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Enzyme-Based Nutritional Cancer Therapy

Dr. Paul Anderson
Facing the Mental-Emotional Challenges of Cancer

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From the Publisher

Rapid Evolution: More Than COVID-19

One of the biggest concerns with the coronavirus vaccines has been how effective they will be against variants. Invariably a spokesperson makes the claim that the vaccine will be effective, albeit probably requiring a booster shot. Given that we are less than 60% full vaccinated in the US. and much less internationally, "booster" shots are hypothetical as none have been tested or are available. The term "variant" may conjure up some mutation has taken place modifying the virus over the past year. More likely, variants represent hardier coronaviruses better able to adapt to ill humans who are incapable of mounting a triumphant defense against infection. While we think of animals adapting over generations taking relatively long time periods, viruses evolve far more quickly. The variant plaguing India will undoubtedly predominate the COVID-19 disease-scape in the months ahead.

In the June 5th *Wall Street Journal* a review of Cal Flyn's new book, *Islands of Abandonment: Nature Rebounding in the Post-Human Landscape* talks about current and past incidents of rapid floral and faunal evolution. The area surrounding Chernobyl that has been closed off to humans for more than three decades is

now replete with wildlife, vegetation, and trees that had been extinguished in the aftermath of the meltdown. Closer to home, Flyn marvels at the return of certain fish in Newark Bay in New Jersey. For centuries the tanneries defiled its waters with sulfuric acid, arsenic, and chromium. Hatters discarded unused mercury there. In the 1950s polychlorinated biphenyls (PCBS) used as insulators and coolants were dumped in the bay. Herbicides such as Agent Orange and its more lethal byproduct, dioxin, were also discharged there. Needless to say, the bay waters were so toxic that all fish and oysters died off.

Flyn writes about the return of the leopard-spotted Atlantic killfish to the Newark Bay in the 1990s. The killfish perished along with most other fish there in the 1950s. For the killfish to return meant that some killfish on the Atlantic seaboard had genes capable of adapting to a very toxic brew. In fact, when scientists compared in 2016 the killfish living in Newark Bay to killfish from non-contaminated waters, they were astounded to find an 8,000% difference in capability of handling toxic chemicals. For the killfish to survive Newark Bay, those variants needed to evolve over three decades – a rapid transformation for fish.

Rapid evolution is hardly a 20th century phenomenon. In Manchester, England, in the 1840s a butterfly naturalist observed that the peppered moth, typically light and pale colored, was increasingly observed as brown toned. Apparently, the lichen on trees that the moth favored was increasingly denuded by the toxic smoke and acid rain of the surrounding mills. The dark color of the moth afforded it safety in blending in with the bark. When Manchester's acrid smoke dissipated with improved industrialization the peppered moth resumed its lighter coloration.

An article in *Nature* in 2011 reported how the tawny owl in Finland changed its primary coloration from a light gray to a dark brown. Finland has seen a diminishing snow level over the past two decades. With a lesser amount of snow, the owl's coloration has changed from gray to brown to better blend in with the trees. The author suggested that this rapid evolution is the first to be directly attributable to climate change.

Animals and plants are adapting to the world impacted by our pollution – in certain cases rapidly. We may not be so adaptable.

Low Dose Naltrexone: The Simple Drug Ignored by Oncology (and Neurology, Rheumatology, Gastroenterology, Dermatology, Psychiatry, and Pain Medicine)

It's been well over 30 years since Bernard Bihari, MD, discovered the dramatic effect of low dose naltrexone for stabilizing the immune system in patients with HIV/AIDS. And it must be emphasized that low dose naltrexone is a very different pharmaceutical from the full dose naltrexone used in treatment of opiate dependency disorders and alcoholism. Bihari's work was disseminated slowly in the days before the internet. One patient with multiple sclerosis, Linda Elsegood, who resided in the UK heard through small patient groups about his work in the US. After suffering with progressive multiple sclerosis with no effective therapy, she heard about low dose naltrexone. A general practitioner agreed to prescribe LDN for her; within weeks Elsegood experienced notable improvements. It is now more than 20 years, and not only is Elsegood's MS in remission but she has been the primary force and advocate of LDN in the international educational resource group, LDNresearchtrust.org.

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From the Publisher

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LDN has a growing list of clinicians who prescribe it, researchers who study it, and patients using it. Still low dose naltrexone is being prescribed as an off-label drug, not recognized by the FDA, and largely unknown to doctors and the scientific community. How can a drug that is beneficial for many medical conditions with minimal adverse effects be so grossly ignored?

This June the LDNresearchtrust.org held its annual meeting virtually. (While some may miss the getting together of the in-person meeting, there is something to be said about being able to attend a very informative meeting from one's kitchen table.) For those who missed the meeting, one can purchase the full presentation and have access to it throughout the year. LDNresearchtrust.org is also offering a master class to certify LDN prescribers. CME credit is available for those purchasing and listening to the 2021 meeting.

This issue we focus on cancer. While we are well acquainted with the role that LDN plays in treating autoimmune disease and modulating the immune system, using LDN in the treatment of cancer has not been greatly appreciated in its off-label applications. At the 2021 conference Andrew McCall, MD, a Glascow, Scotland practitioner discussed his experience prescribing LDN. He discussed a case of a 47-year-old male who presented to him with metastatic melanoma who had undergone six surgical procedures and was given a one-year prognosis. The patient was treated with immunotherapy, which did provide some benefit in controlling his disease. Ultimately it proved to be too painful and needed to be discontinued. Dr. McCall prescribed LDN slowly increasing it to a nightly dose of 4.5 mg. Gradually the patient's pain subsided, and he experienced overall wellness. Dr. McCall has continued to follow him for seven years; the patient shows no sign of recurrence or progressive metastasis.

At the conference Akbar Khan, MD, in Toronto, Canada, discussed several of his 650 patients that he treated with LDN. His first case was an example of how LDN treatment can directly treat cancer as reported in *OHDM* in September 2014.[1] A 60-year-old male presented with tongue cancer. He was advised to undergo radical surgery, including glossectomy, laryngectomy, radiation treatment, and chemotherapy; he refused all of these recommendations. Instead, he sought Dr. Khan's care who agreed to initiated LDN. In addition, he was prescribed high-dose vitamin D3. The patient responded well to the LDN and vitamin D3; the tongue cancer resolved as documented on MRI and has remained in remission over nine years. LDN enabled this patient to avoid radical surgery that would have taken away his tongue and voice box. He had excellent quality of life and did not experience adverse effects. Why is this treatment being ignored by oncologists?

Khan thinks that LDN is capable of exerting anti-cancer activity by its capability of increasing endogenous opiate methione enkephalin and blocade of opiod growth factor based on the work of Ian Zagon, MD.[2] However, Khan is more impressed with LDN's role as an adjuvant treatment in cancer – its ability to act synergistically with other therapies to improve cancer patient outcomes. As an example, he cites a 63-year-old female who had Stage 2A non-Hodgkin's lymphoma. She was initially treated with chemotherapy and targeted immune treatment. After this treatment was completed, she initiated LDN together with other integrative cancer treatments. She is alive now seven years later.

Prof. Angus Dalgleish, professor of oncology at St. George's, University of London, explains that LDN has both direct anti-cancer effects targeting cancer cells and indirect anti-cancer activity "reeducating" the immune system. His research has demonstrated that anti-cancer activity is not carried out entirely by increasing endogenous opiate activity. Instead LDN modulates the "toll-like receptor" (TLR) system acting independently on the immune, endocrine, and neurologic system. Experimentation has demonstrated that LDN is capable of exerting differing effects on TLR receptors. The activation of TLR 9 has an inhibitory effect on IL-6. Because IL-6 drives cancer cell cancer proliferation and growth, its inhibition by TLR 9 exerts a profound anti-cancer effect.[3] Prof. Dalgleish's work should provide ample reason for academicians to research LDN's activity in cancer treatment.

Cancer: The Journey from Diagnosis to Empowerment
by Dr. Paul Anderson

Most naturopathic physicians and integrative doctors are familiar with Paul Anderson, ND, who lectures extensively. Anderson has worked closely with cancer patients and their families over the past 20 years. He and Dr. Mark Stengler are the authors of *Outside the Box Cancer Therapies.* Paul's clinical work has focused on supporting patients who have undergone conventional cancer care, providing supportive strategies and treatment to maintain cancer remission, improve quality of life, and optimize palliative care when cure is not possible. Anderson's work was recognized by the National Institutes of Health when he headed a clinical trial. Beyond the "outside the box" cancer therapies constituting much of Anderson's work, he has focused on the emotional and mental aspects of the cancer patient's survival journey. Such study has led to the publication of his newest book*: Cancer: The Journey from Diagnosis to Empowerment*.

While different cancer diagnosis offers a better or worse prognosis, each patient faces a different cancer course dependent not only on cancer care but on patient mindset, mental wellbeing, and ability to emotionally deal with cancer. Of course, all patients cringe when confronted with a cancer diagnosis, but how the patient approaches his/her life and treatment depends to a greater degree on acceptance of the diagnosis and an openness to explore mental and emotional impediments to healing. Those patients who remain angry and convinced of their doom experience more treatment failure than those who are willing to open up to face their fears and past traumas. We all recognize that mindfulness is an important tool for healing, but how do we get patients and their families to bring this into the healing process? Anderson points out how not only is this invaluable in the adult with cancer, but it is even more important in the family with a child having cancer.

Dr. Anderson's shares with us in this issue how we get from diagnosis to empowerment.

Jonathan Collin, MD

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1. Khan A. Long-term remission of adenoid cystic tongue carcinoma with low dose naltrexone and Vitamin D3 – A case report. *OHDM.* 2014;13,3.
2. Donahue R, Zagon I. The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. *Gynec Oncol.* 2011; 122,2,382-88.
3. Liu W, Dalgleish A. Naltrexone at low doses upregulates a unique gene expression not seen with normal doses: implications for its use in cancer therapy. *Int J Oncol.* 2016; 49, 2, 793-802.

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Pathways to Healing

by Elaine Zablocki

ND Praises Adaptogenic Herbs

Some herbs are natural medicines with the ability to heal specific conditions. For example, foxglove, also called *Digitalis purpurea*, is the source of the medication digoxin, used to treat atrial fibrillation and heart failure.

Other herbs have a more general effect. They produce a nonspecific state of resistance to various stressors; they have an overall normalizing effect on the body. These herbs are called adaptogens. Now, Rachel Rozelle, ND, has written a useful book called *The Essential Guide to Adaptogens: 15 Super Herbs to Relieve Common Ailments.*

Rozelle found these herbs personally useful back when she was a student at the Southwest College of Naturopathic Medicine, in Tempe, Arizona. "As part of our training we learned a great deal about medicinal herbs and their varying effects," she recalls. "I experienced chronic stress at that time; I found that my body responded well to adaptogenic herbs. When you have that wired-and-tired feeling, when you are on edge and jittery, adaptogens sooth your nervous system in a strengthening way."

Rozelle practices at Windhorse Naturopathic in Brattleboro, Vermont, where she specializes in pediatric medicine. She is especially passionate about working with developmental pediatrics and mental health conditions such as autism, anxiety, PANS, PANDAS, and depression. "Everyone benefits from adaptogenic herbs because everyone is bombarded by stress and these herbs specifically help the body recover from these stresses." she says. "The herbs work together synergistically, so people receive an improved effect by using a tincture based on a mixture of herbs. They all work a bit differently, and they help strengthen each other's actions."

The Essential Guide to Adaptogens discusses the benefits of adaptogenic herbs such as ginseng, ashwagandha, cordyceps, holy basil, turmeric, licorice, rhodiola, and schisandra.

The book includes a description of the benefits of each herb plus recipes and tips for using them. It also lists various conditions and suggests useful treatments for each condition.

All the adaptogens have similar effects, but they also have their own unique strengths. "Rhodiola is one of my personal favorites because I find it is a more stimulating adaptogen," Rozelle says. "It has a more energizing and brain-boosting effect; it improves cognition. They've actually done studies showing that it helped decrease mental fatigue and stress related to test taking and led to improved test scores. A similar study in night shift hospital workers found improved mental and physical performance, resulting in decreased clinical errors."

Rachel Rozelle, ND

Holy basil is a very calming adaptogen. It is an easy plant to grow, and you just eat the leaves. "I would say most of my patients need that calming effect, so holy basil is a really nice plant for most people. "Rozelle says. "It is great for brain support, for mental clarity, and for immune support as well. It is antibacterial, it's antiviral, and it's antifungal."

Ashwagandha is one of the most common adaptogens Rozelle uses. "It's really great for so many things," she says. "It binds to the GABA receptors in the brain, so it reduces anxiety. It also supports thyroid function and helps promote normal cortisol patterns in the body. Cortisol is a stress hormone and there's usually cortisol dysfunction with insomnia, so ashwagandha helps promote improved sleep."

In an appendix to the book, Rozelle lists six trusted sources for purchasing adaptogenic or other botanical medicines: BanyanBotanicals.com, GaiaHerbs.com, Herb-Pharm.com, MountainRoseHerbs.com, RebelHerbs.com, and WiseWomanHerbals.com. "You want to make sure you're using high-quality herbs," she says. "These companies have extensive programs, testing the incoming herbs – they really put their heart and soul into the work."

Homeopathic Medicine Effective Treatment for Challenging Conditions

In addition to adaptogenic herbs and many other treatment modalities, Rozelle relies on homeopathic medicine to treat many conditions. "I studied homeopathy in naturopathic medical school. It intrigued me because it is so different from other forms of medicine," she recalls. "It is a challenging treatment modality to learn. I've found it works really well for many different conditions, including autoimmune problems and mental health issues."

Rozelle treats many children with pediatric autoimmune neuropsychiatric disorders, an autoimmune condition attacking

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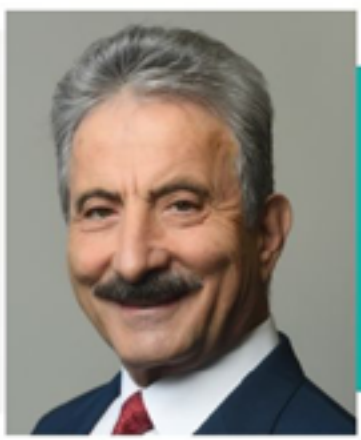

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Pathways to Healing

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the brain, originally triggered by an infection. These children often have behavioral issues such as rage, tics, extreme anxiety and emotional dysregulation. "Homeopathy, it is very gentle but also effective in these cases," Rozelle says. "I found it to be a safe, effective treatment for these conditions. Homeopathic medicine is holistic, individualized, and stimulates true healing in the body. Better yet, there are no side effects!"

Autoimmune and mental health issues are very individualized problems, she notes. The way one person experiences anxiety is very different from the way someone else experiences anxiety. Homeopathic treatment also must be individualized for each patient. "If a remedy doesn't work, that's because it's not the right remedy for that person, in which case you just have to keep trying, to find the remedy that will support that person the most. I've helped people get off of psychiatric medications using homeopathy and other naturopathic treatments."

Rozelle currently lives and practices in Vermont. She used to live in California and is still available there through telemedicine. In Vermont, NDs are considered primary care physicians with a full scope of practice and insurance coverage. When Rozelle practiced in California, her patients had to pay out-of-pocket since her services weren't covered by insurance. "Every state is different," she says. "In California I could only prescribe hormones, while in Vermont we have a full scope of practice, and I can prescribe a range of medications."

When she lived in California, Rozelle was a member of the board of the California Naturopathic Doctors Association. "We met with many state legislators about these issues. Every year we would go to the state capitol and work for insurance coverage and increasing our scope of practice, but it takes time to make these changes."

At the end of her book, Rozelle notes that adaptogens are only one part of a complete health support program that might also include breath work, yoga, massage, or meditation. "Self-inquiry helps us all identify and remove the major stressors in our lives which can be obstacles to our path to healing," she says. "It's important to focus on the foundations of health, such as a good diet, enough sleep, and stress modulation. We need to examine our lives and remove what we call obstacles to cure. That could be excessive stress, or a poor diet, or a toxic personal relationship. If someone takes health supplements but they're also smoking and eating fast food every day, it is like putting a Band-Aid on a wound. We need to remove any obstacles in the way that limit the body's full ability to heal."

Resources

https://www.drrozelle.com/blog: Rozelle's website includes information about her treatment specialties, services, and educational resources for patients. She's written an extremely useful series of articles, posted on her blog, covering diet, inflammation, recovering from trauma, medications, special needs of teenagers, and homeopathy.

Elaine Zablocki is the former editor of CHRF News Files.

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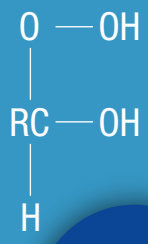

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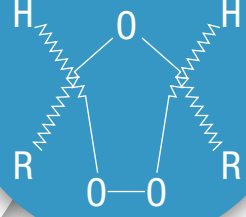

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Shorts

briefed by Jule Klotter
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Protocol for Long Haul COVID-19

In June 2021, Front Line COVID-19 Critical Care Alliance (FLCCC Alliance) released a protocol for Long Haul COVID-19 Syndrome (LHCS). FLCCC Alliance, led by Dr. Paul Marik, is the same group of researchers that developed the MATH+ protocol for COVID-19 patients.

The group's I-RECOVER Management Protocol addresses the many, often debilitating symptoms experienced after infection, including fatigue, headaches, sleep difficulties, smell disorder, decreased appetite, painful joints, dyspnea, chest pain, and cognitive dysfunction. The symptoms are similar to chronic inflammatory response syndrome (CIRS)/myalgic encephalomyelitis/chronic fatigue; but those with LHCS tend to recover on their own, "albeit slowly." Marik reports, "…many consider post-COVID-19 to be a variant of the mast cell activation syndrome."

LHCS can affect people who received a COVID-19 injection ("likely due to monocyte activation by the spike protein from the vaccine") as well those who were infected with the actual virus. Younger people and those who had mild-to-moderate infections appear to be more affected by LHCS than older people or those with co-morbidities. FLCCC Alliance says, "It is likely that delayed treatment (with ivermectin) in the early symptomatic phase will result in a high viral load, which increases the risk and severity of LHCS."

No government health agency has provided guidance on LHCS treatment. I-RECOVER protocol was developed in collaboration with expert clinicians, including Dr. Mobeen Syed, Dr. Ram Yogendra, Dr. Bruce Patterson, and Dr. Tina Peers. Because no clinical treatment trials for LHCS have been conducted, the group says, "these recommendations are based on the pathophysiologic mechanisms of COVID-19 and post-viral illnesses along with our collective experience observing profound and sustained clinical responses achieved with the treatment approaches below."

Ivermectin is the first treatment given to LHCS patients. This inexpensive drug binds to the spike protein, disrupting its ability to attach to ACE-2 receptors. It also has multiple anti-inflammatory and anti-viral effects, as described in a June 2021 review article by Asiya Kamber Zaidi and Puya Dehgani-Mobaraki. Patients with cognitive symptoms are given fluvoxamine. Those with shortness of breath or low oxygen levels need to be assessed for secondary organizing pneumonia.

In addition to a course of ivermectin, patients are also given macrophage/monocyte repolarization therapy consisting of vitamin C, omega-3 fatty acids, atorvastatin, melatonin, and vitamin D3. If all symptoms do not resolve after two-to-four weeks of ivermectin treatment, the protocol recommends treatment with prednisone. If symptoms are still present after ivermectin and prednisone, patients are treated for suspected mast cell activation. The exact protocol with dosages is given at the **flccc.net** website.

The research group states that this protocol is a work in progress: "As with all FLCCC protocols, we must emphasize that multiple aspects of the protocol may change as scientific data and clinical experience in this condition evolve, thus it is important to check back frequently or join the FLCCC Alliance to receive notification of any protocol changes."

Zaidi AK, Dehgani-Mobaraki P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. *J Antibiot (Tokyo).* June 15, 2021: 1–13.

Nagalase, GcMAF, and Cancer

High serum levels of nagalase (alpha-N-acetylgalacto-saminidase) indicate an immune system deficiency and are associated with the presence of cancer, viral infections, and other conditions, including autism. Nagalase, an enzyme, inhibits the production of Gc protein-derived macrophage activating factor (GcMAF); the Gc protein is also known as vitamin D3-binding protein DBP. By inhibiting GcMAF production and the activation of macrophages, nagalase cripples the immune system's ability to detect and destroy unhealthy cells. Nagalase is secreted by cancer cells and is found in the envelope protein that surrounds some types of viruses.

Reducing nagalase levels has produced clinical improvement in patients with diverse cancers, including prostate, breast, pancreas, liver, lung, colon, stomach, kidney, and ovarian cancers as well as mesothelioma, melanoma, fibrosarcoma, glioblastoma, neuroblastoma, and various leukemias. In a 2020 article, Daniel F. Royal, DO, reports, "Nagalase activity is directly proportional to

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viable tumor burden." He uses salicinium, a nagalase inhibitor, intravenously and in oral form (Orasal) to lower nagalase levels. Royal's case report of a patient with lymphoma appears in this issue of *Townsend Letter* (page 22). *Townsend Letter* has also published several articles on salicinium: "Salicinium: An Excellent Addition to My Armamentarium for Cancer Patients" by Carol M. Brown, DO, PhD (August/September 2016); "Salicinium – Disrupting Anaerobic Glycolosis and Improving GcMAF Immune Response" by Virginia Osborne, ND (August/September 2017); "Salicinium Treats and Prevents Cancer and Viral Infections" by Jeffrey J. King, MS (August/September 2019). All are available online.

Another way to decrease nagalase levels is to increase GcMAF levels via supplementation. In addition to increasing macrophage activity, GcMAF also directly binds to and inhibits human nagalase *in vitro*, according to Marco Ruggiero, MD, PhD. Purified human GcMAF, along with other GcMAF-boosting nutrients, have been used to treat cancer with some success. Beta-glucans, glutathione, vitamins D2 and D3, nitric oxide, and bovine colostrum help the body produce GcMAF, according to an article by B. George et al. Also, microorganisms in Bravo Probiotic (Les Alpes, Wellington, New Zealand) produce GcMAF from milk and colostrum Gc-globulin during fermentation. Recently, Ruggiero and colleagues developed a supplement, called imuno® (imuno.org) that reportedly has significantly greater activity against nagalase than GcMAF itself. Imuno® consists of low-molecular-weight microbial chondroitin sulfate, ultrapure phosphatidylcholine, and vitamin D3.

George B, et al. The Orthomolecular Components Needed to optimize the in vivo production of GcMAF. Available at academia.edu.

Health Diagnostics and Research Institute. Nagalase in Blood. Available at http://www.hdri-usa.com/tests/nagalase/

Royal DF. A Clinical Study: Modifying Nagalase with Glycome. *Proccdings of ACIM Researcher.* 2020;2(1).

Ruggiero M. imuno® is over 100 times more effective than pure GcMAF.

Homeopathic Treatment and Non-Small Cell Lung Cancer

A 2020 double-blind, randomized, multicenter Austrian study found that homeopathic treatment improved quality of life and survival in patients diagnosed with late-stage, non-small cell lung cancer (NSCLC). In this three-arm trial, 52 patients received usual care (control group); 51 patients received homeopathic treatment, and 47 patients received placebos that appeared and tasted like homeopathic remedies. The usual-care group acted as the control for the placebo participants who received individual attention from homeopathic physicians.

Homeopathic physicians interviewed each of the treatment and placebo participants and determined an appropriate constitution remedy that primarily addressed mental, emotional, and general symptoms. The constitutional remedies were given in the Q/LM potency (1:50,000) and applied as a liquid. Homeopathics to address adverse symptoms caused by the chemotherapy treatment were prescribed in less diluted potencies (decimal [1:10] or centesimal [1:100]) and delivered as sugar pellets. The doctors faxed their prescriptions for each patient to a pharmacy.

At the pharmacy, patients were randomized into the treatment group or the placebo group. A pharmacist (who did not take part in the randomization) prepared the homeopathic or placebo medications for each patient, packaged them in identical packaging, and mailed them to patients. The investigators, doctors, patients, and the statistician who received the raw data were blinded to treatment allocation until study ended and the data analyses were completed.

Patients in the treatment and placebo arms completed four questionnaires upon entering the study: EORTC QLQ-C30 (measures quality of life), the RAND short-form health survey (SF-36), the Subjective Well-Being Questionnaire, and one that assessed the patient's attitude toward homeopathy and complementary/alternative medicine. Patients completed the same questionnaires after nine weeks when they were assessed by a homeopathic physician, and again at the 18-week assessment. During these appointments, the homeopaths "evaluated whether to continue with the same remedies or change them, based on patient reporting and routine cancer assessment." Each patient was followed for 24 months or until death.

Data from the nine-week questionnaires showed a significant reduction in all symptom scales except pain, diarrhea, and financial difficulties scores in the homeopathy group compared to the placebo group – "by both univariate analysis of the individual symptom scales and by multivariate analysis of all symptoms scales." All symptoms were significantly lower in the homeopathy group after 18 weeks. Also, the homeopathy group showed progressive improvement between visit 1 and visit 2 and, then, between visit 2 and visit 3 – improvement that did not occur in the placebo group.

The homeopathy group also had a longer mean survival time than both the placebo group and the control: "Estimated survival time (hazard ratio for mean) was 477 (95% CI: 410-545) days in homeopathy group, 352 (95% CI: 278-427) days in placebo group and 274 (95% CI: 215-333) days in control group." Moreover, more homeopathic patients were alive after 24 months than placebo or control patients: "Survival rate in the homeopathy group was 45.1% [23 of 51], in the placebo group was 23.4% [11 of 47], and in the control group was 13.5% [7 of 52]." The difference in survival rate between the placebo and control groups was not statistically significant (p=.154).

During the study's five-year recruitment period, conventional treatment for late-stage NSCLC did not include immune-oncologic therapy. The authors say, "Today, immune-oncologic and chemotherapy are established as first-line therapy. Therefore, further studies with immune-oncologic therapy are necessary to investigate the effect of homeopathic therapy with modern forms of therapy." This well-designed study indicates that adding homeopathic care can improve quality of life and survival in cancer patients. Homeopathy has the advantages of not interacting with other treatments and of being low cost.

Frass M, et al. Homeopathic Treatment as an Add-On Therapy May Improve Quality of Life and Prolong Survival in Patients with Non-Small Cell Lung Cancer: A Prospective, Randomized, Placebo-Controlled, Double-blind, Three-Arm, Multicenter Study. *The Oncologist.* 2020;25:e1930-e1955.

Group Drumming for Mental Health

"One of the community music interventions growing in popularity for mental health is group drumming, perhaps due to the inclusiveness of drumming circles, lack of fine motor skill requirements and strong steadying rhythms," write Daisy

continued on page 14 ➤

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Shorts

➤ *continued from page 12*

Fancourt and colleagues. Their 2016 study indicates that engaging in group drumming improves mental wellbeing and decreases depression and anxiety. Surprisingly, it also reduces the inflammatory immune response.

This UK study compared people who attended at least eight of 10 weekly sessions of group drumming (n=30) to a group that regularly attended other non-musical social activities each week (n=15). All participants were receiving mental health services. Over the 10 weeks, a professional drummer, experienced in leading community music activities, taught participants the basics of playing djembe drums as they sat in a circle. The 90-minute drumming sessions consisted of 'call-and-response' exercises, during which participants copied the leader to learn increasingly complex rhythmic patterns. They were also given time to improvise on their own, "creating musical accompaniment to different scenarios such as the sound of water." The drumming leader had no knowledge about the participants' backgrounds or psychological profiles.

Participants in the drumming and control groups completed self-administered questionnaires that measured demographics, anxiety and depression, well-being, stress, and social function at baseline, weeks 6 and 10, and three months after the drumming sessions ended. In addition, drummers had cortisol and cytokine levels assessed with saliva testing.

By week 10, the drumming group showed a significant average decrease of 20% in anxiety and a 38% decrease in depression while the control group's average had no significant change. Social resilience in the drumming group also improved 23%. Wellbeing scores improved in the drumming group (not statistically significant) and remained unchanged in the control. Perceived stress did not change in either group. At the three-month follow-up, the drummers retained much of their improvement.

The saliva tests showed a significant increase in the anti-inflammatory cytokine IL4 while most other measures remained unchanged: "At baseline, a comparison of levels of TNFα and IL4 was elevated towards TNFα (a pro-inflammatory response); however, over the intervention period, there was a shift towards IL4 (an anti-inflammatory response) which reached significance by week 6…." In comparing the psychological and biological measures, the authors found increases in IL4 associated with decreases in anxiety (p=.044) and declines in IL17 correlated to improved social resilience (p=.080).

The authors say, "It would be instructive to focus in future work on specific subgroups, such as those with major depressive disorder or generalized anxiety disorder, to assess where drumming interventions have the greatest therapeutic potential." Given that many people with cancer and other serious illnesses also experience anxiety and depression, I wonder if group drumming might be helpful for them also.

Fancourt D, et al. Effects of Group Drumming Interventions on Anxiety, Depression, Social Resilience and Inflammatory Immune Response among Mental Health Service Users. *PLOS One.* March 14, 2016.

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Publisher Jonathan Collin, MD
Editor Jule Klotter
Contributing Medical Editor Alan Gaby, MD
Managing Editor Barbara Smith
Circulation Manager Joy Reuther-Costa
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Columnists & Writers
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Eleonore Blaurock-Busch, PhD
Jim Cross, ND, LAc
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Contributing Writers
Katherine Duff
Bob Frost
Gary Null, PhD

Layout & Design
Barbara Smith/Sign Me Up! Inc.

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

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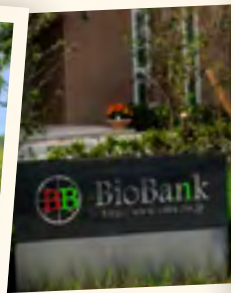

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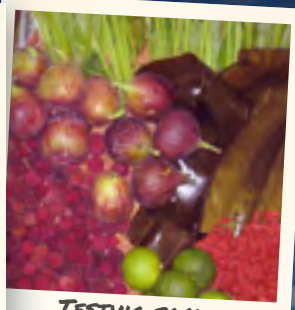

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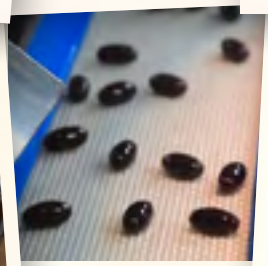

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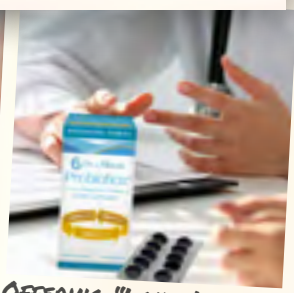

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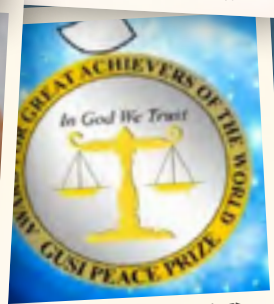

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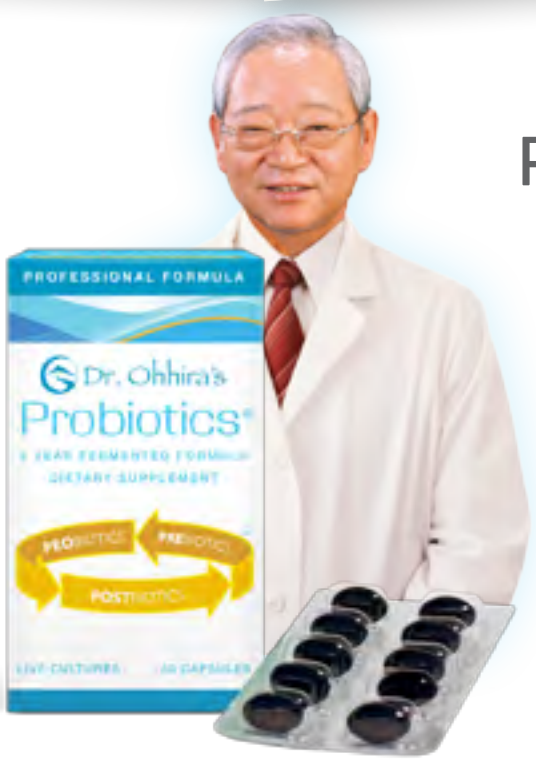

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Paul S. Anderson, ND, is a recognized educator and clinician in integrative and naturopathic medicine. His clinic in Seattle, Washington, specializes in helping people with cancer and chronic diseases. In this issue, he shares excerpts from his new book that offers patients and those who care for them a framework for processing the mental and emotional challenges that so often accompany a cancer diagnosis.

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Literature Review & Commentary

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

Does Eating Too Much Sugar Cause Cancer?

The association between intake of total and added sugar and cancer risk was examined in a prospective cohort study of 101,279 French adults (median age, 40.8 years) participating in the NutriNet-Sante prospective cohort study. During a median follow-up period of 5.9 years, after adjustment for known risk factors (sociodemographic, anthropometric, lifestyle, medical history, and nutritional factors), total sugar intake was positively associated with overall cancer risk. The hazard ratio (HR) comparing the highest and lowest quartiles of intake was 1.17 (p for trend = 0.02). For breast cancer, comparing the highest and lowest quartiles, the HR was 1.51 (p for trend = 0.0007).

Comment: In this study, higher sugar intake was associated with an increased risk of total cancers and breast cancer. Although observational studies cannot prove causation, the possibility that eating too much sugar can promote cancer is biologically plausible. High sugar intake can increase obesity, insulin resistance, inflammation, and oxidative stress; and each of these factors is associated with an increased risk of developing various types of cancer. In addition, refined sugar contains no vitamins and minerals and, therefore, dilutes the diet with respect to potential anti-cancer nutrients such as vitamin C, zinc, and selenium.

Debras C, et al. Total and added sugar intakes, sugar types, and cancer risk: results from the prospective NutriNet-Sante cohort. *Am J Clin Nutr*. 2020;112:1267-1279.

Can Vitamin D Prevent Cancer?

In the Vitamin D and Omega-3 Trial (VITAL), 25,871 men and women (mean age, 67.1 years) in the United States who did not have cardiovascular disease or cancer at baseline were randomly assigned to receive, in double-blind fashion, 2,000 IU per day of vitamin D, 1 g per day of fish oil (Omacor; providing daily 460 mg of eicosapentaenoic acid and 380 mg of docosahexaenoic acid), both treatments, or placebo (olive oil) for a median duration of 5.3 years. As previously reported, no significant differences in cancer incidence were seen in any of the groups. However, in this new secondary analysis, the proportion of participants who developed advanced cancers (metastatic or fatal) was significantly lower in the vitamin D group than in the placebo group (1.7% vs. 2.1%; hazard ratio [HR] = 0.83; p = 0.04). When stratified by body mass index (BMI), the reduction in risk of advanced cancers associated with vitamin D treatment was significant for those with a normal BMI (< 25 kg/m^2; HR = 0.62; 95% confidence interval [CI], 0.45-0.86). In contrast, there was no significant effect of vitamin D in participants who were overweight or obese (BMI of 25 to < 30 kg/m^2: HR = 0.89; 95% CI, 0.68-1.17; BMI of 30 kg/m^2 or higher: HR = 1.05; 95% CI, 0.74-1.49) (p for interaction by BMI = 0.03).

Comment: These findings suggest that vitamin D supplementation can decrease the incidence of advanced cancers in normal-weight individuals, but not in people who are overweight or obese. Since vitamin D had no significant effect on the incidence of cancer, it would seem that vitamin D supplementation prevented the progression of some cancers to an advanced stage. Two possible explanations come to mind regarding why vitamin D was not beneficial for overweight and obese people. First, vitamin D is readily taken up by adipose tissue (of which overweight and obese people have more) and therefore might be less available to exert its various biochemical effects in the rest of the body. Second, obesity is associated with many potentially cancer-promoting biochemical abnormalities such as chronic inflammation, increased oxidative stress, and insulin resistance. Some of these factors might overshadow any potential benefit of vitamin D.

Chandler PD, et al. Effect of vitamin D3 supplements on development of advanced cancer: a secondary analysis of the VITAL randomized clinical trial. *JAMA Netw Open*. 2020;3:e2025850.

Is Testosterone Therapy Safe for Men with a History of Prostate Cancer?

The authors of this study followed 850 patients who underwent radical prostatectomy for prostate cancer, performed by a single surgeon from 2009 to 2018. One hundred fifty-two patients (18.2%) received postoperative testosterone replacement therapy (TRT) because they had a low preoperative calculated free-testosterone level (calculated from serum testosterone and sex hormone-binding globulin levels) and a delayed postoperative recovery of sexual function. These patients were compared with 419 control patients matched by Gleason Grade Group and stage. Biochemical recurrence was defined as two consecutive prostate-specific antigen (PSA) values greater than 0.2 ng/ml. During a median follow-up period of 3.5 years, biochemical recurrence occurred in 7.2% of patients receiving TRT and 12.6% of patients in the control group ($p = 0.07$). In adjusted time-to-event analysis, TRT was an independent predictor of recurrence-free survival. After accounting for Gleason Grade Group, pathological stage, preoperative PSA level, and calculated free-testosterone level, patients receiving TRT were 54% less likely to have a recurrence. In men who had a recurrence, TRT delayed the time to recurrence by an average of 1.5 years. There were no identifiable health complications associated with TRT.

Comment: Androgens promote the development and progression of prostate cancer in experimental models. Concern has therefore been raised that TRT is unsafe for patients with a history of prostate cancer. However, there is no clear evidence that testosterone promotes the development or progression of prostate cancer in humans. The results of the present study are consistent with previous studies, which found no increase in disease progression in prostate cancer patients receiving TRT.

Ahlering TE, et al. Testosterone replacement therapy reduces biochemical recurrence after radical prostatectomy. *BJU Int*. 2020;126:91-96.

Can Whole Grains Prevent Colon Cancer?

The association between intake of whole grains, intake of fiber, and risk of colorectal cancer was examined in a prospective cohort study of 478,994 US adults (aged 50-71 years) participating in the NIH-AARP Diet and Health Study. Diet was assessed using a food-frequency questionnaire at baseline in 1995-1996. During a follow-up period of 16 years, 10,200 cases of colorectal cancer were documented. After adjustment for potential confounding variables (including age, body mass index, physical activity, alcohol intake, smoking, intake of red and processed meat, and family history of cancer), there was an inverse association between intake of whole grains and colorectal cancer. The hazard ratio (HR) comparing the highest and lowest quintiles of intake was 0.84 (p for trend < 0.001). The HR for fiber intake (comparing extreme quintiles) was 0.96 (p for trend = 0.40), and for fiber from grains was 0.89 (p for trend < 0.001). There was no significant association between fiber intake from non-grain sources and colorectal cancer.

Comment: Dietary fiber may have certain actions that could decrease the risk of developing colon cancer. These include binding or diluting carcinogens in the intestinal tract, decreasing the conversion of bile acids to carcinogens, production of anticarcinogenic short chain fatty acids as a byproduct of fiber fermentation, and speeding intestinal transit (thereby decreasing the contact time between carcinogens and the bowel wall).[1,2] In addition to having a number of potential direct anticancer effects, the fiber components of some plants are the main dietary sources of lignans, a group of diphenolic compounds that have anticancer activity.[3]

In the present study, higher intake of whole grains and of fiber from grains (but not fiber from other sources) was associated with a lower incidence of colorectal cancer.

Hullings AG, et al. Whole grain and dietary fiber intake and risk of colorectal cancer in the NIH-AARP Diet and Health Study cohort. *Am J Clin Nutr*, 2020;112:603-612.

Zinc-L-Carnosine Prevents Chemotherapy Side Effect

Ninety-one patients with hematologic cancer who were scheduled for high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT) were randomly assigned to a prevention group (in which zinc-L-carnosine lozenges were started before chemotherapy) or to a control group (in which the lozenges were started immediately after the onset of Grade 2 oral mucositis). Each lozenge contained 18.75 mg of zinc-L-carnosine, and one lozenge was dissolved in the mouth four times per day. Oral mucositis was evaluated daily from the start of chemotherapy until 35 days after transplantation. The incidence of Grade 2-or-higher oral mucositis was significantly lower in the prevention group than in the control group (22.0% vs. 44.7%; $p = 0.025$). Zinc-L-carnosine did not affect the outcome of HSCT.

Comment: L-Carnosine (beta-alanyl-L-histidine) occurs naturally in the body and has demonstrated multiple biochemical actions, including antioxidant and anti-inflammatory activity. In a previous study, oral zinc supplementation (not as lozenges) prevented chemotherapy-induced mucositis, but in another study zinc was ineffective. In the present study, zinc-L-carnosine lozenges prevented Grade 2-or-higher oral mucositis associated with high-dose chemotherapy, without influencing the outcome of the cancer treatment. Further research is needed to determine whether zinc-L-carnosine is more effective than zinc or L-carnosine alone.

Kitagawa J, et al. Polaprezinc for prevention of oral mucositis in patients receiving chemotherapy followed by hematopoietic stem cell transplantation: a multi-institutional randomized controlled trial. *Int J Cancer.* 2021;148:1462-1469.

Zinc-L-Carnosine Prevents Side Effects of Radiation Therapy

Forty patients with breast cancer who were undergoing radiation therapy were randomly assigned to receive 10 ml of a suspension of zinc-L-carnosine or placebo twice a day. According to a personal communication from one of the authors, each 10 ml of suspension contained 38 mg of zinc-L-carnosine. Treatment was started on day 1 of radiation therapy and was continued until radiation therapy was complete or until dysphagia developed, at which point steroid therapy was prescribed. The proportion of patients who developed grade 1 or 2 esophagitis (50% vs. 100%; $p < 0.0001$) and the proportion of patients who needed steroid treatment (15% vs. 85%; $p < 0.0001$) were significantly lower in the zinc-L-carnosine group than in the placebo group.

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Comment: This study demonstrated that treatment with a zinc-L-carnosine suspension markedly decreased the incidence of radiation-induced esophagitis and decreased the need for steroid therapy in patients undergoing radiation therapy for breast cancer.

Saldi S, et al. Zinc-L-carnosine prevented dysphagia in breast cancer patients undergoing adjuvant radiotherapy: Results of a phase III randomized trial. *Breast J*. 2020;26:1882-1884.

Omega-3 Fatty Acids Prevent Oxaliplatin Neurotoxicity

One hundred seventy-nine Chinese patients with colon cancer who were receiving oxaliplatin combined with capecitabine were randomly assigned to receive, in double-blind fashion, capsules containing omega-3 fatty acids (346 mg of docosahexaenoic acid and 64 mg of eicosapentaenoic acid) or placebo three times a day, during chemotherapy and continuing for one month after chemotherapy was completed. All patients had six chemotherapy treatment cycles. The incidence of chemotherapy-induced peripheral neuropathy was significantly lower in the omega-3 group than in the placebo group (52.2% vs. 69.7%; $p < 0.02$). In addition, peripheral neuropathy was significantly less severe in the omega-3 group than in the placebo group ($p < 0.02$). Quality of life, as measured by the Global Health Status score on a questionnaire, was better in the omega-3 group than in the placebo group ($p = 0.03$).

Comment: Peripheral neuropathy is a common side effect of oxaliplatin and is its dose-limiting toxicity. In the present study, supplementation with omega-3 fatty acids decreased the incidence and severity of oxaliplatin-related neurotoxicity and improved quality of life in patients undergoing chemotherapy for colon cancer. The authors of the study suggested that the beneficial effect of omega-3 fatty acids was due to its antioxidant, anti-inflammatory, and neurotrophic effects.

Zhang X, et al. Prevention of oxaliplatin-related neurotoxicity by omega-3 PUFAs: A double-blind randomized study of patients receiving oxaliplatin combined with capecitabine for colon cancer. *Medicine*. 2020;99:e23564.

Curcumin for Polycystic Ovary Syndrome, or More Iranian Research Fraud?

Seventy-two overweight or obese Iranian women were randomly assigned to receive, in double-blind fashion, 500 mg of curcumin three times a day or placebo for three months. The mean fasting plasma glucose level and mean serum dehydroepiandrosterone level decreased to a significantly greater extent in the curcumin group than in the placebo group. In addition, curcumin significantly increased gene expression of peroxisome proliferator activated receptor gamma and the activity of glutathione peroxidase, and nonsignificantly increased gene expression of Sirtuin-1 and superoxide dismutase. The mean change in serum fasting insulin, luteinizing hormone, follicle-stimulating hormone, and estradiol did not differ significantly between groups.

Comment: The data cited above came from two different papers. Each paper apparently measured different laboratory parameters from the same study. That these papers were generated from the same study is supported by the following points: Both papers referred to the same document in the Iranian Registry of Clinical Trials (IRCT). In both papers, there were identical recruitment numbers: 112 patients were assessed for eligibility, 25 did not meet inclusion criteria, 8 declined to participate, and 7 were excluded for other reasons. As with numerous other studies coming from Iran, there are many aspects of these papers that make me wonder whether the research is fraudulent.

1. Discrepancy regarding recruitment periods: In one paper, the recruitment period was October 1, 2018, through the end of May 2019. In the other paper, the recruitment period was January 2019 through June 2019.
2. Discrepancies regarding body mass index (BMI): One of the papers and the IRCT document stated that the participants had to have a BMI between 25 and 30 kg/m^2. However, in the other paper, participants had to have a BMI greater than 25 kg/m^2, with no upper limit. In Table 2 of the first paper cited below, the baseline characteristics indicated BMIs ranging from 17.75 to 39.56 kg/m^2. These baseline BMIs violate the inclusion criteria on both the upper and lower end.
3. Discrepancy regarding inclusion criterion: One paper stated that participants had to be 18 to 49 years of age. The IRCT registration document stated that participants had to be 18 to 50. However, in both papers, the baseline characteristics indicated that at least one of the participants was 52 years old.
4. Discrepancy regarding study design: In the second paper cited below, it was stated that the participants came to the clinic only twice: at baseline and 12 weeks after starting the intervention. However, the paper also stated that the capsule packages were checked at the end of each month, and the number of remaining capsules was counted (presumably to assess compliance). It would not be possible to check the packages after one and two months if the participants did not return to the clinic until 12 weeks.
5. Ethical issue: One of the papers stated that the first patient was recruited on October 1, 2018. However, according to the IRCT document, the study was not approved by the ethics committee until October 28, 2018.
6. Issue regarding the placebo: One of the papers stated that the color of the placebo (maltodextrin) was "completely similar" to that of curcumin. However, curcumin is orange and maltodextrin is white. There was no mention of whether anything was added to the maltodextrin to change its color.
7. Discrepancy regarding funding: One paper stated that no funding was received. The other paper did not mention funding. The IRCT document stated that the study was funded by Iran University of Medical Sciences.

Heshmati J, et al. The effects of curcumin supplementation on oxidative stress, Sirtuin-1 and peroxisome proliferator activated receptor gamma coactivator 1alpha gene expression in polycystic ovarian syndrome (PCOS) patients: A randomized placebo-controlled clinical trial. *Diabetes Metab Syndr*. 2020;14:77-82.

Heshmati J, et al. Effects of curcumin supplementation on blood glucose, insulin resistance and androgens in patients with polycystic ovary syndrome: A randomized double-blind placebo-controlled clinical trial. *Phytomedicine*. 2021;80:153395.

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3. Horwitz C, Walker ARP. Lignans - additional benefits from fiber? *Nutr Cancer*. 1984;6:73-76.

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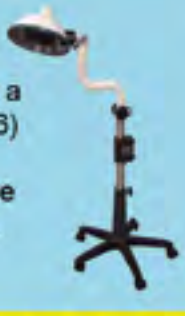

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Rebecca Harder is the author of "Gastra Girl: Saving America One Colon at a Time

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A Case Report – Nagalase Inhibitors and Lymphoma

by Daniel Royal, DO, CTP, JD

On April 10. 2020, Sally Johnson (pseudonym), a 33-year-old black female presented to the Turtle Healing Band Clinic (THBC) in Las Vegas, Nevada. She had developed stomach pain in early February 2020. Her appetite was down. She was also anemic, losing weight, unable to swallow pills, and using a 60 gm CBD oil for pain. The patient was seen in a couple hospitals in Ohio where she was living at the time and found to have lymphoma in her abdomen. She was recommended to have chemotherapy, but the patient refused and sought alternative treatment instead.

When she came to THBC in April 2020, her abdomen was swollen to the point where she appeared to be pregnant. The patient requested IPT (Insulin Potentiation Therapy), but this proved to be too expensive for her. So, a more affordable plan was worked out for the patient. Initially, IV therapy with amino acids was used in combination with a pulsing electromagnetic field (PEMF) treatment in the office. At one point, the patient's albumin began dropping and she developed ascites. A paracentesis was performed in the local hospital. Albumin was thereafter added to her IV to correct this problem from recurring, along with salicinium. Additional labs showed the patient had elevated nagalase and anti-malignin antibody serum ("AMAS") tests. She was then started on THBC's nagalase protocol with Orasal in conjunction with PEMF treatments. Orasal and salicinium are nagalase inhibitors. Her nagalase and AMAS tests continued to improve with treatment until they became "normal."

Patient's AMAS Test Results

AMA ug/m	5/1/2020			9/11/2020		
	S-TAG	F-TAG	Net TAG	S-TAG	F-TAG	Net TAG
500-699						
400-499						
300-399	379			341		
135-299		242	137		268	
100-134						
25-99						73
0-24						

Patient's Nagalase Test Results	Nagalase (U = nmol/min/mg)
4/17/2020	1.04
6/03/2020	1.16
9/10/2020	0.90

Follow-up in September 2020 showed that her anemia had resolved, her abdomen returned to normal size, her energy returned, and she was enjoying normal activities again. A year later, the patient is still completely free of symptoms.

Patient Testimonial (11-20-20)

Thank you so much for saving my life! I was so sick and weak that I couldn't walk with that mass in my belly. It looked like I was 9 months pregnant. And it felt so heavy. Yet, I was losing weight and got down to 73 pounds. I serve and believe God and asked him to please help me. Then, two days before I met you, a holistic doctor in Ohio told my mom about you and the next morning we flew there. God sent me to you with my life draining out of me. You are my hero! I love you. Please keep helping people who have been to doctors, hospitals, and at the end of their rope like me.

On March 1, 2020, the doctors here in Ohio said that if I didn't get a port and let them pour rounds of chemo into me that, "you will be dead in two months," which was two months before my 34th birthday. I ended up signing out of three hospitals (two in Ohio and one in Las Vegas) against medical advice. In each hospital, they were angry with me. In fact, in Ohio, they gave my mom a card and told her to just take me to hospice. My mom said, "No!" We prayed and cried out to God for two more weeks while I remained in horrible pain at home.

Then I flew me out to Las Vegas where I met wonderful doctors and staff at the Turtle Healing Band Clinic, who became my new family. Two months later, on my 34th birthday, and while I was still in your care, I was feeling better and enjoyed my birthday! Now, I am looking forward to my 35th birthday and a new year, already healed and with normal tests! I'm quiet, but I observe everything! God bless you and your family, Dr. Royal! ◆

Tests and Treatments

AMAS Test (Anti-Malignin Antibody in Serum) – This test measures the antibody to malignin, a polypeptide found in most malignant cells. A 1994 review article reported, "The elevation in the concentration of this antibody is associated at high accuracy with the occurrence of cancer cells in the body." Once the type of cancer is identified, the AMAS test can be used to monitor remission after treatment and to look for early signs of recurrence. AMAS is approved by Medicare.

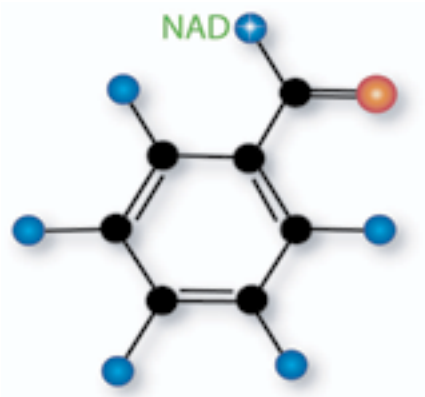
Nagalase in Blood – Nagalase in blood is a sensitive test for monitoring the efficacy of therapy in cancer and certain viral infections. It measures the activity of an enzyme α-N-acetylgalactosaminidase (nagalase) that is produced by cancer cells and in the protein envelope of some viruses. Nagalase prevents the body from making the major macrophage-activating factor (MAF), thus suppressing the macrophage immune response. Nagalase levels directly correlate to cancer tumor burden.

Nagalase Modifier (e.g. Salicinum) – Cancer cells produce energy for growth by fermenting sugars. At the same time, they produce nagalase, which inhibits macrophage activity and the destruction of dysfunctional cells and harmful bacteria. Glycomes, such as salicinum, are complex molecules composed entirely of sugars that bind with the NAD+ coenzyme, found in cancer cells, and inhibit nagalase production. By modifying nagalase production, macrophage activity increases, allowing the destruction of abnormal (eg cancer) cells. Orasal is an oral version of salicinum.

Pulsing Electromagnetic Fields (PEMF) - PEMF uses electrical energy to direct a series of magnetic pulses throughout all the body tissues. Cell behavior and health are dependent upon adequate electromagnetic energy, affecting ion transport, metabolism, absorption of nutrients, and removal of toxins. PEMF recharges blood cells within minutes and harmonizes balance in the autonomic nervous system that regulates all subconscious bodily functions.

Intravenous Nutrient Infusions - Intravenous (IV) nutrient infusions supply nutrients directly into the bloodstream, overcoming deficiencies that can occur in a diseased state. At Turtle Healing Band Clinic, the providers offer amino acids along with minerals, vitamin C, and B vitamins for infusion. The compounds detoxify and nourish the body.

For more information, see the full descriptions of these tests and treatments posted with the full article at townsendletter.com.



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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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Cryoablation Treatment for Cancer

by Ralph Moss, PhD

The medical establishment, epitomized by the US Food and Drug Administration (FDA), is notoriously slow at adopting new methods, however effective they might be. For example, immunotherapy, in the form of Coley's toxins, was demonstrated as effective in ten cases of advanced cancer as early as the early 1890s (Coley 1893). But the FDA did not recognize any form of immunotherapy for cancer until 1990, nearly a century (Tontonoz 2020). Similarly, photodynamic therapy (PDT) was discovered in 1900 (Raab) and was used to treat cancer at Roswell Park Cancer Institute starting in 1974. But the FDA did not approve it until more than two decades later, in 1995.

But the granddaddy of medical delays has to be the cryoablation of malignant tissues. The application of ultra-cold to destroy cancer was demonstrated at the great Crystal Palace Exhibition, which took place in Hyde Park, London, from May to October of 1851.

A surgeon, James Arnott, MD (1797-1883), had been using cold instruments to treat cancer since 1845. He won a medal for his demonstration of cryoablation at the Crystal Palace Exhibition. Tens of thousands of people, including Queen Victoria, Charles Dickens, and Charles Darwin, attended this exhibit, and so cryoablation was hardly a secret. It was publicly available a decade before the American Civil War! (Arnott 1861; Cooper and Dawber, 2001)

For the treatment of cancer, Arnott used a salt and ice solution to attain temperatures of -18° to -24° C (i.e., -0.4° to – 11° F), and to freeze cancers of the breast and cervix. This resulted in decreased tumor size, a reduction in drainage, and the amelioration of pain. Arnott wrote these prophetic words: "Congelation [i.e., freezing] arresting the accompanying inflammation, and destroying the vitality of the cancer cell, is not only calculated to prolong life for a great period but may, not improbably, in the early stage of the disease, exert a curative action."

Nonetheless, this technique disappeared for another century and only started up again in the 1960s, when two New York urologists, Ward A. Soanes, MD, and Maurice J. Gonder, MD, developed the first modern apparatus for the transurethral freezing of the prostate gland. In 1966, the *Journal of the American Medical Association (JAMA)* reported:

> Controlled destruction of tissue by super-freezing has been effective in relieving benign and malignant prostatic obstructions, members of the American Urological Association were told at their annual meeting. Ward A. Soanes, MD, said cryosurgical destruction of prostatic tissue is a further application of pioneer work – primarily in brain surgery – done by others with extreme-cold techniques. (Anon. 1966)

Soames and Gonder used the technique on at least 150 patients "with no mortality and minimal morbidity." It was the beginning of the modern era in cryoablation. Since then, progress has been slow but steady.

But the current version of cryoablation "has almost nothing in common with those versions established in the 1960s and 1970s and further developed in the 1980s and 1990s. The present version," Dr. Witzsch wrote in 2009, "is minimally invasive and has a high efficacy for treatment of high-risk carcinomas and failure of other therapeutic modalities" (Witzsch 2009).

So when did the FDA finally approve cryoablation for cancer? Technically, never, since, as a surgical procedure, it was not subject to regulation by the FDA. But a number of cryoablation systems and cryoprobes have what is called general surgical FDA 510(k) marketing clearance. Examples of cryoablation devices that specifically mention the treatment of prostate cancer in their marketing clearance are two Endocare® Inc. devices, Cryocare CS® and Cryocare CN2® systems, and two Galil Medical devices, Visual-ICE® Cryoablation System and IceRod® CX Cryoablation Needle. Endocare received the first FDA approval in 2006, and the others gained approval in the intervening years. In sum, it took over 150 years from the time that Arnott first demonstrated cryoablation for cancer to the British public to the time it was finally recognized by the FDA and by most insurance plans.

Cryoablation (inaccurately called cryosurgery) is a technique to destroy diseased tissue by applying probes at extremely low temperatures. It is not "surgery" in the ordinary sense, in that no scalpels or other cutting instruments are employed. "Cryo" is increasingly used to treat the following kinds of cancer:

- Prostate cancer – either focally, as a so-called "male lumpectomy," or to destroy the entire gland,
- Select cases of breast cancer,
- Liver cancer (HCC) and liver metastases,
- Retinoblastoma (a childhood cancer affecting the retina of the eye),
- Early-stage basal and squamous cell carcinomas of the skin,
- Precancerous actinic keratosis (skin),
- Precancerous cervical intraepithelial neoplasia (CIN).

It is also used experimentally in tumors of the bone, AIDS-related Kaposi sarcoma, colon, and renal cell carcinoma. It can be used as a stand-alone treatment or in combination with other treatments, such as immunotherapy.

"Cryo" is a very promising and less toxic way of destroying localized tumors or ablating an entire area (such as the entire prostate gland). Not surprisingly, cycles of rapidly freezing and thawing cells bring about tissue destruction. Because of the steady improvement in design and the successful marketing and FDA approval of ultrasound guidance instruments, "cryo" is now a real option for many patients. As word spreads that "cryo" is less damaging than some competing methods, its popularity grows. According to Dr. Bryan J. Donnelly of Calgary: "With longer-term follow-up, the trend favors cryoablation. Significantly fewer positive biopsies were documented after cryoablation than after radiotherapy" (Donnelly 2010, John 2012).

Cryoablation of the prostate gland today is an outpatient procedure, conducted in a relatively brief session under light anesthesia. It is not particularly painful, but it does require the insertion of a catheter (a drainage tube inserted into the bladder) to prevent urinary retention. This is removed after a few days, provided that the patient can urinate on his own.

Third-Generation Cryo

So-called "third-generation" technical refinements include (a) improved 3-Tesla MRI and ultrasound localization of the tumor; (b) the routine use of urethral warmers to prevent collateral damage; and (c) small-gauge delivery systems. The technique uses a fine hollow probe, guided by ultrasound, to penetrate the tumor and introduce liquid nitrogen or argon. This creates a super-cooled area within the tumor, resulting in the ablation of the cancer while leaving healthy tissue unharmed (Hubosk 2007).

Also, probe design and energy sources evolved rapidly over the past two decades. For example, patients with localized liver metastases, which are not accessible to surgery, may still be cryotherapy candidates. The technique is also useful as an adjunct to chemotherapy since chemotherapy, even hepatic arterial infusion (HAI) may be unable to completely destroy tumors or extend life (Bhardwaj 2012).

"Cryo" for liver metastases used to be carried out via laparotomy (a surgical incision made in the wall of the abdomen), but with the increased sensitivity of MRI and ultrasound techniques, percutaneous (i.e., through the intact skin) approaches are now safe and accurate.

There are 500+ PubMed-indexed articles on the use of cryosurgery for liver cancer (HCC) alone. But there is still a lack of knowledge on how well cryoablation stacks up against competing methods. In 2009, British liver surgeons wrote: "Perhaps the time

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has come, therefore, for prospective large-scale randomized control trials to take place comparing ablation modalities to each other and surgical resection" (PubMed ID 19554370). This has been an urgent need for many years (Bhardwaj 2009), but according to www.clinicaltrials.gov such a test has never been performed.

Cryoablation for Breast Cancer

Many breast cancer patients are looking for an alternative to surgery to remove their tumors. Cryoablation has the advantage of a painless, bloodless way of destroying a tumor quickly without the invasiveness of surgery. Instead of having a lumpectomy or mastectomy to remove a breast tumor, doctors insert a thin needle-like device into the mass and then produce a blast of extreme coldness to destroy the malignant tumor. There is no need for sedation or hospitalization, and no pain or scarring. At a growing number of US medical centers, this is considered a viable alternative to surgery for early-stage breast cancers.

An American College of Surgeons Oncology Group carried out a clinical trial affirming this (PubMed ID 27221361). It involved 87 breast cancer patients (with a total of 92 tumors) treated at 19 medical centers around the US. The patients in question all had invasive ductal carcinomas of 2 centimeters or smaller, which could be visualized on ultrasound. Magnetic resonance scans MRIs) were also performed to look at the tumors. After the simple procedure was performed, tissue from the former tumors was examined to see if all the malignant cells were gone. And in fact no remaining cancer was found in 80 out of 92 of the targeted tumors. There was also 100% ablation of tumors smaller than one centimeter in diameter (Simmons 2016).

After a while, the patients' body reabsorbed the killed cancer cells and no traces of it were found on mammograms or other imaging scans. To quote from a 2016 New York-Presbyterian/Weill Cornell Medical Center media release:

> "It's **a huge advance for women** – I think this could be the wave of the future," said the study's lead author, Rache M. Simmons, MD, chief of breast surgery at New York-Presbyterian/Weill Cornell Medical Center. "The beauty of it is it takes less than half an hour, then the patient goes home with a Band-Aid on the tiny incision. There's no recovery time." The procedure can be performed in an outpatient setting with only a topical anesthetic applied to the skin.

US News & World Report ranks New-York Presbyterian as the #1 hospital in New York. It is also ranked #4 of all hospitals in the US. So, this ringing endorsement of cryoablation means a lot. We'll have to see, however, if it can finally put an end to a century and a half of foot-dragging on this topic by conservatives within the medical profession.

NOTE: One should check clinicaltrials.gov for clinical trials employing cryoablation for a particular type of cancer. At the time of writing, using the search terms 'cryoablation' and 'cancer' brought up several dozen trials recruiting patients to treat various cancer types.

Crystal Palace Exhibition

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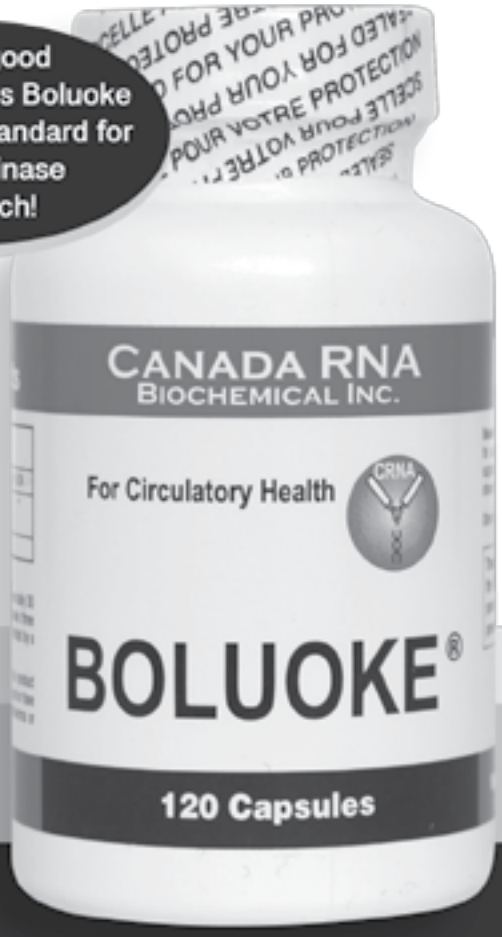

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by Paul S. Anderson, ND
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I wrote *Cancer – The Journey from Diagnosis to Empowerment* after finishing a prior book (*Outside the Box Cancer Therapies* with Dr. Mark Stengler) and realizing there was a great need in the person who has cancer and their support network to have a framework to process the mental, emotional, and ultimately mind-body parts of their cancer journey. In my practice, and mentoring physicians, I saw this was an area of great need but also often not fully addressed simply because the physical aspects of cancer care are so pressing.

My goal with the book was to write a brief guide for patients and loved ones that normalized the common feelings encountered and gave guidance to their journey. That journey, if accepted, is one which moves from shock and victimhood to a place of empowerment. Empowered patients have improved quality of life and often better outcomes from therapies.

The following are excerpts from the book.

From the Introduction

You, as the person with cancer or the person who cares about them, can be confused or angry because of the loss of control over almost everything you feel – an emotional soup that may be different every day. This confusion (or emotional soup) is aggravated by the fact that nobody wants a cancer diagnosis.

This is completely normal. The combination of emotional responses and confusion can lead to a mental drifting that can sabotage your health. The drifting starts from many thoughts, feelings, and emotions crashing in on you, and you cannot process, sort out, and move past it all. You feel lost because you have seen or heard about so many people with cancer, some who do very well and some who do horribly. You may feel stuck not knowing if anything you do really matters.

How can this book help?

The goal of this book is to use the many years of experience I have had with patients and loved ones dealing with cancer and provide you with the tools you need to navigate this difficult terrain. Why? Because the better your internal journey (mental/emotional or mental/emotional/spiritual – whichever you prefer), the healthier you will be, the better your quality of life will be living with cancer, and the outcomes from any medical intervention will generally improve as well. Yes, the internal journey makes that much difference.

Chapter 2

[A note regarding "Gia and Bob" since you are coming in at Chapter 2: I use the stories of two patients (who are, of course, fictionalized) to illustrate the two ends of the spectrum in "moving toward empowerment" I have encountered through the years. Their stories in each chapter are used to illustrate the concepts in the more linear, "how to" portions that follow.]

"I have cancer – I feel lost, angry, confused, and so much more." (You just got some of the worst news a human can get, you're normal.)

Gia's Next Steps: At this stage, she realized, "I have control over the medical process, to a degree, but what about my internal process?" And then she began to reflect, "What about my thoughts, feelings, emotions, and such?" So, Gia embarked on a journey that day. A journey that would change the course of both her "lives."

Having cancer divided Gia's life into a pre-diagnosis "regular life" and the totally unwanted "cancer life." She realized this was the way things were now. She also saw that she held

ultimate control over what she thought, how she felt, and how she processed this new way of being.

She remembered reading about Dr. Viktor Frankl, an Austrian psychiatrist and Holocaust survivor best-known for his 1946 psychological memoir *Man's Search for Meaning*. She decided that if cancer was bad, then someone who lived through a concentration camp might have some insights to help get her out of her angry and obsessive thoughts. She found essays by Frankl online and saw that he believed meaning came from three possible sources: purposeful work, love, and courage in the face of difficulty. He wrote about the "intensification of inner life" that helped prisoners in the death camps stay alive: "Love goes very far beyond the physical person of the beloved. It finds its deepest meaning in his spiritual being, his inner self. Whether or not he is actually present, whether or not he is still alive at all, ceases somehow to be of importance."

This deep realization also helped Frankl process the death of his beloved wife in the camps.

Gia knew she wasn't in a "death camp," but she sure did not feel like she was much better off. "People die of cancer," she would think. So, she took great comfort that someone who survived a death camp and had real insights could provide her with some legitimate wisdom for her journey.

She read another essay in which Frankl quoted Nietzsche: "He who has a why to live for can bear with almost any how." This somehow struck her heart. Yes, she had circumstances she might not be able to change, but she had control over her mind. She recalled the famous idea Frankl shared of his horrific experience in the camps: "Forces beyond your control can take away everything you possess except one thing, your freedom to choose how you will respond to the situation."

"Well," Gia thought. "It sure feels uncomfortable, but it makes sense. I do have control over how I will respond." This day was a turning point for Gia. It wasn't easy, but it was the start of a new chapter in her journey.

Bob's Next Steps: The diagnosis of "probable pancreatic cancer of high stage" dropped on Bob like a bag of cement. … Bob had predetermined that he wasn't going to "process" a cancer diagnosis in any mental or emotional way long before he received this diagnosis. … From an emotional and mental position, there was nothing to work through from his perspective. Bob had seen firsthand pancreatic cancer take lives, and he hated that cancer. "Why couldn't it have just been a massive heart attack?" he thought hopelessly.

In contrast to Gia, Bob was not feeling like progressing or being empowered at all. Bob was stunned and grieving the loss of his life before cancer. Bob became more and more angry. He had spent his life telling himself, and those who would listen, that if he ever got cancer, he would likely end it all. "I've seen it close up, and it's horrible. No way would I ever

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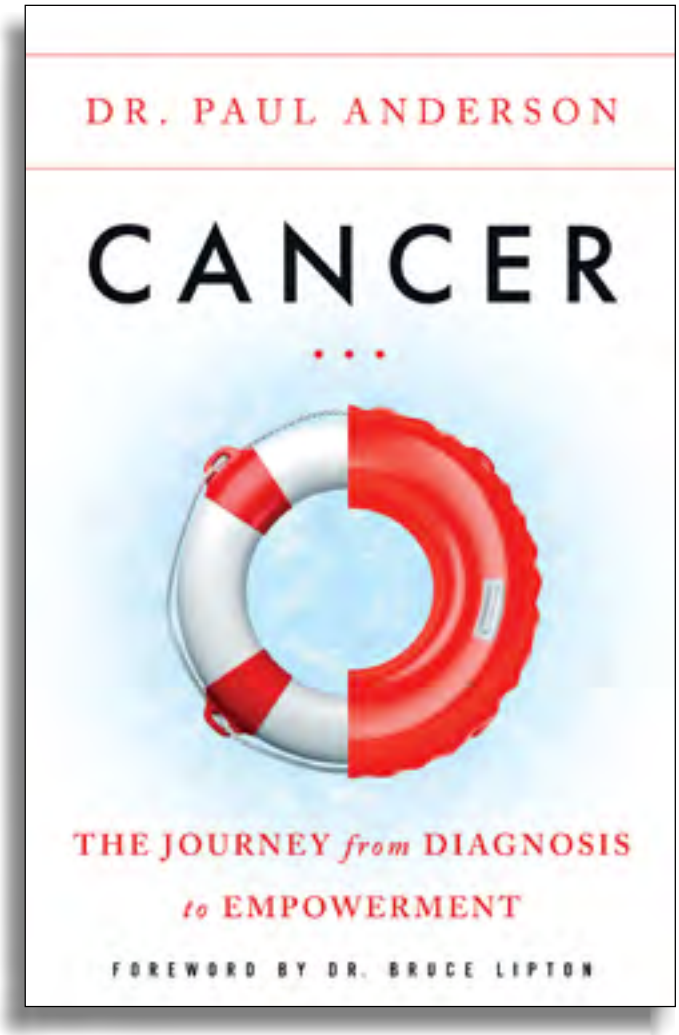
go through that." Bob would recount stories of patients and all the negativity they would experience like the horrific therapies and side effects. He would go on to say, "If it isn't something curable, it's just not worth living."



It became "put up or shut up" time for Bob. He'd spent a career saying all of this. How was that going to play out in his life now?

His partner asked if he would see a counselor and work through the shock, anger, and disbelief. He flatly said, "No. Furthermore, none of that mind-body BS works anyway." This deepened his anger and at times his rage. Nobody argued with him that this was an easy diagnosis, or massively life-changing, or about any detail. His partner simply wished he didn't have to add the mental suffering he was creating on top of everything else.

The stages of grief/processing: Are they real and do they matter? As you can see, the differences between Bob and Gia are unfolding as two opposite methods of coping and processing. Gia is not "happy" with her cancer diagnosis but is open to learning a better way. Bob is ruled by his anger and grief and is not open to learning.

Gia received the news of her cancer as most people do, with surprise and shock. Her initial thoughts were not "constructive," but they were normal. What she did at first was to make sense of what she was thinking and feeling and then work toward a solution focus rather than a fear or anger focus. Was this easy? No. No, it was not. I watched it happen. The important thing is that it did happen.

Upon diagnosis, Bob had the same amount of surprise and shock as Gia. He was, like any human, completely entitled to those thoughts and feelings. He chose to take the step to more anger and agitation.

As I will mention elsewhere in the book, Bob, like anyone else, is entitled to react and do as he pleases. It is a human right, and I would never attempt to deny him. So, I am not judging him or his reaction but rather using it in a clinical sense as a counterpoint to what I have seen as more helpful strategies in moving toward empowerment.

Most people have heard of the stages of grief originally written by Elizabeth Kubler-Ross, which include denial, anger, bargaining, depression, and acceptance. These stages were developed to describe the process patients go through as they come to terms with their terminal illness.

While there is some debate about the accuracy of these stages in all people, I can certainly tell you from years of working with patients during some of the hardest moments of their lives, the stages of grief are excellent observations.

These are common stages that both patients and loved ones go through. What I have seen, and many people relate to, is that a person often gets "stuck" in a stage and, once stuck, has a great deal of difficulty progressing.

Nobody (or very few people) would argue that a person diagnosed with cancer should not feel these things. That is the human condition. And it stands to reason that as we are all individuals, we may experience a stage or two more or less intensely than another. The important aspect is that we continue to move through these completely valid feelings and stages to arrive at a point that affords us maximum health and benefit as we (or our loved ones) live with our cancer journey.

Your Next Steps: Here are some factors I have seen that make the realization and processing of the grieving stages work toward better outcomes and eventually lead to empowerment.

1. Recognizing the stages are real. Honor them. They are normal and not a sign of human frailty. You are wired to process large shocks this way.

We may choose different words to describe the phases of this process, but most people go through them in the same order. However, you may process them in a different order or move rapidly through one and not the other. As I will discuss later in the book, there can be "cycles" or "grief within grief," all of which is completely normal.

Based on our individual past experiences, personality, and other factors, we all process the diagnosis and every other part of cancer at varying speeds. Some people experience more denial while others experience more anger. There is no

right or wrong way to process. The important thing is to let the process happen. While there are predictable steps in the process, you may know where you will take longer to process (or it may surprise you). This book provides insight as to where you may need help, support, and personal growth.

2. Know that however you move through them, it is YOUR way. Moving, processing, and growing are the important parts. You will not do this like others, and that is perfectly normal.

3. Know that close supporters and loved ones are going through their version of this as well. Those around us may not realize this will happen. Often, they know they have shock and sadness but do not realize they have to process the entire diagnosis, change in life, and relationships as well. This often helps you, the patient, to understand others' reactions as well as to help or suggest help for them.

4. Realize that acceptance is not resignation. The act of acceptance is embracing the reality of the journey and all it encompasses while also knowing that you have control over your responses to and interpretation of the process. Acceptance allows you to reset and move on to an empowered, proactive, and progressive state, which, in my experience, is healthier and associated with better outcomes throughout the journey.

5. Find outside help if you cannot process through a stage, need help understanding a loved ones' processes, or feel lost in your own process.

For flow and simplicity, I will use the term "counselor" throughout the book to represent whatever form of outside help you choose. You may find a psychiatrist, psychologist, counselor, spiritual advisor, or one of the many other helpers to facilitate your journey. The important thing is that you resonate with them and that they resonate with you. As a note, you may already have a relationship with a counselor. If not, know that the process of finding the right person takes time. Ask friends or professionals for referrals (your healthcare team will likely have many), and work with someone you feel you resonate with.

Cancer – The Journey from Diagnosis to Empowerment is available in print, audio and electronic editions. Links available at https://drabooks.com/cancer-diagnosis-to-empowerment/.

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Nutraceutical Use in Prostate Cancer

by Geo Espinosa, ND, LAc, IFMCP, CNS

Introduction

Prostate cancer (PrCa) is the second most common cancer in men after lung cancer and accounts for more than 1.2 million newly diagnosed cases a year worldwide. Furthermore, this disease globally kills over 350,000 annually.[1]

Here in the United States roughly 250,000 men are diagnosed with PrCa yearly, accounting for about 35,000 deaths from the disease.[2]

Numerous environmental and lifestyle factors, such as diet, obesity, smoking, and exercise, have been linked to PrCa. Nutrition and diet have long been thought to be associated with PrCa development and progression.

The use of nutraceuticals, prescribed by holistic practitioners or self-prescribed by the patient, to mitigate PrCa has increased by 128% from 1996 to 2016 for sole therapeutic purposes or in an integrative fashion combined with conventional medical approaches.[3]

As such, PrCa patients need expert guidance with the proper use of targeted nutraceuticals to manage their disease and optimize quality of life

The purpose of this article is to present the nutraceuticals I use most in the management/co-management of PrCa patients and in what disease stage I use them.

I attempt to provide objective evidence when possible and offer reasoning with my approach, dictated by almost twenty years of practice in working mainly with PrCa patients.

Dr. Geo Espinosa Nutraceutical Approach to Prostate Cancer

The goal with treating patients with PrCa is to treat the biological soil or, as many in the integrative/holistic oncology field would call, "the terrain." Such ideas of treating the microenvironment are not new. In the late 1880s, Dr. Steven Paget published his "seed and soil" theory proposing that the spread of tumor cells is governed by interaction and cooperation between the cancer cells (seed) and the host organ (soil).[4] The goal then is to make such biological soil in the patient hostile to cancer.

In PrCa, an inhospitable cancer microenvironment is done by the following:

1. Reducing pro-carcinogenic inflammatory processes like factor NF-kB and inflammatory cytokines such as TNF-α and IL-6,[5]
2. Minimizing oxidative stress by modulating uncontrolled cellular reactive oxygen species (ROS) – a contributor to PrCa development and progression,[6]
3. Optimize immune and natural killer (NK) cell function. Robust NK cell activity may improve the prognosis of PrCa patients,[7]
4. Improve insulin levels and optimize glucose metabolism in pre-treatment patients or those on androgen deprivation therapy (ADT). Insulin resistance and glucose metabolic dysfunction are contributory to PrCa.[8]

Secondly, nutraceuticals work as part of applying other lifestyle practices, like a plant-based, whole food focused diet, rigorous physical exercise, and good sleep. Thus, nutraceuticals/dietary supplements complement lifestyle practices to support patients with PrCa.

Lastly, the nutraceuticals suggested here are the most common recommendations for PrCa patients in my practice and may not be complete for the sake of brevity as a full book can be written on the topic.

The methods implemented in my practice are broken down into three categories of PrCa patients:

1. The active surveillance patient.
2. The post-procedure patient.
3. The patient on androgen deprivation therapy (ADT) for advanced disease.

Again, despite the category the patient fits in from the above description, nutraceuticals/dietary supplements should be one element and complement targeted lifestyle interventions with diet, physical exercise, and good quality sleep to minimize progression of PrCa and optimize quality of life despite the disease or side effects from associated medical treatments.

In general, the key nutraceuticals I recommend for patients with PrCa include curcumin, grape seed extract, medicinal mushrooms, active hexose correlated compounds (AHCC), brocolli extract, vitamin D, zinc, selenium from selenized yeast, green tea extract (EGCG), vitamin E (high in gamma-tocopherol), Andrographis, magnolia bark, and modified citrus pectin (MCP). Further down in this article, scientific support for most recommendations is provided.

The Active-Surveillance Patient

This type of patient has low-risk PrCa, does not need medical treatment at diagnosis, and is fit for active surveillance (AS) by his medical physician. Low-risk disease is described by a patient with reduced stage PrCa, relatively low PSA <10, and thought unlikely to die from prostate cancer if untreated with medical interventions.

Investigators have found that patients eligible for AS are at low risk of dying from prostate cancer or developing metastatic disease at 10 or 15 years (less than 1%.)[9]

The goal here is to closely monitor men on AS for changes in the aggressiveness of their cancer via serial biopsies and PSA measurements and, if an unfavorable change is detected, to offer definitive local therapy with curative intent.[10]

A holistic view with patients on AS is essential since many men in this category often die prematurely from something other than prostate cancer, like heart disease.

While reducing the risk of prostate cancer progression is essential, the nutraceutical approach should help avoid/manage prostate-related, lower urinary tract symptoms, lower the risk of cardiovascular disease as this is the number one killer in men, mitigate overall cancer formation in the body, or decrease the risk of any other illness the patients is genetically predisposed to.

The nutraceutical recommendations for the AS patient are the following botanicals and nutrients, emphasizing prostate health-supporting ingredients like rye pollen extract, quercetin, ginger extract, cranberry extract, and other nutraceuticals based on patients' overall individual needs. The therapeutic goal is to lower the risk of PrCa progression where hopefully, aggressive medical interventions are unnecessary and reduce the risk of premature mortality from all causes.

The Post-Procedure Patient

This patient has a low to intermediate stage of PrCa and has undergone a medical procedure for his disease. The goal with this type of patient is to keep him from developing PrCa recurrence or minimize the need for aggressive medical interventions, if possible after PrCa recurs.

The post-procedure patient likely has intermediate-grade prostate cancer, PSA 10 to 20, likely underwent surgical removal of the prostate or radiation therapy, and either has no recurrence or mild recurrence after medical treatment.

The nutraceutical recommendations for the post-procedure patient are the following botanicals and nutrients, emphasizing Agaricus mushroom and about 4 grams of curcumin. The therapeutic goal is to lower the risk of cancer recurrence or cancer progression.

The Androgen-Deprivation Patient

This patient may have advanced PrCa with or without metastasis and is on constant or intermittent medically induced chemical castration with ADT.

Androgen deprivation therapy (ADT), also known as hormone therapy, is a form of chemical castration and is one of the common treatments for advanced prostate cancer. The types of ADT include luteinizing hormone-releasing hormone (LHRH) agonists, which prevent the pituitary gland from secreting the luteinizing hormone (LH) due to the presence of high levels of LHRH.

LHRH agonist drugs include leuprolide (Lupron), goserelin (Zoladex), and triptorelin (Trelstar).

Another method of chemical castration in patients with advanced prostate cancer is LHRH antagonists, which prevent LH secretion by blocking the release of LHRH. LHRH antagonist drugs include degarelix (Firmagon).

Other categories of ADT (and chemical castration) include androgen synthesis inhibitors.

Androgen synthesis inhibitors work by preventing the production of androgens by all tissues, including the adrenal glands, by inhibiting the CYP17 enzyme responsible for producing testosterone. Androgen synthesis inhibitors include abiraterone (Zytiga) and ketoconazole.

Lastly, yet another form of medically induced castration is antiandrogens. Antiandrogens work by blocking the androgen receptors from the binding of androgens and include, apalutamide (Erleada), bicalutamide (Casodex), enzalutamide (Xtandi), and darolutamide (Nubeqa)

Despite the mechanism of action, hormone therapy for advanced prostate cancer induces chemical castration, which comes along with unwanted side effects. ADT's adverse events include hot flashes in about 60% of men, metabolic syndrome, cardiovascular events, anemia, memory, and cognitive decline, and osteosporosis.[11] Other adverse events from antiandrogens include hypertension, fluid retention, and hypokalemia.[12]

The nutraceutical recommendations for the ADT patient include ingredients that mitigate cognitive decline, improve physical energy, support bone health, and lower the frequency of hot flushes. Nutraceutical recommendations to minimize adverse effects from ADT are the following:

- Brain function and cognition: acetyl-L-carnitine, lion's mane, ashwagandha
- Improve physical energy: ashwagandha or any other adaptogenic botanicals and cordyceps
- Hot flushes and night sweats: black cohosh
- Bone health: vitamin K2, boron, and black cohosh

Nutraceuticals can minimize cancer progression.

The therapeutic goal for patients on ADT is to support medical treatments with natural and lifestyle practices to mitigate disease progression while minimizing adverse events from ADT for the patient to sustain quality of life.

Nutraceutical Recommendations for Prostate Cancer Patients with Scientific Support

Selenium seems protective for PrCa in most studies. One of those landmark studies was the Nutritional Prevention of Cancer (NPC) study. Participants received selenium in the form of selenized yeast at 200 mcg/day. Researchers here looked at the effects of selenized yeast on skin cancer and noticed a 65% reduction of prostate cancer in the group on selenium from the yeast compared to placebo as a secondary study outcome.[13]

Shortly after the publication of the NPC results in the late 1990s, I began working with prostate cancer patients and remembered selenium being a favorable hot topic for PrCa at urological conferences. The enthusiasm for the mineral died down after the results of the SELECT study was published.

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The SELECT trial (SELenium and Vitamin E Cancer Prevention Trial) ended early in 2008 when no benefit for prostate cancer prevention with the use of either vitamin E or selenium.[14]

Later reports from SELECT demonstrated that selenium supplementation increased the risk of high-grade prostate cancer (by 91%) among men with a high baseline toenail selenium concentration only in the arm for selenomethionine, not the group taking both vitamin E and selenium. There were no adverse events in the group taking both vitamin E and selenium, suggesting possible synergistic activity between the two nutrients.[15]

The use of selenomethionine (SeMet) instead of selenized yeast in SELECT was controversial as the choice to use SeMet was for logistical reasons, i.e., batch-to-batch variability in selenized yeast, etc., not due to evidence that L-selenomethionine is the superior form of selenium for prostate cancer.[16] Besides, the NPC trial showing a significant risk reduction in PrCa used selenized yeast, not L-selenomethionine.[13]

While L-selenomethionine is the predominant form of selenium in selenized yeast, the yeast contains numerous other mineral forms – also includes selenocysteine and methyl selenocysteine – with varying chemopreventive properties.[16]

When comparing the selenized yeast form of selenium to selenomethionine in a small group of men with prostate cancer, one study suggests that SeMet does not decrease oxidative stress and therefore doesn't protect cells or prevent cancer compared to selenium from selenized yeast.[17]

Recommendation: 200 mcg of selenium in the form of selenized yeast.

Vitamin E is a nutrient I frequently use with patients with PrCa but mainly in mixed tocopherol. Gamma tocopherol is the most prevalent form of vitamin E in the diet, whereas alpha-tocopherol, found in dietary supplements, is the most biologically available form.[18] Numerous studies looking at gamma-tocopherol vitamin E have shown an inverse association with prostate cancer risk.[19]

Alpha-tocopherol supplementation has shown up to a 40% decrease in development and mortality in men consuming 50 International Units (IU) compared to placebo – a result that was sustained two years after the study ended.[20]

Interestingly, higher concentrations of plasma gamma-tocopherol were associated with a statistically significantly lower risk of developing prostate cancer. Studies show protective associations between selenium and alpha-tocopherol concentrations and subsequent prostate cancer only in the presence of higher concentrations of gamma-tocopherol.[21]

The SELECT trial found no protective effect from vitamin E in the form of alpha-tocopherol at 400 IU a day, taken alone or in combination with selenium. Further published SELECT research showed an increased risk of prostate cancer in the vitamin E, alpha-tocopherol arm but not in the combination intervention.

Three flaws from SELECT as it relates to vitamin E and PrCa:

1. They used a synthetic, unnatural version of the vitamin in dl-alpha-tocopherol, not a natural mixed tocopherol version.
2. Gamma tocopherol (in combination with alpha-tocopherol) seems to be essential in protecting against prostate cancer.
3. The dose in alpha-tocopherol vitamin E in SELECT was eight times higher than that from the ATBC study, 400 IU vs. 50 IU, respectively. Such a high dose of a substandard form of vitamin E in alpha-tocopherol may potentially promote prostate cancer.

Recommendation: 400 IU of vitamin E, mixed tocopherol with higher gamma-tocopherol.

Zinc. The human prostate contains one of the highest amounts of zinc of all tissues in the body. Zinc continuously decreases in the prostate in early to late cancer cells. One study shows supplemental zinc intake was associated with a reduced risk of clinically relevant advanced PrCa.[22]

Another Swedish study looked at men with high zinc intake and showed lower PrCa specific mortality, especially in men with localized tumors.[23]

Too high zinc consumption of over 100 mg/day may significantly increase the risk of being diagnosed with advanced prostate cancer. In one cohort, approximately 32% of the total zinc intake was from dietary supplements, representing the largest zinc source. So, while there is no evidence of causation in higher amounts of zinc causing PrCa, there is a correlation.[24]

Recommendation: 15 to 30 mg of zinc daily.

Vitamin D. Numerous studies on prostate cancer patients with the lowest prediagnostic 25(OH)D levels show a significantly greater risk of prostate cancer-specific mortality.[25]

Although some studies show no benefit of vitamin D on prostate cancer,[26] in one non-randomized, small human study, vitamin D(3) supplementation at 4000 IU/d, revealed a decrease in serum levels of prostate-specific antigen (PSA) or the rate of progression of PrCa. The study concluded that patients with low-risk prostate cancer under active surveillance might benefit from vitamin D(3) supplementation at 4000 IU/d.[27]

Recommendation: I recommend a reasonable dosage of vitamin D3, between 2000 IU and 4000 IU a day, or an amount necessary to get serum levels to 40 to 60 ng/ml. Though the benefits of vitamin D and PrCa are not definitive, vitamin D may prevent fatal cancer of all types.[28]

Botanicals

Curcumin, a polyphenol extracted from the rhizomes of *Curcuma longa*, belongs to the most promising group of bioactive natural compounds, especially in treating several cancer types. Curcumin exhibits anti-cancer ability by targeting different cell signaling pathways, including growth factors, cytokines, transcription factors, and genes modulating cellular proliferation and apoptosis.[29]

Curcumin may be beneficial in men who are undergoing radiation therapy for prostate cancer. One study observed a reduction in the severity of radiotherapy-related urinary symptoms while increasing antioxidant capacity from curcumin consumption.[30]

Men on AS or watchful waiting for localized prostate cancer took a polyphenol-rich food supplement that contained a blend of pomegranate, green

tea, broccoli, and turmeric (*Curcuma longa*) or placebo; PSA levels progressed significantly less in the group taking the supplement combination.[31]

Recommendation: 600 mg to 4000 mg of curcumin. Up to 8 grams a day seems safe in most patients, but I have not seen higher than 5000 mg a day be more beneficial in PrCa patients.

Grape seed extract (GSE). Preclinical studies demonstrate the apoptotic abilities of grape seed extract on prostate cancer cells.[32]

A cohort of men were studied to observe the association of PrCa with dietary supplements taken. Researchers noticed no associations with PrCa and the use of many forms of dietary supplements, except with grape seed supplementation, where a 41% risk reduction of PrCa was observed.[33]

Recommendation: 400 mg a day of GSE.

Medicinal mushrooms. Chinese medicine and naturopathic doctors have used a variety of medicinal mushrooms for centuries for therapeutic purposes. Various research studies have shown that extracts of Asian mushrooms and common mushrooms fight against prostate cancer. These particular fungi, including cordyceps, maitake, oyster, reishi, *Coriolus versicolor*, shiitake, and white button, contain components valued for their anti-cancer abilities.

Men who habitually consumed mushrooms 1–2 times weekly had an 8% lower risk of prostate cancer, and those who ate mushrooms ≥3 times weekly had a 17% lower risk than the men who had mushrooms once weekly or less. The study lacked information on the intake of dietary supplements.[34]

Strong evidence for the use of medicinal mushrooms as an anti-cancer agent is scarce.

Ganoderma (reishi mushroom) is the most popular and intensely investigated genus among medically active mushrooms. Plenty of its species are famous for their antiviral, antibacterial, antifungal, anti-cancer, and immune-stimulating activities and have been used traditionally in the folk medicine of Eastern countries for centuries.

Despite scarce human studies on *Ganoderma* on prostate cancer, I use this mushroom for its ability to boost the activity of lymphocytes, such as natural killer cells (NK), T-cells and B-cells, tumor necrosis factor (TNF), and phagocytes (which ingest other cells).[35]

Recommendation: 250 mg to 500 mg of *Ganoderma lucidium* (reishi) mushroom.

Active Hexose Correlated Compound (AHCC), a fermented extract produced from the mycelia of shiitake mushroom, is a rich source of alpha-1,4-glucans, which are thought to enhance its biological effects. Preclinical studies have shown that it has anti-inflammatory and antioxidant effects, enhances resistance against bacterial and viral infections, and exerts anti-cancer effects.[36]

Recommendation: 1.5 to 3 grams of AHCC.

Agaricus mushrooms. One study of 36 men with biochemical recurrence ➤

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of prostate cancer studying a species of *Agaricus* (white button mushroom) powder therapy was associated with declining PSA levels in 36% of patients. These results indicate that mushroom intake can modulate PSA levels in biochemically recurrent prostate cancer.[37]

Recommendation: 250 mg to 500 mg of *Agaricus* species.

Andrographis. Components in the Andrographis plant have potent IL-6 inhibitor abilities that induce apoptosis and suppress prostate cancer tumor growth. Researchers suggest that andrographolide, a common herbal medicine used in China and India, may be developed as a potential therapeutic agent to treat prostate cancer.[38] IL-6 may have unwanted protective abilities against PrCa cells initiated by androgen deprivation.[39] Andrographis has many protective qualities, and being an IL-6 inhibitor may be an important one in PrCa.

Recommendation: 200 mg to 500 mg of Andrographis.

Green tea extract. The inhibitory action on cancer cells from green tea is attributed to its active compounds present in higher amounts called polyphenols, which consist mainly of catechins, especially epigallocatechin-3-gallate (EGCG), which accounts for more than 50% of total polyphenols.[40]

A meta-analysis of thirteen observational studies in Asian populations has documented a moderately significant inverse association between green tea intake and prostate cancer risk.[41]

A systematic review and stratified analyses of observational studies and randomized controlled trials (RCTs) using stringent inclusion criteria have concluded that green tea is an effective chemopreventive agent, particularly in prostate cancer patients with high-grade prostate intraepithelial neoplasia.[42]

In patients with high-grade prostatic intraepithelial neoplasia, a pre-prostate cancer precursor, supplementation with green tea catechins was associated with lower prostate cancer incidence, reduced PSA level, delay in the onset of prostate cancer, and reduced prostate cancer, lower urinary tract symptoms and a further improvement in quality of life.[43]

Recommendation: 500 mg to 1000 mg of green tea extract. A higher amount than 1000 mg may elevate liver enzymes in my clinical experience, so some precaution with a very high dosage of green tea extract is advised.

Broccoli extract. Cruciferous vegetables contain high levels of glucosinolates, whose major breakdown product, by the action of myrosinase enzymes, is indole-3-carbinol, which has exhibited potent anticarcinogenic properties against prostate cancer. Another phytochemical that occurs ubiquitously in cruciferous vegetables is an isothiocyanate called sulforaphane. Sulforaphane can induce arrest of prostate cancer development and progression via disruption of signaling within tumor microenvironments and activation of apoptotic cell death.[44]

The first meta-analysis of 13 studies (seven were cohort and six population-based case–control studies) evaluating the association between consumption of cruciferous vegetables and prostate cancer risk has found that high consumption of cruciferous vegetables was significantly associated with 10% decreased risk of prostate cancer.

In a double-blinded, randomized placebo-controlled multicenter trial, 78 prostate cancer patients who had rising levels in PSA after radical prostatectomy were treated with either 60 mg sulforaphane or placebo for six months and then followed for two months with no treatment. PSA increased significantly in the placebo group compared with the sulforaphane group. Also, the doubling time of PSA (good prognostic indicator) was 86% longer in the sulforaphane compared with the placebo group.[45]

Another meta-analysis of studies conducted over 18 years in Europe, including a total of 1294 prostate cancer patients and 11,492 controls, has shown that consumption of cruciferous vegetables was associated with a 13% reduction in prostate cancer risk.[46]

Consumption of cruciferous vegetables might not always be a practical way to obtain the required daily quantities of sulforaphane and Indole-3-carbinol as the concentration of sulforaphane and Indole-3-carbinol in cruciferous vegetables is highly variable depending on various factors, including the amount of sunlight, soil, rainfall, seed strain, and myrosinase enzyme activity. Extracts of cruciferous vegetables may be more practical.[47]

Recommendation: 100 mg to 500 mg of broccoli extract day.

One in six men are diagnosed with PrCa; and as the incidences increase, more will seek the care of naturopathic and integrative medical experts. I believe a properly designed nutraceutical protocol is an essential component for the longevity and wellbeing of PrCa patients.

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Dr. Geo Espinosa is a naturopathic doctor, licensed acupuncturist, and certified functional medicine practitioner recognized as an authority in holistic urology and men's health. He is faculty and holistic clinician in urology at New York University Langone Medical Center and faculty at the Institute for Functional Medicine (IFM). As an avid researcher and writer, Dr. Geo has authored numerous scientific papers and books including co-editing the book *Integrative Sexual Health* and author of the best-selling prostate cancer book *Thrive, Don't Only Survive*. Dr. Geo is the chief medical officer (CMO) and formulator at XY Wellness, LLC, and lectures internationally on the application of science-based holistic treatments for urological conditions. In his free time, he enjoys writing on his popular blog, DrGeo.com, spending time with his wife and three kids, and practicing the Israeli martial art, Krav Maga.

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Fasting, IGF-1, and HER-2 Breast Cancer

by Jacob Schor, ND, FABNO

Two interesting studies published in early 2020 are relevant to our use of fasting during cancer treatment. Stefanie de Groot and her team of Dutch researchers reported in *Nature Communications* that in a randomized trial of 129 human epidermal growth factor receptor-2 (HER-2) negative breast cancer patients, about half of whom followed a fast-mimicking diet (FMD) for three days prior to and during chemotherapy, that the intervention significantly increased the likelihood of a complete or partial response to treatment, presumably because the caloric restriction had lowered IGF-1 levels.[1]

In late April, Yiwei Tong's team in China reported surprising, though somewhat confusing, information about insulin-like growth factor-1 (IGF-1) in HER-2 positive breast cancer patients.[2] Tong's results contrasted what many of us would have predicted. It will be important to integrate their data into our understanding as we move forward.

De Groot's work continued Valter Longo's research on fast-mimicking diets. Longo has methodically researched the effects that fasting and diets that mimic fasting have on cancer treatment. His earliest efforts to research water fasting met with poor patient compliance so he developed a fast-mimicking diet (FMD)—a low-calorie, low-protein, plant-based, intermittent meal plan that triggers similar metabolic effects as fasting. We've encouraged patients to use Longo's products or imitate his eating plan for a dozen years. An article by Jennifer Couzin published in *Science* in August 2008 was the first we heard of Longo and his theory.[3] Couzin had written about the Raffaghello study published two months prior that suggested fasting mice were more tolerant of high-dose chemo than those on a regular diet.[4] By the time her August article appeared, our patients had begun trying Longo's fasting at home.

According to Longo and de Groot, healthy cells switch from a proliferative state to a maintenance and repair state during fasting, while malignant cells are unable to adapt to a nutrient-scarce existence. Fasting deprives proliferating cancer cells of nutrients, growth and other factors, rendering them sensitive to cancer therapy and increasing their cell death.[5]

De Groot's data came from a multicenter, open label, phase II trial, that enrolled 129 patients from February 2014 to January 2018. They were randomly assigned to continue their regular diet or follow Longo's fast-mimicking diet for the three days prior to and during the first day of chemo.

Thirty of the patients received six cycles of FEC-T chemotherapy (5-fluorouracil, epirubicin, cyclophosphamide, and docetaxel), while the remaining 99 received eight cycles of AC-T (doxorubicin, cyclophosphamide, docetaxel). The control group, but not the FMD group, also received dexamethasone pretreatment to minimize nausea and vomiting.

While the FMD diet is easier than fasting, it is still a challenge. Of the 65 patients randomized to the FMD, 81.5% followed the diet during their first round of chemo, around half followed the diet through two rounds, but only 20% followed it all the way through treatment.

Radiologically complete or partial responses occurred about three times more often in the FMD group than the control group in both univariate (OR 2.886) and multivariate (OR 3.168) analyses. The number of patients who had stable or progressive disease as determined by x-ray was quite a bit lower in the FMD group (11.3%) than in the control group (26.9%). The more closely a patient followed the diet, the better their response.

Toxic reactions to the chemo did not differ between groups, but recall the FMD group were not given steroids to prevent side effects. In other words, fasting worked as well as steroids at reducing chemo-induced nausea.

These results de Groot reported were satisfying but not unexpected; they support Longo's earlier work. Tong's results, on the other hand, left me scratching my head.

Tong ran a retrospective study analyzing data from 679 Chinese breast cancer patients, who were positive for human epidermal growth factor receptor-2 (HER-2+) and had been treated in Shanghai, China, between 2012 and 2017. Of these patients, 209 also had metabolic syndrome MetS). Overweight was defined by body mass index (BMI) ≥ 24.0 kg/m^2. This is the largest study to date looking at IGF-1 and HER-2-positive breast cancer.

Tong's researchers tracked several key measures, in particular recurrence-free survival (RFS) and overall survival (OS). Insulin-like growth factor-1 (IGF-1) was used to classify participants into high or low IGF-1 sub-groups. The usual parameters of metabolic syndrome were followed, including basal metabolic index (BMI), fasting glucose,

IGF-1, IGFBP-3, insulin, C- peptide, triglycerides, TC, HDL-C, and LDL-C to see if they changed disease outcome. Tumor size, node involvement, histological grade, hormone receptor status, proliferation index, HER2-enrichment intrinsic subtype, and anti-HER2 therapy were tracked as well, as these are clear prognostic factors for HER-2+ cancers.

The theory that Valter Longo and his collaborators have bandied about since 2008 is that fasting is beneficial because it lowers IGF-1. The fast-mimicking diet used in the de Groot study was developed by trial and error to keep IGF-1 as low as possible.

After a median follow up of three years, 52 women had disease recurrence. IGF-1 levels were not associated with recurrence-free survival (RFS, *P* = 0.620). That was unexpected.

However, when the women were divided into two subgroups based on whether they were normal or overweight using body mass index (BMI), everything changed. Dividing the group at a BMI ≥ 24.0 kg/m^2 revealed a clear association between IGF-1 and recurrence free survival (RFS). For normal-weight women, high IGF-1 was associated with a superior four-years RFS (91.1% vs. 85.0%; HR 0.53) compared with women with a low IGF-1 level. In contrast, for the overweight women, high IGF-1 was associated with an impaired four-years RFS (88.3 vs. 95.7%, HR 3.20).

It wasn't just recurrence-free survival that varied with weight. High IGF-1 levels were independently associated with better overall survival (OS) in the whole cohort (HR 0.26 *P* = 0.044) as well as in the non-overweight population (HR 0.15, 95% *P* = 0.005). High IGF-1 was protective in non-overweight patients but appeared to be bad news for the overweight. As our colleague Dr. Ian Biers so often reminds me, progression-free survival and recurrence-free survival do not predict overall survival. We often look to these recurrence measures as they are easier for researchers to obtain than overall survival data, and many people falsely assume the two are related. They are not. Thus, these associations between IGF-1 and superior OS should be underlined.

Treatment with 'targeted therapy' (trastuzumab aka Herceptin) non-significantly improved OS from 96.7% to 97.7% (*P* = 0.149). However, significantly better four-year OS was seen in the high IGF-1 group compared to the low IGF-1 group (99.2 vs. 95.8%, *P* = 0.044). One might surmise having high IGF-1 was a better bet than Herceptin for staying alive. Subgroup analysis showed a modest but insignificant interaction of IGF-1 and BMI in predicting OS (*P* for interaction = 0.054). High IGF-1 level was associated with improved OS in normal-weight patients (4-years OS 99.4 vs. 93.7%, *P* = 0.005; HR 0.15), but not in overweight ones (4-years OS 98.7 vs. 98.9%, *P* = 0.438; HR 2.51, 95% CI 0.23–27.63, *P* for interaction = 0.054).

What's all this mean?

Recall that de Groot examined only HER-2 negative cancers while Tong looked at only HER-2 positive cancers. For the moment let us assume that these findings only apply to these respective HER-2 types. The de Groot study is relatively clear. Fasting for the few days prior to chemo, as has been suggested by Longo et al over the years, seems to do what they have predicted based on animal studies; it reduces side effects of the drugs and increases odds for a good long-term outcome.

The Tong results are more difficult to describe and far more difficult to explain. For overweight HER-2+ women, lower IGF-1 levels were associated with better outcomes. We should underline "overweight" in that sentence. Fasting, because it lowers IGF-1, might be helpful for overweight women. That doesn't change anything. It was the normal-weight women's results that blindsided us. High IGF-1 was associated with better outcomes in these women, both short term when measured as time to progression and long term when measured as overall survival.

These findings should outweigh our general recommendations regarding fasting made in the past. In HER-2+ BC we may even want to fine-tune diet recommendations based on BMI and IGF-1 levels. Our goal in HER-2+ normal weight women should now be to increase their IGF-1 levels. High animal protein diets raise IGF-1 levels while low animal protein diets are associated with decreased IGF-1. We should be extremely cautious with fasting normal-weight women and instead probably encourage high animal protein diets to increase IGF-1. While for the overweight women they should be encouraged toward caloric restriction, fasting, and a possibly a vegan diet. Obviously, we can no longer make decisions without knowing the BMI and IGF-1 levels of these patients. And of course, what I just said applies to HER-2 positive BC.

It seems that the interaction leptin has with other growth factors should be our new focus of attention.

Least we think that these data impact only a small subgroup of patients, keep in mind that in the United States, 70% of adults and 37% of adolescents are overweight or obese.[6]

Although Tong's conclusions stand in contrast to what many of us would have predicted, our basic understanding remains that insulin-like growth factor (IGF) is critical to the growth, development, and maintenance of many tissues in the human body.[7] IGF-1 is especially important during neonatal and pubertal growth, and acts by simulating cell proliferation and interrupting programmed cell death.[8] IGF-1 is of particular importance in breast tissue development.[9] Binding of IGF-1 to its receptor (IGF-1R) stimulates activation of the phosphatidylinositol 3-kinase (PI3K) and mitogen activated protein kinase (MAPK) pathways that cause cell proliferation. The bottom line remains that IGF-1 signaling is involved in 87% of invasive breast cancers.

For several years we have relied on a hypothesis that crosstalk exists between the IGF-1 pathway, insulin, and the

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epidermal growth factor receptor family; increased IGF signaling should lead to progression of breast cancer, metastatic invasion, and promote resistance to therapies such as chemotherapy and radiotherapy.[10,11] Elevated insulin levels bind to certain IGF-1 receptors on breast cancer cells and stimulate proliferation. This has been our rationale for encouraging these patients to reduce excess carbohydrate consumption as this might lower insulin production. An increase in IGF should lead in turn to a decrease in breast cancer survival[12] and an increased all-cause mortality in HER-2+ patients. Or at least this is what we thought.

We are left with seemingly conflicting ideas; fasting, which lowers IGF-1, seems helpful for breast cancer patients in general but, lowering IGF-1 may worsen prognosis for women with HER-2+ breast cancer.

Although De Groot's results seem to confirm that our general theories about IGF-1 and breast cancer are on target, Tong's data hint that other growth inducers outweigh the effect of IGF-1, at least for HER-2 + breast cancers. Biology, it turns out, is more complicated than we thought, and there are a range of chemical factors in the body which drive cancer growth beside estrogen, insulin, and IG-1. Tong's data suggest some other factor is at play, one associated with obesity.

We should note that this isn't the first report to differentiate the effect of IGF-1in breast cancer based on BMI. In 2013, Catherine Duggan et al reported that increased IGF-1 levels were associated with an approximate two-fold greater risk of BC-specific mortality in participants with a BMI >25 kg/m^2, than in lean women. On the other hand, they also found that high serum levels of IGF-1 and the IGF-1/IGFBP-3 ratio were associated with increased risk of all-cause mortality in women with breast cancer.[13] Duggan's study participants were not limited by HER-2 status, and their findings suggest that a similar division by BMI might apply to broad range of breast cancer patients.

We must ask why obesity has such a profound impact on cancer. Tong et al offer no theory to explain their results. The answer to the question Tong's data elicit is probably why obesity is so closely tied to cancer in general, a phenomenon we are all aware of but tend to not pay much attention to. Probably one of those elephants in the room things.

Having unexplained and curious phenomenon in the universe, mysteries, as we might term them, is a source of delight and wonderment for many. For some people, unexplained mysteries niggle at the back of our awareness, begging for explanation. Why does obesity change cancer outcomes so much and now in particular, why this peculiar IGF-1 and obesity relationship? Let me offer up my current thinking, with the caveat that I do possess a BS degree and that by the time this is in print, the theories will have changed.

Obesity is the elephant in the cancer room; only smoking carries a greater risk of cancer. Yet surprisingly little work elucidates the actual mechanisms by which obesity promotes cancer. Perhaps this is a result of our efforts to be socially proper and not notice or make a fuss if someone is overweight? On a tissue level obesity causes a chronic inflammatory state resembling chronic injury[14]; but at this point, a better explanation seems necessary.

The confusing action obesity has in the Tong study is not uncommon. There are a number of cancers in which obesity increases risk, speeds progression and then, oddly provides a survival advantage. This is referred to as the "obesity paradox."[15,16]

One plausible explanation appeared in *Lancet Oncology* back in 2018. Jennifer McQuade at MD Anderson reported that checkpoint inhibitor drugs that target PD-1 work better in obese patients than in normal weight ones. In 330 advanced melanoma patients, those who were male and overweight lived an average of almost 27 months compared to normal weight patients who averaged only 14 months. At the start of the study her assumption had been that obesity would worsen prognosis, not improve it.[17] Being fat is supposed to be bad for cancer, after all.

Tumors grow faster in obese mice and obese people, and this is apparently because their T-cells are "exhausted," no longer capable of performing their role in limiting cancer growth. The T-cells stop proliferating and become sluggish at secreting proteins that stimulate the immune system. The T-cells also display more than average PD-1, meaning cancer cells are better at suppressing T-cell function, telling these defenders to "leave me alone."[18-19]

These effects all appear to be driven by the hormone leptin, which is closely linked to obesity. This may explain why these drugs that inhibit PD-1 work well in both obese tumor-bearing mice and overweight cancer patients. PD-1 protects cancer cells better, or more effectively, in fat bodies; it is the chronically elevated leptin levels that exhausts the T-cell so that the immune system cannot defend against cancer.

Jacob Schor graduated from National College of Naturopathic Medicine in 1991 and practiced in Denver until his recent retirement. He was active in the Colorado Association of Naturopathic Doctors, the Oncology Association of Naturopathic Physicians, and the American Association of Naturopathic Physicians. He continues to contribute regularly to the *Townsend Letter*, the *Natural Medicine Journal*, and NDNR.

Remember, high leptin increases PD-1 expression on the T-cells leaving them more vulnerable to being shut down. PD-1 inhibitor drugs reawaken the T-cells and lead to a renewed immune defense. Thus, in the obese, PD-1 inhibitor drugs can have a greater impact.[20]

Leptin, the hormone most linked with obesity, is associated with improved outcomes in breast cancer. In 2019 Yan Kong et al reported that in their study of 325 breast cancer patients, those who had a complete response to chemo treatment, had higher serum leptin levels and more leptin receptors than in patients whose disease progressed.[21]

Reports now link obesity with improved overall survival and progression-free survival in patients with metastatic melanoma, bladder cancer, colorectal cancer, lung cancer, and renal cell carcinoma treated with targeted or immunotherapy and high leptin seems to be the common denominator.[22-27]

Kong's breast cancer data wasn't looking at patients undergoing immunotherapy treatment so we must consider and guess whether the results were related to changing leptin levels. Which brings us back to fasting and fast-mimicking diets. Caloric restriction in humans dramatically lowers leptin. One human trial of eight weeks reported leptin dropping nearly 50%.[28] We may need to reinterpret our concept of fasting and caloric restriction; it does more than lower IGF-1. Caloric restriction also lowers leptin, perhaps profoundly. Fasting may also act to reawaken exhausted T-cells.

Taken together, these studies suggest that there are multiple hormones that interact to promote breast cancer growth and that we cannot expect to make sense when examining them one at a time; leptin interacts with IGF-1, IGF-binding protein-3, insulin and estrogen in breast cancer. All of these need to be examined and their interactions understood.[29] Our desire for simple explanations will not bring us the answers we require.

In research using human breast cancer cell lines, leptin increased HER-2 protein levels and enhanced the responsiveness of HER-2+ breast cancer cells to other growth promoting chemicals.[30] It is possible that leptin and IGF-1 have a greater impact on HER2+ breast cancer and this is why Tong's data were so striking.

It seems that the interaction leptin has with other growth factors should be our new focus of attention. But should we even bother to measure leptin in our cancer patients? Or is the old BMI calculation enough to estimate it? I don't know the answer yet. As I wrote early on, Tong's results have left me confused, sitting at my desk scratching my head. ◆

References and article are available online at www.townsendletter.com.

The Work Continues: Two Cases of Metastatic Cancer Treated with an Enzyme-Based Nutritional Protocol

by Linda L. Isaacs, MD

Since the death of my long-time colleague and friend, Nicholas Gonzalez, MD, I have continued to offer the same protocol that we used for patients with cancer and other degenerative diseases. The method is based on the work of William Donald Kelley, DDS; Nick had reviewed Kelley's records and found many remarkable patient outcomes, as detailed in his book *One Man Alone*.[1] Nick and I co-authored an article with 30 case reports in *Alternative Therapies in Health and Medicine* in 2007.[2] At the time of his death, Nick was working on a collection of case reports from his practice and mine, which was subsequently published in two volumes.[3,4]

In a 2019 article, I reported the outcomes of two patients I first saw around the time of Nick's death in 2015.[5] Below, I provide an update of their status.

Patient 1: Metastatic Colon Cancer

Patient 1 had a right colectomy in May 2014, for a 4.5 cm adenocarcinoma with metastases in 2/32 lymph nodes. CT scan July 2014 showed three hepatic hemangiomas.

Instead of the recommended chemotherapy, Patient 1 followed a self-designed nutritional plan. CT December 2014 showed the three hepatic hemangiomas seen previously, and a low-attenuation lesion described as unchanged from previous exams. PET scan was negative; but his CEA was steadily rising, so he began chemotherapy with FOLFOX. CT scan June 2015 showed, in addition to the three hemangiomas, a new 0.8 x 0.9 cm low attenuation lesion in the liver. He discontinued chemotherapy at that time.

By December 2015, the liver lesion had grown to 1.7 x 1.5 cm. In February 2016, he underwent partial resection of the right lobe of the liver. The pathology report stated: "Metastatic adenocarcinoma, consistent with colonic primary, extending focally to margin of resection."

He began a nutritional program under my direction in April 2016. Around the same time, a scan showed "Enlarging low attenuation lesion within the right lobe of the liver suspicious for metastatic disease."

After two months on his protocol, abdominal CT showed a low attenuation hepatic mass, and CT of the chest showed a new "slight lobulated nodule … measuring 0.9 x 0.8 cm." His oncologist strongly recommended resection of the lung nodule and the liver mass, as well as resumption of chemotherapy. However, Patient 1 told me that FOLFOX made him so sick that he would rather be dead.

In mid-July 2016, he underwent resection of the right lobe of the liver which contained a 1.5 x 4.0 x 2.7 cm well-circumscribed lesion. Microscopic examination showed "Metastatic nodule of colorectal-type adenocarcinoma with no residual viable tumor identified." The finding of necrotic tissue, rather than viable cancer, is interesting since he had not received chemotherapy for more than a year.

He refused resection of the lung mass and continued on the protocol I prescribed, with no other treatment. A series of CTs have shown no further activity in the liver, and gradual shrinkage and disappearance of the lung mass. In March 2021, he told me that his oncologist marvels at the resolution of his Stage IV disease. Patient 1 has never told his oncologist about his nutritional program.

In summary, a liver metastasis developed in this patient while he was receiving FOLFOX chemotherapy. It was resected, and he began treatment with me roughly 10 weeks after surgery. Ten weeks later, scans demonstrated a recurrent liver lesion and a new lung lesion. The liver lesion was removed, and pathology showed "no residual viable tumor"; he had received no orthodox treatment of any kind during this window. Since then, the patient has had gradual resolution of the lung lesion, with no evidence for disease in several scans, while pursuing only the prescribed nutritional protocol.

In a review and meta-analysis of palliative chemotherapy for colon cancer, median survival was estimated to be 8.0 months for untreated patients and 11.7 months for the chemotherapy group.[6] Patient 1 is now more than five years out from the discovery of metastatic disease.

Patient 2: Metastatic Non-Small Cell Lung Cancer

In October 2013, Patient 2 reported vision changes, vertigo, and headaches to his local doctor. Scans showed masses

in his lung and brain, and in February 2014, the brain mass was resected. Pathology demonstrated "metastatic adenocarcinoma, most consistent with a non-small cell lung primary."

March 2014 PET/CT revealed a 7 mm pulmonary nodule with intense uptake, and focal activity in the hilum. MRI of the head showed enhancement along the resection cavity. He then underwent radiation to the brain.

He was told he would most likely be dead in six months regardless of treatment, so he refused chemotherapy and began a self-designed nutritional plan. On this, his disease progressed. Chest CT August 2014 showed the lung lesion was larger at 1.5 cm, the hilar node also larger at 2.5 cm, and several new small nodules were seen, felt to be metastases. MRI of the brain September 2014 showed a new 1 cm tumor in the frontal lobe; in a repeat scan in December, the frontal lobe mass measured 1.7 cm, and a new mass had developed in the cerebellum.

I first saw Patient 2 in late December 2014. At that time, he felt well, though he did report visual changes caused by his original brain surgery. He had no symptoms from his pulmonary disease.

In January 2015, he started the protocol I prescribed, but he also proceeded with glucocorticoids followed by radiation to both tumors in his brain, because of concerns about impending herniation. After completing radiation, he developed excruciating headaches, and was found to have extensive vasogenic edema with midline shift. In June 2015, he called to let me know that despite all these issues, he had stayed on the prescribed nutritional program. Chest CT August 2015 showed that the previously seen masses had resolved. MRI of the brain September 2015 was unchanged from a June study. In March 2016, he let me know that a recent MRI of the brain demonstrated a slight decrease of enhancement in the resection bed, to the amazement of his neurologist.

During 2017 and 2018, he continued in his usual state of health, with visual problems felt due to his brain surgery and radiation. MRI of the brain April 2018, compared to a June 2016 scan, was read as "persistent right cerebral masses, slightly enlarged." Then in late June 2018, he called me to report episodes of left-sided weakness and shaking. I told him to go the emergency room.

In the hospital, chest CT July 2018 showed "No evidence of metastatic disease or primary neoplasm involving the thorax." An MRI of the brain, compared with the April 2018 study, showed "Interval increase in size of right frontal mass with signs of recent hemorrhage … with increased surrounding vasogenic edema … stable right parietotemporal mass with surrounding vasogenic edema." His physicians concluded that the brain masses represented post-radiation changes, with the acute clinical change due to hemorrhage, and he was discharged on a glucocorticoid taper and levetiracetam.

I told him at the time that despite the clear chest CT, he should not assume that his cancer was gone, and should not stop his nutritional protocol. Unfortunately, because of his poor vision, and left-sided weakness from the June 2018 hemorrhage, he was never able to resume it. He lived alone, with very little social support, and was having great difficulty managing daily activities such as shopping, cooking, and cleaning. He contacted me occasionally to update me about his situation, and then again to let me know that his disease had recurred with a vengeance. He passed away in May 2020.

In summary, this patient with non-small cell lung cancer had one brain metastasis removed, then radiation to recurrent brain lesions, but had no systemic treatment and no treatment of any kind to the lung lesion or the hilar nodes. While he was able to continue his nutritional program, there was no evidence of disease in the thorax; but after his neurological deterioration due to hemorrhage, he could no longer follow it; his disease recurred, and he expired.

In a review of cases of non-small cell lung cancer metastatic to the brain, median survival was about 10 months.[7] Patient 2's six-year survival is remarkable, as is the resolution of the lung tumor without orthodox therapy of any kind during the period he was able to follow his nutritional protocol. And while I am saddened by his death, in our last conversation he told me he was grateful for the extra time he had, and he promised he would put in a good word with St. Peter for me.

Kelley found that pancreatic enzyme ingestion could lead to flu-like symptoms that were relieved by coffee enemas.

Discussion

The treatment protocol used with these patients involves three components: large doses of a pancreas product naturally rich in enzymes; diet and nutritional supplementation designed to address autonomic nervous system imbalance; and detoxification with several modalities, including coffee enemas. All three aspects are necessary for success.

Pancreas product. The theoretical mechanisms behind the use of pancreatic enzymes against cancer have been reviewed in detail elsewhere.[8,9] To summarize, more than a century ago, the British embryologist John Beard noted the similarity between cancer and the trophoblast, the early stage of the placenta.[10] Both tissues are undifferentiated, invasive, and able to create a blood supply. But at a certain point in gestation, the trophoblast modifies its aggressive behavior and transforms into the mature placenta. Beard observed that this transformation occurred at the same time the fetal pancreas began to synthesize enzymes, and speculated that pancreatic enzymes might play a role in cancer prevention and treatment.

Research has confirmed that trophoblast cells and cancer cells use similar mechanisms to invade and create a blood supply.[11] More recent studies

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demonstrate receptors for proteases on the surfaces of both types of cells.[12,13]

During Beard's life, physicians used enzyme preparations with variable success, which Beard felt was due to the erratic quality of the products used. Quality, dosing, and patient non-adherence all make for challenges in implementing this form of therapy. For some patients, it is difficult to accept that treatment will have to continue for years. Our belief is that cancer develops due to inadequate pancreatic enzyme manufacture by the body, and that just as an insulin-dependent diabetic requires insulin indefinitely, many of our patients require some additional pancreas product indefinitely or the cancer will recur. Patient 2's story illustrates this.

Some patients over the years have decided that only the pancreas product is important and that they could minimize or eliminate the following aspects of the protocol. Kelley, Nick, and I all found that those patients do not succeed.

Diet, supplements, and the autonomic nervous system. Dietary advice for all patients includes organic food, unprocessed and unrefined, with no white flour, white sugar, or inflammatory oils. Beyond that, in this model, different patients need different diets, from nearly vegetarian to a diet replete with animal protein and fat, in addition to root and cruciferous vegetables. Different patients also need different supplement protocols, with the vegetarian patients doing well with magnesium and potassium, the carnivores needing more calcium.

The model is based on Kelley's clinical observations, with support from the work of Dr. Francis Pottenger and Dr. Ernst Gellhorn.[14,15] The two parts of the autonomic system, the sympathetic "fight-flight-freeze" system and the parasympathetic "rest-digest" system, ideally operate in a balanced way. Genetic predisposition, environmental stressors and aging can push one system or the other to be overactive, resulting in poor health. Health can be improved by improving the balance of the autonomic system.

The sympathetic nervous system can be toned down by an alkalinizing diet and by magnesium and potassium but is stimulated by calcium. Patients with an overactive parasympathetic system tend to be too alkaline and do well with red meat, fat, and supplemental calcium. Patients whose metabolism is balanced need a variety of foods and moderate amounts of magnesium, potassium, and calcium. A detailed explanation of this, with a review of Pottenger's and Gellhorn's work, can be found in Nick's book *Nutrition and the Autonomic Nervous System*.[16]

Kelley predicted that an overactive sympathetic system contributes to carcinomas, such as lung, breast, pancreas, colon or prostate cancer. Patients with an overactive para-sympathetic system would develop cancers of the immune system, such as myeloma, leukemia, and lymphoma.

Nick told me once that the principles of autonomic imbalance could help make sense out of many of the bits and pieces that would float past in the medical and nutritional literature. As an example, researchers have found that breast cancer patients who were prescribed beta-blockers (for reasons other than breast cancer, such as hypertension or heart disease) do better than patients who were not prescribed this medication.[17] In Kelley's model, breast cancer patients have an overactive sympathetic nervous system, and beta-blockers specifically block the beta-adrenergic receptor of the sympathetic nervous system, bringing these patients' metabolisms closer to balance.

In another study, administration of calcium supplements slightly raised the risk of heart attack.[18] A subsequent article, pooling the results of many studies, suggested that there was no such increased risk.[19] Calcium, as a stimulator of the sympathetic nervous system, could well be an instigator of heart attacks if given to patients whose sympathetic nervous systems are already too active. In the Kelley model, patients with overactive parasympathetic nervous systems need and thrive on high doses of calcium

Linda L. Isaacs, MD, received her Bachelor of Science from the University of Kentucky. After medical school at Vanderbilt University, she completed her residency in internal medicine and is certified by the American Board of Internal Medicine. In her practice, she uses nutritional protocols to treat patients diagnosed with cancer and other serious degenerative illnesses. She and her colleague, the late Dr. Nicholas Gonzalez, published articles about 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*. Visit her website at www.drlindai.com

supplements, while patients with overactive sympathetic systems need very little. The patients in the study showing increased risk might well have been made up mostly of those with overactive sympathetic systems. Larger analyses, pooling data from many studies with patients of a variety of metabolic types, would show no risk.

In contrast to Kelley, Nick and myself, others in the integrative nutritional world state that everyone should be on the same diet, which might be anywhere from vegan to low-carb – usually the diet that the prescribing practitioners feel best eating for themselves. With our methods, I will find myself recommending for some patients a diet with less animal protein than works for me, and for others a diet with much much more. Two of my patients, who were included in our 2007 article in *Alternative Therapies in Health and Medicine*,[2] illustrate this point; one, with pancreatic cancer, was told to eat a near-vegetarian diet, the other, with lymphoma, was told to eat large amounts of animal protein. Both patients are alive and well today, twenty years or more since diagnosis. Each continues to eat the prescribed diet with relish. The vast majority of the time, patients feel well with the recommendations we give.

Many other nutritional supplements besides magnesium, potassium and calcium have an effect on autonomic nervous system balance as well, which is why I warn my patients not to add to or modify their protocol without talking to me first. Emotional states and stress are also important, since negative emotions can activate the sympathetic nervous system powerfully.[20]

Detoxification. Detoxification, primarily with the use of coffee enemas, is the third component of the work I do. Coffee enemas were widely used in mainstream medicine in the nineteenth and the first half of the twentieth century for the treatment of poisoning and in postoperative care.[21-27] Theoretically, coffee enemas stimulate bile flow from the liver and gallbladder, thereby assisting removal of wastes. Support for this comes from a 2014 article describing their use in clearing bile prior to capsule endoscopy.[28] *Alternative Therapies in Health and Medicine* recently published an article of mine reviewing this subject.[29]

Kelley found that pancreatic enzyme ingestion could lead to flu-like symptoms that were relieved by coffee enemas, and so he incorporated them as a key component of his treatment regimen. On a practical level, Nick and I have had patients decide that the enemas were unnecessary, and none have done well. Most patients immediately feel better when they do them, so compliance with this aspect is better than I would have predicted before I tried them myself. However, some patients cut corners because of the time it takes, as well as a fundamental lack of appreciation of the importance of detoxification. Dietary quality and avoidance of environmental pollutants also fit into the category of detoxification, because bringing in unnecessary toxins slows the whole process down.

Conclusion

In an ideal world, methodologies that look promising in case reports are then evaluated in a formal clinical trial.[30] Nick and I tried our best, starting with a pilot study in pancreatic cancer published in 1999.[31]

The clinical trial that followed was, in our opinion, rendered worthless because of problems in study design, mismanagement, and poor compliance on the part of the majority of the patients enrolled.[32,33] The academic researchers involved did not discuss compliance in their publication of the results, even though this had been discussed extensively as the trial progressed.[34,35] The oncology community was profoundly unsupportive of the trial, and I believe this affected patient compliance with the protocol.

Nick and I have focused on publication of case reports over the years, but one of the most common questions, from both patients and other practitioners, has been, "What is your success rate?" Understandably, patients want to know what the likelihood of success is for their particular situation. Unfortunately, it is a question that is impossible to answer in a scientifically rigorous and responsible way, due to a heterogeneous patient population, variations in adherence, and difficulty finding an appropriate comparison group in the medical literature. Nick and I addressed this in the last article we wrote together, published a few months before his death in 2015.[36]

My goal in continuing to practice and publish case reports is to keep this work alive to help interested patients with no curative options, or those who have completed their orthodox therapy. It is my hope that one day the medical world will be more receptive and willing to fairly investigate the results. ◆

References and article are available online at www.townsendletter.com.

A Case Study of Stage 4 Melanoma in Remission

by Leigh Erin Connealy, MD, and Bita Badakhshan, MD

Integrative Cancer Therapies

- **Intravenous (IV) vitamin C:** Very high blood levels of vitamin C, which can only be achieved with IV administration of high doses of ascorbate, form hydrogen peroxide, which kills cancer cells without harming normal tissues. Used alone or with other cancer treatments, IV vitamin C has been shown in numerous clinical trials to slow disease progression and increase survival time.[8]
- **Additional IV therapies**: Other IV therapies that target cancer include **dichloroacetate sodium** (**DCA**, which kills cancer cells by interrupting their metabolism[9]), **Poly MVA** (a proprietary blend of palladium bound to alpha lipoic acid, B-vitamins, and trace minerals), and **artesunate** (an antimalarial drug that has been shown to bind with iron in the body and trigger cancer cell death[10]). IV **curcumin** and **selenium** are also administered for their anti-inflammatory, antioxidant, and anti-cancer properties.
- **Hyperbaric oxygen therapy (HBOT):** When 100% oxygen is breathed in a pressurized chamber, oxygen diffuses into the plasma, lymph, and cerebrospinal fluid and is transported throughout the body, dramatically increasing oxygen levels.[11] In addition to creating a less hospitable environment for cancer cells, which largely rely on anaerobic metabolism, HBOT enhances the effectiveness of cancer treatments and reduces their adverse side effects.
- **Pulsed electromagnetic field therapy (PEMF):** Administered in conjunction with IV vitamin C and/or HBOT, PEMF treatments induce electromagnetic fields in the 0–300 Hz range to boost ATP production and help restore cellular function and integrity. When used as an adjunct to chemotherapy and radiation, it also reduces side effects and improves prognosis.[12]
- **Supportive Oligonucleotide Therapy (SOT):** This personalized cancer treatment harnesses the power of oligonucleotides (short DNA or RNA molecules).[13] Each treatment is individually tailored to target and bind to the patient's circulating tumor cells and block the expression of genes required for growth and proliferation.
- **Ozone therapy:** Treatments involve exposing a small amount of the patient's blood to ozone, then reinfusing it back into the body. This oxidative therapy increases the vulnerability of cancer cells while triggering antioxidant and immune defenses that protect normal cells.[14]
- **Light Beam Generator (LBG):** LBG is a noninvasive therapy that focuses on the lymph system. By stimulating lymph flow with specific wavelengths of light, LBG eliminates excess lymphatic fluid and cellular wastes.
- **Hyperthermia:** Hyperthermia treatment, which involves raising the temperature of specific areas or the entire body to above normal levels, damages cancer cells and helps shrink tumors. It also sensitizes cancer cells to other treatment modalities.[15]
- **EDTA chelation therapy:** EDTA is the treatment of choice for heavy metal toxicity. Infused intravenously, it binds to lead, iron, and other minerals in the blood and enables them to be excreted from the body.[16]
- **Nutritional support:** Dietary advice and individualized supplement regimens, based on nutritional evaluation, are a mainstay of integrative cancer therapy. Common supplement protocols include alpha lipoic acid, vitamin D3, B-complex vitamins, probiotics, and pancreatic enzymes.

Abstract

Melanoma accounts for just 1% of all skin cancers but is responsible for the majority of skin cancer deaths.[1] Although surgical removal is often curative in early-stage melanoma, the risk of recurrence increases and prognosis worsens in advanced disease. We report on the case of a patient with recurrent stage 4 melanoma with metastasis to the liver. Early detection of recurrence with specialized blood tests of cancer biomarkers and treatment with integrative therapies led to an excellent response, and the patient is now in remission.

Introduction

Melanoma incidence is increasing in the US, with a 1.4% rise in new cases per year from 2009 through 2018.[2] The prognosis for localized early-stage melanoma is excellent, but the five-year survival rate for metastatic melanoma is just 27%.[3] Therefore, investigation into novel blood tests and effective therapies is needed to improve early detection and outcomes in melanoma and other cancers.

Several specialized blood tests are excellent adjuncts for early detection of cancer.[4] Although these tests are underutilized in conventional oncology, they identify biomarkers indicative of cancer activity before signs and symptoms are evident on physical exam, routine blood tests, and imaging scans. They include the following:

- Phosphohexose isomerase (PHI), also called autocrine motility factor, is an enzyme involved in anaerobic metabolism. Elevations have been linked with increased tumor activity

in cancers of the skin, liver, and other sites.[5] *Normal range: 15.6–31.4 U/L*

- Circulating tumor cells (CTC) are cancer cells that are sloughed off from tumors and released into the bloodstream. Recurrence or metastasis occurs when these circulating cells take up residence in the initial tumor site or in other organs.[6] CTCs can be detected by RGCC's "liquid biopsy." *Normal range: 0 cells/mL*
- Nagalase, or alpha-N-acetylgalacto-saminidase, is an enzyme that inhibits Gc macrophage-activating factor (GcMAF) and interferes with the production of macrophages. Patients with cancer have elevated levels of nagalase, and the higher the level, the greater the tumor burden and the more aggressive the cancer.[7] *Normal range: below 0.95 nmol/min/mg*

These tests are also useful for monitoring the effectiveness of therapeutic interventions and guiding treatment protocols, both conventional and integrative. (See sidebar on page 46 for a brief description of integrative cancer therapies.)

Here, we discuss a patient with MRI-documented recurrence of melanoma, diagnosed as stage 4 with metastasis to the liver, that was initially suspected based on PHI, CTC, and nagalase test results. Early detection of cancer activity plus a comprehensive integrative treatment program with a number of anti-cancer and supportive therapies resulted in regression and ultimate disease remission.

Case Description

A 50-year-old male consulted us in January 2016 for monitoring and treatment. He had been diagnosed with stage 3 melanoma in June 2014, with surgical removal of lesions on his back and left shin. Twelve lymph nodes were also removed, and one had microscopic metastasis. A PET scan in September 2014 was clear, and no further treatment was recommended. He was monitored by his oncologist with blood work every three to six months and had a CT scan at the end of 2015 that was negative. The patient also has a history of thyroid cancer, diagnosed and treated in 2014, and is status post radiation and thyroidectomy.

When we first saw the patient in January 2016, he had no complaints but, given his history of cancer, wanted to enhance his immune function and overall health. Blood work at the patient's initial exam revealed that complete blood count (CBC), comprehensive metabolic panel (CMP), and high-sensitivity C-reactive protein (hs-CRP) were within the normal range and, in fact, remained so throughout his treatment course. However, his PHI and CTC were high at 60 U/L and 9.3 cells/mL, respectively, suggestive of ongoing cancer activity.

Early indications of cancer activity enabled us to begin treatment months before the December 2016 MRI confirmation of metastatic melanoma.

Therefore, we started the patient on a three-month protocol consisting of hyperbaric oxygen therapy (HBOT) three times a week, intravenous vitamin C and dichloroacetate sodium **(**DCA) plus pulsed electromagnetic field therapy **(**PEMF) twice a week, and Light Beam Generator (LBG) and ozone therapy once a week. We also recommended four Supportive Oligonucleotide Therapy (SOT) treatments, spaced out several months apart, beginning in October 2016.

Although his PHI and CTC levels initially declined, by late 2016 his PHI spiked up to a very high 92.9 U/L, his CTC was 9.5, and his nagalase was elevated at 1.97 nmol/min/mg, so scans were ordered in December 2016. CT of the lungs was negative, but abdominal CT revealed two adjacent hypodense lesions in the left lobe of the liver measuring 10 mm and 11 mm, an increase from 3 mm each previously. A contrast-enhanced MRI of the abdomen was positive for two lesions on left hepatic lobe measuring 10.8 mm and 6.4 mm *consistent with metastasis to liver*. There were also several cystic lesions.

Following his diagnosis of metastatic melanoma, the patient resumed HBOT three times a week plus PEMF and IV therapies (vitamin C, DCA, poly MVA, selenium, and artesunate) twice a week. He also began weekly LBG and hyperthermia treatments twice a week and started taking metformin 500 mg twice a day. He had a second SOT treatment in March 2017. Abdominal MRI in April 2017 showed that the larger lesion had shrunk to 9.6 mm compared to the previous 10.8 mm, and the second lesion was stable at 6.4 mm. Small cystic lesions were noted, but no new lesions were present. MRI of the pelvis and CT of the chest were negative. CTC levels in April dropped to 7.9 cells/mL, and PHI was in the normal range at 30.7 U/L. Nagalase also declined to a high-normal level of 0.94 nmol/min/mg.

Over the next few months, the patient continued IV vitamin C plus IV selenium and artesunate weekly. He received his third SOT treatment in August 2017 and continued to do well. MRI that month showed further shrinkage of the two lesions to 4 mm and 6 mm, with small cystic lesions but nothing new. He had a fourth SOT treatment in January 2018 and HBOT two or three times a week. Blood tests in February 2018 revealed that his PHI had dropped to 31.5 U/L and his nagalase to 0.66 nmol/min/mg, both within the normal range. Abdominal MRI in April 2018 showed stable lesions measuring 4 mm and 6 mm with small cystic lesions and no new lesions.

We continued to follow the patient with regular treatments and blood tests throughout 2018. His CTC further declined to 7.0 cells/ml in June. PHI also gradually declined. Interestingly, when the patient decreased his treatments, his PHI crept up. When he resumed IVs and HBOT, it normalized. By December 2018, MRI of the abdomen showed further decrease in the two liver lesions, now measuring 2 mm and 4 mm with small cystic lesions that were unchanged.

We stepped up his IV therapies in 2019, and in June his PHI and nagalase levels were in the normal range at

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28.1 U/L and 0.75 nmol/min/mg, respectively. MRI of the abdomen in June 2019 showed calcification of the liver lesions with no additional lesions except for the cystic lesions and no evidence of metastatic disease. MRI of the pelvis was also negative for metastasis. The patient's stage 4 melanoma has been in remission since June 2019. Abdominal MRI with and without contrast in December 2019 noted the presence of tiny stable hepatic cysts and no evidence of abdominal neoplasm.

The patient returns for follow up with periodic testing and supportive treatments. His most recent CTC test was 5.2 cells/mL, a significant improvement from his initial 2016 test result of 9.3 cells/mL. His PHI levels have also been in the normal range except for a spike in January 2021, which rapidly returned to normal. This could be due to high levels of palladium, a toxic heavy metal that suppresses immune function. He has received multiple EDTA chelation treatments with significant improvements in previously high levels of lead, gadolinium, platinum, uranium, and other metals, and his palladium level is slowly decreasing.

Discussion

This patient has been in remission with stage 4 melanoma since June 2019. Initially diagnosed with stage 3 melanoma in June 2014, he was treated with surgical excision of lesions on his back and left shin plus removal of 12 lymph nodes. He had a normal PET scan in late 2015 with no further treatment recommendations.

After consulting us for monitoring in early 2016, we suspected a recurrence based on elevated PHI, CTC, and nagalase levels suggestive of tumor activity. We started him on a comprehensive treatment program consisting of HBOT, IV vitamin C and DCA, PEMF, LBG, and ozone therapy, with the later addition of SOT. An MRI in December 2016 confirmed recurrence, with metastasis to the liver (two lesions and multiple liver cysts) and a diagnosis of stage 4 melanoma.

Given that the patient's recommended follow up by his oncologist was blood work every three to six months, it is possible that this recurrence would have gone unnoticed, had active cancer biomarkers not been detected by PHI, CTC, and nagalase tests. Early indications of cancer activity enabled us to begin treatment months before the December 2016 MRI confirmation of metastatic melanoma.

Over the next five years, we treated the patient with a comprehensive treatment program, making periodic additions and adjustments to include additional IV therapies (Poly MVA, selenium, curcumin, and artesunate), hyperthermia, nutritional support, and EDTA chelation. During that time, his PHI, CTC, and nagalase slowly returned to normal levels, indicative of a reduction in cancer activity. This

mirrored findings on CT and MRI scans, as the two liver lesions slowly regressed from an initial 10.8 and 6.4 mm, to 2 and 4 mm a year later, and, in June 2019, to calcification of the two liver lesions, no additional lesions, and "no evidence of metastatic disease."

This is a remarkable recovery, given the aggressiveness and mortality risk of metastatic melanoma. Over the past decade, significant progress has been made in the treatment of stage 4 melanoma, which historically had a five-year survival rate of less than 10%. Newer immunotherapy regimens, which help the patient's immune system identify and fight cancer, are a promising and welcomed treatment option with lasting remission for some patients with advanced melanoma.[17] However, immunotherapy does not work for everyone, and many patients still face a challenging prognosis.

Some of the complementary therapies we used to treat this patient have direct anti-cancer effects. Others stimulate various aspects of the immune system or enhance overall health. An added bonus is they are well tolerated, do not damage healthy tissues, and actually protect against the adverse effects of conventional cancer treatments. The patient had few side effects throughout his treatment course and reported stable energy and appetite and no pain or other symptoms.

Nearly 1.9 million new cancer cases are predicted in the US in 2021, along with an estimated 608,507 cancer deaths. Approximately 39% of Americans will be diagnosed with cancer of some kind during their lifetime.[18] The outcomes this patient and many other patients with a variety of cancers have experienced attest to the efficacy of these and other integrative cancer treatments – not only for melanoma but most types of cancers.

The underutilized cancer biomarkers (PHI, CTC, and nagalase) and integrative therapies we have presented merit broader use as well as future research, including randomized clinical trials, to elucidate their mode of action, safety, and ability to increase long-term survival.

Note: The patient has provided informed consent to use his information for educational purposes.

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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 47,000 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 and Integrative Doctors in the US.

Cancer Center for Healing, 6 Hughes, Irvine, California 92618, 949-581-HOPE (4673) https://www.cancercenterforhealing.com/

Bita Badakhshan, MD, was raised in Sweden and moved to Southern California in 1996. She attended medical school at St. George University, finishing her family medicine residency at North Shore-Long Island Jewish Health System. After a brief stay in the New York City area, Dr. Badakhshan returned to Southern California in 2011. Under the mentorship of Dr. Connealy, Dr. Badakhshan has placed special career focus on cancer, cancer prevention, and integrative cancer treatments. Dr Bita works closely with all Stage 1-4 cancer patients. She is a member of the American Board of Integrative Holistic Medicine.

Lyme Disease: Highlights of Diagnosis and Naturopathic Treatment

by Darin Ingels, ND, FAAEM

The Basics

- Lyme disease has become the fastest growing insect-borne infectious disease in the United States, Europe, and Asia. Lyme disease affects more than 476,000 people each year in the United States and 65,000 people in Europe.
- There are over 100 different species of *Borrelia* in the United States and more than 300 worldwide.
- There is poor consensus among physicians on the diagnosis and treatment of Lyme disease and the conventional medical understanding of Lyme disease is often limited to those who have acute infection.
- Chronic Lyme disease or post-Lyme syndrome has become controversial, and many patients are dismissed when they complete their treatment for acute Lyme disease, yet still have symptoms.
- Evidence of persister cells that are resistant to antibiotics in those who have undergone treatment add credibility to the likelihood of persistent or chronic Lyme disease.

Symptoms of Acute Lyme Disease

- Fever
- Chills
- Throbbing headaches or migraines
- Profound fatigue
- Neuropathy
- Muscle and joint pain, especially migratory joint pain
- Swollen lymph nodes
- Bell's palsy
- Erythema migrans (EM) rash ("bull's eye rash")

Symptoms of Chronic Lyme Disease

- Any of the symptoms seen with acute Lyme disease, plus:
- Abdominal pain and bowel changes
- Memory loss or cognitive impairment
- Light or sound sensitivity
- Dizziness or vertigo
- Sleep disturbances
- Cardiac problems: mitral valve prolapse, heart block, palpitations, chest pain
- Balance or coordination deficits
- Endocrine disruption: hypothyroidism, irregular menses, etc.

Lyme Testing

- Lyme disease is a clinical diagnosis according to the CDC and not solely based on a lab test alone.
- The Lyme screen test is less than 46 percent sensitive and misses most people with Lyme disease.
- Lyme Western Blot testing is more sensitive and specific.
- False positive Lyme tests are uncommon, whereas false negative tests are common and therefore a negative test cannot rule out the possibility of having Lyme disease.

Conventional Treatment of Lyme Disease

- The conventional medical treatment for Lyme disease is to take antibiotics for up to 3 weeks after diagnosis.
- The International Lyme and Associated Diseases Society (ILADS) will use longer courses of antibiotics, both oral and intravenous, for longer periods of time due to the slow growing nature of *Borrelia*.
- Use of long-term antibiotics may cause imbalances of normal gut microbiome and damage to the mitochondria, so risks and benefits need to be weighed with each patient.

Herbal Treatment of Lyme Disease

- Numerous herbal therapies have been shown to be effective in the treatment of Lyme disease and are generally regarded as safe.
- *Artemisia annua* (sweet wormwood/sweet annie) and *Uncaria tomentosa* (cat's claw) are effective at killing *Borrelia* in its stationary and growth phases. *Artemisia annua* is also effective against *Babesia duncani.*
- *Uncaria tomentosa* is anti-inflammatory, antioxidant, immune stimulating, adaptogenic and hepatoprotective. Dr. Eva Sapi reported in *Townsend Letter* in July 2010 that *Uncaria tomentosa* and *Otaba species* were more effective than doxycycline at eliminating *Borrelia burgdorferi* in both its spirochetal and round body forms.
- *Houttuynia cordata* (chameleon plant) has been used in Traditional Chinese Medicine to treat leptospirosis, which is also a spirochete. This herb has been useful in modulating inflammation in Lyme patients, as well as helping prevent and treat secondary opportunistic viral illness.
- Coptis (*Coptis chinensis*) is rich in coptisine and berberine, which have anti-cancer, anti-inflammatory, and anti-bacterial effects. It may also help reduce oxidative stress and protect against neuronal damage.
- *Cordyceps sinensis* (Cordyceps) is a medicinal mushroom that contains beta-glucans, which are well-known to help stimulate the immune system. Like many of its other medicinal mushroom cousins, its immune activation targets mostly T cells and NK cells.
- *Hericium erinaceus* (Lion's Mane) is another medicinal mushroom that can help reduce depression and improve cognitive function. There is additional evidence to suggest lion's mane may also help with remyelination of damaged neurons.

Summary

- Lyme disease is a complex medical illness that is often overlooked in medical practice.
- Early diagnosis and treatment are important in helping patients overcome their illness.
- Antibiotics can be effective in acute Lyme disease, but have limited benefits in long-term Lyme treatment.
- Herbal therapies can be effective at targeting Lyme disease and coinfections but can also help support the immune system, reduce inflammation, and provide other health benefits to the patient.
- A personalized medicine approach can be custom tailored to each patient so that herbal prescriptions fit the individual needs.

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Interview with Dr. Serge Jurasunas on Immuno-Oncology: The Latest Advances in Cancer Treatment and Lifestyle

by Dr. Jamie Turndorf

JT – What personal event launched your career of over a half-century journey in treating cancer?

SJ – This is a long story because my interest in treating cancer began back in 1967 or 1968 when I was in Montreal, Canada, and found Dr. Max Gerson's book, *A Cancer Therapy – Results of Fifty Cases*. I was at the beginning of my practice and knew nothing about cancer, but this book fascinated me since also I could see some correlation with the work of Dr. Bernard Jensen concerning the use of fresh organic vegetable juice, especially carrot and beet juice. Max Gerson's approach made sense to me since it offered cancer theory and a diet. In truth, I have in my memory the sad story of both my father and mother who both died of cancer. At that time our house smelled of all kinds of medications that caused me to develop repulsion for these remedies. This maybe is the reason why I decided to spend more time learning about cancer – having been my fight for over the past 50 years. However, I found myself limited and decided to learn more about cancer and also iridology, since I started to use it in my practice from Dr. Jensen's teaching.

So, I decided to close my consulting office and flew back to Europe, then traveled to Germany to see if I could get more information about cancer and therapy. I was lucky to meet pioneers like Dr. Paul G. Seeger, cancer researcher, biologist, and physician, who conducted several experiments, beginning in 1938 at the Robert Koch Institute in Berlin. In 1957, he demonstrated that the cause of cancer and its growth was the destruction of important enzymes in the respiratory chain in the mitochondria – a discovery was made similar to Otto Warburg's. He published over 300 scientific papers and several books and was twice nominated for the Nobel Prize in 1979 and again in 1980. Unfortunately, today, Dr. Seeger remains unknown even after having been a great researcher.

I also met Dr. Siegfried Wolz, a biotechnology engineer who also collaborated with Dr. P. G. Seeger. S. Wolz was the owner of the Wolz Laboratory; we kept in contact over many years before he died. Dr. Seeger asked him to develop a product that could regenerate cellular respiration. He then developed the famous Enzyme Yeast Cells during the same year we had met. In 1990, they both published a very important book called, *Successful Biological Control of Cancer*, offering a full description of his research since 1938, about the theories on mitochondria and cellular respiration, explaining how to reactivate cellular respiration using selected enzymes and other compounds. Now for me, it was a basis to understand what cancer is and to start treating it. My first article published in the *Townsend Letter* in 1999, was about the theory of cellular respiration. To my surprise, I received so many letters from both naturopaths as well as physicians showing major interest. In 2011, I subsequently published a more complete article.

JT – You were born in France and immigrated to the US in 1959 where you met Dr. Bernard Jensen. Then you spent time in Canada where you began your studies in naturopathy after which you came back to France, traveled to Germany, and finally settled in Portugal. Why did you choose to permanently reside in Portugal?

SJ – We can never know what life has decided for you, what you will do, or where you will go. For me, it is like a puzzle. When very young, I decided to immigrate by myself to the US. Luckily, I landed in Los Angeles where under some predestined circumstance, I met Dr. Bernard Jensen, who profoundly changed my life and guided me to this new world of natural medicine. The reason why I then moved to Montreal was to enroll in a course of naturopathy in the French language rather than in English since I also didn't know where to go to study in the US; but at the same time, I started to read many health books. I also began my first homeopathy correspondence course with the French College of Homeopathy in Paris. Before graduation, I opened a consulting office and was lucky to have many patients. But as previously explained I found my knowledge limited and decided to return to France and traveled to Germany. So you see for some reason, life brought me back to Europe.

In Paris, I registered for advanced courses at the French School of Naturopathy in evening classes and then collaborated to offer some courses in iridology and Dr. Jensen's nutritional and detox method. The French Federation of Naturopathy

organized a yearly congress where I met a young Portuguese doctor, speaking fluent French who was attracted by my knowledge of naturopathy.

Back then, iridology was practically unknown in Portugal. He invited me to come and work in his Lisbon clinic. Of course, the language could at first be an obstacle, but I was not very satisfied with my life in France after living in the US and Canada. I decided to accept his offer and see what life would bring me.

One year later I met my wife Lucie, a professor of French philosophy, who was very enthusiastic about the philosophy of naturopathic medicine and natural food. We decided to open my own consulting office, while at the same time we created a small company to import the best natural products for our patients, including the important Enzyme Yeast Cell preparation from Dr. Wolz. Of course, my wife gave up her profession, and we began to educate people, publish our health magazine, started to travel, and then later opened several health food stores. In 1976 I opened my first large clinic in Lisbon, where the weather was excellent, the food still natural, etc. Now I permanently reside in Portugal because I was well accepted by patients, people who were very open, friendly, who understood how I treated disease. They were especially attracted by iridology. My mission was to help them and offer some meaningful education. Of course, we grew and developed a large [line of] natural products.

In 1985, we decided to open our own pharmaceutical manufacturing facility, not only for pharmaceutical products but for high-quality natural products to fulfill the need of my patients and supply our health food stores. Today we export to about 28 countries. In 1983, I opened a second, large, three-story clinic outside of Lisbon that became a school where doctors from several countries came for my teaching. This explains the reason why I settled in Portugal; but of course, I never forget the US, having made many good contacts with doctors. I went back several times to lecture, offer seminars, and collaborated with some institutions. I even obtained a license as a naturopathic physician and even as a homeopathic physician, but this was many years ago. I also traveled to lecture in about 36 countries worldwide.

JT – In your book you speak about your personal experience in treating cancer. Please tell us how you approach this disease.

SJ – When I speak about my personal experience I am referring to having a cancer patient facing you, which is one aspect of the disease along with the disease itself. Just treating the cancer is not like treating Parkinson's disease or arthritis since cancer is a killing disease that causes serious physical and psychological suffering. We have to know how to handle and help patients in this battle. I felt it takes years or even decades before you understand what cancer means and how to approach both the disease and the patient. I have treated thousands of cancer patients of all types, grades, and ages; but this disease is so complex that you never finish discovering more mechanisms. You never know when cancer cells start to develop resistance, what mechanisms support the migration of cancer cells; and of course, it all depends on the patient's attitude, lifestyle, dietary style, the way he/she reacts when diagnosed. We also must consider whether or not if the cancer was previously diagnosed without metastasis or as cancer with metastasis, which makes an overwhelming difference when treating the disease.

Science is far from discovering everything there is to know about the human body, especially what is cancer? On one hand, you have to describe the disease to your patient,

p53 gene expression is one of the main keys when treating cancer, especially breast cancer.

collect several factors associated with lifestyle, all the organic function or dysfunction including the nervous system, the energy level being also important, along with an emotional profile, oxidative stress profile, and the nutritional profile maybe through an LBA (Live Blood Analysis) examination. But if you want to treat patients like I do, you do molecular markers testing, and only then do you have a better way to understand the cancer of each patient. Maybe the patient needs a chemical brain analysis as I offer, to get an idea about the function of the neurotransmitters, which also may affect the immune system and need to be balanced.

One other very important step when treating cancer is to determine the activity of the p53 tumor suppressor gene and p53 protein levels. For instance, a high level of mutated p53 is considered a poor prognosis and you have to know how to reverse this situation. This is the way I approach the disease, but it requires time to learn and be organized. I believe the p53 gene is the most important gene protecting us against cancer. Just as an example, a few years ago a team of researchers from the US and Israel made an investigation with elephants to find out why they practically do not die from cancer. In their lifetime elephants develop only a 5% risk of cancer and a 5% risk of dying from cancer, while for a human it goes up to 55%. So where is the answer? Could you believe this, but the answer is associated with the p53 gene, but why? While humans have only two copies of the p53 gene, elephants have 40 copies and are highly protected. The published article suggests that the p53 gene may be the answer to cancer prevention and treatment.

JT – Can you give us an overview of your research on this topic?

SJ – Let's say that for the past 15 years I have concentrated my research in two main directions. First, I focus on apoptosis – related to the function of the p53 tumor suppressor gene since p53 mutation is necessary for the development of many forms of cancer along with other apoptotic players and inhibitors of apoptosis. We then perform specialized blood testing on the patient where the results give you the information you need for diagnosis, prognosis, treatment follow-up, and how to build your treatment.

Now, remember that cancer cells can be killed directly or indirectly even with chemotherapy, but always through

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apoptosis. Dysregulation of apoptosis occurs in cancer cells and has not only been implicated in tumor progression but also plays an important role in response to therapy; this is important to remember. Now doing such testing gives you the result you need to tailor your treatment, and it works also as a prognosis but sometimes you get a very bad prognosis. We may call this diagnostic procedure molecular markers testing, and we do it in a laboratory, as I have explained in several articles in the *Townsend Letter*.

In the beginning, when I started to use this molecular blood testing, I was obliged to spend considerable time studying and understanding the function of each gene. Of course, you have to know how to select natural agents that can reverse, activate, and inhibit various genes. I initially worked by experimentation and intuition. But it makes an overwhelming difference if you have a cancer patient with a mutated p53 gene or high levels of mutated p53 proteins, where the treatment has to be tailored according to the result. But this serves as only one example.

The other direction is the immune system which I have studied for decades but more seriously since I started to use RBAC [rice bran arabinoxylan compound]. Today we hear a different story, and nobody is currently just looking for the magic bullet to cure cancer. A few years ago, I began to develop more interest in the immune system fighting against cancer. Subsequently what surprised me, after oncologists denied and even criticized the power of immune cells to fight cancer, was a recent Sloan Kettering large public announcement that everyone is born with a defense system against cancer, meaning **YOU!** We already knew about this for a long time. The advertising said: Now oncology has introduced the latest breakthrough in cancer therapy. Can you believe this?! In any event, I have concentrated my research on the NK cell activity related to cancer and how to activate apoptosis using RBAC, but we never stop learning and reading updated documents.

When I started writing this book I was obliged if I may add, to engage in even more study about NK cells and update results about RBAC. Now RBAC is perhaps the most documented compound functioning as a biological response modifier that according to me should be included in all cancer protocols. In Japan, RBAC is considered a functional food and even used in more than 100 hospitals conjointly with chemotherapy and recommended by over 5000 doctors around the world. So by both studying and working with my patients, this has shown me how RBAC contributes to reduce tumor size, decrease tumor markers, how it works in synergy with various anticancer agents and natural compounds like curcumin, for instance, to prevent or eliminate metastasis. RBAC contributes to increased lifespan with quality of life, but even better you can read about it in my book and see some examples with clinical cases illustrated with scans before and after the treatment. I can say that writing this book was beneficial for me since I was motivated to have done more studies.

One instance was more study about the anticancer properties of curcumin and a new excellent study on the synergistic apoptotic effects of both RBAC and curcumin in human MM cell lines in vitro. I wanted to see this for myself and made several experiments with metastatic breast cancer and a huge stomach tumor using only RBAC and liposomal curcumin. If together you target angiogenesis, for instance, using the C-statin compound from bindweed herb, with strong angiogenic properties you can expect some good results; but as I said, individual experience is the key to success since at the same time you are facing the patient and the success depends on how you handle it, as well as its attributes.

JT – Why were you inspired to write a new book focusing on immuno-oncology using rice bran arabinoxylan?

SJ – OK, first let me tell you that boosting the immune system with a cancer patient is not new to me for over 40 years. In 1986 I published in France, a book on cancer where I mentioned that the channel of immunotherapy may be the only way to treat cancer. It took an additional 35 years before oncology came to this conclusion. Immunotherapy has now become the fourth pillar of oncology, but again using toxic agents – not to mention the cost is very expensive and once again it turned into a big business. For me the story of the RBAC began in 1992 when I was visited by one of my Japanese contacts who told me about a new compound developed in Japan, a rice bran arabinoxylan called Biobran, being very powerful to stimulate the immune system, especially the NK cells. I then began to experiment with my patients culminating in the excellent results we have today. In June 2017, I was participating in the 5th International Biobran (RBAC) workshop in Krakow, Poland, with the participation of various oncologists that themselves used RBAC. You can see my report in the *Townsend Letter* of October 2017.

Back then, for the first time, I met the general manager of Daiwa Lab (Japan), Mr. Nori Shirai, who after seeing my one-hour presentation, including several clinical cases with the protocol, came to me looking real enthusiastic, saying I should write a book including many clinical cases such as the ones that I had presented. I know what it means to write a book when after you start, during the next two or three years, you'll be busy writing, searching, changing and not even have time for your own life. So, I asked for time to consider and see how I would develop the contents of the book.

While it was a challenge for me to write this book, I wanted to offer a new orientation to treat cancer, through activation of the immune cells, especially NK cells by using RBAC, which has shown efficacy over the past years. Not only is RBAC a strong immuno-modulator, but it has anti-inflammatory properties, decreases free radical activity, and is important for me that it modulates the Bcl2/Bax ratio, meaning an increase in apoptosis, but this has only been shown recently in a new study. During the past three years, I saw so many published articles speaking of a revolution in oncology by stimulating the immune system, I realized I had been given a reason to write this book.

I showed my own clinical experience in other approaches and diet and included a selection of 25 well-documented clinical cases. Daiwa's president was pleased with the project, where Daiwa was in charge to publish the book. Having it

distributed in over 50 countries, including the US, offered more reason for me to write the book. However, I didn't expect so much time and energy would be spent to get the book finished in perfect US language. I devoted three years to this book, but in the end, I was rewarded.

JT – In your new book, you explain the role of p53 gene expression as the guardian of our immunity. This p53 gene is better known as the tumor suppressor gene. Can you tell us more?

SJ – Yes, most of us are acquainted with the p53 tumor suppressor gene as the guardian of our genome, being implicated in about half of all cancers. We know even less about some other important functions of the p53 gene, for instance, being the guardian of our immune integrity, which is one of the last discoveries of science concerning the p53 gene. Of course, this is all new and may be difficult to understand, but we just realized that the p53 gene is the maestro in a complex network of genes implicated in the case of cancer with immunosuppression, angiogenesis, inflammation, tumor invasion, and survival. If functioning normally, p53 gene can activate several immune mechanisms.

Another example, p53 is a transcription factor that can modulate checkpoints PD-1 and PD-L1 expression that blocks the immune system, specifically T-cells, and become a target in immunotherapy using the checkpoint drugs, Keytruda and Optivo. However, so far the results were still low, about 35%, along with side effects. There are at least two other mechanisms by which the p53 gene can activate immune cells to destroy cancer cells, such as by activation of an anti-tumor response via direct transcriptional regulation of the NK cell. The p53 gene can also modulate the tumor microenvironment that cancer cells use to grow and expand. Today the microenvironment is considered just as important as the tumor itself and needs a specific approach as well. This p53 gene can alter the host immune response, which is an additional way to increase the immune function to fight cancer.

But one other practically unknown function of p53 is the relation between the vitamin D receptor (VDR) gene that mediates the effects of vitamin D. We know that vitamin D modulates the activity of numerous immune cells. The expression of the VDR gene and then absorption of the vitamin D is induced by the normal p53 function but not by mutant p53.

Now we can understand why the p53 gene is so important when treating cancer and activating the immune system. The idea is to reactivate normal p53 function, using several selected natural compounds used to reverse immunosuppression and enhance anti-tumor activity. Of course, this is only a brief explanation, but you find all the details in my book.

This is why as I explained in the beginning, I wanted to devote a special chapter in my book about the p53 gene and its various functions, especially those linked with the immune system. Now we may better understand my response to attacking cancer cells both from direct activation of the immune cells and NK cells, while at the same time activating or reactivating p53 normal function, which contributes to an overall increased immune response. Why not call this a breakthrough in cancer treatment?

Interview with Dr. Jurasunas

JT – Why do you believe oncologists do not focus more attention on the p53 gene in clinical practice?

SJ – We could also ask why they pay no attention to using other alternative methods when they face treatment failure? Today you find over 70,000 scientific publications about the p53 tumor suppressor gene, p53, and cancer. Every year there are conferences and a world congress organized on mutant p53, where reactivating mutant p53 is considered as an anticancer therapy, so what is the problem with oncologists? More recently researchers in Ireland have found a promising treatment for patients with TNBC, the most aggressive known breast cancer. They published the result of their study in the *International Journal of Cancer* under, "Mutant p53 a Novel target for the treatment of a patient with TNBC," describing how a drug that targets the mutated p53 protein can largely inhibit the TNC cell proliferation and migration. So now we can say that the p53 gene may be one of the main keys in the treatment of cancer! According to my clinical experience, I can say yes.

Unfortunately, cancer theory is based on a deep-rooted dogma, and for far too long chemotherapy and radiation have remained the routine cornerstone of research by a laboratory in search of new miraculous drugs. I believe that today oncologists just work like robotic computers following what they all learned, conforming to what they are being told to do in the hospital. They are not yet ready to change their protocol, even if p53 mutation is an obstacle to chemotherapy.

Considering p53 mutation in clinical practice would support a new treatment paradigm with the use of natural compounds besides chemotherapy for which I believe oncologists are not yet prepared. Also, consider many alternative-medicine cancer doctors still do not understand the importance of the p53 tumor suppressor gene concerning cancer. I could give a further example when on one occasion where after sending my abstract to speak at an International Congress of Alternative Breast Cancer in the US, I received a negative reply: Not sufficient interest in a topic for this Congress! I could not believe such an attitude from alternative doctors knowing that p53 gene expression is one of the main keys when treating cancer, especially breast cancer. But on both sides require an open mind.

Let me quote you from Professor Ben Peiffer, oncologist at the Aesculap Clinic in Switzerland who also works with RBAC in his cancer protocol who has often stated, "You need to have an open mind." He was a professor of oncology in New York, but one day his sister was diagnosed with cancer and came to New York for treatment by her brother, but unfortunately she died. That woke him up but as he said, it is very difficult to get out of the system that you have been taught. He decided to return to Switzerland and opened a clinic where he could treat cancer patients differently. His cancer protocol included stimulation of the immune system using RBAC and activation of apoptosis.

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Unfortunately, in the Western world, most oncologists are still closed to any new paradigm, even those with scientific support such as the p53 tumor suppressor gene that responds to the use of natural compounds, simply because they are not independent and must be under the umbrella of Big Pharma or chemotherapy/radiation, so this may answer your question.

JT – What lifestyle and dietary rules and habits do you follow personally?

SJ – This is an interesting question because I have many colleagues that just live without dietary rules since they just do a job like any other and over the years most have passed on from heart disease or cancer. First, you have to be convinced that you need certain rules regarding food and a balanced lifestyle or way of living. Don't forget that naturopathy is also a philosophy of life.

Now let me tell you upon meeting Dr. Bernard Jensen back in 1962, he enthusiastically invited me to his Hidden Valley Health Ranch. I saw for myself the importance of nutrition and a balanced food diet not only as a recovery therapy but as a way to keep our body and mind healthy. So at that time, it changed my own life and my food style because for me it was a way to show more respect for my body and just stay on natural organic food and not junk food. All my life and also for my wife, we adhere to some important dietary rules, the first with food quality. We buy only organic vegetables and fruits, but we also have our own small organic garden. We only use natural organic non-industrial food, whole food, fresh fish caught during the night in the market the following morning. We also prepare every day our fresh organic vegetable juice that always include red beets, which to me is one of the most healthy of the main anticancer foods. In my book, *Health and Disease Begin in the Colon*, I have included 10 recipes for healthy soups, for a different purpose than we usually eat at home. We do follow mini-fasting in our diet with 16-18 hours between dinner and breakfast the next day, when we have only a cocktail of vegetable juice or some fruit with kefir or a salad in the afternoon. This is important, because at our age it keeps us healthier, you can be sure of this. We offer ourselves as an example of being healthy.

During the past 50 years, we always take several daily supplements but always include coenzyme Q10, vitamin C, magnesium, selenium, NADH, enzyme yeast cell preparation, CGF, chlorella tablets, and RBAC, to offer a few examples. Concerning my lifestyle, it is more difficult when you have been busy as I have been for several decades, traveling as I did; but I always set aside time for some sports, a lot of swimming, running, and participated in several triathlon competitions. But now I just build my lifestyle according to my age and keep swimming in my pool or spend summers at the beach and take a daily walk in the forest where I live. To tell you the truth at the moment we have to worry more about our health and immune system facing not only the risk of cancer but this pandemic; and good nutrition, dietary styles are our best weapon to keep away from infection and cancer.

JT – Can you please summarize the latest cancer treatment breakthroughs?

SJ – For over 20 years we have been used to reading about cancer in magazines like the *New York Times*, that this is the breakthrough we've been waiting for. Now, this is new ammunition in the war against cancer. Not a joke, but in 2007 the director of the National Cancer Institute announced the year 2015 as a deadline for the elimination of suffering and death caused by cancer. Of course, this false declaration was reported with pleasure by the media, yet where are we today with cancer and suffering patients? Where are we today with all the promised breakthroughs? We are still far from realizing this declaration since cancer is still dangerously on the increase. Finally, we all agree that classical treatment is not giving the desired results.

Mechanisms that are now considered as treatment using the body's [ability to] attack are the reason for the title of my book called, *Cancer Treatment Breakthrough*, but I should better say breakthroughs since I am explaining other advances in cancer. If the fight is within, then besides the immune system, we have to recognize that apoptosis through the function of the p53 gene expression is also as much or even more important; and when it will be recognized, then we can speak of another breakthrough. I have read somewhere in an article calling to boost tumor death, that cancer treatment needed two important approaches. Optimize both p53 and immune support, but this is what I have already been doing for so many years.

Now you have to understand that with either classical oncology or alternative medicine there is no one miraculous remedy that can cure cancer. We need to set up multiple approaches, which today are recognized by many oncologists. Now please remember that each patient is an individual from a genetic standpoint. We have many types of cancers since it is not just one disease; we also have different stages of cancer. We have cancer cells with resistance, tumors without metastasis, or cancers that have spread in various organs; so you can better understand the complexity of treating cancer because each patient has his/her unique cancer.

President Obama proclaimed the only theoretical advancement of medicine is to present what they call a personalized and precision medicine, but by doing what? Cancers look similar, but there are differences in the way they grow and spread. This is what we accomplish with our molecular markers testing since no two patients with similar cancer show the same molecular markers testing results; both are different.

I have researched and read a paper online called, "Advances and Breakthroughs in Cancer Treatment"'; but it only discusses the classical approach of surgery, chemo/radiation, monoclonal antibodies, cart-t-cell therapy, immunotherapy, mutations in the cancer cells, but there is nothing different. What about apoptosis and if the p53 tumor suppressor gene is mutated, which occurs in about 50% of all cancers? What is oncology doing about testing patients?

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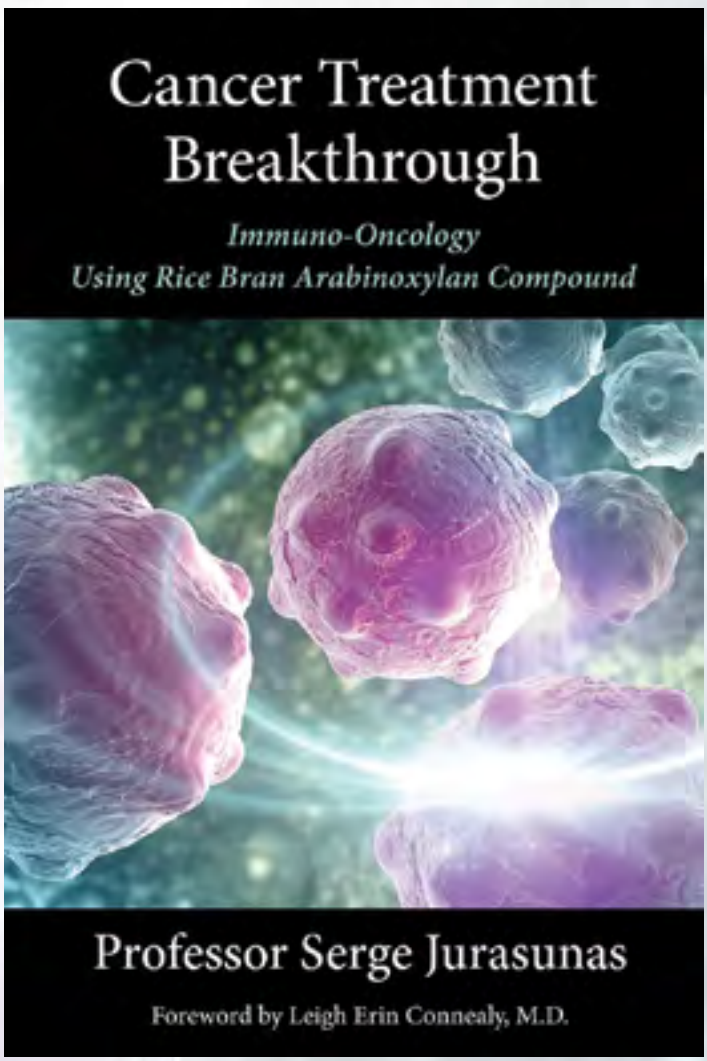
Cancer Treatment Breakthrough

Immuno-Oncology
Using Rice Bran Arabinoxylan Compound

Dr Serge Jurasunas

Professor Serge Jurasunas is a Doctor of Naturopathic Medicine and Oncology. He is an internationally renowned medical researcher and iridologist who has worked for over half a century improving the lives of cancer patients using Rice Bran Arabinoxylan Compound (RBAC). RBAC is a natural, innovative ingredient that can activate the NK cells against cancer cells.

Dr Serge Jurasunas has written 7 books on natural health. He has had over 100 papers and articles published and translated into several languages and has delivered conference presentations in more than 45 countries.



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Interview with Dr. Jurasunas

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Oncology is missing something important, but we know that science and medicine never get along since today medicine is too industrialized to move in other directions. The real breakthrough in cancer must include a combination of therapies that attack cancer in as many directions as possible using non-toxic agents. I have presented this approach in my book. I have included a chapter on the p53 gene since, as I have already explained, it is also known as the guardian of our immunity, inhibits glucose transporters, and modulates telomerase activity. When recognized it will be another breakthrough. Of course, restoring the activity of NK cells is important, since they are really special immune cells that can kill cancer cells directly. We know that in cancer NK cells are functioning only from 20-50% of their activity, they are not always ready to fight; and it seems that NK cells are more important than any other immune cells but lately seem to attract more attention in cancer treatment.

In *Cancers* (Volume 11, Issue 1, January 2019) the main article title on the cover is named, "NK cell-based immunotherapy in cancer metastasis," and is presented as a new way to treat cancer. You'll see in my book, case study examples on metastasis elimination. Do we now have a new breakthrough?!

Now another advance I would like to mention which I am working on for a couple of years is associated with the telomerase/p53 ratio, which I discussed in my last article in the *Townsend Letter* (August/Sept 2020). I believe we have here a new advance in diagnostic and treatment since we know that telomerase activity is expressed in 85% of cancer but modulated by normal active p53 gene while telomerase is activated when p53 gene is mutated. With highly activated telomerase, cancer cells increase survival and even become immortal. This is a new way to diagnose cancer by measuring the ratio telomerase/p53 gene, but this has never been done before; but I believe it may be one of the most important breakthroughs. We can reverse the bad ratio by using several natural agents, for example, curcumin and genistein. I believe we have here a new way to diagnose cancer and make a prognostic, so here we have a personalized and precision medicine. Now by using a total immune approach – NK cells, p53 gene, the microbiome – we can call integrative immuno-oncology. I developed a poster, "Holistic Approach to Cancer Treatment," with a figure that shows exactly how cancer must be approached that I use in my clinic with cancer patients. I will gladly send this poster to any doctor who asks.

JT – Why do people currently face such a high risk of contracting cancer and today the various SARS-COVID viruses?

SJ – Yes, we all are asking why so many people today are at high risk to develop cancer. Now in the year 1900, one person out of 100 was at risk of developing cancer but now we are at one out of three people, so the important question is why? I believe that the increased risk of cancer is associated with the development of our industrial society – the abuse of chemicals in the air, food, water, electromagnetic fields, but also, and we don't mention, the excess of pharmaceutical drugs. Now, if we blame pollution to be the first factor that may lead to cancer, let me tell you that pharmaceutical drugs may also come in at first or second place. Pharmaceutical drugs en masse appeared over 50 years ago.

When I first arrived in Portugal, cancer was a rare disease, where today you have two or three family members with cancer. For example, between 2005 and 2015, cancer diagnoses increased by 33% worldwide with prostate and breast cancers. Both cancers are hormone-disrupting diseases. Thanks to the entry of Portugal in the ECC, this opened the door to the importation of industrial food and other modern food along with establishing industrial agriculture and pharmaceutical companies. As a result, medicine became an industry. Today junk food, McDonald's, is the favorite food of juveniles and even whole families. Over the past decade, humans have abused pharmaceutical drugs in such a way that it has deteriorated our bodies. Today, as a result, people are without any defense against the current pandemic.

Did you know that many drugs, including antibiotics, are damaging to mitochondria function, and we know now that mitochondria are directly associated with cancer? Over the generations, the body has lost much of the capacity of its defense mechanism; and it is true for the immune defense, one important line of protection against cancer.

I have read the interesting article by Ross Pelton, PhD, "The Microbiome-COVID-19 Connection," in the *Townsend Letter* (May 2021) where he proposed that mankind has experienced a gradual decline in immune function and disruption of the gut microbiome. I totally agree with him. Today many people have a serious deficiency in detoxification enzymes; and, if living or working in a polluted environment, they have a high risk of cancer. Pollution may also affect NK cells and cause mutation of the p53 gene – insecticide, for example – so here again we have the risk of cancer.

Another wrong theory is that cancer is a disease of age, but not anymore. It's found more and more in those middle-aged and younger. Just let me give one example among many others: A 26-year-old woman ballet dancer was diagnosed with lung cancer and metastasis already spread to the bone and the liver. She came with her family to my clinic. Of course, she got worse from chemotherapy with metastasis having spread to the brain. She started smoking only three years before being diagnosed, so probably her cancer started long before smoking but this is only one example of what has gone wrong in our society

Over the years we have in a way, created a condition where our body is no longer in a position to defend itself against disease. This gives you the answer for people with the risk of SARS and COVID-19 viruses. Lately, it has been shown that people infected with the SARS virus have a serious deficiency in vitamins C, D, zinc, and selenium. In both cases with cancer and COVID-19, the natural killer cells are implicated. Now during a pandemic, you see who is healthy or not. Without changing our lifestyle, food styles need to be more independent from toxic pharmaceutical drugs and vaccination. I am afraid that

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Defend: v.t.[ME. defenden, L. defendere] To ward off, repel.
1a. BRM4 1b. To guard from attack; keep from harm; protect.

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Interview with Dr. Jurasunas

➤ *continued from page 58*

we will have to face increased cancer risk and more pandemics in the near future if we do not improve our health condition.

JT – Where have you taught and lectured?

SJ – Well, I'll just answer briefly. I have traveled and lectured in about 36 countries on three continents. During 1970-1980 when I started to travel, I gave my first lecture in September 1972 in New York City at the International Congress of Cancer Victims and Friends and again at the same congress in 1974 in Los Angeles. At that time, we didn't have Google, and we could learn only by meeting other colleagues at conferences, going to some clinics to learn, read books, etc. I came back several times to the US and participated in several seminars on integrative medicine and worked to develop the oxidative dried blood test with my late friend, Robert Bradford, PhD, who organized several seminars in San Diego, but also in different cities in Europe annually. I also had a very good experience after being invited in 1985 to Sri Lanka to speak at a large world congress of alternative medicine. At that time, I met the health minister and the minister of traditional medicine. Immediately the health minister invited me to stay in Colombo for some time to learn how I treat cancer patients in the Hospital of Colombo, which I did. One other nice experience was to be invited by the University of Vilnius, Faculty of Medicine, Lithuania to give a seminar on the topic, "A Complementary and Alternative Lecture on New Avenues for Treatment in Oncology," where I presented, in a combination therapy, the activation of the immune system using RBAC followed by clinical cases. Can you believe such a thing happening in other European countries?

I also lectured in Korea, invited by the President of the Korean Society of Traditional Medicine. More recently I was surprised but honored to be invited to the BIT's 4th Annual Congress and exposition of molecular diagnosis in Beijing, China, to present my work on the p53 tumor suppressor gene and therapy. Travel became for me a reason not only to offer lectures but, especially, to learn from the other lecturers. Learning more is part of my life, and still today I spend considerable time studying and learning.

Serge Jurasunas is an internationally well-known practitioner and researcher in complementary oncology and molecular medicine, a pioneer in naturopathic medicine and live blood analysis, with 55 years of experience in a private clinic. He is a professor of naturopathic oncology and has delivered lectures all over the world. He has been a frequent contributor to the *Townsend Letter* for 22 years. He is the author of two books in English, including *Cancer Treatment Breakthrough – Immuno-Oncology using Rice Bran Arabinoxylan Compound*, and *Health and Disease Begin in the Colon Featuring Prof. Serge Jurasunas' Natural Medicine*.
Email: sergejurasunas@gmail.com;
Blog: https/naturopathiconcology.blogspot.com;
Skype: serge jurasunas

Dr. Jamie Turndorf is known to millions as Dr. Love through her website: Ask DrLove.com. She is the host of the "Love Never Dies" radio show, syndicated in 136 countries. Dr. Turndorf talks about love on Binge Network TV. She is the author of many international bestsellers, including her latest book, *If You Think You Don't Have PTSD – Think Again.*

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Integrative Oncology and the Repurposing of Pharmaceutical Medications and Natural Supplements

by Sean Devlin, DO, HMD, MS

Integrative oncology, in general, refers to the use of a combination of complementary and alternative medicine (CAM) therapies in conjunction with conventional cancer treatments. It has been defined in different ways, but there is no widely accepted definition. For our purposes in this article, I will provide you a couple of definitions below.

1. Integrative oncology is a branch of medicine that utilizes a wide variety of resources to empower patients with information and treatment, involving everything from lifestyle modification to prescriptive therapies. These involve exercise, diet, and nutritional recommendations. It also includes mind-body medicine, spirituality and spiritual practices, natural medicines, homeopathic remedies, body work, counseling, acupuncture, Chinese herbal medicine/traditional Chinese medicine, detoxification, oxidative therapy, ortho-molecular medicine, naturopathic remedies and immunotherapy, traditional herbal medicines, 'Off Label' prescriptive medications (repurposed drugs), fractioned chemotherapy, metronomic chemotherapy, dose dense chemotherapy, targeted therapies, hormone modulation and/or blockade, pharmaceutical immunotherapies, radiation therapy (including brachytherapy, hyperthermia and proton beam therapy), and general supportive care.
2. The *Journal of the National Cancer Institute* definition: "Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment."

There is a looming explosion of cancer diagnoses on the horizon. From the aging 'Baby Boomer' generation to the 'lost year' of cancer screenings due to COVID -19, we face a growing wave of future cancer cases. Advanced stage cancer is one of the most lethal and anxiety-provoking diagnoses anyone can get, and it is growing at a significant rate around the world. It carries with it a high level of morbidity and mortality, not to mention a high financial burden to the patient and our healthcare system.

Even as our knowledge base grows in the field of oncology, we are still struggling with advanced staged cancers. Diagnostically we have been gradually adopting advanced genomic testing of patients and their tumors to better provide personalized treatment plans. We have added numerous targeted therapies, small molecules, Car-T therapy, and immunotherapies to our armamentarium. However, we regularly rely on more 'old school' chemotherapy that has been in use for over 80 years. Patients often fear the effects of chemotherapy and look outside the box for other options that may be less caustic. One of the biggest problems that comes from the realm of cancer drug development is that the development of brand-new drugs is a long, complicated, and costly process; and there is no guarantee that the drug will be successful and/or tolerable.

One solution that has been explored and utilized by integrative practitioners and oncologists has been the use of repurposed medications and natural supplements. Drug repurposing is the idea of using an already approved drug for another disease or disorder away from its initial indication. Medication repurposing of approved non-chemotherapy drugs is an effective strategy to develop new therapeutic options for the treatment of cancer patients, with potentially fewer side effects and at a more affordable cost. Drug repurposing identifies new ways for the use of already FDA-approved and/or investigational drugs (Figure 1).

Concordantly, the Right to Try Act was signed into law in the United States on May 30, 2018. This law is another way for patients who have been diagnosed with life-threatening diseases like advanced stage cancer, who have tried all approved treatment options without satisfactory response, and who are unable to participate in a clinical trial to access certain unapproved, experimental and/or investigational treatments.

Several drugs across numerous pharmacological categories have displayed potential anti-cancer activity in laboratory

Drug discovery vs repurposing timeline from the journal *Nature*

Figure 1

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and clinical studies by regulating several key molecular mechanisms and oncogenic pathways in human cancer and cancer cell lines. Even though many of these medications have been through clinical trials and are mostly FDA approved, they may not have the indication for 'anti-cancer' purposes. We will focus on several of these medications, including anti-diabetic drugs, cholesterol medication, antibiotics, and antifungals.

In the world of naturopathic medicine there exists a long list of herbs, extracts, hormones and vitamins that have been used in the prevention, support, and treatment of the cancer patient. For the purposes of this article, we will review a few of the clinically relevant substances.

Many of these natural therapies are safe and complementary to standard medical interventions.

As always, we encourage our readers to work closely with their integrative physicians, oncologists, surgeons, and radiation oncologists, as we feel it takes a village to provide the best possible care to the cancer patient.

Due to the breadth and depth of this topic, we will review some of the more popular medications and natural remedies being used by integrative oncologists in the US and abroad.

Below we have listed them and will discuss some of their background and potential mechanisms of action in regard to cancer therapy.

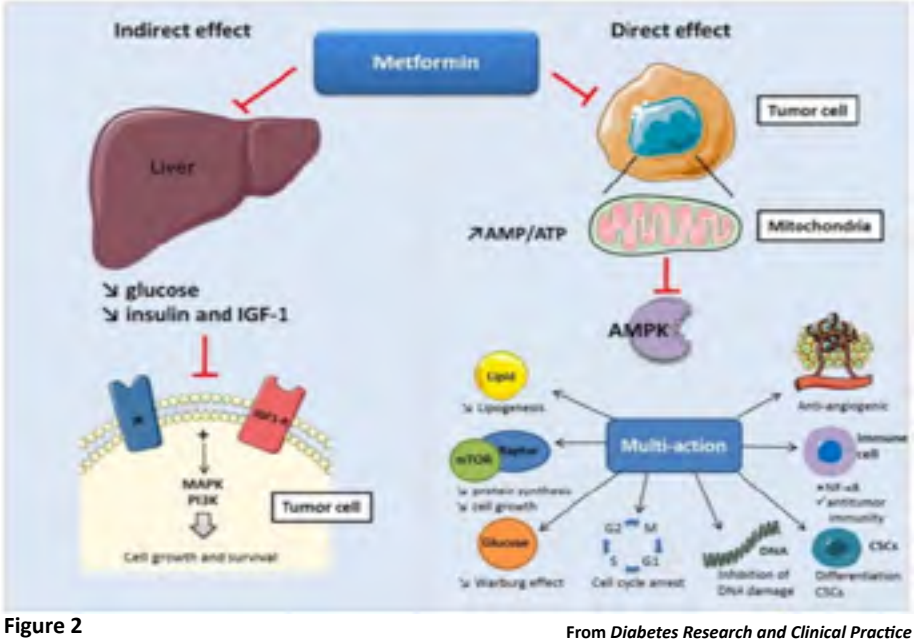

Figure 2

From *Diabetes Research and Clinical Practice*

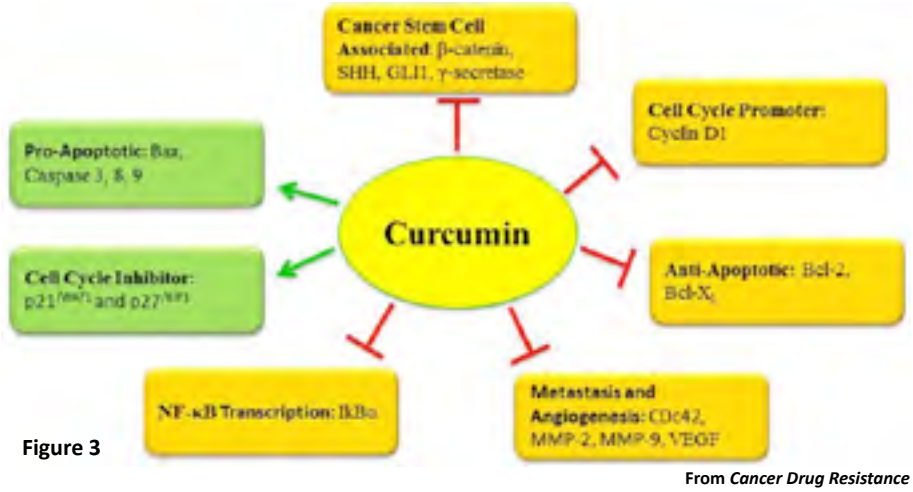

Figure 3

From *Cancer Drug Resistance*

Metformin: Let's start with one of the most well-known repurposed medications for supporting the cancer patient. That drug is metformin, a biguanide, which is used as a first-line oral agent for the treatment and prevention of type 2 diabetes mellitus. Metformin has been used in many studies as a single agent or in combination with other drugs for treatment as well as prevention of cancer. Metformin is known to have an antitumor effect through activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, the EMT signaling pathway, via epigenetic modification and possible immune modulation.[1] Metformin may also decrease the amount of circulating insulin and decrease the risks associated with insulin resistance, diabetes and cancer.[2] By lowering circulating insulin there is a decreased anabolic drive for some cancers that over express IGF-1 and insulin receptors (Figure 2).[3-5]

Doxycycline: Doxycycline is used to treat infections caused by bacteria. It is in a class of medications called tetracycline antibiotics. Doxycycline can stop the growth of bacteria by allosterically binding to the 30S prokaryotic ribosomal unit during protein synthesis. Its mechanism of action in cancer cells and cancer stem cells is just becoming elucidated. In the pancreatic cancer stem cell model, it appears that doxycycline inhibits the FAK/PI3K/AKT pathway and significantly inhibited migration and invasion ability of pancreatic cancer cells.[6,7] Further research evidence suggests that doxycycline had synergistic effects with cisplatin, oxaliplatin, 5-FU, sorafenib, and gemcitabine. Dosing is 100 mg a day and can be taken in a month-on month-off fashion with some of the anti-helminthic repurposed medications. It is important to also regularly use prebiotics and probiotic while taking this antibiotic.

Ivermectin: Initially, the antiparasitic drug ivermectin was approved in humans back in late 1980s to treat onchocerciasis, also known as river blindness, caused by the blackfly-transmitted parasite *Onchocerca volvulus* in poor populations around the equator.

Research demonstrates that ivermectin exerts antitumor effects in different types of cancer. Ivermectin interacts with several targets, including the multidrug resistance protein (MDR), the Akt/mTOR and WNT-TCF pathways, the purinergic

receptors, PAK-1 protein, certain cancer-related epigenetic deregulators such as SIN3A and SIN3B, RNA helicase, chloride channel receptors and preferentially target cancer stem-cell like populations.[8,9] Through the PAK-1 protein, ivermectin can induce autophagy (which is the self-eating cell death process). Ivermectin induces caspase-dependent apoptosis, which has two pathways an intrinsic and extrinsic one. Both ultimately lead to cancer cell suicide. Ivermectin inhibits mitochondrial respiration by decreasing the activity of respiratory complex I enzyme. For many patients with healthy livers, ivermectin can be introduced alongside other chemotherapeutics and treatment programs as an adjunct anti-cancer therapy.[10] Also of interest, ivermectin is currently being looked at strongly as an agent to treat and possibly prevent COVID-19. Dosing may vary between 150-200 mg/kg and given on an intermittent or pulsed schedule.

Atorvastatin: Atorvastatin is a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. Atorvastatin reduces levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, and very low-density lipoprotein (VLDL)-cholesterol and increases high-density lipoprotein (HDL)-cholesterol (which is cardioprotective). It is commonly used in adult primary care and by cardiologists to treat elevated cholesterol and dyslipidemia. Large data pools were analyzed recently due to the thoughts that statin use may cause cancer or contribute to cancer progression. The analysis found that statin use was not associated with increased risk and that the use of statins was significantly associated with a reduction of mortality in colorectal cancer patients. Several mechanisms responsible for anticancer effect in colorectal cancer patients were the induction of apoptosis by down-regulating anti-apoptotic proteins, inhibition of cellular proliferation, or inhibition of angiogenesis.[11] This statin also triggered autophagy (cancer cell self-eating) in cervical cancer tumor xenografts. Dosing of this medication ranges from 20-80 mg. Labs need to be closely monitored; the side effects of myositis and general muscle soreness is the usual reason this medicine is stopped. Also of note, it may be necessary to use CoQ10 as a supplement as these statins can deplete this coenzyme.

Mabendazole/Albendazole: Mebendazole is a broad-spectrum anti-helminthic drug, in the same class as albendazole, flubendazole, oxfendazole, and fenbedazole. Anti-parasitic action of azoles is due to their action as a microtubule-disrupting agent acting to prevent the signaling of growth and maturation of tubulin in the gut of helminths, causing the parasites to die.
Tubulin is vital to cell division and is therefore a cancer target for several chemotherapy drugs, including paclitaxel, colchicine, and vincristine.[12,13] Dosing can range from 100-200 mg orally, and this medicine is best tolerated when taken with food.

Niclosamide: Niclosamide is an FDA-approved anti-helminthic drug and may elicit antineoplastic effects through direct STAT3 (Signal transducer and activator of transcription 3) inhibition. The STAT3 signaling pathways regulate the gene expression of proliferation, survival, migration and invasion, as well as angiogenesis that supports the growth of cancer cells and tumors. This anit-helminthic drug may also help checkpoint immunotherapy work better in non-small

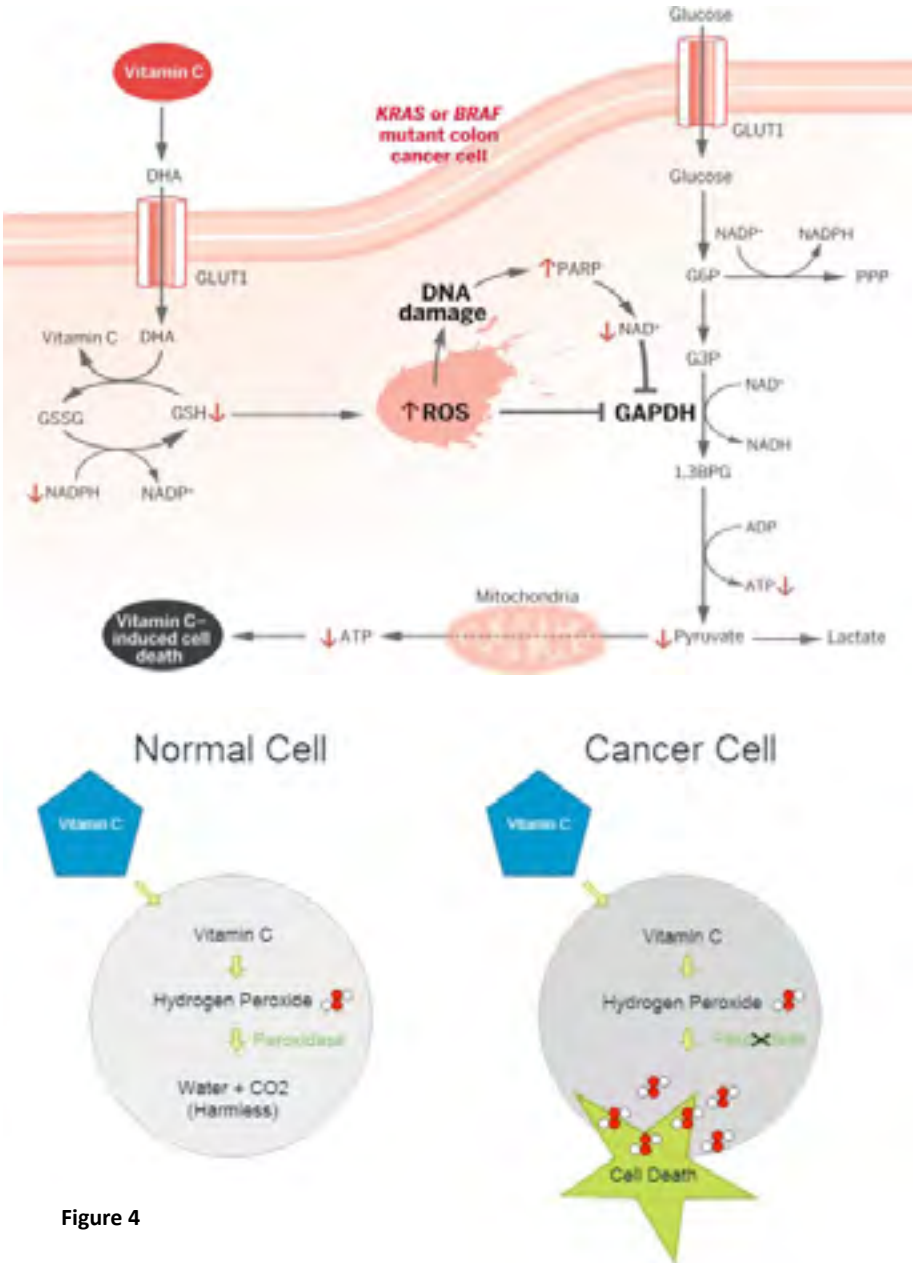

Figure 4

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cell lung cancer.[14,15] Dosing ranges from 1500-4500 mg per day.

Artemisinin: Artemisinin and its derivatives are commonly used anti-malarial drugs that have been shown to have anti-neoplastic properties. Artesunate is a semi-synthetic derivative of artemisinin that comes from the Chinese herb sweet wormwood. Artesunate has been proven as an effective cytotoxic agent against ovarian, breast, colon, melanoma, leukemia, renal, and prostate cancer cell cultures. Artesunate can also induce apoptosis in a variety of cancer cell lines. Artesunate prompts cell cycle arrest in the G2/M phase by increasing the expression of the initiator of autophagy, specifically Beclin 1.[16] Some evidence suggests that artesunate may cause cell cycle arrest and apoptosis in some breast cancer cell lines, including triple negative breast cancer.[17] The low toxicity profile and long history of use of artemisinin for malaria world-wide make this substance and its derivatives a very interesting source of anti-cancer therapeutics.[18] Dosing varies based on oral or IV administration.

Melatonin: Melatonin is a 'sleep hormone' and neurotransmitter released by the pineal gland. It is also a highly efficient antioxidant. It is one of the prime regulators of our circadian rhythm and sleep. Melatonin has been ascribed anti-inflammatory, immunomodulatory, pro-apoptotic, anti-proliferative, and anti-angiogenic properties that make it a powerful antitumor agent. One effect that is garnering interest is melatonin's ability to modulate inflammation and free radical expression through epigenetic on and off mechanisms. The actions of melatonin are primarily mediated by the G-protein coupled MT1 and MT2 receptors. The oncostatic action of melatonin is through multiple actions, including upregulation of apoptosis, the arrest of the cell cycle, inhibition of metastasis, and antioxidant activity.[18-20] Beyond supporting healthy sleep this molecule appears to have a wide variety of direct and indirect effects on cancer. Dosing usually starts low (3-5 mg) taken right before bedtime, then it can be increased slowly as tolerated and tapered up to 240 mg or higher. Dosing can be split up over the day as it increases and as is tolerated.

Milk Thistle: Milk thistle/Silymarin (*Silybum marianum*) has been traditionally used in medicine, particularly in the treatment of liver diseases. Silimarin has been demonstrated to "inhibit cell proliferation and to induce apoptosis, while also having anti-angiogenic properties." The induction of apoptosis in cancer cells has been mediated by the involvement of cellular stress. Milk thistle has the potential to operate as a STAT3 inhibitor as well as an inhibitor of the upregulation of the PD-L1 protein, that can allow the cancer to hide from the immune system, which has been the target of some checkpoint inhibitors. These influences may prevent cancer cell growth and immune system evasion.[21] Silimarin appears to work on epithelial-mesenchymal transition (EMT) regulators, whereby epithelial cells are converted into mesenchymal cells, which are frequently activated during cancer invasion and metastasis—thus being a promising therapy for certain cancers, including non-small cell lung cancer. It has also been documented to suppress cancer cells by means of down-regulating actin cytoskeleton and PI3K/Akt molecular pathways. Silymarin has been shown to help sensitize cancer cells to chemotherapy, and silymarin may also reduce the toxic effects of chemotherapy on vital organs or on healthy cells.[18,22] Hyperactivation of PI3K signaling cascades is one among the most ordinary events in human cancers. Dosing ranges from 1,000-3,000 mg per day.

Berberine: Berberine is an isoquinoline alkaloid extracted from the root, rhizome, and stem of *Rhizoma coptidis*. Berberine contributes to cell death by inducing cancer cell apoptosis through different mechanisms. Berberine contributes through multiple mechanisms to the inhibition of metastasis and cell invasion.[18] Berberine decreases insulin resistance through upregulation of insulin receptor expression in normal cells. Obesity, insulin resistance, and type 2 diabetes (T2D) increase the prevalence and worsens the prognosis of more than a dozen different cancer types. Berberine appears to also provide protection for patients receiving radiation therapy. Several signaling pathways are affected by berberine, including the MAP (mitogen-activated protein) kinase and Wnt/β-catenin pathways, which are critical for reducing cellular migration and sensitivity to various growth factors involved in promoting cancer cell proliferation.[23] Dosing ranges from 1,000-3,000 mg when taken orally.

Curcumin: Curcumin, a polyphenol extracted from the rhizomes of *Curcuma longa*, also known as turmeric, belongs to the most promising group of bioactive natural compounds, especially in the treatment of several cancer types. Curcumin has a variety of pharmacological effects such as antioxidant, anti-cancer,

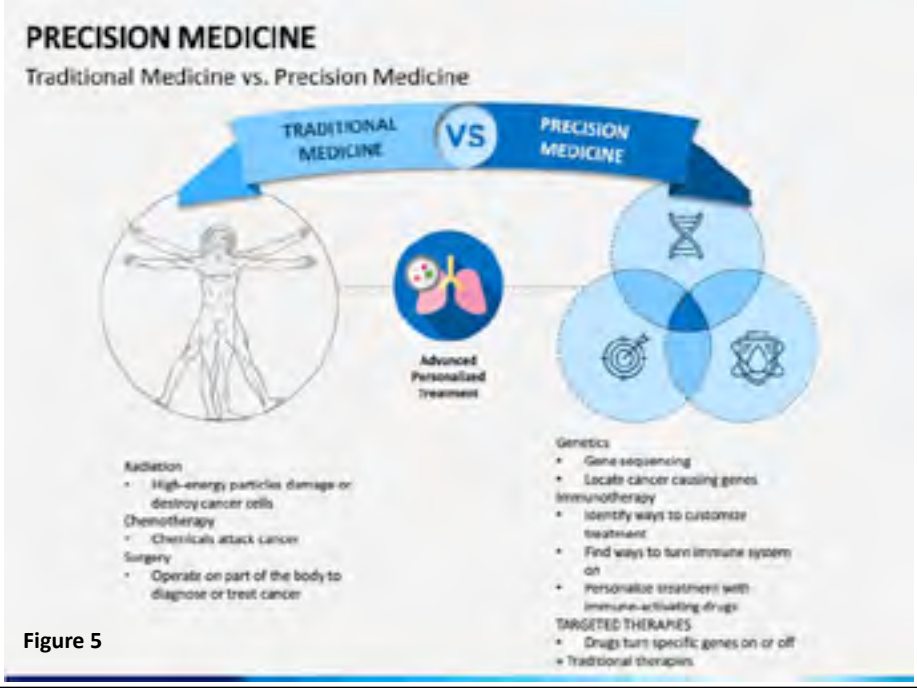

Figure 5

anti-inflammatory, and anti-microbial activities. Anti- cancer effects of curcumin are due to targeting of a wide range of cellular and molecular pathways involved in cancer pathogenesis, including NF-kB, MAPK, PTEN, P53, and microRNAs (miRNA) network.[18,24] Curcumin extract taken orally can be dosed from 800-8,000 mg per day. IV curcumin has been used when in a liposomal delivery form, and those doses are usually much lower (Figure 3).

Quercetin: Quercetin is a naturally occurring flavonoid present in many commonly consumed food items. Quercetin glycosides are the dominant flavonoid content that can be found in propolis along with other healthy foods, including onion, broccoli, apple, tea, as well as red wine. Quercetin governs numerous intracellular targets, including the proteins involved in apoptosis, cell cycle arrest, detoxification, antioxidant replication, and angiogenesis. Quercetin may mediate apoptosis through several mechanisms, including mitochondrial disruption, DNA intercalation or down regulation of survival signals like PI3K/Akt and NFkappaB.[25] Quercetin has been shown to work well in combination with many chemotherapeutic agents.[26-28] Quercetin is a flavonoid with antioxidant properties. The ability of quercetin to exert many beneficial effects on health, including protection against various diseases such as osteoporosis, lung cancer, and cardiovascular disease makes it a flavonoid of great interest amongst integrative practitioners. Dosing varies but ranges between 400-1,600 mg, split up over several doses throughout the day.

Vitamin C (Ascorbic acid): Knowledge regarding the pharmacokinetic properties of ascorbic acid or vitamin C, has in recent preclinical studies, sparked interest in the utilization of high-dose vitamin C for cancer treatment. Studies have shown that pharmacological vitamin C (doses given intravenously) targets many of the mechanisms that cancer cells utilize for their expansion and survival. The main components of ascorbate-induced cell death are DNA double-strand breaks *via* the production of hydroxyl radical (H_2O_2) and ATP depletion due to the activation of poly (ADP-ribose) polymerase 1.[7,29,30] Some early animal studies have shown a synergy with some immunotherapy checkpoint inhibitors.[31] Due to the general safety and tolerance of this vitamin, there is much excitement about its use alone and in conjunction with other modalities such as chemotherapy and CAM therapeutics. Dosing of vitamin C given intravenously can range from 60-100 grams over several hours (Figure 4).

Vitamin D: A low vitamin D status is associated with an increased risk of various cancers, such as of colon, breast, prostate and hematological cancers. Several epidemiological studies have suggested that ultraviolet-B exposure can help reduce cancer risk and prevalence, indicating a potential role for vitamin D as a feasible agent to prevent cancer incidence and recurrence.

Vitamin D stimulates the innate immune system in fighting more efficiently against bacterial infections, such as tuberculosis, while it prevents overreactions of the adaptive immune system that may cause autoimmune diseases, such as multiple sclerosis. Some of the strongest research evidence suggests it may play a role in cancer prevention.[32] There have been two randomized controlled trials using vitamin D and calcium that found a beneficial effect in reducing cancer incidence. One showed a clear relationship with supplemental vitamin D reducing the relative risk of breast cancer in post-menopausal women while the other from data from the Women's Health Initiative study showed a significant decrease in breast cancer risk in vitamin D supplemented participants.[33,34] Dosing really is individualized to keep serum levels between 70-100 ng/ml and usually requires it be taken with K2 in order to maintain calcium homeostasis.

Our efforts in the field of integrative oncology have always been to focus on the personalization of care. By providing individualized and patient-focused care, we believe that outcomes for both quality of life and length of life can be improved. Many people have put off their preventative cancer screenings (colonoscopies, physical exams, etc.) over this past year due to COVID-19. We in the field of integrative medicine feel prevention and early intervention is critical in taming the beast that is cancer.

As we enter the era of precision medicine with our eyes on the horizon, we see molecular technologies like CRISPR Cas-9, personalized cancer vaccines, novel small molecules and individualized targeted therapies and the newly discovered Retron Library Recombineering (RLR) gene editing tool, offering hope to those who develop cancer in the future (Figure 5). Like many things in this world, the future is never clear; however, this is an exciting time and some of that excitement comes in the form of repurposed medications and CAM therapies for the treatment of cancer. By integrating some of these tools into oncology practices today, it might be possible to increase treatment efficacy and improve response rates for patients with a wide array of cancer types. If you or someone you know is interested in using some of these tools to address a cancer diagnosis, please consult with your primary physician, oncologist, and integrative oncologist to learn more. Never attempt to self-diagnose or self-treat any illness, including cancer, by yourself. Cancer is a complex illness and requires a team ◆

References and article are available online at www.townsendletter.com.

Dr. Devlin 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. He currently sits on IOICP advisory board. Dr. Devlin is a board-certified family physician and board eligible in emergency medicine. He also is board certified and fellowship trained in anti-aging and regenerative medicine and fellowship trained in integrative cancer therapeutics. Dr. Devlin holds a master's degree in biochemistry and has pursued doctoral studies in pharmacology with an emphasis on the evaluation of novel antineoplastic agents. Dr. Devlin has been honored to lecture nationally and internationally on a variety of medical topics and is regularly sought to provide his expertise through direct consultation and lectures from a variety of medical organizations.

Dr. Devlin can be reached directly at Gerber Medical Clinic in Reno, Nevada, at 775-826-1900, Highland Springs Wellness Center in Grass Valley, California at 530-274-2274; and Advanced Dermatology and Cosmetic Surgery in Lake Tahoe at 775-588-5000.

Mastering the Art and Science of Integrative Cancer Medicine

by Robert Zieve, MD

Being a skilled integrative cancer practitioner involves the art of synergizing three major areas of care:

1. Our observation of the patient. This entails sharpening our perceptions, spending time with each patient, listening well, and trusting our intuition.
2. Our understanding of the patient's terrain, which may be evaluated through lab tests.
3. Our understanding of the patient's cancer dynamics.

In this article I will demonstrate with specific cases how to increase your skills, through the lens of four of my patients, and through the practitioner toolbox of therapeutic approaches. In this toolbox of therapies, we may include diet, botanical and nutritional medicine, IV therapies like vitamin C, mistletoe therapies either subcutaneous or IV, and sometimes low dose (metronomic) chemotherapy approaches when combined with systemic hyperthermia, as well as through prescription drugs like low dose naltrexone or metformin.

Of these four patients, two are ongoing cases, one is a current patient now in NED (No Evident Disease), and one has passed. I think it is important to learn from our "failures," so one of these cases will be a patient who has passed on from her cancer.

Many integrative cancer practitioners have had successes with their cancer patients. My endeavor is to learn from my patients, to understand the process with each patient and how each is unique in terms of quality of life, their tumor microenvironment or terrain as it is evaluated through data and published studies, as well as in their cancer pathology itself, to appreciate the art of how we integrate these into therapy programs that make sense and work.

Estrogen-Positive Post-Menopausal Breast Cancer Patient in NED

A post-menopausal woman who 10 years ago was diagnosed with an ER+ breast cancer, had a lumpectomy and declined radiation therapy. Subsequently, in the next six years, she developed several estrogen positive recurrences but no metastases. One recurrence was treated with chemotherapy but recurred again a couple years later. The most recent recurrence, three years ago, became a near triple negative cancer. She then underwent lumpectomy, radiation therapy, and chemotherapy. After her treatments, in addition to a robust oral protocol, she was prescribed TM, or tetra thiomolybdate, an anti-angiogenic agent that in studies at the University of Michigan was shown to help prevent growth and spread of sub-angiogenic tumor colonies (which we cannot see with scans but can only presume the presence of) when prescribed for patients in NED. She took TM for nearly three years. University of Michigan studies done in the early 2000s showed that when a patient in NED follows this protocol, subsequent relapse is rare, even after TM is discontinued.[1] She is now in NED, or No Evident Disease.

What can we learn from this case?

Let's discuss radiation therapy after a lumpectomy, which is the modern oncology approach. What were the consequences of not doing radiation therapy at that time of her first cancer diagnosis? She went on to have four more recurrences of the cancer in the same breast that required further treatments.

The issue of radiation therapy after a lumpectomy is controversial today. Lumpectomy plus adjuvant radiation is considered equal to a mastectomy in terms of local recurrence risk reduction. Adding adjuvant radiation to lumpectomy, especially if the cancer features are of a higher risk, or the surgical margins are not widely clear (we do not know if this was the case with this patient), reduces subsequent local recurrence risk by as much as an absolute 30%. That is not an insignificant risk reduction.

BUT, women do not die of breast cancer that recurs locally in the breast. Also, breast irradiation has NOT been shown to benefit long-term overall breast cancer specific survival – because women with breast cancer are at risk of dying of metastatic disease rather than local recurrences, which local radiation does not prevent. This woman chose not to do radiation therapy after her original lumpectomy. She developed four recurrences of the same cancer, but with no metastases. This is an important point.

It really comes down to personal choice: How willing is a woman to be vigilant for and potentially re-treat breast cancer if it recurs in the same breast? Generally, but not always, if it recurs, mastectomy is indicated – since lumpectomy has already been performed. Is a woman willing and able to engage a robust prevention plan after a lumpectomy, one that includes botanicals, nutrients, TM for two-to-three years, and possibly subcutaneous mistletoe for two-to-three years?

We have seen a few women who have chosen to forego adjuvant radiation therapy over the years and still experience a recurrence of their cancer in the breast in a fairly short time frame. Of course,

adjuvant radiation would not have guaranteed prevention, but it would have reduced the risk in these situations. However, some women do not experience any metastases after a lumpectomy and no radiation therapy. Much today is a mystery to all of us, like why there have been spontaneous remissions in some people.

There are potential risks of radiation to weigh into the equation. Radiation can cause cell mutations, potentially worsening cancer cell behavior. Left-sided radiation can impact the heart, especially if delivered to the chest wall, and radiation to either breast can impact underlying lung tissue and lead to radiation fibrosis. And radiation to the axilla following node removal increases risk of localized fibrosis that can lead to lymphedema.

Then there is the issue of stem cells. In an article entitled "Radiation Treatment Generates Therapy Resistant Cancer Stem Cells from Aggressive Breast Cancer Cells," researchers from the Department of Radiation Oncology at the UCLA Jonsson Comprehensive Cancer Center reported that radiation treatment actually drives breast cancer cells into greater malignancy.[2] It is believed that this is due to stem cells that remain after radiation therapy. These stem cells also often remain after chemotherapy.

The researchers found that even when radiation kills half of the tumor cells treated, the surviving cells which are resistant to treatment, known as induced breast cancer stem cells (iBCSCs), were up to 30 times more likely to form tumors than the nonirradiated breast cancer cells. In other words, the radiation treatment regresses the total population of cancer cells, generating the false appearance that the treatment is working. However, the treatment actually increases the ratio of highly malignant to benign cells within that tumor, eventually leading to the iatrogenic (treatment-induced) death of the patient.[3]

Tumors are composed of a wide range of cells, many of which are entirely benign. The most deadly type of cells within a tumor or blood cancer, known as cancer stem cells (CSCs), have the ability to give rise to all the cell types found within that cancer. They are capable of dividing by mitosis to form either two stem cells (increasing the size of the stem population), or one daughter cell that goes on to differentiate into a variety of cell types, and another daughter cell that retains stem-cell properties.

This means CSCs are tumorigenic (tumor-forming) and should be the primary target of cancer treatment because they are capable of both initiating and sustaining cancer. They are also increasingly recognized to be the cause of relapse and metastasis following conventional treatment.

Protocols must be adjusted to the individual.

CSCs are exceptionally resistant to conventional treatment for the following reasons:

1. CSCs account for less than 1 in 10,000 cells within a particular cancer, making them difficult to destroy without destroying the vast majority of other cells comprising the tumor;
2. CSCs are slow to replicate, making them less likely to be destroyed by chemotherapy and radiation treatments that target cells, which more rapidly divide.

And then, as discussed previously, there is the risk of post-radiation fibrosis that can affect the lungs and restrict air movement years after treatment. But there is something we can prescribe after radiation therapy to help prevent this.

Pentoxifylline (Trental), along with vitamin E and other "blood moving botanicals" can help to offset this risk after radiation therapy, and to help prevent radiation fibrosis. However, is a woman willing to use this combination for one or more years after completing radiation therapy? There is good data on this combination, and it is inexpensive, yet few oncologists are aware of this approach. But how many of us take the time to educate our patients to these proven therapies?

The Pentoxifylline/vitamin E combination, along with other blood moving herbs in TCM, can help to offset this risk after radiation therapy. However, in my experience people in remission from cancer who have undergone radiation therapy are typically not likely to persist with a therapy for that length of time.[4,5]

Note: The author is aware that some of these studies are dated, when compared with how fast data is being published today. However, this in no way renders them inaccurate. The botanicals we prescribe for many people with cancer have thousands of years of outcomes-based experience as testimonials, as well as decades of good institutional research.

Then there is this: Regarding radiation therapy in breast cancer, an article published in 2019, called "Omitting Radiation in Older Breast Cancer Patients," concluded:

> …most women aged 70 and above with clinical stage 1, ER+ cancers do not need radiation therapy after lumpectomy. Furthermore, studies regarding the use of genomic signatures in younger women with low-risk tumors might ultimately demonstrate an additional subgroup that may avoid radiation therapy. Radiation oncologists are on the verge of joining breast surgeons and medical oncologists in decreasing the cost and morbidity of breast cancer treatment without negatively impacting survival or quality of life.[6]

It has been very gratifying to guide this woman to a successful outcome from her near triple negative breast cancer (a dangerous cancer) that had developed years after her original estrogen receptor positive cancer. As we can see, achieving this result requires that we integrate our understanding of tumor dynamics with good, published data and experience to guide us, all the while being aware of the pressure the patient was receiving from her oncologists to do regular oncology therapies. In her case, after the fifth recurrence, the integration of low dose carboplatin and paclitaxel with a robust protective oral program and mistletoe therapy was successful in helping her get to NED and have a good quality of life with natural medicine addressing the chronic insomnia she has had since anesthesia at the time of original lumpectomy.

There is much we can learn from this case and the studies therein. First, that there is current rethinking of radiation therapy after lumpectomy. Second, that it is a woman's choice, and the more fully informed our patients are, the better to be able TO make a decision that is right for them. Third, our task is not only to address the cancer itself, but also the

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patient's quality of life. To be clear, there is no one-size-fits-all approach, only what is right for a given women in a particular situation.

Patient with Stomach Cancer

What can we learn from our patients who have passed while under our care? Are these our failures?

This person had been diagnosed in 2018 with a known poorly differentiated adenocarcinoma of the greater curvature of stomach, with small mets to the peritoneum. She lived a good quality of life until 2021 when she passed rather suddenly after bowel obstruction surgery. She did quite well for several years with her chemo and an integrative oncology approach, which included a robust supportive oral protocol, IV vitamin C, and IV mistletoe twice a week. She was on a regimen of 5 FU, cisplatin, and leucovorin.

Tumor dynamics revealed that her cancer was her2neu negative. (Note: some types of cancer are her2neu positive, such as lung adenocarcinoma, prostate cancers, and some gastric cancers, though this is never checked for by her oncologist, and if so, most oncologists will not include Herceptin in a treatment regimen. In large part this is because Herceptin is not approved outside of her2neu positive breast cancers.) Yet our toolbox in integrative cancer medicine is full of good data on herbs and nutrients in her2neu positive cancer patients.

She had some leukopenia from her chemotherapy. Her oncologist wanted to give her either Neulasta or Neupogen.

I advised her to take a week off from chemo if her oncologist wanted to give her either of these two drugs. She followed my guidance, and this permitted her WBC to come back into normal range so she could continue with her chemo. There are studies in the *British Journal of Cancer* in 2017 that conclude that the occurrence of a low white count during chemotherapy is an independent predictor of increased response in several forms of cancer.

There are other reasons, which I learned in Mederi Foundation trainings that I participate in, to advise against either of these two bone-marrow stimulating drugs:

- It may play a role in worsening anemia in patients receiving adjuvant epirubicin and cyclophosphamide.[7-9]
- Granulocyte colony-stimulating factor, or Neupogen, suppresses autologous tumor killing activity of the peripheral blood lymphocytes in the patients with ovarian carcinoma.

This woman had a gastric cancer. She was probably given Neupogen unbeknownst to me, before she consulted me. Also, had her WBC or ANC dropped significantly and not come up with waiting a week more for more chemo, the other option that was suggested by integrative oncologist Dwight McKee, MD, was Leukine or sargramostim. Both are similar to Neulasta but are also anti-angiogenic, which is important in many cancers. This drug is a recombinant granulocyte macrophage colony-stimulating factor (GM-CSF) that functions as an immuno-stimulator.[10]

By September of 2019, she had done quite well with her chemo and an integrative oncology approach. She was active, travelling, and had a good quality of life. CT in October 2019 still showed the same mesenteric LUQ nodularity, as well as the implant on the greater curvature of the stomach about the same. A few mesenteric nodules consistent with peritoneal carcinomatosis appeared stable without new lesions. Her oncologist commented to her that he had not seen a patient with this type of metastatic cancer do so well, and even asked about the IV mistletoe she was receiving.

Unfortunately and sadly, even on her chemotherapy and her integrative oncology program, her cancer progressed, and she developed a small bowel obstruction that required surgery. After this, she sadly deteriorated and passed within three months. She remained the vibrant and hopeful woman whom she was, right up until she deteriorated. Working with such a person was highly motivating for me to continue to deepen my work in integrative cancer medicine.

What can we learn from this patient? That people can live a good quality of life while receiving therapies that keep an aggressive cancer at bay and stable. But this requires vigilance on the part of physician and patient and staying with a program that is working, as well as a patient who can afford these integrative therapies.

Triple Positive Breast Cancer Doing Well

A 49-year-old pre-menopausal woman with a diagnosis of triple positive breast cancer (ER+/PR+/Her2neu+) came to see me in September 2019. She had a lumpectomy on January 15, 2020. Five nodes were removed and were all clear. Of note is that her KI 67 proliferation marker on biopsy was very low. This often means a cancer may not respond to chemotherapy.

She was doing the Wylie Protocol under guidance from her oncologist for over a year after her diagnosis, which involves bioidentical forms of estrogen and progesterone. She had her estrogen metabolites monitored by another physician.

Because of the pandemic, her oncologist prescribed a subcu form of Herceptin called Herceptin-Hylecta every three weeks, which we administered to her.

Unfortunately, PTEN was never checked on her biopsy. This would have been good to order because PTEN, as a tumor suppressor gene, if mutated, can predict which patients with her2neu+ cancers will be resistant to Herceptin and Herceptin-like drugs. A 2009 published article stated that PTEN, a tumor suppressor gene, is a potential decision-making tool for trastuzumab use in breast cancer.[11]

Had it been mutated, there are no pharmaceuticals that address this mutation, but there are natural medicines for this. Jim Roach, MD, in *Vital Strategies in Cancer*, and Donald Yance, CH, MH(AHG) of the Mederi Foundation, have documented this published research.

Serum her2neu, a good marker in such cancers, ranged between 7-12.3. More than 15 is of concern, and likely means that the cancer has developed a resistance to Herceptin or Herceptin class drugs.[12,13]

Her oral program while on the subcutaneous Herceptin-like drug Hylecta included 10 olives per day and a lot of olive oil. *Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2 neu expression and synergistically enhances the growth inhibitory effects of Herceptin*.[14]

Because there is a higher risk of brain metastases after 10 years in people with

her2neu positive cancers, I suggested that she ask her oncologist to prescribe Lapatinib, or Tykerb, an oral tyrosine kinase inhibitor which crosses blood brain barrier (unlike Herceptin), instead of subcutaneous Herceptin-Hycleta. Such brain metastases are a late complication because the brain gets seeded in her2neu+ cancer cells.

Lapatinib is a small molecule dual tyrosine kinase inhibitor of both HER1/EGFR. Had she been on this and developed a rash, that is a good sign of drug effectiveness. Quercetin is an effective treatment that not only helps relieve the rash but also enhances HER2 targeting drugs.[15]

Her oncologist declined to prescribe this drug, perhaps because it would not have been approved by her insurance company.

This woman's case reminds us to be observant and pay attention to the person and their lifestyle. She is a somewhat high-strung successful businesswoman. Premenopausal women with her2neu cancers tend to be overachievers, according to the clinical experience of Donald Yance, CH, MH(AHG), of the Mederi Center.

Catecholamines can stimulate Her2 mRNA expression and promoter activity. In one study, the antitumor activities of herceptin (trastuzumab) were significantly impeded by chronic catecholamine stimulation in gastric cancer cells and in the mice bearing human gastric cancer xenografts. Propanolol in low doses, like 10 mg daily, which is part of the CARE Oncology protocol, can keep this risk of overstimulation low. Propanolol in low doses in the morning, when added to Herceptin therapies, improves cancer survival by about 25%.[16]

There is also good data on the herb rauwolfia, when dosed correctly, in such cancers.[17]

Of course, there are herbs and nutrients, with good data backing them, that can achieve the same results, like Kava and glycine.

Why is this important? Epinephrine, a catecholamine, is a daytime driver of her2neu receptors. The risk in such patients is that catecholamine-induced β2 -adrenergic receptor (β2-AR) activation leads to Herceptin resistance. One study demonstrated that a correlation of β2-AR level with Her2 status was demonstrated in breast cancer tissue. Catecholamines stimulate Her2 mRNA expression.[18]

With this patient, there was concern she was in a borderline hyperthyroid state, with a very low TSH of .0008, and high free T4 and free T3, while not taking any thyroid medication. Thus, the concern for excessive catecholamine release. She has a history of a partial thyroidectomy, reason unclear.

The conclusion of a study published in *BMC Medicine* in August of 2020 was that hyperthyroidism is associated with an increased risk of breast cancer, particularly for patients with toxic nodular goiter.[19] This woman did not have this goiter diagnosis at present, nor was she taking excessive amounts of iodine, so it was presumed her abnormal hyperthyroid-leaning tests were lifestyle related. Her reverse T3 was quite high, indicating adrenal stress and catecholamine overdrive. This was discussed with her, and she was supported with herbs often used in hyperthyroid patients, such as leonarus, lycopus, and gromswell, as well as kava.

It was obvious to me from the beginning that she was not going to change her lifestyle behavior patterns that made her successful professionally. So, I attempted to work around that with relaxing herbs that would strengthen the parasympathetic nervous system, such as products with glycine and kava.[20]

Included in her oral program was quercetin, which is a type of flavonoid that suppresses invasion of breast cancer cells by controlling β2- adrenergic signaling and may be a dietary chemo-preventive factor for stress- related breast cancer.

Some people are not ready to look deeper and make the lifestyle changes they may need to make in order to heal, and it is not our task to force people to do this.

As of April 2021, she is doing well, off Hylecta, in NED, and with a normal bilateral breast MRI.

Stage 3 Melanoma Patient, Stable

A 61-year-old woman consulted with me early in 2021 for help with her stage 3 melanoma which began in 2018 and which was initially excised from her back. It then subsequently spread to lymph nodes in her groin. Her oncologist wanted her to start on immunotherapy to protect against brain and other metastases. She was resistant to this suggestion, having read the side effects, and consulted with me.

Other mutations that are not uncommon in melanoma, such as the V-600 E mutation, "has also led researchers to accomplish newer therapeutic strategies that lead to improved disease-response and grant survival benefits. Vemurafenib, a *BRAF* inhibitor agent, is one of the few available targeted therapies that is FDA approved and provides promising results in metastatic disease. However, its resistance at an early stage is of great concern. Recent implementation of combinational therapies including *targeted therapy*, immunotherapy, and biological agents has appealed many researchers to define the adjunctive role of available therapies and their limitations in advanced stage and metastatic melanoma."[21]

Approximately one-half of advanced (unresectable or metastatic) **melanomas** harbor a **mutation** in the **BRAF** gene, with **V600E** being the most common **mutation**. Targeted therapy with **BRAF** and MEK inhibitors is associated with significant long-term treatment benefit in patients with **BRAF V600-mutated melanoma**.[22]

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The lesson here, being aware of this more updated clinical research, is that modern oncology continues to develop strategies for cancer treatment. And the additional lesson is that there are combinations of integrative therapies that can support the use of these therapies so as to prevent serious side effects and to potentiate them. A discussion of this subject is beyond the scope of this article. Suffice to add here that a well-recognized potential side effect of immunotherapy is autoimmune conditions.

Regarding lab tests pertinent to melanoma, her LDH (a good tumor marker in melanoma) continues to be normal, as does her beta 2 microglobulin.

Her serum S-100B levels are high at 137 (0-96). This is a great marker for micrometastases in melanoma. S100 calcium-binding protein B (S100B) is a protein of the S-100 protein family. S100 proteins are localized in the cytoplasm and nucleus of a wide range of cells and are involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation. This protein may function in the proliferation of melanoma cells, as well as in other cancers, notably when there is nervous system damage. Her serum CoQ10 level is normal and has stayed normal. When this is low, there is a greater risk of metastases.[23]

I advised the patient to add high-dose quercetin to her program, and perhaps a general antihistamine, which published studies suggest may help in melanomas. In a research letter, "Antihistamines May Improve Survival Among Patients with Malignant Melanoma" in the journal *Allergy*, researchers reported that the common allergy medications desloratadine and loratadine may be associated with improved survival in patients with malignant melanoma. And the *ASCO Post* reported in May 2020, "Antihistamines May Improve Survival Among Patients with Malignant Melanoma."[24] Also, "Users of two common antihistamines – desloratadine and loratadine – have lower mortality rates from cutaneous malignant melanoma than patients who use other antihistamines," researchers reported in March 2020.[25]

In addition to a robust oral protocol and IV vitamin C, she was started on subcutaneous mistletoe, and developed a significant rash with even the lowest strength, so this dose was titrated for an optimal response. Mistletoe is a form of immunotherapy, though this is not often recognized or acknowledged in oncology. From the beginning, this woman was very sensitive to low doses of subcutaneous mistletoe, which enables us to see that there are no formulas in medicine, and that protocols must be adjusted to the individual.

She continues as my patient and is clinically doing well. Follow-up MRI and CT have both been stable with no progression of her melanoma.

What this case demonstrates is how to help someone with an aggressive cancer type:

- By understanding the intricacies of her cancer and her terrain, and the importance of specific lab test markers in melanoma;
- Helping her to steer through the oncology world and to remain with a stable but dangerous cancer;
- Maintain a good quality of life;
- Follow a well thought out integrative cancer program;
- Prepare for any eventual need for immunotherapy, which her oncologist wants her to do now, but she is hesitant.

She is a very pleasant and intelligent person who has researched her condition well, and who understandably is under stress regarding her condition and the advice she is receiving. She continues to be reticent to undergo immunotherapy, due to the potential of side effects. Of course, if her subsequent MRIs and CTs show any further spread of this aggressive cancer, she is open to immunotherapy.

Rekindling Passion Every Day

In the beginning, what works best for me, when I walk through the door into an exam room to see a cancer patient, or when the patient walks into my office, is to recognize and feel the individuality of that patient. My initial task is to empty myself of any preconceived notions I may have, and to strive to become the best integrative cancer physician I may be.

I observe the following things:

- What is my initial sense when the patient walks in?
- What is his or her state of mind?
- Do I feel fear and anxiety from the patient, or confidence and trust?

It is the manner in which I combine and make sense out of what I feel and perceive with what I know about the person's terrain and the cancer itself, including treatments, that the art and alchemy of discovering a path towards healing for the person in front of me may come to fruition.

In taking this approach, we rediscover each day, through our patients, our passion for this work. This passion can help each of us deal with the issues of life in which we ourselves may be struggling. That helps us to find our way to the feeling that we have fulfilled our task for that person and that day. This is holy work, and it is holy ground. ◆

Robert Zieve, MD, practices integrative cancer medicine in Scottsdale, Arizona, and in Boulder, Colorado. He is on the staff of Holistica Integrative Care in Boulder, as well as MindBody Medicine Center in Scottsdale. Dr. Zieve also provides national integrative cancer consultations independently of these two clinics. Having practiced as an integrative medical doctor for over 35 years, and simultaneously as a board-certified specialist in emergency medicine from 1983-2003, Dr. Zieve is one of the most experienced and well-trained physicians in integrative cancer medicine in the United States.

He was an instructor at the Southwest College of Naturopathic Medicine in Tempe, AZ in the 1990's, and was President of the Arizona Homeopathic and Integrative Medical Association for two terms in the late 1990's. From 1999-2001 he was Medical Director of Paracelsus Fox Hollow Clinic near Louisville, Kentucky, which was the US affiliate of Paracelsus Klinik, an internationally known cancer clinic in Lustmuhle, Switzerland.

In an effort to further the national education of physicians in integrative cancer medicine, Dr. Zieve, MD is the Medical Director of Healthy Medicine Academy and the editor-in-chief of the *Cancer Strategies Journal*. He was the host of Healthy Medicine Radio in Northern Arizona, which broadcast for five years.

He uses many treatment modalities with his patients, including person and cancer-specific applications of herbs, nutrients, and food programs, IV Vitamin C therapy; botanical IVs, and injectable mistletoe therapies, along with the broad range of lab tests, scans, and procedures that are often required when one has a cancer diagnosis.

www.robertzievemd.com

References and article are available online at www.townsendletter.com.

The Milk Thistle Chimera?

by Dr. Douglas Lobay, BSc, ND

Nick came into my office wanting another bottle of Detox pills. He was a big man over six feet tall with thick, tattooed arms, ruddy, sun-damaged complexion, and the mass of a football lineman. He came to see me about a year prior complaining about fatigue, indigestion, and psoriasis. His dietary habits reflected his appearance. He told me he drank too much and had no intentions of quitting. He said the Detox pills seemed to help his skin a lot, his gas and bloating decreased, and he was feeling a little better. Detox was the name I gave to a blended product that I compounded for liver support and detoxification. The main ingredient in Detox was milk thistle along with a few other ancillary herbs.

I attended Bastyr College of Naturopathic Medicine in the late 1980s when there was a resurgence and explosion of scientific data on natural medicine. I was particularly fascinated by the research on herbs and botanical medicines. I remember that students at our small college each had a mailbox in front of the administration office on the third floor. Every month a stack of the new issue of the *Townsend Letter* would appear on top of the mailbox. It was supplied free of charge to college students, and I raced to get a copy before they disappeared. I read it from cover to cover and was mesmerized by all the new scientific explanations of natural medicine. Kudos to the staff of *TL*, and I am forever grateful for their generosity.

At school I was inculcated by the new science behind and supporting various natural therapies and medicines by a few zealous instructors. I began to collect references from various books and medical journals that I would photocopy at the college or the University of Washington. I recall reading some referenced works about the use of milk thistle in liver disease. Adjectives used by these natural medicine research gurus to describe single studies included "remarkable," "dramatic," "tremendous," and "amazing." I still refer to my research files as much as I do the internet. Now as a practicing naturopathic physician with close to thirty years of experience, I can look back and critically re-evaluate the clinical efficacy of milk thistle in the treatment of liver disease.

Milk thistle or *Silybum marianum* grows from one to three meters in height and has large prickly leaves and purple and red flowers. Milk thistle is indigenous to Asia and is also found in Europe and North America from Canada to Mexico. The ancient Greeks used the plant medicinally and named it "silybum" meaning thistle. During the Middle Ages monks introduced the plant to Europe and regarded it with mythical and religious adoration. Milk thistle has been used in folk medicine to treat liver disorders, including jaundice, gallstones, peritonitis, hemorrhage, bronchitis, and varicose veins. In the 18th century milk thistle was the treatment of choice for liver disorders. The leaves, seeds and fruit have been used for medicinal purposes.[1,2]

The crude extract obtained from milk thistle was originally termed silymarin. Silymarin represents a mixture of flavonoid compounds called flavonolignans. Three major flavonolignans identified in silymarin are silybin, silydianin, and silychristin. While these flavonoids are found in the leaves and fruit, they are found in highest concentration in the ripe seeds. The ripe seeds contain 4.0 to 6.0% silymarin. Silymarin has been identified as the active ingredient in milk thistle responsible for its purported medicinal effects. Concentrated extracts standardized to contain 70 to 80% silymarin content have been developed.[1,2]

Bijak explained that silybin is the major flavonolignan isolated in silymarin from milk thistle. Silybin is made of two separate units: taxifolin and phenylpropanoid joined together by an oxeran ring. Kostek and others tried to identify the mechanism of action of silybin. They concluded that the activity of silybin was complex and multifactorial. Silybin protected hepatocytes, blocked penetration of various toxins, prevented apoptosis, protected the liver from oxidative intracellular damage, increased superoxide dismutase enzyme activity along with glutathione, and increased the activity of peroxidase, strengthened and stabilized cell membranes, inhibited synthesis of prostaglandins associated with lipid peroxidation, and promoted liver cell regeneration by promoting protein synthesis and new cell production.[3,4]

Loguercio and Festi stated that extracts of milk thistle, silymarin and silybin, are the most prescribed natural compounds for liver disease, yet has no definitive results in terms of clinical efficacy. Sixty-five percent of patients with liver disease in the US and Europe are reported to take some sort of herbal medicine. In Germany alone the cost of milk thistle products accounts for 180 million dollars per year. Despite the wealth of data, no firm clinical evidence exists to recommend the use of these substances in clinical practice.

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Discrepancies are attributable to various factors such as quality of clinical trials, heterogeneity of diagnosis, lack of standardized properties, frequent inconsistent dosing and variable outcome parameters.

Silymarin refers to a group of at least seven different flavonolignans. Silybin accounts for 50 to 70% of silymarin content. Silymarin has poor and erratic bioavailablity. The silymarin absorption rate is between 20 to 50% percent. It has low water solubility, low bioavailabilty, and poor intestinal absorption. Some products conjugate silymarin with other compounds to enhance absorption like silymarin phytosome.

The administration of 240 milligrams of pure silybin induced a peak concentration in plasma of 240 ng/ml at about two hours and persisted for four hours. After administration of 560 milligrams of silymarin, the fraction of free sulfated and glucuronidated silymarin was about 17%, 28%, and 55% respectively. Silymarin has been showed to be over 70% protein bound. Both free and conjugated silymarin have rapid plasma and tissue distribution reaching a maximum level within one hour after administration.

Silymarin showed none or only mild interference with cytochrome p450 enzyme pathways including CYP2E1, CYP2D6, CYP2C1, CYP1A2, CYP2A6 and CYP3A4. It did show interference with UGT1A pathway involving inhibition of glycuronyl transferase. In thirteen patients with prostate cancer a dose of 2.5 to 20 grams of silymarin per day induced an asymptomatic hyperbilirubinemia that was resolved with discontinuation of the product. Silymarin has demonstrated antioxidant effects by decreasing the formation of ROS (reactive oxygen species) by acting as an iron chelator, decreasing formation of superoxide anions, and scavenging for lipid peroxide free radicals.

Silymarin has demonstrated anti-inflammatory effects by interfering with nuclear factor kappa beta which is a transcription factor for many different inflammatory compounds and pathways. As a result, a decrease in levels of pro-inflammatory phosphorylation, protein kinase, leukotriene, and caspase activity was observed.

Silymarin has demonstrated some direct antiviral effects. Silymarin also demonstrated some antifibrotic activity. Silymarin has also demonstrated moderate metabolic effects by decreasing uptake and production of glucose in gluconeogenesis and glycogenolysis. Silymarin has also demonstrated cell signaling effects by a decreasing nuclear factor kappa beta, VEGF (vascular endothelial growth factor), and other cell cycle regulators. Hepatoprotective effects have been demonstrated with chemotherapy drugs, including docetaxol, gemcitabine, and methotrexate. Silymarin blocks intestinal beta-glucuronidase, an enzyme that removes glucuronate and that can potentially reactivate conjugated toxins from glucuronyl pathway.[5]

Mulrow et al reviewed 11 electronic databases including Cochrane, Embase and Medline through July 1999. Sixteen prospective studies were identified with 14 randomized, placebo-controlled trials of milk thistle in liver disease. Also, sixteen additional non-placebo-controlled trials were analyzed. Four studies reported significant improvement in at least one measureable liver function parameter, including aminotransferase levels, albumin, malondialdehyde, and histiologic hepatocyte appearance. Three studies of unspecified liver etiology showed improvement in at least one liver function marker compared to placebo. Two studies showed an overall decrease in mortality. Three placebo controlled double blind trials of 28-day duration in patients with viral hepatitis showed significant improvement in multiple parameters. A longer duration study up to one year showed a consistent decrease in aminotransferase liver enzyme levels. Two trials involving patients with alcoholic cirrhosis showed a non-significant improvement in liver function, hepatocytes, jaundice, ascites and swelling. Also, another study of 30-day duration showed a significant improvement in liver aminotransferase levels compared to placebo. Side effects reported include gastrointestinal problems (diarrhea, gas, bloating and a change in bowel habits), headache, eczema, pruritus, fatigue, arthralgia, and rhinoconjunctivitis.

A pooled meta-analysis review of these studies concluded that clinical efficacy of milk thistle in the treatment of liver disease was not clearly established despite improvements that some individual studies showed. The authors further reported that poor study design, poor quality of reporting, poor heterogeneity of etiology, sample size, study methods, duration, dosing, and variations in functional assessment contributed to non-significant outcomes. Most benefits reported appeared to be related to a decrease in liver aminotransferase levels, although some studies showed an increase and decrease. The mechanism of action of milk thistle was not clearly identified or established in most studies and was surmised to be multifactorial. More good quality trials were recommended to fill in the gaps that this meta-analysis identified.[6]

Jacobs et al searched 13 databases and identified 14 studies that met their inclusion criteria. Three studies showed an inverse relationship between histologic benefit and milk thistle compared to placebo. No difference in aminotransferase enzymes, including ALT, AST, albumin and prothrombin levels was found between milk thistle and placebo. The only statistically significant improvement noted was a consistent decrease in ALT enzyme levels compared to placebo. An average reduction of 9 IU/ml of ALT was noted with a 95% confidence interval between -18 to -1 IU/ml with a probability of 0.05. Milk thistle showed low levels of adverse effects and was generally well tolerated. The researchers concluded that there was no reduction of mortality, improvement in histology of liver biopsy, or biochemical markers of liver function. The overall efficacy of milk thistle remained inconclusive.[7]

Saller et al provided an updated systematic review of the potential benefits of milk thistle. Nineteen studies were identified as double or single blind. There was no evidence of favorable influence of milk thistle in the evolution

of viral hepatitis, especially hepatitis C. In alcoholic liver disease, a decrease in AST was noted; but there was no change in alkaline phosphatase. In liver cirrhosis, overall mortality was 16.1% with milk thistle compared to 20.5% placebo. Liver-related mortality was 10.0% with milk thistle versus 17.3% placebo.[8]

Rambaldi et al's Cochrane review provided no evidence supporting the use of milk thistle in liver disease. They further noted that low quality trials showed beneficial effects, while high quality trials showed no statistical benefit. Thirteen randomized trials assessed milk thistle in 915 patients with liver disease caused by viral infection and alcohol consumption. Only 26% of the trials showed adequate allocation concealment and only 46% showed adequate double blinding. Milk thistle significantly improved liver-related mortality in all trials, but had no effect on overall mortality. The researchers were disappointed by the lack of high-quality studies and further questioned the beneficial effects of milk thistle in liver disease. They concluded that the evidence was lacking and better high-quality studies comparing milk thistle to placebo are needed.[9]

Ribeiro de Avalar et al conducted a systematic review with meta-analysis of randomized controlled trials of the effects of milk thistle on liver disease. Seventeen studies of 10,904 searched on electronic databases met inclusion criteria. Six of these studies were included in the meta-analysis. A small but statistically significant decrease in ALT levels of 0.26 IU/ml and in AST levels of 0.53 IU/ml was observed. The researchers noted that there was a high degree of heterogeneity and low methodological quality in the studies analyzed.[10]

Zhong et al studied the therapeutic effects of milk thistle in eight randomized controlled trials involving 587 patients. AST and ALT levels were significantly reduced in the silymarin group versus placebo. AST levels decreased an average of -6.57 IU/ml with 95% confidence interval ranging from -10.03 to -3.12 with a p value of 0.05. ALT levels decreased an average of -9.16 IU/ml with a 95% confidence interval ranging from -16.24 to – 2.08 with a p value of 0.01. The researchers concluded that silymarin has potential efficacy in reducing transaminase levels in patients with NAFLD or non-alcoholic fatty liver disease.[11]

Yang et al evaluated the efficacy of silymarin in chronic hepatitis C infected patients. Five randomized controlled trials using intravenous silymarin or sibinin in 167 patients were analyzed. No difference in alt levels, quality of life, and HCV RNA levels were noted.[12]

Toth examined a pool of four randomized controlled trials involving 491 patients. After three months of consumption, milk thistle significantly decreased LDL cholesterol, total cholesterol, and fasting glucose. However, there were no significant improvements in HDL cholesterol, triglycerides, or body mass index. It did not significantly affect ALT and AST liver enzymes of creatine kinase.[13]

And finally, an analysis of milk thistle would not be complete without a discussion of its reported effects on mushroom poisoning. Mengs et al stated that 90% of all fatal mushroom poisoning worldwide were due to *Amanita phalloides* mushroom poisoning. Symptoms of Amanita toxicity include abdominal cramps, vomiting and severe diarrhea usually starting six to eight hours after mushroom consumption. In 1500 documented cases, administration of intravenous silybinin reduced the mortality rate to 20% with other treatments to 10% along with aggressive fluid rehydration. The authors concluded the used of silybinin was justified in the treatment of acute Amanita mushroom poisoning. It should be pointed out that a double-blind placebo-controlled trial of milk thistle extract in fulminant mushroom poisoning might by unethical. As such, conclusions should be made with some degree of cautious optimism.[14]

The clinical efficacy of milk thistle in the treatment of liver disease is still debatable and uncertain. While positive individual studies of milk thistle are often reported in the lay natural medical literature, a review of several meta-analyses of the scientific studies in PubMed and other medical databases are less favorable and not quite as glowing. Obviously, there are still questions concerning the effectiveness of milk thistle. More high-quality double-blind placebo-controlled trials may be revealing. As is the case with natural products, more questions are asked than answers revealed. For instance, what dose and product type is best in the treatment of liver disease. Obviously, there may be a lack of standardization of product variety that is not revealed or specified in a meta-analysis. Unless something better comes along, milk thistle is still my benchmark medicine for liver problems. It also has a very good safety record and reports minimal side effects. Having said that, I am still happy prescribing milk thistle products in the treatment of liver disease and other allied health conditions. My patient Nick is also happy with the results.

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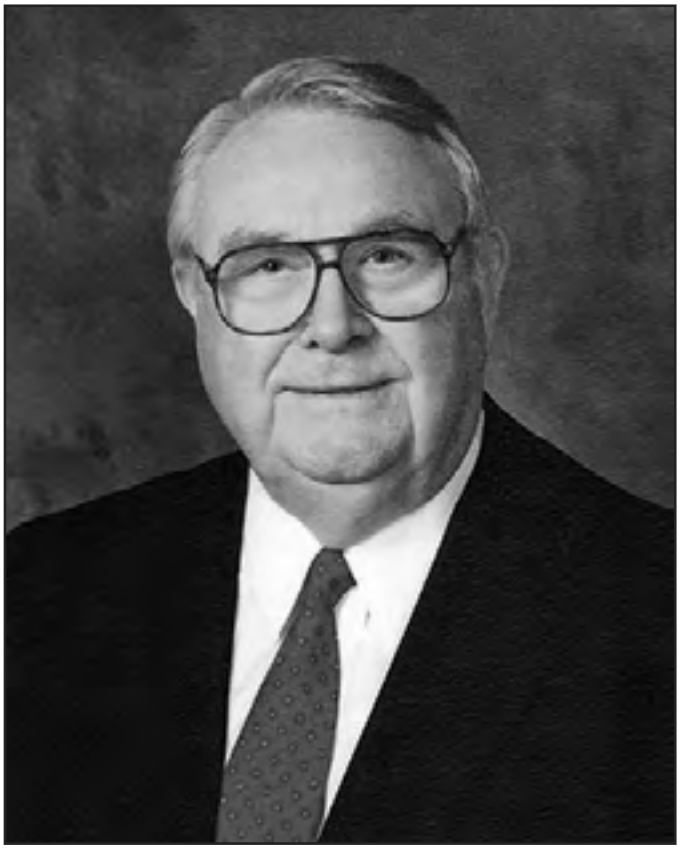
In Memoriam



Robert McRee Battle, MD

July 23, 1933 – June 17, 2021

We have lost a great doctor (teacher), friend and mentor. It's been many years ago that I met Dr. Bob Battle, and we gradually built a warm, strong relationship. It occurred to me that so many of his colleagues have not had the opportunity to learn from him. He had lots to teach. I never once heard him do a presentation. I thought I might get him to share and put something together. We did a Zoom meeting I recorded when ICIM was at Dallas in March 2020. I could not get him on track to divulge his pearls and secrets. It was an early Zoom attempt for me, and he couldn't hear my questions. He used that time to review his life, and luckily I saved that file.

I visited him and his wife Ceci Delgado just a few weeks ago in May. He was struggling but continued to make huge efforts to see a few patients that needed help. He hoped to find someone to join his practice and transition his patients; but even at 87, there was no way he'd abandon them. A few years ago, Ceci, had a serious health problem which they resolved. Afterwards, she told me "I believe him." She totally trusted in his caretaking.

What pearls might he have shared that I could share in turn? At our last visit, he emphasized several times: "It all boils down to the autonomic nervous system." I know he was inspired by Dr. Dietrich Klinghardt. He was at many Klinghardt meetings. In fact, he was at a lot of meetings. He delighted in anything he could learn. We shared many meals and telephone calls discussing the new information that we came upon. As he had gotten less able to travel, he would call to get reports and highlights. If he was unable to attend an ICIM meeting, it wasn't long before we talked so he could get a recap.

Here's a pearl from him. He put his patients who were over 60 on C-PAPs with an oxygen concentrator. He reported that his patients had very few cardiac issues if they would do this. My husband, Donn, was suffering with congestive heart disease, and Bob insisted that I bring him over. We arrived late in the evening, but Bob was prepared to have Donn use the C-PAP and oxygen concentrator. By morning, the swelling in his legs had completely disappeared with no drugs and especially no diuretics.

I told him about Dr. Michael Platt's recommendations for prostatic hypertrophy. Dr. Platt uses about 300 mg progesterone daily to the perineum. He promptly called Dr. Platt for further discussion and treated several of his patients in this fashion. Of course, this was only done with a positive response with autonomic response testing (again Dr. Klinghardt). He told me several times, he was astonished that men tested for so much progesterone; but it was working – and working without any diminution of sexual function and interest.

He kept his medical grab bag full. He offered chelation, ozone therapies, peptides, hormones, IV nutrients, neural therapy, homeopathic remedies and was very fond of the UNDA numbers. He felt that he could help most people with cancer.

Dr. John Trowbridge assisted him in the last few months to try to navigate the medical system. He expressed his gratefulness for that friendship over and over when I visited.

Bob was a tireless fighter for keeping options available to his patients. He had numerous skirmishes with his medical board and always he stayed standing.

My last message from Bob was on May 27th. He wrote, "So after all this long wait, let nature take her course…healing!" He was strong in his belief in God, and God's strength was in him.

And so, as we mourn the loss of our friend and teacher, our lives have nonetheless been enriched. We were able to share in his great enthusiasm for whatever he undertook but particularly for his love of caring for people.

I will no longer get a phone call on my birthday with Bob and Ceci singing and I will miss that. But thank you, Bob, for putting the color and joy into the fabric of our lives. He cherished the extended family he found with ICIM and through our memories he will always be with us.

Carol Petersen

Letters to the Editor

Assessing Liver Function

I would like to comment on Dr. Douglas Lobay's article "Assessing Liver Function?" in the June 2021 edition of the *Townsend Letter*.

My motivation in writing to ask for a clarification is because we are now experiencing an epidemic of fatty liver disease, which has become – when it progresses to NASH – the number one cause for being placed on the liver transplant list in the United States. I think it's essential that we all have a better grasp of hepatology.

Dr. Lobay writes "the average current lab values for ALT on most chemistry panels are between 5-43 units/ml.... The average current lab values of GGT on most chemistry panels are between 5-60 units/ml."

In hepatology, there is a consensus that normal levels of ALT are below 30 in a male and below 20 in a female. Anything above that value should be considered an abnormal result and repeated within six months. A second elevated value needs to be assessed and acted upon with further testing to rule out liver disease, alcohol or substance abuse or medication toxicity. (pers. commun. Robert Gish, MD) My hepatologist colleagues have been trying to educate the rest of the medical profession about this, but labs will not change their reference ranges. They continue to include diabetics in their reference populations, which only serves to allow those with liver disease to fall through the cracks.

The story with GGT is even more serious. Kazemi-Shirazi et al. have looked at mortality risk in 283,483 attendees of the Vienna General Hospital, all of whom had GGT monitoring as part of their standard health assessments. Participants were all followed for up to 13 years, and outcomes were matched against the general population of Austria. They looked at GGT levels for gender and age groups in 37% of the general study population (104,888 adults). The upper limit for GGT was considered 14 U/L for men and 9 U/L for women. In those with GGT levels between 9 U/L-17 U/L for women and between 14 U/L-27 U/L for men (approximately 85,000 people), there was a 20 percent increased risk of all-cause mortality. Individuals in this highest risk category: GGT levels above 56 U/L for men and 36 U/L for women had a doubling of risk for dying: 130% for cancer mortality; 60% for both vascular mortality and death due to ischemic heart disease; and 40% for stroke deaths. In this group there was a 15.1 times increased risk of death from liver/bile duct disease and 18.5 times increased risk of death from liver cancer.

Multiple studies have seen the correlation with GGT and increasing risk for cardiovascular disease, metabolic syndrome, gestational diabetes, type 2 diabetes, and chronic kidney disease for both men and women with GGT levels as low as 20 U/L (Koenig, Seneff 2015). Following standard lab reference ranges in hepatology is dangerous as we can miss not only ongoing damage but sentinel blood markers like GGT that predict oxidative stress, glutathione depletion, cellular damage, and overt disease.

We cannot be lazy and make clinical decisions based on our clinical lab reference ranges and Wikipedia (really?), but we have to look at the epidemiological evidence and listen to our hepatology colleagues who have the experience and training to know what they're talking about.

Respectfully
Lyn Patrick, ND

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Chelation of Arsenic

I read with interest the review of arsenic and type 2 Diabetes in "Shorts" in the May 2021 edition of the *Townsend Letter*. I would like to comment on the statement "Perhaps, the first step, as Yuxin Hu, et al, advise, would be to reduce the amount of arsenic in the body by avoiding sources, whenever possible, and by safe chelation with DMPS and/or DMSA."

The half-life of arsenic in the body is very short – inorganic arsenic is about 10 h, and 50 to 80 percent is excreted in about 3 days. The biological half-life of methylated arsenic is about 30 hours. (Goyer and Clarkson, 2001). Very little arsenic is sequestered in the body; the damage is done while the arsenic is quickly passing through the lungs, liver, endothelium, kidney and bladder (where cardiovascular disease and cancers occur) and is excreted in the skin, nails, and hair as well as the urine. Therefore, chelation therapy is only appropriate in acute poisoning situations, where individuals have greater than 50 mcg./gm creatinine in their urine.

Arsenic IS a huge problem in the US where over 11 million Americans are at risk for exposure from well water and municipal drinking water systems. And, according to Dr. Ana Navas-Acien at Columbia University, who has published extensively on arsenic exposure, levels as low as 12 mcg/gm creatinine inorganic arsenic in the urine, increase risk for cardiovascular disease. (pers comm Ana-Navas Acien MD). Dr Navas-Acien has been leading the research group for the Strong Heart Study and the article reviewed in "Shorts" on type2 diabetes.

Thank you for this opportunity to shed a little light on the serious problem of arsenic toxicity. Thank you so much for your helpful reviews in the *Townsend Letter*, I've been a grateful subscriber these past 30 years.

Warmly,
Lyn Patrick ND
EMEI global, emeiglobal.com

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Ask Dr. J

by Jim Cross, ND, LAc

thias1020@yahoo.com

Not Speaking In Tongues

John Maynard Keynes has a terrific line: "The difficulty lies not so much in developing new ideas as in escaping from old ones." For me, the mark of a truly innovative scientist/health care practitioner lies in the ability to alter their way of thinking when present-day ideas/facts evolve from old paradigms. We are witnessing this presently with exciting new information about COVID-19 and its supposed "vaccine." We could and hopefully will see this same phenomenon with regards to cancer prevention.

I had an interesting "brain wave" walking in the forest this morning: cancer cells speak a different language than our healthy human cells and our even more prevalent microbiota. So, to prevent and treat cancer, we must be so lucky as to decipher cancer's uniquely original language.

By learning cancer's language, you gain the ability to understand what essentially defines who it is and what constitutes its strengths and weaknesses.

We Were Soldiers is an excellent Vietnam War movie that accentuated the above strategy. Mel Gibson played Lieutenant Colonel Hal Moore, who commanded US forces at the Battle of La Drang in 1965. The movie shows Col. Moore, before he was sent to Vietnam, reading about the battle of Dien Bien Phu in 1954 – in which the Vietnamese, led by Viet Minh commander Nguyen Huu An, decisively beat the French and drove them from Indochina. Moore had discerned the strategy the Viet Minh general had used to defeat the French. Because of this understanding, he was able to predict the same general's moves at La Drang and make successful counter moves that saved some of his men and caused the general to withdraw.[1]

For me, preventing cancer means addressing key areas in our lives whose healthy, optimal "language" could be co-opted into a dysfunctional, pro-cancer "dialect" that fuels cancer growth.

To me, these key areas are the types of food consumed, stress reduction, introducing continual daily movement into a person's life, modification of genetic SNPs in the body, and identifying the emotional and chemical toxins to which each person is inevitably exposed. Keeping these areas humming with vitality can prevent their language from being subverted by cancer and used to fuel its growth. For sake of brevity, I will focus on the seemingly simple topic of food.

In an article many moons ago for *The Townsend Letter*, I penned my mantra for optimal, individual food consumption: ***eat local, photon-rich, nutrient-dense, fiber-rich food – not too much – according to your genetic make-up, in a calm, relaxed manner***. I find that following these simple food rules is one basis for chronic disease prevention, including cancer. Next, I will proceed to look at a few sections of my mantra and their relationship to cancer prevention.

I have a favorite line I use with patients: your genes are smarter than you; try not to get in their way. Referencing my "according to your genetic make-up" above, the Inuit represent a society where this idea seems to hold true. Their genetic make-up had been virtually unchanged until about seventy years ago, but their lifestyle was about to undergo a dramatic transformation.

Descriptions from 1923 suggest that cancer was essentially nonexistent in their population[2] and a report from 1949

discovered 14 cases over a 10-year span.[3] In the years following WWII, many Inuit were forced to relocate to large urban centers, which converted their traditional, low carbohydrate, high fat, and high protein diet of mostly fish and sea mammals into one that consisted mainly of grains and sugars. This resulted in an age-adjusted rate of traditional cancers that almost quadrupled from 1975 - 1981.[4] Thus, their genetic blueprints, which appeared to prevent cancer, were manipulated dietarily to accommodate cancer cells as their lifestyle and, as a result, their internal milieu had changed.

Another direction in which to probe from my mantra is "nutrient–dense food." Much food consumed in America today is calorie rich. These excess calories originate mostly in neocarbs: white and whole wheat flour and sugar. Neocarbs strongly stimulate insulin secretion. Insulin is a highly potent growth factor. A prospective cohort study using data from the National Health and Nutrition Examination Survey of 1999-2010 found that among all participants – obese and non-obese – cancer mortality was significantly higher in those with hyperinsulinemia.[5] Another study found that hyperinsulinemia was a significant risk factor for postmenopausal breast cancer, which was independent of adiposity. It also found that insulin may be driving the development of breast tumors.[6]

Let me end by fleshing out the "in a calm, relaxed manner" portion. With regards to the health of your gastrointestinal system, stress is beginning to be appreciated as a linchpin to optimal working order. With patients, I always ask them if they have been through a carwash. The vast majority say "yes." I then convey to them that their GI tracts can be similar to a great carwash: having their cars vigorously sprayed and shaken, not stirred around a little. I tell them this is what happens when their GI tracts are happy and every integral GI part is functioning full on. They are hosing down the food with digestive enzymes and mixing in those secretions utilizing peristaltic waves and segmentation. What makes a GI tract happy/functional? It lies being in parasympathetic nervous system/relaxation mode during meals more than sympathetic nervous system/stressful mode.

Before modern civilization entered the fray, stressful situations tended to be short, sweet, and hopefully survivable. However, when one partakes in a stressful situation, human bodies need to make specific physiological adaptations so that a ravenous tiger doesn't eat them or an inhospitable human doesn't spear them. This requires blood being diverted to the skeletal muscles and heart and away from the GI tract, in particular. (This is why your parents told you not to swim out into the lake after a heavy meal.)

What happens if your GI tract does not receive sufficient, positive attention/blood flow?

- The gastroesophageal/cardiac sphincter doesn't close fully → reflux.
- Stomach acid secretion is reduced → suboptimal protein digestion and lower liver, gall bladder, and pancreas secretions.
- Lower liver/GB secretions → impaired digestion of fats.
- Lower pancreas secretions → lower neutralization of acid and substandard digestion of carbohydrates, proteins, and fats.
- Decreased peristalsis/segmentation → longer overall transit time, especially in the large intestine, which leads to prolonged contact of the colonic mucosa with carcinogens.
- Altered Microbiota → barrier dysfunction/leaky gut which has systemic pathological consequences.[7]

Every one of the above negatives lead to a GI system out of balance. This adversely alters the language of every system of the body, which can make it vulnerable to an invasion of cancer.

Hippocrates has an excellent quote: "Illnesses do not come upon us out of the blue. They are developed from small, daily sins against Nature. When enough sins have accumulated, illnesses will suddenly appear."[8] So, to really prevent cancer, one must be vigilant daily and take the preventive steps to ensure that our defenses resemble a medieval castle with impenetrable walls and a 100-foot moat around the castle laced with a plethora of hungry crocodiles. Having a healthy and optimally functioning GI tract is one part of this extremely intricate puzzle known as cancer prevention.

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Healing with Homeopathy

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

A Quick Homeopathic Cure for Debilitating Night Sweats

I normally wait a good year and a half or more before presenting a homeopathic case as cured. I am making an exception here in order to dispel the widespread myth that homeopathy works slowly. I have heard that so often, wherever I have gone. But, when a homeopath is able to understand the patient at a deep level, and find the *simillimum* (one best remedy), as happened with Kristin, rapid change is possible.

I had treated Kristin for several years much earlier in her life, beginning in 2004. Her symptoms and state were very different, but I was able to help her at the time. Recently, many years later, she was suffering from terrible night sweats, and her husband suggested that she give me a call. Fortunately, she did, two months ago, at the age of fifty-eight.

"Incredible Night Sweats"

"I finally entered menopause in the middle of 2019. Since then, I've had incredible night sweats. I sleep on towels. I'm dripping wet. They're almost always between 3 and 3:15 AM. Occasionally 2-2:30. Then again around 4 AM. Then 4:45. A women's health doctor prescribed compounded hormones in micro-doses, which has reduced the intensity of the sweats. And it's helped the frequency somewhat.

"I had odd perimenopausal symptoms. I'd wake about 3 or 4 AM with pain in my thoracic vertebrae, and irritability. And I felt exhausted. So much so that I would sit down after work and be asleep. Like I was drugged. Just out. Bleary. Nothing has helped me with that.

"I also get intestinal gas which progresses through the day. When I get up, my size feels appropriate. Towards 5:30 I start to feel more and more bloated. Almost like my intestines are full of water... Like I am filled with water. My whole abdomen has a thick, watery feeling... It reminds me of the past when my upper body was literally swollen, moving down to the lower body.

"I'm a chiropractor specializing in athletes. I love my work, but it's exhausting. The young athletes are being taken advantage of and I was wearing it on my heart. I was treating an 8-year-old skating champion. She would tell me all the horrible things her mother would say to her. The coaches push the kids so hard. I care incredibly for these kids. They may get gold medals, but they end up having surgeries. And they are emotionally stunted. They're like racehorses... I'd feel heartbroken. Happy for them but know how screwed up they were.... It would wear me out... I remember one fifteen-year-old star skater who could barely walk. The dark side of the Olympic training world wore me out. The pandemic has put a hold on that work for now."

I asked Kristin to tell me about the night sweats. "I'm drenched. My hair is so wet that it sticks to my face. It feels slippery... The night sweats came with the odd, visceral feeling that my bones were being squeezed really tight, boiling hot. Then the night sweat would come. They're boiling... The bone part is incredibly painful... it's like the marrow is boiling. It's so uncomfortable I wouldn't wish it on anybody... They're physically exhausting. I'm drained of energy. It's like you've done an incredibly physical feat. Like all your nutrients were gone... In the morning I'm mentally dull for a while."

I asked Kristin to share with me more about the feeling in her abdomen. "It feels gurgly. Like there's thick water in my abdomen... it makes my skin feel taut around my belly... Not as thick as cake batter. But it's in this container that's so stretched." Wondering if a sensitive woman like Kristin might need a plant remedy, I asked the opposite of the thick sensation. "Something that moves easily. A sense of ease, freedom... Heavy, weighted. Like your entire abdomen is swollen."

What Is Unique About Kristin and What Remedy to Give Her?

I found Kristin to be remarkably articulate in conveying her symptoms to me. Her sensitivity to and empathy for the children whom she treated was impressive and palpable, which might suggest a plant remedy. Yet, according to the *Sensation Method*, which I use, there should be a clear and recurrent

plant sensation running though all the symptoms as well as its opposite. So, by the end of the appointment, I did not know, as I often do, just which remedy to prescribe.

I use the *Synergy* (previously *MacRepertory* and *ReferenceWorks)* most of the time to analyze cases to search the homeopathic literature for the best remedy. In this case I took the shortcut of searching for "Perspiration" within three words of "Profuse" in the same remedy as "Abdomen" within three words of "Water" in the same remedy as "Gurgling" within three words of "Abdomen." This was just a quick way to begin to search for a remedy that matched all of these main features of Kristin's case. From there I could search further in *Materia Medica, Repertory*... the possibilities with the *Synergy* program, originally the brainstorm of my dear friend, David Warkentin, are endless.

Two remedies stood out in black type in this search: *China* and *Phosphoric acid.* There was nothing about *China* that fit mentally and emotionally. Kristin didn't use words like "drained," and she lacked the daydreamy overactivity of the *Rubiaceae* family mind. But *Phosphoric acid* brought forth an immediate "Aha!" *Phosphoric acid*, like the other acids, is an excellent remedy for exhaustion, often from the dehydration resulting from diarrhea. But this was another kind of dehydration: from profuse sweating. The strong desire for carbonated drinks was absent. But *Phosphorus* is an exuberant, bubbly, bleeding heart kind of remedy. Kristin had shared with me, in fact, her heartbreak about the terrible physical beating that these young athletes endured both physically and emotionally.

When I searched further some of the rubrics of *Phosphoric acid*, I found "Perspiration, clammy"; "Perspiration, climacteric"; and "Perspiration debilitating, exhausting." This was an "Aha!" moment in which I felt fairly sure about the remedy though I never know until the follow-up visit six weeks later. I gave Kristin four doses of *Phosphoric acid* 1M twelve hours apart.

Six Weeks Later

You can imagine my elation when Kristin told me, "I'm doing great. I am seriously doing 100% better! The symptoms are completely gone. I don't even have remnants of them. That happened within a week or so of taking the remedy... The night sweats have pretty much gone away. I get a little warmish around 3:30 AM, but it passes very quickly, and I go back to sleep easily. That is when I used to have the night sweats. There is no gurgling in my intestines. The night sweats [being gone] is a ginormous relief!.. I'm feeling more whole."

I shared with Kristin in depth about what I had given her and why, because she has excellent insight into her own state, and because I worried that if she resumed doing work that left her heartbroken, there could again be repercussions, even worse. When I spoke with Kristin more about the remedy and its indications, she confirmed that she did indeed like juicy fruits, a keynote of the remedy (it is not surprising that the body would have this mechanism of helping to deal with dehydration). She also shared that her partner of many years would see how burned-out Kristin was from her work and would question her as to whether she was sure that she wanted to continue.

Obviously, this is only the first follow-up in this cycle of Kristin's homeopathic care. But the response was profound, rapid, and there is no reason to believe it will not continue.

Dr. Judyth Reichenberg-Ullman is the author of *Whole Woman Homeopathy*, and co-author, with Dr. Robert Ullman, of six books on homeopathy*: Ritalin-Free Kids, Homeopathic Self Care, The Savvy Traveler's Guide to Homeopathy and Natural Medicine, A Drug-Free Approach to Asperger Syndrome and Autism, The Homeopathic Treatment of Depression, Anxiety, and Bipolar Disorder,* and *Rage-Free Kids* as well as *Mystics, Masters, Saints and Sages—Stories of Enlightenment*. They have been columnists for the *Townsend Letter* since the early 90s, and they have taught internationally. They live on Whidbey Island Washington, and in Pucón, Chile.

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

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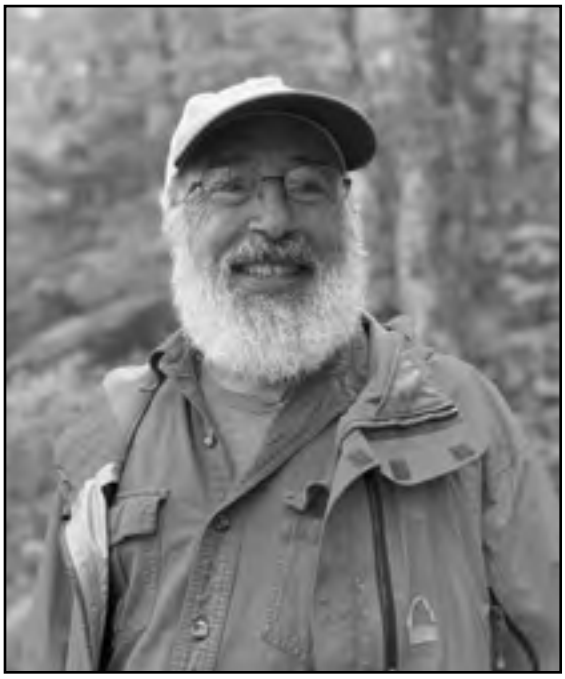

Curmudgeon's Corner

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

Acid Alkaline Diets and Cancer – An Ethical Question

Do the ends justify the means? A cancer patient reports they are following an alkalinizing diet to combat their cancer and asks my approval. I tell them that while the theory is malarkey the diet is a good idea never the less.

People like to be told what to eat. Any basic sort of religion came with dietary codes telling adherents what not to eat. As our adherence to these religious strictures weaken, people turn elsewhere for guidance. There is an almost universal need to categorize foods into good or bad. It's Kosher or Halal, natural, preservative-free, organic, gluten-free, non-GMO, or low carb. An old classification system that won't go away is the idea of acid and alkaline foods.

We need to go all the way back to Marcellin Berthelot (October 25, 1827 - March 18, 1907) to understand where this concept of acid and alkaline diets originated. Berthelot was a French chemist, famous for numerous important discoveries not relevant to this article. In 1864, Berthelot moved on from other interests to the study of thermochemistry. In his 1879 book *Mecanique Chimique*, in which he introduced the concepts of 'endothermic' and 'exothermic' reactions, he described a laboratory apparatus he had invented for his experiments called a bomb calorimeter. Such things are still in use.

A bomb calorimeter consists of a chamber pressurized with oxygen and suspended in a water bath. A sample is added to the chamber and once everything is set up, ignited. The pressurized oxygen guarantees that whatever is inside the bomb rapidly incinerates and is reduced to ash. The heat released by this controlled explosion is absorbed by the water bath and the water's increase in temperature is equivalent to the calories of heat given off by the sample. This is how food's calorie content is determined to this day.

After the experiment is done, all that is left inside the bomb calorimeter is ash. If one adds water to this leftover ash, one can measure its pH and tell whether it is acidic or alkaline. This measurement is the basis of describing some foods as alkaline or acidic. In 1912, Sherman and Gettler published a paper that listed foods that had been tested in this fashion, classifying them as acidic or alkaline based on the pH of their leftover 'bomb ash.'[1]

The current alkaline-ash diet is based on this once-upon-a-time list. This is not what we call cutting-edge science. In general, fruits and vegetables leave an alkaline ash, and meats and grains leave acidic ash.

Bomb calorimeter

There is a widespread belief that following an alkalinizing diet, that is avoiding foods that produce acidic ash and choosing to eat foods that leave an alkaline ash, is a valid treatment for cancer.

Dr. Neil McKinney, who teaches naturopathic oncology at Boucher Institute of Naturopathic Medicine doesn't think much of this theory. "To put it bluntly, suggesting cancer can be treated or cured by alkalinizing the body is pure rubbish. Treatments based on alkalizing are quackery."

McKinney tells me that this fallacy began with Otto Warburg, whose research on the biochemistry of sugar metabolism in

the 1920s to 1940s won him a Nobel Prize. Warburg found that cancer cells often live in hypoxic, very low oxygen, and acidic conditions and that they derive energy from sugars by fermenting them the way yeast do. He came up with a theory that these low oxygen and high acidic conditions were the cause of cancer.

> Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar. – Dr. Otto H. Warburg

Current science explains this phenomenon differently. For a tumor to survive it needs to stimulate the growth of blood vessels. Otherwise, it can't get all the oxygen it needs to metabolize sugar. Tumor cells stimulate blood vessel growth by producing vascular endothelial growth factor (VEGF). Even with this stimulation, tumor cells often outpace the growth of new blood vessels. When they do so, they don't have enough oxygen.

[Even this theory has fallen from favor, and we now generally account for tumor acidity as a result of cancer cells expressing an excess of proton pumps on their cell membranes and that they pump metabolic wastes out of the cells, generating an acidic environment in the tumor proximity. One example, "Metastatic breast cancer cells from pleural effusions were up to 200-fold more active in acidifying their extracellular milieu than non-malignant mammary cells cultured in the same conditions…" [2]]

When oxygen is deficient, tumors change how their cells metabolize sugar. They start breaking it down through fermentation. This isn't ideal; fermentation releases only about 5% of the energy that would have been produced if oxygen were available. The tumor cells do this to survive, not because they like to. Fermentation of sugar without adequate oxygen produces lactic acid. This is because not only aren't there enough blood vessels to bring oxygen to the tumor cells, there are also inadequate blood vessels to remove waste products like lactic acid. This was a good theory a hundred years ago. Now it is tumor cell proton pumps that get the credit for the acidic tumor environment. Low oxygen and acidic tissue environments are no longer considered the cause of cancer but instead it is the other way around. Cancer cells create an environment that is acidic and short of oxygen.

The idea persists that neutralizing the acid produced by tumors and bringing oxygen to tumor cells can cure cancer. Changing the pH of a tumor does not change its growth rate significantly, nor does it seem to lead to cell death. In 2004, Wenzel and Daniel published results of several experiments using quercetin and other flavones that trigger apoptosis (cellular suicide) in cancer cells. They found that apoptosis occurred independent of changes in alkalinity or acidity of the cellular environment, altering pH did not appreciably effect survival or death of cancer cells.[3]

Even if it were true that raising the pH of a tumor was a useful therapy, there is no easy way to make this happen. The body holds the pH in blood and body fluids within a narrow range. Even a slight shift in pH would change the way enzymes act and the body does everything it can to prevent this from happening. Mechanisms in the body buffer any attempt at raising or lowering the body's pH.

Dr. McKinney writes, "I worked for years in radiation therapy research on the hypoxic cell problem. Cancer does not ever form due to an acidic or a low oxygen environment—rather, advanced tumors create these conditions as they outstrip their angiogenesis capacity. It is not possible to alkalize tumors by any oral supplement, … even IV bicarb will not harm tumors."

The idea that oxygen will kill cancer cells is equally absurd. Cancer cells like oxygen; lack of oxygen slows their growth. Remember those angiotensin inhibitor drugs, bevacizumab (Avastin) is a prime example; by preventing the growth of new blood vessels to tumors, they suffocate the cancer cells. But let's stick with this alkaline and acid pH business.

This misplaced and outdated desire to increase the cancer's pH has gotten cobbled together with the even older old bomb calorimeter ash data. Books and especially websites urge cancer patients to eat alkaline ash-producing foods on the theory that this will neutralize the acidic environment that created cancer.

Warburg's theory was interesting 100 years ago. When we look for compelling research which might confirm the benefits of following this alkaline diet we come up with slim pickings.

T.R. Fenton has led several studies that looked at this alkaline diet business. The first was published in 2009 and looked at this diet as a treatment for osteoporosis. It has long been suggested by proponents that eating highly acidic ash foods would rob the body of calcium and lead to osteoporosis. Fenton's conclusion after conducting a meta-analysis of all published data found: "Promotion of the "alkaline diet" to prevent calcium loss is not justified."[4]

Fenton conducted a second meta-analysis published in 2011, and came to the same conclusion that any suggested association between eating a diet high in acid ash foods and osteoporosis is not supported: "…and there is no evidence that an alkaline diet is protective of bone health."[5]

A systematic review published in 2016 that examined alkaline and acid diets in relation to cancer risk found that "… there is almost no actual research to either support or disprove these ideas. This systematic review of the literature revealed a lack of evidence for or against diet acid load and/or alkaline water for the initiation or treatment of cancer. Promotion of alkaline diet …. to the public for cancer prevention or treatment is not justified."[6]

Given all this, one would think I'm opposed to patients believing these ideas. I hesitate to say anything negative to patients about this diet. That's because fruits and vegetables top the list of foods that burn down to alkaline ash. The theory behind this whole business may be nonsense, but the results are good for most people. Getting someone to eat more alkaline foods is equivalent to telling them to eat more fruits and vegetables, foods that contain chemicals proven to prevent and fight cancer. Telling someone to avoid eating foods that produce acidic ash is telling them to avoid foods that increase the risk of cancer. These outcomes may have nothing to do with pH; they have everything to do with the other nutrients present in the foods.

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Curmudgeon's Corner

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So here is an ethical question: Do we let people believe in outdated science for the purpose of getting them to do something that is good for them? Do we let our patients follow these alkaline food lists, knowing that the theory that supports their diet is malarkey?

Some days working with patients is like parenting a three-year old; we have to pick our battles, and fighting this one just might not be worth the effort. I confess, I sometimes let the truth slide and leave people believing something we know to be false, but knowing that this crazy idea is inspiring them to eat a healthier diet. Am I wrong to do this?

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CALENDAR

AUGUST 5-6: EUROPEAN ENDOCRINOLOGY AND DIABETES CONGRESS online. CONTACT: https://endocrinology.conferenceseries.com/

AUGUST 6-8: INSTITUTE FOR FUNCTIONAL MEDICINE BIOENERGETICS MODULE – Clinical Solutions for Mitochondrial and Metabolic Dysfunctions livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modules-apm-bioenergetics-formerly-energy-2021/

AUGUST 13-15: A4M/MMI ENDOCRINOLOGY online. CONTACT: https://www.a4m.com/endocrinology-2021.html

AUGUST 16-17: 16th WORLD CONGRESS ON TRADITIONAL AND COMPLEMENTARY MEDICINE online. CONTACT: https://traditionalmed.conferenceseries.com/

AUGUST 24-25: 16th INTERNATIONAL CONFERENCE ON FRONTIERS IN TRADITIONAL AND ALTERNATIVE MEDICINE online. CONTACT: https://alternativemedicine.conferenceseries.com/

AUGUST 24-25: 16th INTERNATIONAL CONFERENCE ON ALTERNATIVE MEDICINE – Innovation for Treatment of COVID-19 online. CONTACT: https://alternativemedicine.naturalproductsconference.com/

AUGUST 26-29: ACUPUNCTURE MERIDIAN ASSESSMENT (AMA) TRAINING For Doctors, Dentists & Health Professionals: Detecting Parasites, Dental & Fungal with Simon Yu, MD, in St. Louis, Missouri. CONTACT: www.preventionandhealing.com; 314-432-7802.

AUGUST 26-29: 12th ANNUAL INTEGRATIVE MEDICINE FOR MENTAL HEALTH CONFERENCE in Atlanta, Georgia, and live online. CONTACT: https://www.immh2021.com/

SEPTEMBER 9-11: A4M/MMI BIO-IDENTICAL HORMONE REPLACEMENT THERAPY SYMPOSIUM in Anaheim, California. CONTACT: https://www.a4m.com/bio-identical-hormone-replacement-symposium-september-a4m-2021.html

SEPTEMBER 17: 4th INTERNATIONAL CONGRESS ON EPIGENETICS AND HUMAN DISEASES online. CONTACT: https://epitranscriptomics.geneticconferences.com/

SEPTEMBER 18: BUILDING LIFETIME IMMUNITY PROFESSIONAL CERTIFICATE TRAINING in San Antonio, Texas, with Cornell Richard Neel, MD. Also, OCTOBER 20. Sponsored by Children's Future Foundation. CONTACT: 442-234-3263; Lifetimeimmunity.com

SEPTEMBER 22-23: 7th INTERNATIONAL CONFERENCE ON INFECTIOUS AND RARE DISEASES in Vancouver, Canada. CONTACT: https://infection.conferenceseries.com/

SEPTEMBER 24-26: 8th INTERNATIONAL CONGRESS ON COMPLEMENTARY & ALTERNATIVE MEDICINE in Montreal, Canada. CONTACT: https://complementarymedicine.conferenceseries.com/

SEPTEMBER 24-26: ADVANCED INTEGRATIVE ONCOLOGY in Scottsdale, Arizona, and live online. CMEs available. CONTACT: Sharon Phillips, phone 954-540-1896; Email: sharon@aampconferences.com; https://aampconferences.com/

SEPTEMBER 29-OCTOBER 3: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE (ICIM) FALL MEETING – Vaccines and Immunology: Truth and Fiction in Fort Worth, Texas. CONTACT: https://icimed.com/

OCTOBER 1: THE ACADEMY OF INTEGRATIVE HEALTH AND MEDICINE (AIHM) INTERNATIONAL FELLOWSHIP IN INTEGRATIVE HEALTH & MEDICINE begins its next session. Scholarships available for this 1000-hour hybrid program for clinicians who aim to become leaders in integrative health and medicine. CONTACT: https://aihm.org/

OCTOBER 1-3: THE BIOREGULATORY MEDICINE INSTITUTE (BRMI) presents Optimizing Clinical Skills and Knowledge in Scottsdale, Arizona. Featured Guest - Dr. Ralf Oettmeier of Switzerland's Alpstein Clinic. CONTACT: https://www.biologicalmedicineinstitute.com/upcoming-events

OCTOBER 1-3: MID-ATLANTIC NATUROPATHIC CONTINUING EDUCATION CONFERENCE online. CONTACT: https://www.njanp.org/2021conference

OCTOBER 1-3: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Cardiometabolic UK 2021 livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-cardiometabolic-uk-2021/

OCTOBER 14-17: AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE FALL CONFERENCE – Immunity, Inflammation, and Autoimmunity in San Diego, California. CONTACT: http://aaemconference.com/

OCTOBER 14-17: 16th ANNUAL CARDIOMETABOLIC HEALTH CONGRESS in National Harbor, Maryland. CONTACT: https://www.cardiometabolichealth.org/2021/cmhc-16th-annual.html

OCTOBER 14-17: ACADEMY OF INTEGRATIVE HEALTH & MEDICINE VIRTUAL CONFERENCE online. CONTACT: https://aihm.org/conference/

OCTOBER 22-24: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Restoring Gastrointestinal Equilibrium livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-gi-2021/

OCTOBER 29-30: 12th ANNUAL BIOMARKERS AND CLINICAL RESEARCH CONGRESS in Vancouver, Canada. CONTACT: https://biomarkers.conferenceseries.com/

OCTOBER 29-30: 8th INTERNATIONAL CONFERENCE ON NATURAL, TRADITIONAL, & ALTERNATIVE MEDICINE in Vancouver, British Columbia, Canada. CONTACT: https://naturalmedicine.conferenceseries.com/

NOVEMBER 5-6: NEW HAMPSHIRE ASSOCIATION OF NATUROPATHIC DOCTORS (NHAND) 2021 ANNUAL CONFERENCE: Science, Spirit & Clinical Pearls. In-person and Livestream. CONTACT: conference@nhand.org; https://www.nhand.org/annual-conference/

NOVEMBER 5-7: 21st ANNUAL CONFERENCE OF THE WESTON A. PRICE FOUNDATION – Staying Healthy in a Toxic World in Allen Texas (near Dallas). CONTACT: https://www.wisetraditions.org/

NOVEMBER 19-21: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – ENVIRONMENTAL HEALTH 2021 livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-environmental-health-formerly-detox-2021/

DECEMBER 9-12: A4M/MMI 29th ANNUAL WORLD CONFERENCE – Unmasking the Hidden Epidemic in Las Vegas, Nevada. CONTACT: https://www.a4m.com/29th-annual-world-congress.html

JANUARY 21-23, 2022: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – Cardiometabolic livestream online. CONTACT: https://www.ifm.org/learning-center/functional-mfunctional-medicine-advanced-practice-modulesapm-cardiometabolic-2022/

FEBRUARY 25-27: IFM FUNCTIONAL MEDICINE ADVANCED PRACTICE MODULE – The Many Faces of Immune Dysregulation and Inflammation livestream online. CONTACT: https://www.ifm.org/learning-center/functional-medicine-advanced-practice-modulesapm-immune-2022/

FEBRUARY 26-MARCH 2: NATIONAL CONFERENCE ON WILDERNESS MEDICINE in Big Sky Ski Resort, Montana. CONTACT: https://wilderness-medicine.com/cme-conferences/ski-big-sky-montana/

APRIL 22-24: JOINT AMERICAN HOMEOPATHIC CONFERENCE in Reston, Virginia and virtual online. CONTACT: https://www.homeopathycenter.org/

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Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Screening Mammography Recommendations for Average Risk Women – Confusions Revisited

I first covered this issue of screening mammogram guidelines for this column in 2014. I hope to review some history here and revisit the status of where things are now. Regular screening mammography is conducted in an attempt to reduce mortality from breast cancer. The practice is based on the presumption that screening mammograms detect breast cancers that are smaller than those detected by physical breast exams, meaning they can be detected sooner, on average, than clinically palpable breast cancers. This "early detection" is hoped to result in better prognosis than later detection of larger tumors. However, avoiding breast cancer–related deaths is not the only outcome to consider. Two other outcomes need attention as well: false alarms and overdiagnosis. And, how meaningful is this early detection and better prognosis assertion?

According to a 2010 review in *JAMA Internal Medicine* by Welch and Passow, "Among 1,000 US women aged 50 years who are screened annually for a decade, 0.3 to 3.2 will avoid a breast cancer death, 490 to 670 will have at least 1 false alarm, and 3 to 14 will be over diagnosed and be treated needlessly."[1]

According to randomized trials conducted from the 1960s to the 1980s, screening mammography reduced breast cancer mortality.[2] A significant insight into these studies is the plausibility that screening mammography was more effective in the past when breast cancer treatments were less effective. Researchers with this perspective point out, "If women with new breast lumps now present earlier for evaluation, the benefit of screening will be less. If clinically detected breast cancer has now improved, the benefit of screening will be less."[3] They also point out that these randomized trials occurred before 1990, and since then we no longer have randomized trials but observational studies in the United States.

There has been much debate about the benefit versus harm of mammography in the last few years, especially since the United States Preventive Services Task Force (USPSTF) guidelines were published in 2009.[4] USPSTF guidelines differed from the major advisory groups on this subject at that time, (ie, the American College of Obstetrics and Gynecology [ACOG], the American College of Radiology [ACR] and the American Cancer Society [ACS]). We will update those in this article, shortly.

In 2014, controversy and lack of clarity bubbled up again with the published Canadian National Breast Screening Study and its findings from 25 years of follow-up in a screening mammography trial.[5] It was initiated in 1980 and included almost 90,000 women ages 40–59. All the women received baseline mammograms. Women aged 40–49 were randomized to five annual mammograms plus annual breast exams or to usual care. Women in the 50–59 age group were randomized to five annual mammograms plus breast exams or to only annual breast exams. Over the next 25 years, approximately the same number of incidences of and deaths from breast cancer occurred in each group. In short, annual screening mammography in women aged 40–59 did not reduce mortality from breast cancer any better than physical exam or usual care (when access to adjuvant therapy for breast cancer is free and available via the Canadian healthcare system). In addition, 22% of screening detected cancers (106/484) represented overdiagnosed breast tumors.

This Canadian study is not the only study that has cast doubt on the value of screening mammography. Other findings in the last few years have revealed similar findings. These include the Kalager et al study in Norway,[6] the Mandelblatt et al study,[7] and the Autier et al study.[8] In 2012, Bleyer and Welch published a large analysis of three decades of screening mammography and breast cancer incidence using Surveillance, Epidemiology and End Results (SEER) data to examine data from 1976 through 2008. They concluded that, yes, there were substantial increases in the number of cases of early-stage breast cancers detected through screening mammography, but it only slightly reduced the rate at which women presented with advanced breast cancer – suggesting that there is substantial overdiagnosis of approximately one-third of the cases. They also concluded that, at best, screening had only a small effect on the rate of death from breast cancer.[9] In a 2011 publication of Swedish data based on three decades of follow-up, major benefits of screening were observed, with a 31% lowered risk of breast cancer mortality in the screening

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group; however, the number of women needed to screen for seven years to prevent one breast cancer death was 414.[10]

In his stunning NEJM editorial after the Kalager et al Norwegian study,[6] Gilbert Welch concluded an even more alarming mathematical calculation that it would take screening 2,500 women every year over a 10-year period to avoid one death from breast cancer.[3] These studies collectively have contributed greatly to the ongoing debate over the risk and benefit of screening mammography.

Critiques of the Canadian study point out that the Canadian study dates back to a time when women had more primitive mammograms. Between 1980 and 1984, the technology and equipment were limited and mammograms could only detect 30% of breast cancers. Mammography today is in the range of being able to detect 70% to 80% of breast cancers. You can see the problem. Yes, the Canadian study is a randomized controlled study, and over 25 years, but it's generated by technology from 34 years ago. Another critique is that the study was not truly randomized in that nurses and doctors preferentially put the patient into the mammography arm when a breast lump/mass was detected.

Critics of any conclusion other than an endorsement of screening mammography starting at age 40 also point out that many of the editorials and analyses of benefits and risks are based on calculations and numerical predictions rather than actual studies. ACOG, ACS, ACR, and many clinicians and surgeons amidst those groups insist we look at the actual studies, randomized and observational, that conclude that screening mammograms saves lives (ie, early detection – and thus earlier treatment – leads to fewer deaths from breast cancer). Others point out that, in fact, there has not been a randomized trial in the United States on this subject for about 50 years; and again, the earlier randomized trials showing benefit also occurred when there were less effective treatments and less awareness of breast cancer and exams.

Ok, now let's get current. The current status is that USPSTF, ACOG, ACS and ACR have all been offering up differing guidelines for screening mammography in average-risk women. Please do note, this conversation is all about average-risk women. Particularly, the guidelines for age 40-49 years old differ. In a review published in February 2018 in the *American Journal of Roentgenology*, Ray et al assert that the majority of the data from randomized controlled trials supports the use of mammography in this age group.[11]

The authors of this review found eight relevant trials of screening mammography among women between ages 40 and 49 years. The results from these trials indicate that routine screening with mammography in average-risk women has been associated with a statistically significant 15% to 18% reduction in the risk for breast cancer mortality. Only one study did not find a significant improvement in the risk for breast cancer mortality associated with mammography. It should be pointed out that these trials were done before the routine use of digital mammography and tomosynthesis. These technologies have improved detection and have reduced risk for false-positive mammogram results, especially in this age group.

This attempt of mine at an updated summary of guidelines started with the reading of the updated UK Age trial, which set out to assess if screening should begin at a younger age and if that might lead to overdiagnosis of breast cancer. The first UK Age trial was published in 2015.[12]

Results from the study's 17-year follow-up,[13] showed a reduction in breast cancer mortality with annual screening, beginning at age 40 years, which was significant in the first 10 years after participants were randomly assigned. Yearly screening mammography starting around the age of 40 reduced breast cancer mortality over the next 10 years, but it did not reduce mortality further once women started regular mammography screening at the age of 50.

For women who started screening mammography between the ages of 39 and 41 years, there was a 25% reduction in death from breast cancer over the next 10 years at a relative risk reduction of 0.75 compared to women who started screening later at about the age of 50.

The rate of false-positive mammography results at the initial screen was 4.9% and subsequent rates of false-positive results were 3.2%

They also note that fewer deaths due to breast cancer are achieved in women who begin screening mammography at age 40. But…the researchers estimate that 1,150 women would have to be screened in their forties to prevent one breast cancer death. On the other hand, one-sixth of all breast cancers are diagnosed before age 50, and many of these cancers are the more aggressive types of breast cancer. If you are feeling tossed around by pros and cons of screening mammography starting at age 40, it's understandable.

Let's break down the current guidelines from different organizations, and maybe that will help sort out the practicalities of what options we have about screening mammography advice.

Current Guideline Recommendations

From Medscape, updated September 23, 2020: The US Preventive Services Task Force (USPSTF) recommends:

> For women younger than 40 years at average risk for breast cancer, there have no been randomized studies done to suggest a benefit to screening. The various experts groups have not reached a consensus among them, but several recommend a clinical breast exam (CBE) every 3 years and a discussion about the benefits and limitations of breast self exam (BSE).
>
> For women over the age of 40 years at average risk for breast cancer, many expert groups recommend CBE annually. In terms of imaging, the most widely recommended screening approach in the United States for this group has been annual mammography, however, current guidelines vary with respect to the recommended age to start regular mammography (eg, 40, 45, or 50 years) and whether to perform mammography annually or biennially.

Recommendations regarding discontinuation of mammography also vary, with both age – typically, 75 years – and life expectancy as criteria. For example, the American College of Radiology recommends annual screening mammography until the life expectancy is less than 5 to 7 years, based on comorbidities.

Although mammography guidelines have been in place for over 30 years, 20-30% of women still do not undergo screening as indicated. The 2 most significant factors in determining whether a woman undergoes mammography are physician recommendation and access to health insurance. Non-white women and those of lower socioeconomic status remain less likely to obtain mammography services.

Here are the current specifics from leading organizations:

The USPSTF: Screening for average risk women to start at age 50 and then every other year between the ages of 50 and 74 years. These recommendations do not apply to women who are at excess risk for breast cancer due to known genetic mutations or histories of chest radiation

The 2017 update of the American College of Obstetricians and Gynecologists guidelines on screening in average-risk women includes the following recommendations:

- Use shared decision-making to select screening choices.
- Clinical breast examination may be offered every 1-3 years for women aged 29-39 years and annually for women aged ≥ 40 years.
- Start offering mammography at age 40 years; initiate after counseling, if patient desires.
- Recommend starting mammography screening by no later than age 50 years.
- Mammography may be annual or biennial; biennial screening is particularly reasonable after age 55 years.
- Continue mammography until age 75 years, then discuss discontinuation, with the woman's health status and longevity as considerations.

The American College of Radiology and Society of Breast Imaging both recommend annual mammograms starting at age 40 years and continuing "as long as they are in good health."

The American Cancer Society (ACS) guidelines for women at **average risk** for breast cancer states that for screening purposes, a woman is considered to be at average risk if she doesn't have a personal history of breast cancer, a strong family history of breast cancer, or a genetic mutation known to increase risk of breast cancer (such as in a *BRCA* gene) and has not had chest radiation therapy before the age of 30.

Women between 40 and 44 have the option to start screening with a mammogram every year.

Women 45 to 54 should get mammograms every year.

Women 55 and older can switch to a mammogram every other year, or they can choose to continue yearly mammograms. Screening should continue as long as a woman is in good health and is expected to live at least 10 more years.

All women should understand what to expect when getting a mammogram for breast cancer screening – what the test can and cannot do.

Screening Mammography

Women who are at high risk for breast cancer based on certain factors should get a breast MRI and a mammogram every year, typically starting at age 30. This includes women who

- Have a lifetime risk of breast cancer of about 20% to 25% or greater, according to risk assessment tools that are based mainly on family history (see below);
- Have a known BRCA1 *or* BRCA2 *gene mutation* (based on having had genetic testing);
- Have a first-degree relative (parent, brother, sister, or child) with a *BRCA1* or *BRCA2* gene mutation, and have not had genetic testing themselves;
- Had radiation therapy to the chest when they were between the ages of 10 and 30 years;
- Have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have first-degree relatives with one of these syndromes.

Lastly, according to the ACS, clinical breast exams are not recommended for breast cancer screening among average-risk women at any age.

In the United Kingdom, a national breast cancer screening program offers mammography to women between the ages of 50 and 70 years every three years. But Duffy, the lead author of the UK Age trial of 2015, noted that the current screening protocol for mammograms of every three years works well in women over the age of 50 years; but for younger women, more frequent screening would be needed.

Duffy goes on to say that "the results not only from our study but from others around the world suggest that this [3-year screening interval] would not be very effective in women under 50, due partly to the denser breast tissue of younger women and partly to the faster progression on average of cancers diagnosed in younger women….Some counties in Sweden, for example, offer screening to women under 50 at 18-month intervals, which seems more realistic."

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What Do We Tell Our Patients?

When speaking with patients, I let them know that there are in general, four camps regarding screening mammography for average-risk women and that they differ greatly:

Camp 1 is essentially ACOG and ACR with some nuanced differences: screening mammography yearly starting at age 40 and ending approximately mid-70s, although this is based on individual health and ability to withstand treatment regimens.

Camp 2 is held by the USPSTF, which is quite a bit different with screening mammography. This recommendation is not to start mammography screening in average risk women until age 50, and then to do it every other year.

Camp 3 is a model common in many European countries: screening mammography every three years, some starting at age 40 and others at 50.

Camp 4. No screening at all in average risk women, based on calculations from one of the leading US researchers on analyzing screening mammography data. As mentioned earlier, his conclusions are that it would be necessary to screen 2,500 women every year for 10 years to avoid one death from breast cancer.[3]

I also point out a few caveats to my patients. The first is that the data does not explain whether avoiding screening mammograms (and their potential for earlier detection) will result in exposing women to more aggressive treatments and the ensuing impacts on quality of life and adverse effects. The second is that breast cancer diagnosed in younger women, ages 40–49, tends to be more aggressive. So, screening mammography in this age group might in fact be more important than screening mammography after age 50 or so.

After sharing all the above information, I feel that my patients are reasonably well informed and can make their own decisions, with my support.

Final Comments

Here's the remarkable thing to me, and a rationale for NOT supporting routine annual screening in average risk women in this 40-49 age group: Remember, the researchers calculated that 1150 women needed to undergo screening in the age group of 40 to 49 years to prevent one breast cancer death, or about one breast cancer death prevented per 1000 screened. However, their point of view is that results indicate that screening before age 50 does prevent deaths from breast cancer, with a minimal additional burden of overdiagnosis. I can see their arguable point: we have the opportunity to prevent one cancer death per 1,000 women screened. But my point would be, that is a lot of women getting screening mammograms to ONLY prevent one death. And, could our efforts and money for education be better spent on the known and proven modifiable breast cancer risk reduction strategies: less alcohol, more exercise, reduce breast density, and avoid overweight/obesity.

Some readers might conclude that they won't recommend screening mammography at all or may instead choose to recommend breast thermography. Before going the route of thermography, I recommend the excellent article by Walker and Kaczor: "Breast Thermography: History, Theory, and Use."[14] My conclusion for that excellent review of the research is that breast thermography is not a reliable tool for screening or diagnosis.

The recent research pointing to more serious questions about the benefits vs harm of screening mammography in average-risk women has not caused me to stop recommending screening mammography or to suggest thermography. Instead, it has caused me to have an increased awareness that the mortality benefit is possibly modest and that my recommendations and my patients' decisions may in fact be a close call with trade-offs of modest benefit and modest harm. This highlights the need for us to make individual recommendations based on known risk factors for breast cancer, including obesity, more than seven alcohol drinks per week, a first-degree relative with breast cancer history, BRCA mutations, and the slight increased risk incurred after estrogen with progestin (and not necessarily progesterone and not estrogen only) use for more than three-to-four years in postmenopausal women. A systemic dose of estrogen and progestin is associated with one more woman with breast cancer per 1,000 women, per year. This is a very, very slight increased risk, and it's lower with estrogen alone or estrogen and bio-identical progesterone.

I always try to present information and recommendations in a manner that provides my patients with quality and up-to-date information and encouragement to decide what they are comfortable with and what choice they want to make for themselves.

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group (27 vs. 53 hours; p<0.001). Hospital mortality was 16.4% in the intervention group and 19% in the placebo group (p = 0.65).[4]

Eighty patients in China with sepsis or septic shock were randomly assigned to receive, in single-blind fashion, the Marik protocol or placebo for four days (with hydrocortisone continued for 7 days). Twenty-eight day mortality was nonsignificantly lower in the intervention group than in the placebo group (27.5% vs. 35%; 21.4% reduction p = 0.47). The mean improvement in the SOFA score at 72 hours was significantly greater in the intervention group than in the placebo group (3.5 vs. 1.8; p = 0.02).[5]

Two hundred five patients at 14 centers in the United States who had septic shock were randomly assigned to receive, in double-blind fashion, the Marik protocol or placebo for four days. Patients were enrolled within 24 hours of diagnosis. Median time from initiation of vasopressor therapy to initiation of study medication was 14.5 hours in the intervention group and 13.0 hours in the placebo group. The proportion of patients who died within 30 days was nonsignificantly higher in the intervention group than in the placebo group (34.7% vs. 29.3%; p = 0.26). There were no significant differences between groups with respect to mean change in SOFA score during the first 72 hours or incidence of kidney failure.[6]

One hundred patients in northern India diagnosed with sepsis (85% of whom had septic shock) received standard treatment and were randomly assigned to receive or not to receive (control group) the Marik protocol for four days or until discharge from the ICU (hydrocortisone was given for seven days or until ICU discharge, followed by a taper over 3 days). In-hospital mortality was nonsignificantly lower in the intervention group than in the control group (24% vs. 28%; 14.3% reduction; p = 0.82). Thirty-day mortality was 40% in the intervention group and 42% in the control group. Mean duration of vasopressor use was significantly lower in the intervention group than in the control group (75.7 vs. 96.1 hours; p = 0.01). The intervention group may have been sicker than the control group at baseline, since the admission diagnosis was septic shock in 92% of patients in the intervention group and 76% of those in the control group.[7]

Two hundred eleven patients at 10 intensive care units in Australia, New Zealand, and Brazil with septic shock were randomly assigned to receive the Marik protocol or hydrocortisone alone (control group) until cessation of vasopressor administration or until any of the other criteria for stopping the intervention were met, or for a maximum of 10 days. Patients were enrolled a maximum of 24 hours after they fulfilled the diagnostic criteria for septic shock. The median time from meeting eligibility criteria until the first dose of vitamin C was 12.1 hours. Patients in the control group were allowed to receive thiamine at the discretion of the treating physician. There was no significant difference between groups in the primary outcome measure, which was the time alive and free of vasopressor administration up to day 7. Ninety-day mortality was 28.6% in the intervention group and 24.5% in the control group.[8]

Possible Explanations for the Less-Than-Impressive Results

Although there was some evidence of a modest benefit from the randomized trials reviewed above, the results were far less impressive than those reported by Marik and by some other ICUs units around the world that adopted his protocol. Marik and associates have argued that the failure of the randomized trials to confirm their results may have been due to two factors.[9,10] First, the researchers may have waited too long to begin the treatment. In Marik's series of patients, almost all were given vitamin C, hydrocortisone, and thiamine within six hours of diagnosis. In contrast, among the studies that provided such data, many or most patients did not receive the Marik protocol until 12 or more hours after severe sepsis or septic shock was diagnosed. A retrospective cohort study of 206 patients treated for septic shock at a Wisconsin tertiary academic center found that ICU mortality was markedly lower among patients who received the Marik protocol within six hours of diagnosis than among those whose treatment was started six to 24 hours after diagnosis. Second, Marik's group argued that excessive amounts of fluid may have been administered in the randomized trials, and that giving too much fluid can greatly interfere with the beneficial effects of vitamin C, hydrocortisone, and thiamine.

Editorial

I am not an expert in the treatment of septic shock, so I am not in a position to evaluate the arguments made by Marik and colleagues. However, I am aware of many apparently effective treatments that yielded negative results in randomized controlled trials because the investigators deviated from the protocol used in the successful trials. Dr. Marik is a renowned authority on critical care, having written over 400 peer-reviewed journal articles, 50 book chapters, and four books on critical care. In recognition of his expertise and considering that countless lives could be saved if his observations turn out to be correct, researchers should conduct a large, randomized trial that adheres exactly to the methods Marik and associates found to be so successful.

Alan R. Gaby, MD

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Intravenous Vitamin C, Hydrocortisone, and Thiamine for Septic Shock: Update

In the October 2017 issue of the *Townsend Letter* I reviewed evidence that the combination of intravenous vitamin C, thiamine, and hydrocortisone can decrease mortality by nearly 80% in patients with severe sepsis and septic shock. These findings were reported in a retrospective study by Dr. Paul Marik and coworkers at Sentara Norfolk General Hospital (which is affiliated with Eastern Virginia Medical School). Beginning in January 2016, these doctors began administering this combination treatment to all patients with severe sepsis or septic shock.[1] Their protocol was instituted after the doctors observed a dramatic recovery in three patients with fulminant sepsis who were almost certainly going to die from septic shock. After treatment with intravenous vitamin C and hydrocortisone, all three patients recovered rapidly with no residual organ dysfunction. Hydrocortisone (without vitamin C) is frequently given to patients with severe sepsis, although a randomized controlled trial found that it does not improve outcomes.[2] Marik and associates included hydrocortisone in their protocol because of evidence that it may act synergistically with vitamin C in patients with severe sepsis. Thiamine was also given, because thiamine deficiency is common in septic patients and is associated with an increased risk of death.

The treatment protocol was as follows (all treatments were given intravenously): Vitamin C: 1.5 g every six hours for four days or until discharge from the intensive care unit (ICU). Hydrocortisone: 50 mg every six hours for seven days or until ICU discharge, followed by a tapering dose over three days. Thiamine: 200 mg every 12 hours for four days or until ICU discharge. The 47 patients who received this treatment (intervention group) were compared with a control group of 47 patients with severe sepsis or septic shock treated at the same hospital between June 2015 and December 2015. None of the patients in the control group received intravenous vitamin C or thiamine, but 60% received intravenous hydrocortisone at the discretion of the treating physician.

The hospital mortality rate was 8.5% (4 of 47) in the intervention group and 40.4% (19 of 47) in the control group (78.9% reduction; $p < 0.01$). None of the patients in the intervention group died of complications related to sepsis; rather, the four patients who died succumbed to complications of their underlying disease. The Sequential Organ Failure Assessment (SOFA) score decreased (improved) in all patients in the intervention group, and none developed progressive organ failure. Approximately two-thirds of the patients in each group had acute kidney injury at presentation. However, significantly fewer patients in the intervention group than in the control group ended up requiring dialysis or other renal replacement therapy (10% vs. 37%; $p = 0.02$). All patients in the intervention group were weaned off vasopressors at a mean of 18.3 hours after starting vitamin C, and the dose of vasopressors was typically reduced at two-to-four hours after the first vitamin C infusion. In contrast, nine patients in the control group required increasing doses of vasopressors and died of refractory septic shock. In the intervention group, renal function improved in all patients with acute kidney injury.

This report created great excitement, as it potentially represented a major advance in the treatment of critically ill patients. More than 50 medical centers around the world began using Marik's protocol, and many reportedly observed the same dramatic benefits.[3] Marik's report also led numerous research groups around the world to conduct randomized controlled trials to determine whether the benefits of vitamin C, thiamine, and hydrocortisone could be confirmed. The results of some trials were positive, while others found no benefit. In none of the randomized trials were the results even nearly as impressive as those reported by Marik and associates. Some of these studies are reviewed below.

Randomized Controlled Trials

One hundred thirty-nine patients in New Jersey with sepsis or septic shock were randomly assigned to receive, in double-blind fashion, the Marik protocol or placebo for a maximum of four days. The mean time that patients required vasopressors was significantly less in the intervention group than in the placebo

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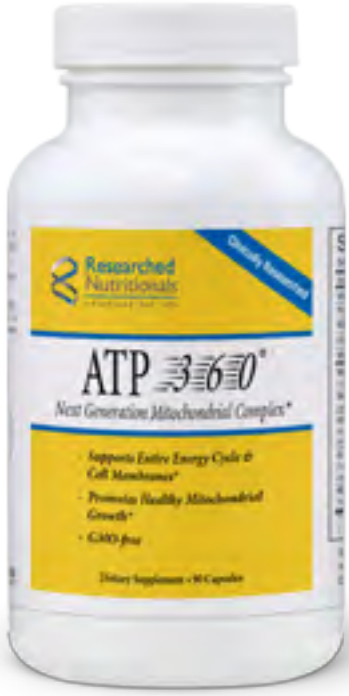

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