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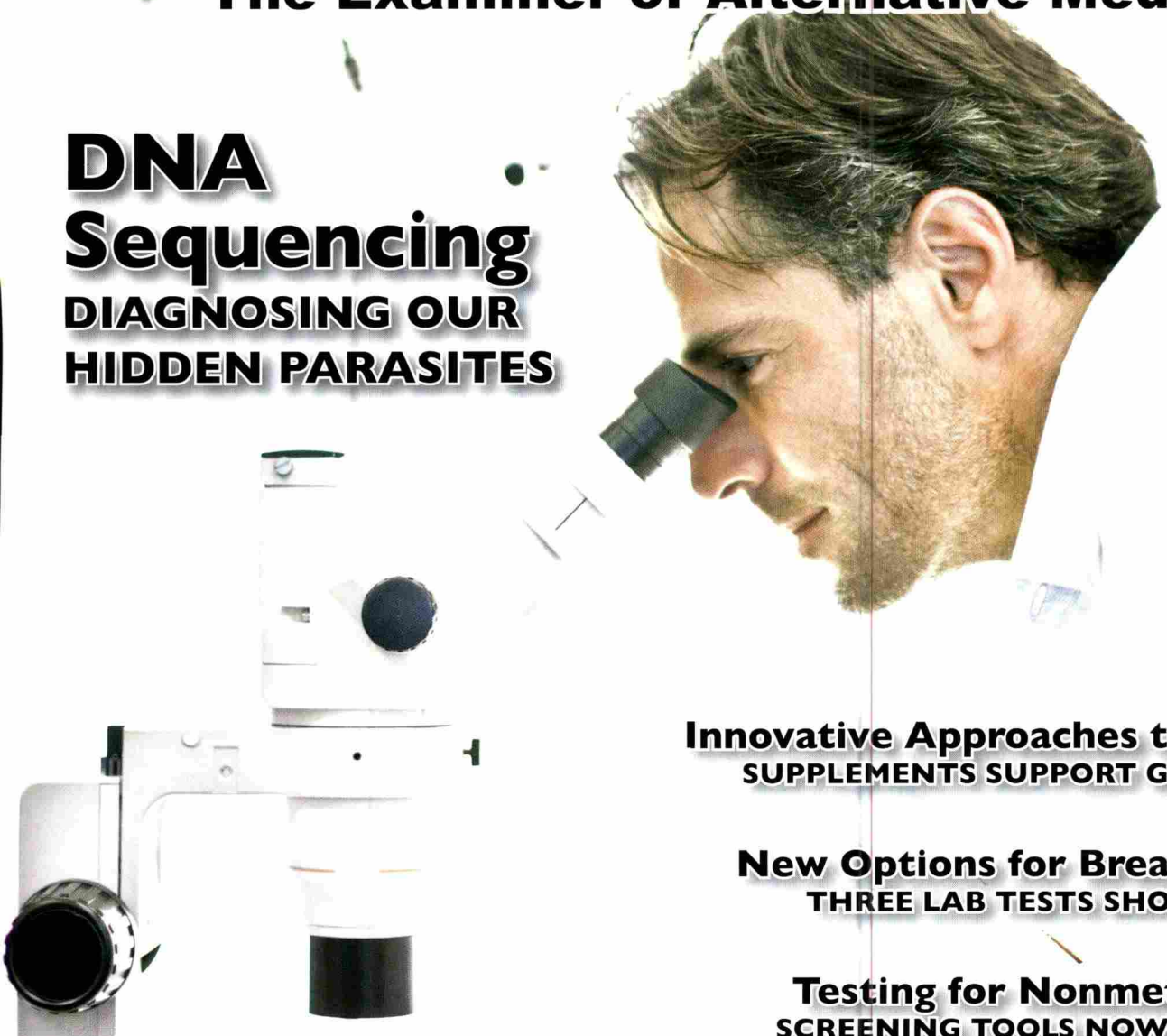

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From the Publisher

Shantaram

The holiday season is behind us. Perhaps a work of fiction might be just the thing for a doctor who seems to have no time to break loose and relax. A book that I just read had everything you might want from a novel – an adventure story based on the author's life, written surprisingly well for a first-time novelist, with character development and description that ignites the imagination far more than the proverbial "picture worth a thousand words." The plot is introduced in the first few pages: a man brought low by divorce, who is imprisoned for robbery to maintain his drug habit, escapes prison, takes on a new identity, lands in Bombay (Mumbai) as a fugitive attempting to remake his life.

Gregory Roberts, the author of *Shantaram*, did become addicted to heroin following a divorce, engaged in repeated armed robbery, and eventually was sentenced to 19 years. After boldly breaking out of prison, he fled from his native Australia to New Zealand, assuming a new name. One day when authorities grew too close, he decided that Bombay would be the right place to get lost in – a city of millions with multiple cultures, languages, religions, and ethnicities. *Shantaram*'s protagonist, assuming the first name of Lindsay, takes us into the mind, soul, and physicality of a person who is creating life anew. Lindsay is content with immersing himself in what Bombay offers; his experience with a smiling, contented slum-dweller, who escorts tourists to local hotel and eateries, develops into a very intimate friendship. Prabu introduces him to expats who are linked to a leading Mafia chieftain. Slowly learning Hindi, while becoming familiar with Bombay, "Linbaba" eventually is robbed of money and passport, and is compelled to survive at the edges. Moving to the slum that his tourist guide/taxi driver lives in, he becomes a doctor/healer of sorts for the families who live happily in the shanty village, even though he has no medical training – but he does have a good knowledge of first aid.

Linbaba's life unfurls like that of a character in the *Odyssey* or *Don Quixote*, except that his is rooted in1980s India.

continued on page 6 ➤

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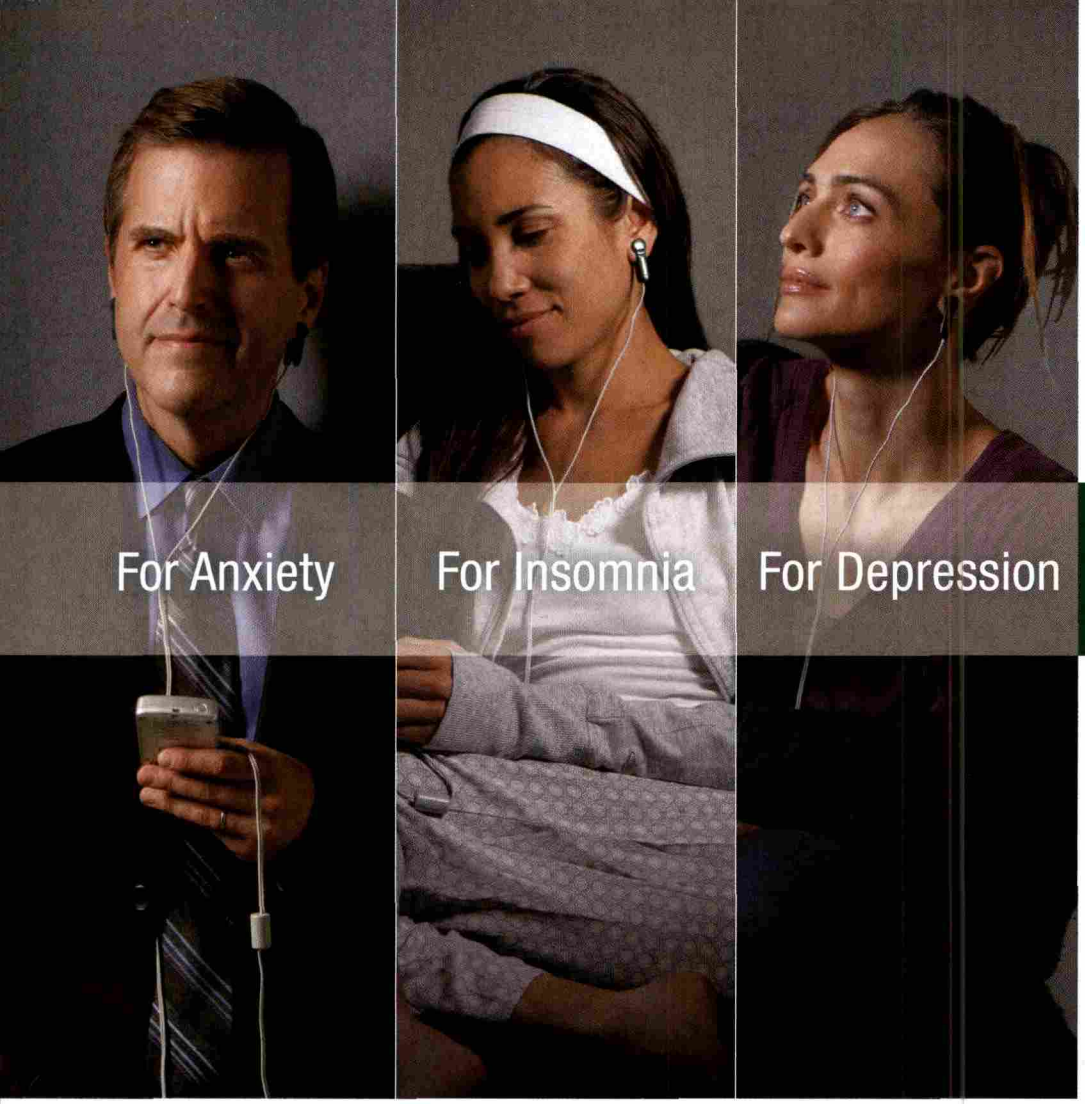

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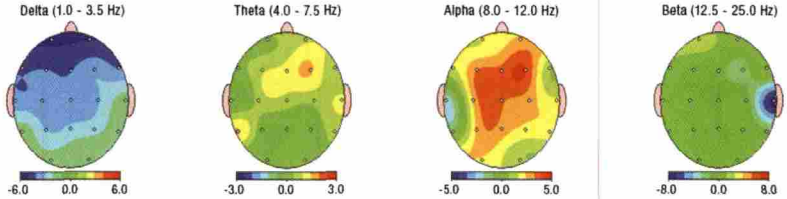

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*Kennerly R. Changes in quantitative EEG and low resolution tomography following cranial electrotherapy stimulation. PhD Dissertation, the University of North Texas. 2006;529 pp., 81 tables, 233 figures, 171 references.

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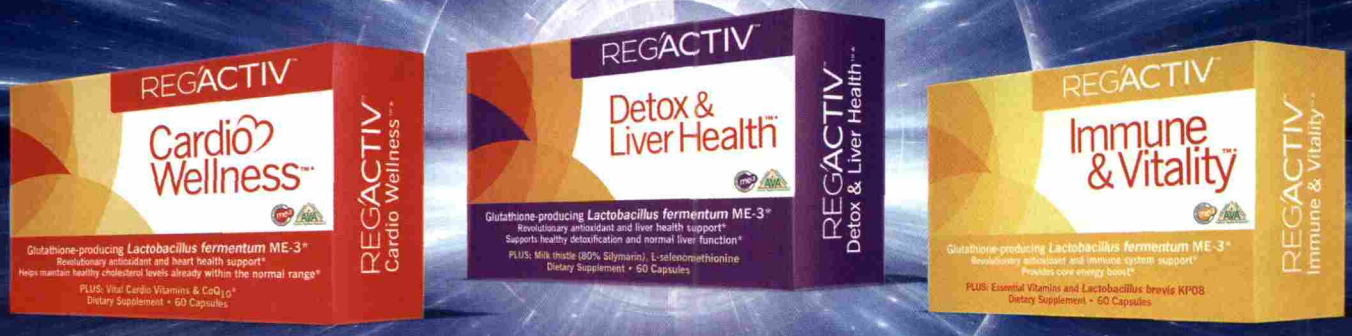

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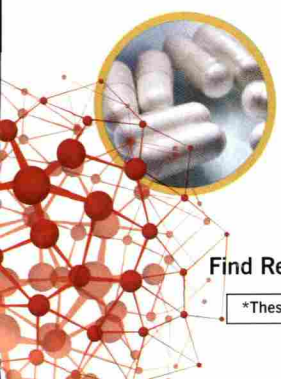

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Letter from the Publisher

➤ continued from page 1

Corruption in India is rampant; the right amount of bribery keeps the authorities at bay, if order is maintained. Illegal currency changing, money laundering, fraudulent passport bookmaking, gun trade, and drug sales are all part and parcel of Bombay life. Like it or not, Linbaba's life becomes entrenched in the Hindu and Muslim crime gang. What differentiates this from a *Godfather* story is the heart and soul that Linbaba/Roberts experiences in participating in so many bizarre situations – from the moblike violence targeted at a driver who carelessly injures another in a car accident, to the hellacious, penned-in, vermin-infected, starvation conditions facing anyone unfortunate enough to be jailed in Bombay. Linbaba copes well with adversity, even hopelessly pursing an unrequited love, but in every situation he is torn between the need to survive and see life from the eyes of the crime lord, slum dweller, and bureaucrat.

It is strange, yet invigorating, to find oneself sorting through the difficult moral and ethical choices of a fugitive. *Shantaram* makes the case that one can experience happiness while living in poverty. More importantly, it gives insight into how much of the thinking of gang members is not only rational but also heartfelt. *Shantaram* is an epic read, and one that never disappoints.

At What Point Are We Overutilizing Laboratory Testing?

I attended the Emerson Ecologics IGNITE conference in mid-November in lovely Carlsbad, California. The OMNI La Costa is one of those plush getaways that you imagine hosts meetings for executives of a Fortune 500 company, and the bedroom-deep bath with marble flooring did not disappoint. Jeffrey Bland, PhD, who has played a pivotal role in introducing and educating me (and most of you) on functional medicine, gave the keynote. After an early workshop on nutritional intervention in treating diabetes, the talks focused on the business of medicine. Among the speakers instructing us on tips to build our practice was Peter Osborne, DC, founder of Gluten Free Society, and author of the soon-to-be published book *No Grain, No Pain*. Osborne's work has focused on the deleterious role that gluten plays in people's health; his book reviews his clinical experience working with patients over the past 15 years. He promises that his book will expand upon Perlmutter's *Grain Brain* and Davis's *Wheat Belly*. Emerson Ecologics is to be congratulated for catering the weekend events with highly palatable – in fact, delicious – gluten-free, dairy-free fare.

Osborne's talk, however, was not focused on reviewing his rationale for counseling patients on being gluten free. He outlined his multipronged strategy for practitioners to substantially increase their incomes. Osborne is charismatic and persuasive and very steadfast on his message. He thinks that practitioners of functional medicine, spearheading the medicine of the future, deserve to be financially rewarded for offering patients the best diagnosis and treatment.

continued on page 8 ➤

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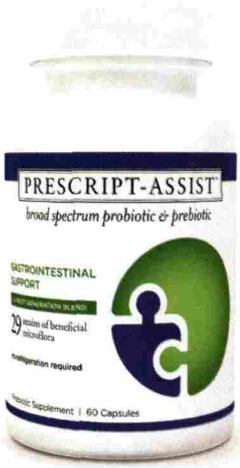

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[1] Pennisi, E. (2011). Body's Hardworking Microbes Get Some Overdue Respect. *Science, 330* (December 2010), 1619.

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Letter from the Publisher

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Osborne has developed "protocols" for diagnosing patients that require extensive functional medicine testing. Without that testing, Osborne contends, a practitioner will miss key biochemical and physiological abnormalities that are not diagnosed by most MDs. Osborne considers that all incoming patients need extensive laboratory testing including genomic analysis, toxic metal evaluation, comprehensive vitamin and mineral testing, screening for fungal toxins and candida, food allergy evaluation, comprehensive stool analysis with parasitology, and other assessments. Such laboratory testing is routinely done with all new patients. Based on the lab results, protocols are created requiring nutritional and diet changes, and costly supplementation orders are implemented. Due to difficulties with insurance company authorization, his laboratory services are directly billed to the patient, not insurance or Medicare.

The question is, is this functional medicine? Is functional medicine a diagnosis based on an array of out-of-range laboratory tests that are flagged and then automatically treated? How do the physical exam, history, imaging studies, and pathology factor into the functional-medicine diagnosis? If the patient is receiving prescription treatment, do the laboratory abnormalities alone provide the basis for modifying the medical treatment? What about legitimate concerns about erroneous laboratory testing?

Elsewhere Alan Gaby, MD, has argued that less testing is better; we should use our clinical acumen to diagnose and treat the patient. Horror stories abound about patients becoming alarmed after being informed of a diagnosis based on incorrect pathology and imaging reports. While erroneous functional medicine testing is unlikely to cause alarm, for example, a wrong vitamin B12 level, generating a massive compilation of out-of-range test scores that may not be fully understood does not yield a "true" medical diagnosis. From a medical legal basis, the lab abnormalities will not counter malpractice based on failing to provide usual and customary care.

Practitioners may generate fabulous incomes based on ordering extensive lab testing leading to protocols requiring purchase of quantities of supplements, but this is income-based medicine, not functional medicine.

Is the Shutdown of Vemma the Death-Knell for MLM Vitamin Companies?

On August 27, 2015, the Federal Trade Commission (FTC) shut down Vemma, a multilevel-marketing company. Vemma touts itself as a premier producer of energy drinks and other nutritional supplement products. Like other MLMs, Vemma sales depend on signing up people who contract to purchase a package of supplements monthly. In order for the member to earn income, other individuals are recruited to become "downline" members and contract to buy monthly supplements. And, like other MLMs, the compensation

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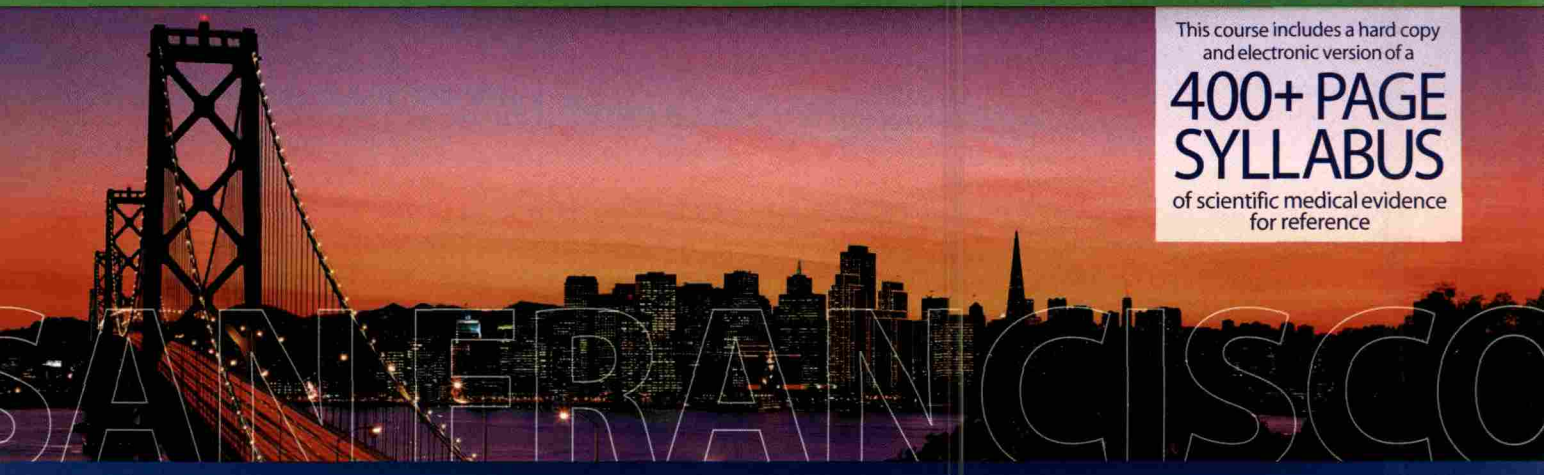

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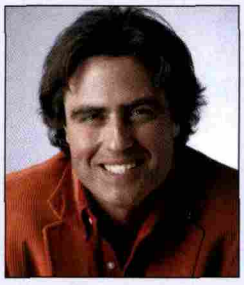

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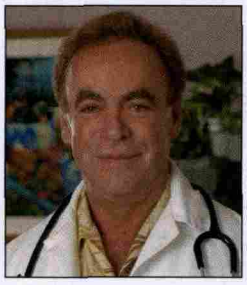

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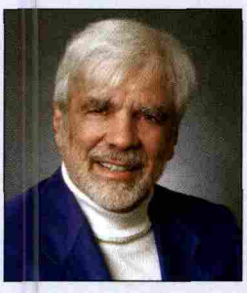

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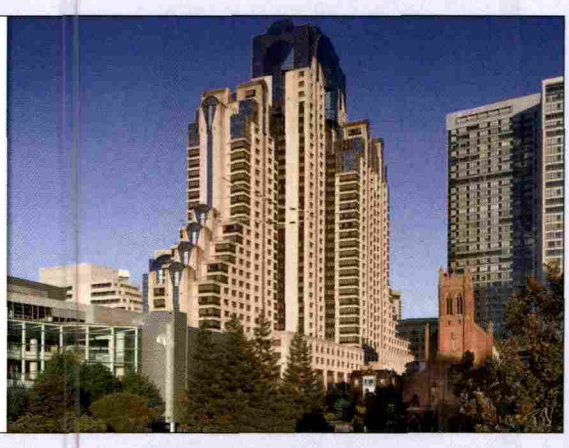

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Letter from the Publisher

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formula is set up to offer a trivial income for the downline member, while upline members who have signed up the downline earn the lion's share of the compensation. Typically for MLM companies, most individuals discover that they are unable to sign up a sufficient number of downline members to actively recruit new members expanding the downline. Once the member fails to achieve an active downline, he or she quits, not wishing to pay the expensive prices for the purchase of energy drinks.

I would wish to report this story as a dispassionate editor, but I was enticed to become a member of the Vemma organization and signed up for a membership including a monthly shipment of supplements. The upline for me was not a consumer patient but an integrative physician whom I respected highly. I did think that the Vemma daily drink was beneficial as a supplement. However, like most MLM products, it was expensive. In addition, not long after I became a member, Vemma's nighttime sleep aid drink – the primary draw for my participation – was withdrawn due to FDA oversight. One or more ingredients in the product were found to cause liver toxicity. For me, that drink's discontinuation, as well as the general problems with any MLM participation, led me to cease using the products. Of course, I never succeeded in receiving compensation for selling Vemma.

Vemma products are currently unavailable until the company has its day in court. Vemma is a private MLM company. Of greater concern, at least for stock market investors, is the fate of one traded company. Herbalife has been in business as long as I have been in practice. Not a few of my patients have used Herbalife supplements. Part of the problem with MLM participants is that they are convinced that their supplements are superior to other products in the marketplace. When the doctor advises the need to use different nutrient combinations, there is resistance on the patient's part to either stoping the MLM supplements or using formulations that are not part of their MLM product line. My experience with patients who have been active in Herbalife is that they could fund a portion of their monthly costs for purchasing supplements through their downline sales. They did not succeed in supplementing their income.

Herbalife is now wrangling with a hedge fund manager who made a giant bet 2 years earlier that the FTC will shut it down for being an illegal pyramid scheme. What is the difference between multilevel marketing and an illegal pyramid scheme? Not much. However, when the FTC attempted to claim that Amway was a pyramid scheme in the 1990s, it failed. Now the FTC is claiming that Vemma is a pyramid scheme and it also has Herbalife in its sights.

We may be seeing the beginning of the end of MLM supplement companies.

continued on page 22 ➤

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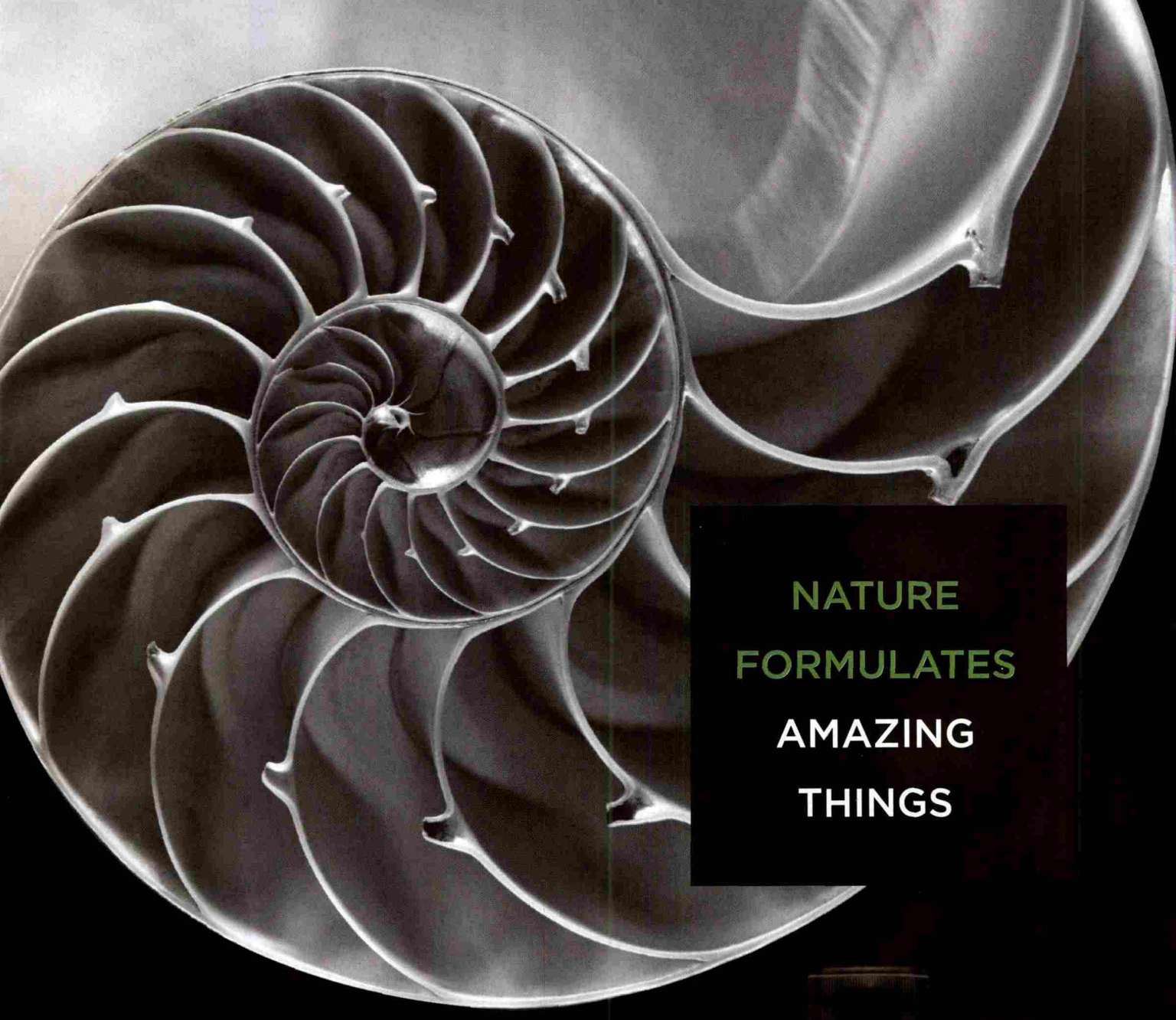

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The Current State of Mental Health Care in the US: Conventional vs. Holistic

by Ira L. Goodman, MD, ABIHM, FAARM

One of the many advantages of living in San Diego is the plethora of medical meetings that rotates through. Last month I was invited to attend two back-to-back international mental health conferences, which were remarkable more for their contrasting styles than for their similar content.

The first was Psych Congress, which was held at the San Diego Convention Center. It is one of the two large psychiatric meetings held annually and it attracted over 3000 attendees, mostly conventional psychiatrists. It was, as expected, heavily sponsored by Big Pharma, including lavish exhibits hawking every conceivable psychotropic drug in all their varieties. The exhibit hall must have taken days to set up with custom carpeting, cappuccino stands, "food" stands (mostly items that I would never consider consuming), large video displays, attractive reps summoning passersby into their areas, and even street artists performing – anything to get the attention of their marks – the ones writing the prescriptions. Even the poster area was basically one study after another comparing one drug with another, praising the sponsor's product. There was one exhibit featuring a folic acid product, but other than that there was basically no mention of anything like diet, nutraceuticals, HRT, energy medicine, exercise, or lifestyle in the exhibit hall. However, the lectures did have token coverage of lifestyle, and one even mentioned the microbiome, but it was very rudimentary. There was one interesting moment when a high-functioning schizophrenic got up in front of 2000 psychiatrists and told her life story, which included multiple meds, hospitalizations, discrimination, and accomplishments. She received a standing ovation when she thanked the psychiatrists. The patient, remarkably, graduated from Yale Law School and wrote a book. Apparently there are rare schizophrenic patients who manage to overcome this disease. I also learned something about the drug prazosin, which is an alpha blocker typically used for BPH and hypertension but can be used off label for PTSD and insomnia at very low doses. There are now studies supporting this off-label indication. Other than that, I could not wait to get out of this conference. It was biased and commercial – not an atmosphere of intellectual discovery or honesty.

The second meeting was the Integrative Medicine for Mental Health (IMMH) conference, an annual event attracting about 400 attendees from a variety of disciplines. I fully admit to a functional medicine bias, but this conference was one of the best I have been to in years. Almost every lecture was on point, informative, and even enlightening. The exhibits were a cornucopia of useful devices, supplements, home aids, and cutting-edge new companies displaying their wares. Each lecture was followed by a lively question session that usually took 30 minutes or more, as well as audience discussions in separate groups. There were many fascinating topics covered, including integrative medicine for depression and anxiety, HRT and metabolic treatments for mental health, food allergies, the microbiome's effect on mental health, lithium as an agent for cognitive function and mood, the latest thinking on autism, metabolic disorders mimicking psychosis and other mental disorders, multiple sclerosis, cognitive decline, and a new inflammatory marker PLA2. I cannot possibly discuss all the lectures adequately in this relatively small report, but I will mention a few items of special interest. One is the increasing use of low-dose lithium (1–20 mg p.o.) for many different mental disorders, including cognitive decline, mood elevation, manic depression, and anxiety. As most readers probably know, lithium has been used for years by conventional psychiatry for bipolar disorder in doses of 300 to 600 mg/d with several significant side effects. However, these side effects can be mitigated with low doses of the drug, and lithium levels are not even measurable in the serum. Nevertheless, clinical benefits are almost always evident, including the avoidance of standard-of-care drugs that can be very dangerous for a number of reasons. The beverage 7UP used to have low-dose lithium in it until 1950. (Lithium has a molecular weight of 6.94, so it was rounded up to 7 and the beverage was frequently advertised as a mood elevator, hence the name 7UP.) In areas of the country with high lithium soil content, epidemiological studies show fewer suicides and victims of depression. It is a naturally occurring element typically found in hair samples even without supplementation. Several physicians (including Jonathan Wright) have been using it for cognitive decline prophylaxis and mood elevation. This mineral is worthy of any functional medicine practitioner's tool kit.

Another noteworthy item that I learned about at this conference was the new inflammatory marker PLA2 (phospholipase A2), which is measured in the urine by the Great Plains Laboratory (although other labs are sure to follow). There are 10 types of PLA2 produced, 9 of which are measurable in the urine and only 1 measurable in the serum since the molecule is too large to make it through the kidneys (lipoprotein-associated PLA2). The LpPLA2 that most functional medicine practitioners and some cardiologists use is the one associated with vascular inflammation and is supposed to portend a CV event. The other 9 PLA2 molecules can indicate brain inflammation as well as inflammation elsewhere. The exciting thing is that a new product called CDP choline can reduce high PLA2 levels and presumably brain inflammation as well. It can be used in many neurological degenerative conditions and even as a prophylactic nutraceutical for brain health.

This is cutting-edge material developed and researched by Dr. William Shaw, who gave several clear and convincing lectures at the IMMH conference. His work on the association between Tylenol (acetaminophen) and autism is groundbreaking and well worth viewing. Dr. Daniel Amen also gave a well-received lecture on his work with SPECT brain scans, pointing out that psychiatry is the only specialty that still practices as it did over 100 years ago without looking at the organ that it claims to be expert in. Dr. Neal Rouzier gave an excellent talk on the association of hormone deficiencies (specifically testosterone and thyroid) with a number of mental health issues.

I was a little disappointed that neither meeting mentioned the work of Robert Whitaker that he describes in his two books, *Anatomy of an Epidemic* and *Psychiatry Under the Influence*. Whitaker postulates that the introduction of psychotropics (starting with Thorazine in the 1950s) resulted in dramatic increases in the incidence and severity of mental health disorders due to the perturbation of the neurotransmitter levels which results in permanent changes in receptor density and sensitivity in the brains of treated patients. This creates a situation that leads to greatly increased recurrences of the mental disorders that the drugs temporarily ameliorate. This is exactly what is seen epidemiologically. Neither meeting mentioned the work by Irving Kirsch, PhD, in his book *The Emperor's New Drugs*, in which he proves that psychotropics work no better than placebos. A more complete description of these two books is beyond the purview of this article, but I wanted to mention them here since they are highly relevant to any serious student of this subject.

As an advanced fellow in functional medicine, board examiner, and author, I found these two conferences fascinating. Clearly my bias is toward less invasive, less toxic, and more effective treatments in anything I am called upon to treat. This should be the same motivation of any physician, but the forces of industry create a cognitive dissonance that seems almost impossible to overcome. It is my hope that the readers of this article will be motivated to resist commercial influences and make logical choices based on evidence and unbiased thinking. ◆

In Memoriam: Nicholas J. Gonzalez, MD

by Linda L. Isaacs, MD

I met Nick Gonzalez on October 31, 1983, on the first day of my internal medicine rotation as a third-year medical student at Vanderbilt University Medical School; he was the intern on the team. He was striking: a fast-walking, fast-talking New Yorker, brilliant and witty. He was incredibly efficient, one of the first interns to be able to leave the hospital at the end of the day, but his work was always done and his patients loved him.

On the last day of the rotation, he asked me for a date. Three months later, I contacted him and we met for lunch. That was when I began to learn more about him: a former journalist, he had developed an interest in nutrition from interviewing various luminaries in the field and had decided to go to medical school. While at Cornell Medical College, he met a dentist, William Donald Kelley, who had developed a nutritional approach to cancer that included dietary modifications, large quantities of pancreatic enzymes, and detoxification measures such as coffee enemas. Dr. Kelley invited Nick to investigate his work, and Nick found large numbers of patients with appropriately diagnosed cancer who had done extraordinarily well. However, Nick's research project found no favor with the faculty at Cornell, so he had not gotten the recommendations needed to get into the highly competitive residency programs in his beloved New York City. He wound up in Nashville, Tennessee, where he clearly felt out of place. And every day, he pushed himself to get home as quickly as possible so that he could make a few calls, write a few letters, to continue his Kelley project.

As we got to know each other in the following weeks, I heard more about the patients whom he had discovered in Dr. Kelley's practice. He told me of a patient with widely metastatic prostate cancer, admitted to the hospital for pain control, who after his discharge began the Kelley program; years later, he was completely well and playing in a ragtime band. Another patient, who had uterine cancer metastatic to the lungs, had a repeat chest X-ray after several years on the Kelley program that showed no evidence of disease. And there were many more, all compelling, all making it very clear to me why this brilliant man had put his career on the line to follow up with this work.

In July 1984, Nick moved to Oklahoma City to pursue a fellowship in immunology under the direction of Dr. Robert A. Good, the former president of the Sloan Kettering Institute and Nick's mentor as he worked on his Kelley project. It was unusual to start a fellowship immediately after an internship, but Dr. Good promised Nick that he would be able to devote much of his time to his study of Dr. Kelley's work. Meanwhile, I was completing medical school in Nashville, and Nick and I stayed in touch by phone. Nick frequently visited Dr. Kelley in his office in Dallas, and Nick and Dr. Good even saw one of Dr. Kelley's patients in their clinic during that time.

Nick and I were married in May 1985, a week after I graduated from medical school. Dr. Good was the best man at our wedding; Dr. Kelley attended the ceremony. We moved to Florida, where Nick completed his fellowship with Dr. Good at All-Children's Hospital in St. Petersburg, while I did my internship in internal medicine at the University of South Florida. Nick continued his research on Dr. Kelley, assembling his findings into a lengthy monograph, then submitting some of the individual case reports to various medical journals for publication. The reception took both Nick and Dr. Good aback. A number of editors thought that the results had to be fraudulent despite the extensive documentation in the provided medical records. Some warned Dr. Good that his reputation would be tarnished by continued association with this project. It became obvious that Dr. Good could not help Nick get the results published

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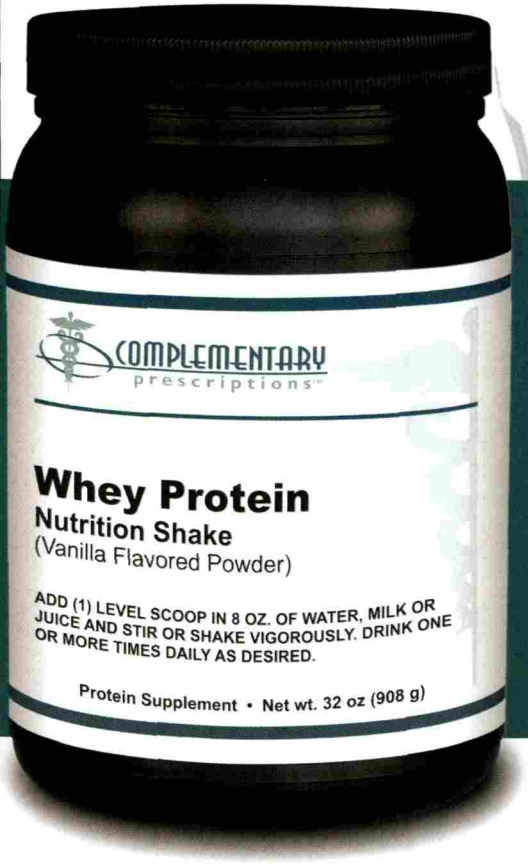

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Nicholas J. Gonzalez, MD

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or get funding for further research, so Nick made plans to leave at the end of his fellowship in June 1986.

Meanwhile, my own health was faltering. In medical school, I had begun to have fatigue and difficulty concentrating, and while I managed to complete my internship and pass my licensure examinations, by 1986 I had a full-blown case of what would later be called chronic fatigue syndrome. I resigned from my residency program, and Nick and I headed north to spend time with Dr. Kelley, who had moved to Pennsylvania to live with an ardent supporter of his work, Dr. Carol Morrison. The plan was that Nick would complete his Kelley monograph, get a literary agent, and get the work published, while I would begin the Kelley program myself to get well.

At this point, Dr. Kelley's work was in shambles. He had been involved in the treatment of the actor Steve McQueen and was pilloried in the press when McQueen died. He had trained a network of practitioners to administer his program, but their success in implementing it had been widely variable. He had lost faith in the company which manufactured the supplements that he recommended. Patients still contacted him looking for treatment, but he was increasingly fearful of proceeding.

Nick's efforts to get the monograph published did not go well. Even though he had a reputable agent, some editors at publishing houses still questioned the truthfulness of the patient histories, despite the inclusion of the patients' medical records. Other editors said that the medical divisions of their publishing companies would have serious concerns if the book was accepted. As Dr. Kelley's hopes of the book's publication died, his behavior became increasingly strange. He dispatched letter after letter to his mailing list, his paranoia becoming increasingly evident, and he became suspicious of Nick and me. Finally, Nick decided that we should leave and try to recreate the work independently, as Dr. Kelley was clearly not functional.

We left for New York City in the spring of 1987, to live in Nick's mother's house. We had no money, no office, and no place to refer prospective patients to purchase the supplements that they would need. With characteristic doggedness, Nick set to work. He investigated the manufacturing processes and potencies of various pancreas products and decided which one was most likely to work. He found supplements with which we could recreate, as closely as possible, the customized programs that Dr. Kelley had devised for different types of patients. The family of a former Kelley patient was willing to serve as the distributor of supplements to the patients. A contact from Nick's journalism days offered office space, first at night and on the weekends, then during regular office hours. And a number of alternative cancer referral sources, such as the Cancer Control Society, helped get the word out that Dr. Nick Gonzalez was offering his version of Dr. Kelley's work from his office in New York City. Dr. Robert Atkins had Nick on his radio show multiple times, and this too helped recruit patients.

Meanwhile, I continued my efforts to improve my own health, and with the better-quality products that we were using, I finally felt well enough to resume my interrupted medical residency in June 1989. I completed it without difficulty and passed my internal medicine boards in 1991. During my residency, our marriage disintegrated, in retrospect I believe due partly to communication issues stemming from our very different cultural backgrounds. We also had a few too many 2 a.m. conversations about enzyme chemistry; we both eventually remarried to people outside the medical profession, limiting how much we could talk shop during "off" hours. But just as many divorced parents forge a new working relationship for the good of their children, so our joint commitment to our work helped us weather the divorce and build a new friendship. After I completed my residency, I joined him in his practice, and in 1993 we moved to a new office space where we could both see patients.

By this time, Nick had started to accumulate his own long-term success stories among his patients. I remember particularly a patient with breast cancer metastatic to the liver and brain, with documented resolution of disease on the therapy; and another patient with renal cancer who had a metastatic lesion the size of an egg protruding from his skull, whose disease regressed after he began his protocol. In articles and at conferences, Nick discussed his and Dr. Kelley's successes, and this drew attention from both supporters and critics. In 1993, he was invited to present cases at the National Cancer Institute by the associate director of the Cancer Therapy Evaluation Program, as part of its early effort to consider nontraditional therapies. Nick and I compiled the records for 25 cases, with a variety of cancer types. After the session, the associate director suggested a pilot study with pancreatic cancer, though no funding for such a study was volunteered.

Shortly thereafter, the Nestec Corporation (Nestlé) provided the funding and the trial began. But around the same time, someone filed a complaint with the state medical board, and this gave it the opening to begin a lengthy investigation of Nick's competence. Hundreds of thousands of dollars in legal bills later, the state board placed Nick on probation pending evaluation and "retraining." The evaluation process revealed only that Nick's handwriting was terrible, and to the office staff's relief, he began to use a dictation service. And the oncologist who subsequently sat in on Nick's patient visits as part of the "retraining" became a lifelong friend and supporter. Nick completed the requirements of the state board and the probation ended, but the damage to his reputation remained.

Meanwhile, the pilot study for patients with pancreatic cancer was under way. One of the patients on the trial was an employee of Procter & Gamble. Intrigued by how well this patient did, the vice president for health care contacted the office, and eventually Procter & Gamble entered into a research agreement with Nick, providing welcome scientific input. During that time, we were able to improve the process by which the enzymes for our program were made.

The pilot study ended in 1998, and the results were published in the June 1999 issue of *Nutrition and Cancer*.[1] Of 11 patients followed in the trial, 8 suffered stage IV disease.

Nine (81%) lived 1 year, 5 lived 2 years (45%), 4 lived 3 years (36%), and 2 lived longer than 4 years. In comparison, in a trial of the drug gemcitabine, of 126 patients with pancreatic cancer, not a single patient lived longer than 19 months.[2]

Our happiness at the acceptance and publication of this article was muted by other concurrent events. In the 1990s, Nick lost two malpractice lawsuits. The more serious of the two involved a woman with uterine cancer who had called the office twice to ask for an appointment and had been turned away with instructions to get surgery. Months after her initial contact, she finally did, and was found on hysterectomy to have an adenocarcinoma with papillary and clear cell features, a particularly aggressive type of cancer. She was offered entry into a clinical trial for high-risk and recurrent endometrial cancer, but instead contacted the office and became Nick's patient. Around 9 months later, she developed back pain and was found to have a metastatic tumor in the spine which was surgically removed. She discontinued her nutritional program and began chemotherapy, and subsequently went blind. Her lawyers claimed that had she entered the clinical trial that she was offered and received treatment immediately, instead of waiting until a recurrence was found, she would never have had the recurrence and would not have gone blind.

Some facts about the case are not included in this scenario. The pathologist who reviewed the slides from the surgically removed tumor in the spine stated that what was present was necrotic debris, and that no viable cancer was seen. And most remarkable was the patient's survival. Metastatic uterine cancer of any variety is a rapidly terminal disease, regardless of treatment. Yet the patient was still alive at the time of the malpractice trial, years after the spinal tumor was found; she eventually passed away nearly 20 years after her original diagnosis.

The records are compatible with the patient's having had undiagnosed metastatic disease to the spine at the time the uterus was removed, with the enzyme treatment having rendered the disease necrotic, the necrotic tissue becoming inflamed and symptomatic, and the subsequent chemotherapy unnecessary. But the jury found in favor of the plaintiff, with an award in excess of Nick's malpractice policy.

Nick eventually won a legal malpractice case against the attorney who had ineptly defended him. But again, the damage to his reputation and to his finances had been done. He was forced to declare bankruptcy and to sell the apartment that he loved. The medical practice survived, but it was a horribly stressful time, with financial struggles, with endless paperwork demands from attorneys, with reporters call to request interviews, and with articles in the press both positive and negative.

In the midst of all this, in 1998, the National Cancer Institute, in conjunction with the National Center for Complementary and Alternative Medicine, approved funding for a large-scale controlled trial evaluating our approach against chemotherapy, again in patients diagnosed with pancreatic cancer. Unfortunately, despite our initial enthusiasm for the project, it was ineptly managed by the academicians involved, who published an article about it without our consent in 2009.[3] Nick's book *What Went Wrong: The Truth Behind the Clinical Trial of the Enzyme Treatment of Cancer* details the problems with the trial quite thoroughly, and spells out why we did not think the published paper's results were valid.[4]

I recently wrote an article about the problems in the study's design that doomed it from the outset.[5] Even as I wrote it, I wondered why we had ever agreed to proceed. But in the wake of Nick's sudden death, I have found myself thinking back to the 1990s and to all the terrible things that we endured back then. Had Nick not been subjected to the injustices of the state board investigation and a malpractice suit by a woman whose life he may well have saved, had we not been coping with an onslaught of unnecessary work brought on by these issues, we might have had the clarity of mind and the willpower to fight for a better trial design.

However, even after the bitter disappointment of the clinical trial, we continued to treat patients, with continued success. Nick's book about Dr. Kelley's patients was finally published, and Nick had been working on a book of case reports at the time of his death.[6] In the days afterwards, I heard from patients of mine with condolences; a patient with melanoma with biopsy-proven lung metastases, now 4 years out from that diagnosis, another patient with pancreatic cancer now 14 years from diagnosis. I have seen many more patients, his and mine, whose lives have been transformed by the methods he fought so hard to preserve and study. These patients and their stories help give me the determination to do what I can to keep Nick's memory alive, and to continue the work so that perhaps a future generation of researchers can pick up where we left off.

Nick rarely spoke publicly about the obstacles and injustices that he had to deal with as he pursued his work. But I think it is important, as a witness to many of them and as a part of his legacy, to chronicle them. He had many opportunities to turn aside and pursue a more conventional and comfortable path as an academic researcher. He never did; he fought on for what he believed was right, and for that I will always honor him.

Notes

1. Gonzalez NJ, Isaacs LL. Evaluation of pancreatic proteolytic enzyme treatment of adenocarcinoma of the pancreas, with nutrition and detoxification support. *Nutr Cancer*. 1999;33(2):117–124.
2. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413.
3. Chabot JA, Tsai WY, Fine RL, et al. Pancreatic proteolytic enzyme therapy compared with gemcitabine-based chemotherapy for the treatment of pancreatic cancer. *J Clin Oncol*. 2010;28(12):2058–2063.
4. Gonzalez NJ. *What Went Wrong: The Truth Behind the Clinical Trial of the Enzyme Treatment of Cancer*. New York: New Spring Press; 2012.
5. Isaacs LL. Research battles: survival tips from a veteran. *Integr Med Clin J*. In press.
6. Gonzalez NJ. *One Man Alone: An Investigation of Nutrition, Cancer, and William Donald Kelley*. New York: New Spring Press; 2010.

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National Institutes of Health Awards Funds for Planning a Second Chelation Study

The National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH) has awarded $800,000 to Mount Sinai Medical Center of Florida and the Duke Clinical Research Institute to initiate a planning year for the second Trial to Assess Chelation Therapy (TACT2). Chelation is a process by which a medication, such as edetate disodium, can "grab" toxic metals such as lead or cadmium within the body – present in most individuals – and allow their removal through the urine.

Planning for TACT2 follows up on the positive results of TACT, an NIH-sponsored multicenter, double-blind efficacy trial, which took place from 2002 to 2012 and was conducted in 134 sites across the US and Canada. The study chairman was Dr. Gervasio Lamas, chairman of medicine and chief of the Columbia University Division of Cardiology at Mount Sinai Medical Center in Miami Beach, Florida. During TACT, 1708 heart-attack patients were randomized to receive 40 infusions of a 500 mL edetate disodium-based chelation solution or a placebo infusion, with a second randomization to an oral vitamin and mineral regimen or an oral placebo.

TACT demonstrated a reduction in recurrent heart events in patients who already had sustained a heart attack. Recurrent heart events measured in the study were death, heart attack, stroke, coronary revascularization, and hospitalization for angina. In a subgroup of 633 diabetic patients, there was evidence of even larger benefit than seen in the overall trial, with a 41% reduction in recurrent heart events and a 43% reduction in deaths.

"A subgroup analysis of the original trial results suggests major benefit in diabetics with cardiovascular disease. The disease burden in this group of

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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.

patients is devastating, so a replication of these findings is of some urgency," said Josephine P. Briggs, MD, director of the National Center for Complementary and Integrative Health.

The TACT clinical results were presented at the American Heart Association's Scientific Sessions in 2012 and published in the *Journal of the American Medical Association* in 2013, *Circulation: Quality and Outcomes* in 2014, and the *American Heart Journal* in 2014.

"The hallmark of science is the ability to replicate results," said Lamas. "Therefore, in collaboration with the Duke Clinical Research Institute and NIH scientists, we are planning TACT2."

"The results of TACT were both surprising and intriguing. I am very pleased that TACT2 is building on these findings to determine if they can be replicated in diabetic patients who have experienced a myocardial infarction – a particularly high risk group of patients in need of effective therapy," said Eugene Braunwald, MD, Distinguished Hersey Professor of Medicine at Harvard Medical School and Faculty Dean for Academic Programs at Partners Healthcare Systems.

Plans for TACT2 include targeting the population of patients who received the greatest benefits from edetate disodium treatment – those with a prior heart attack and diabetes. The NCCIH has approved a planning year for TACT2. If the planning phase is successful, the study team will request support for the full scale trial, in order to replicate the clinically significant results of TACT in patients with diabetes. By narrowing the patient population, TACT2's focus will be more precise and refined, allowing researchers to reduce the size, duration and cost of the trial relative to TACT.

"The excess heart disease that continues to accompany diabetes is a major public health problem with enormous human and economic costs. If the original findings in the TACT study are replicated in TACT2, we will have a new and powerful weapon to ameliorate heart disease in diabetes," said David M. Nathan, MD, director of the Diabetes Center at Massachusetts General Hospital and a professor of medicine at Harvard Medical School.

The planning phase for TACT2 will include finalizing the research protocol for the trial and having it approved by the NIH. During this phase the investigators will also identify the clinical research sites that will enroll patients and finalize enrollment targets for the trial. If the implementation phase is approved, the resulting trial will pragmatically and efficiently retest the TACT results.

"Unless we can show a consistent effect across the two TACT Trials and establish a similar mechanism to deliver the treatment safely, it will be difficult for chelation to enter the mainstream of other cardiovascular therapies," Lamas said.

TACT2 planning activities will be undertaken by a study team including a clinical coordinating center led by Lamas and a data coordinating center led by Kevin J. Anstrom, PhD, and Daniel B. Mark, MD, MPH, from the Duke Clinical Research Institute (DCRI).

"Although not approved by the Food and Drug Administration for treating heart disease, chelation therapy has been used for nearly 60 years and has generally been believed by conventional medical practitioners and cardiologists to be without value, though TACT suggested otherwise. A definitive answer on chelation therapy that will be embraced by the cardiology community will require this additional research," said Lamas. Added Mark from the DCRI Coordinating Center, "Funding for the planning phase of TACT2 is critical, as it is the first step toward replicating what we found in TACT."

This research is supported by cooperative agreements AT9149 and AT9150 from NIH's National Center for Complementary and Integrative Health.

For more information on the planning phase of TACT2, please contact Dr. Lamas at gervasio.lamas@msmc.com.

About Mount Sinai Medical Center

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About the Duke Clinical Research Institute (DCRI)

The DCRI is the largest academic research organization in the world, with a mission to develop and share knowledge that improves the care of patients through innovative clinical research. The DCRI conducts groundbreaking multinational clinical trials, manages major national patient registries, and performs landmark outcomes research. DCRI research spans multiple disciplines, from pediatrics to geriatrics, primary care to subspecialty medicine, and genomics to proteomics. The DCRI also is home to the Duke Databank for Cardiovascular Diseases, the largest and oldest institutional cardiovascular database in the world, which continues to inform clinical decision-making 40 years after its founding.

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Letter from the Publisher

➤ continued from page 10

Q Fever Following Anti-Aging Treatment with Sheep Fetal Cells

The spas in Europe have had a long tradition of providing healing water therapies much favored by the rich and famous. Since the 1930s, a few clinics in Switzerland and Germany have administered ovine or bovine fetal cells promising to rejuvenate the body. Paul Niehans, a Swiss doctor, who injected live sheep cells directly in the buttock, was one of the developers of cell therapy. Cells harvested from the sheep's brain, liver, spleen, kidneys, pancreas, heart, intestine, and thymus were thought to activate a healing effect on the patient's ailing organs. Niehans later used injections of lyophilized cells, considering them as effective as live cells. His patients included Pope Pius XII as well as Charlie Chaplin. Although Niehans achieved great acclaim, writing about his treatment in *Die Zellulartherapie* (*Cellular Therapy*, in German and English), he did not have any published studies.

In 2014, at an undisclosed German clinic, six patients from the US and Canada developed Q fever one week following administration of live sheep cell therapy.[1]

The patients experienced fever, fatigue, headaches, and other symptoms. Infectious disease workup revealed *Coxiella burnetii*, the causative agent for Q fever. The organism is morphologically similar but distinct from *Rickettsia* and other tick-borne organisms. Coxiella is treatable with tetracycline or doxycycline. Nevertheless, three patients continued to have symptoms 10 months after the cell therapy administration.

The authors of the *MMRW* report cite adverse events following sheep cell therapy, which they label as xenotransplantation, including radiculopathy, anaphylaxis, vasculitis, encephalitis, clostridial infection, and death. They warn that patients having these treatments should be on the alert for zoonotic disease (disease transmitted directly from animal to human). Q fever may also be transmitted directly from human to human.

Next-Generation Sequencing and Infectious Disease

The aforementioned case of *Coxiella* infection compels us to reconsider infectious disease etiology in patients with acute and chronic medical conditions. Unfortunately, most chronic disease does not present with fever, chills, exanthem, nausea, diarrhea, and related symptoms. Practitioners are faced with patients having signs of secondary symptoms – neurologic, musculoskeletal, cerebral, gastrointestinal, endocrine, and cardiac symptomatology. Could it be that irritable bowel syndrome, neurologic paresis, fibromyalgia, adrenal fatigue, and angina have underlying etiologies of undiagnosed infectious disease? Stephen Fry, MD, argues that, yes, indeed there may be an *undiagnosed microorganism culprit*.

In this issue, Fry explains the exciting new diagnostic methodologies being implemented to explore infectious disease diagnosis. Of particular interest is next-generation DNA sequencing (NGS). This method permits sequencing many DNA segments at relatively low cost. NGS enables one to use DNA sequencing to identify a wide range of microorganisms, including organisms not suspected as pathologic. Rather than requiring lengthy culturing, NGS enables rapid bacterial, protozoal, fungal, and viral identification. Infectious disease often depends on serology testing to establish a diagnosis. However, antibody testing is fraught with difficulties, particularly in patients in whom the antibody levels are borderline. The advantage of NGS is that it is unnecessary to specifically test for one organism; NGS enables the identification of organisms that would not be suspected as being the causative agent. The other major advantage is that testing is not limited to blood, urine, stool, and CSF. One may also use wound tissue and other infected materials for diagnosis.

The next time that the patient's testing reveals significantly abnormal inflammatory markers, consider an infectious disease workup.

Jonathan Collin, MD

Notes

1. Robyn MP, Newman AP, et al. Q Fever outbreak among travelers to Germany who received live cell therapy – US and Canada. *MMWR*. Oct. 2, 2015. 64 (38): 1071–1073.

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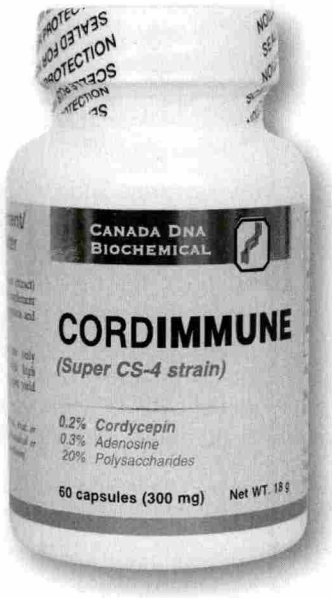

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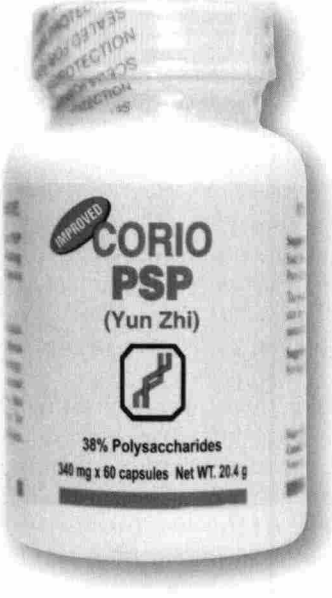

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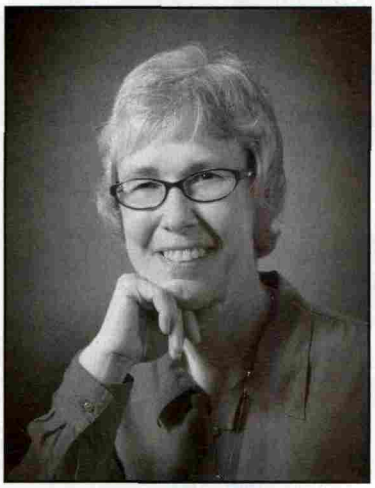

Shorts

briefed by Jule Klotter
jule@townsendletter.com

Aluminum and Alzheimer's Disease

Although industry keeps asserting that aluminum is safe and has no role in Alzheimer's disease (AD), scientific review articles show otherwise. Aluminum is "the most abundant naturally occurring neurotoxic element to which we are exposed," write Suriyadipta Bhattacharjee and colleagues. The aluminum content of drinking water directly correlates with the incidence of AD in epidemiologic studies. In their 2014 review articles, Bhattacharjee et al. list several research observations that support a causative link between aluminum and Alzheimer's disease. First, aluminum "strongly promotes amyloid aggregation and accumulation" in the brain, a defining characteristic of AD. In addition, aluminum exposure increases both inflammatory signaling and the level of certain brain gene messenger RNAs and micro-RNAs found in people with Alzheimer's. Bhattacharjee and colleagues say, "Perhaps most importantly ... of all pharmaceutical treatment approaches directed against AD to date, chelation using the antioxidant and trivalent iron/aluminum chelator desferrioxamine has been shown to be one of the most effective therapeutic strategies [for moderate- to late-stage AD] yet devised."

In addition to being ingestible in food and drinking water, particulate aluminum can be inhaled, moving directly to the hippocampus. Christopher Exley and Thomas Vickers present a 2014 case report of a 58-year-old man who was diagnosed with Alzheimer's in 2003. For eight years preceding his diagnosis, the man had daily work exposure to aluminum sulfate "dust." Initially, the man experienced headaches, fatigue, and mouth ulcers. By 1999, memory problems and depression had developed. Brain tissue samples, taken after his death at age 66, showed a mean aluminum level of 2.98 μg/g dry weight in the frontal lobe – "more than three times higher than a mean value 0.83 μg/g dry weight previously recorded for multiple samples of frontal lobe from multiple individuals." In addition, one-third of the 46 samples taken from the man's brain had "potentially pathological" aluminum levels exceeding 3.50 μg/g dry weight. Exley says that a third possible source of aluminum is vaccination and allergy immunotherapy that use aluminum adjuvants. Immune cells are known to take up aluminum adjuvant particulate after a vaccine or allergy immunotherapy injection and move the metal throughout the body and into the brain.

The body eliminates aluminum via urine and perspiration. Exley proposes using the biologically available form of silicon, silicic acid, to increase the metal's removal from the body. "This therapy is based upon the observation that drinking silicon-rich mineral waters increases the excretion of aluminum in urine," he writes. He discovered in the late 1990s that silicon reduced acute aluminum toxicity in fish. Exley and his colleagues have not yet verified whether silicon-rich mineral water also increases aluminum excretion through perspiration.

Bhattacharjee S, Zhao Y, Hill JM, Percy ME, Lukiw WJ. Aluminum and its potential contribution to Alzheimer's disease. *Front Aging Neurosci.* 2014;6:62. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3986683. Accessed October 19, 2015.

Exley C. Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease. *Front Neurol.* October 2014;5:212. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC4209859. Accessed July 8, 2015.

Exley C, Vickers T. Elevated brain aluminium and early onset Alzheimer's disease in an individual occupationally exposed to aluminium: a case report. *J Med Case Rep.* 2014;8:41. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3923550. Accessed October 19, 2015.

Breath Analysis and VOCs

For millennia, physicians have noticed that some diseases produce characteristic breath odors. Technology now permits researchers to identify the volatile organic compounds (VOCs) that cause the odors. Researchers have identified over 3400 VOCs in deep alveolar breath, many of which result from metabolic processes throughout the body, according to a 2014 review article led by Nicholas J. W. Rattray. VOC patterns in exhaled breath potentially offer a noninvasive method for diagnosing multiple conditions. Research, however, has proceeded slowly since Linus Pauling first presented a paper on a typical human breath signature to the National Academy of Sciences in 1971, primarily because of technological challenges.

Breath analysis is quite complex. While many VOCs arise during metabolism, others come from exogenous sources such as inhalation of car exhaust or cigarette smoke or the ingestion of certain foods or beverages, explain Frank S. Cikach Jr. and Raed A. Dweik. Their 2012 review article discusses the use of breath analysis in cardiovascular illness. Protocols for reliably capturing a breath sample, technology that can detect compounds at very low concentrations, and methods for separating potential biomarkers from other signals need to be addressed before breath analysis can be used to diagnose nonpulmonary illnesses. Also, the technological hardware

needs to be smaller and less complex for widespread clinical use.

In addition to solving technological issues, researchers must accurately identify the VOC patterns that correlate with targeted diseases. Rattray and colleagues say that no single VOC is likely to indicate a specific illness: "Specific combinations or classes of compounds (i.e., fingerprints) are more likely to form the basis of a 'compound biomarker panel' for a disease. ... "

Ibrahim A. Hanouneh and colleagues conducted a 2014 study that involved patients with alcoholic hepatitis and cirrhosis (n = 40), patients with non-alcohol-related cirrhosis with acute decompensation (n = 40), and a control group of people without liver disease (n = 43). People with chronic liver disease have "'a distinctive musty, sweet breath odor. ... '" Hanouneh and colleagues found six compounds (2-propanol, acetaldehyde, acetone, ethanol, pentane, and trimethylamine [TMA]) with elevated levels in the patients with liver disease compared with controls. Furthermore, the patients with alcoholic hepatitis had higher mean concentrations of TMA, acetone, and pentane in their breath, compared with the other patient group or with controls (for both, $p < .001$). The authors report that TMA, acetone, and pentane scores of 36 or higher identified the patients with alcoholic hepatitis with 90% sensitivity and 80% specificity. In addition to aiding diagnosis, the researchers hope to eventually use breath analysis to assess severity of the disease and to monitor treatment. In the case of liver disease, biopsy – an invasive procedure with risk of complications – is the gold standard for assessing disease severity.

Breath analysis has not yet reached the stage of blood panels or urine analysis for disease detection; but once technology improves and standards for breath collection and VOC profiles are set, it may become a valuable noninvasive window into the body's metabolic processes.

Cikach FS, Dweik RA. Cardiovascular biomarkers in exhaled breath. *Prog Cardiovasc Dis*. 2012;55(1):34–43. Available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4205725. Accessed October 25, 2015.

Hanouneh IA, Zein NN, Cikach F et al. The breathprints in patients with liver disease identify novel breath biomarkers in alcoholic hepatitis. *Clin Gastroenterol Hepatol*. March 2014; 12(3):516–523. Available at http://europepmc.org/articles/pmc3971429. Accessed October 25, 2015.

Rattray NJW, Hamrang Z, Trivedi DK, Goodacre R, Fowler SJ. Taking your breath away: metabolomics breathes life in to personalized medicine. *Trends Biotechnol*. August 2014. Available at www.researchgate.net/publication/265163243. Accessed October 25, 2015.

Cost-Effectiveness

The Patient Protection and Affordable Care Act expanded the number of people with health insurance, but the cost of medical care and health insurance premiums continues to rise. Nonetheless, the US – unlike other countries – shies away from using cost-effectiveness data to make decisions about health coverage. As physician Aaron E. Carroll explains in his December 2014 editorial, one way to assess cost-effectiveness is to divide an intervention's cost by the number of quality-adjusted life years (QALYs) it typically produces. Countries such as Britain consider QALYs and cost-effectiveness along with benefits and risks when recommending an intervention's coverage by the National Health Service.

When passing the Affordable Care Act, US legislators refused to include cost-effectiveness measures because of concerns that looking at cost would lead to health care-rationing – that is, making hard (and unpopular) decisions about coverage. The law mandates that insurers must cover all services rated A or B by the US Preventive Services Task Force (USPSTF), without any cost sharing by consumers. In addition, insurance must cover all vaccinations recommended by the Advisory Committee on Immunization Practices (ACIP). In their analysis of effectiveness, these two agencies very rarely consider a preventive service's cost-effectiveness. Carroll says, "That means that we are all paying for these therapies [in the form of insurance premiums], even if they are incredibly inefficient."

Moreover, the Affordable Care Act authorized the Patient Centered Outcomes Research Institute (PCORI), a nongovernmental organization, to do comparable effectiveness research. PCORI states on its website that it will not fund any proposed research that includes a formal cost-effectiveness analysis or directly compares the costs of alternative treatment approaches. The organization will fund studies that look at the effect of a treatment's direct cost to patients, such as out-of-pocket, hardship, or barriers to care access. Apparently, insurers' costs that get passed onto consumers via higher premiums are not an issue. As PCORI says on its website, "We don't consider cost effectiveness to be an outcome of direct importance to patients." Carroll says, "I think understanding how much bang for the buck I, my patients, and the public are getting from our health care spending is of great importance."

Mark V. Pauly, Frank A. Sloan, and Sean D. Sullivan suggest that an economic advisory body could help agencies such as the USPSTF and the Advisory Committee on Immunization Practices (ACIP) consider cost-effectiveness. In making their

recommendations, expert panels look solely at health benefits and risks; panel members have medical, not economic, expertise. Pauly and colleagues suggest that advisers with expertise in both health management and economics could calculate the cost per unit of additional benefit provided by a more expensive and effective alternative and compare it with a benchmark value to determine economic efficiency. Preventive services whose cost-effectiveness exceeds a to-be-determined threshold would be recommended for full insurance coverage. Other services would be available but not routinely covered by insurance. Instead, consumers would have access to information about a service's effectiveness and cost so that they could make their own decisions. Pauly and colleagues believe that including cost-effectiveness is necessary because the costs of new drugs and the many vaccines entering the market are becoming increasingly expensive.

"If we are going to mandate that recommendations and interventions must be covered by health insurance, and if our willingness to pay the cost of this insurance is not unlimited," says Carroll, "it seems logical that we at least consider their economic value. The cost effectiveness of a therapy need not be the only thing we use to approve coverage, but ignoring it is akin to putting our heads in the sand."

Carroll AE. Forbidden topic in health policy debate: cost effectiveness. *New York Times*. December 15, 2014. Available at http://www.nytimes.com/2014/12/16/upshot/forbidden-topic-in-health-policy-debate-cost-effectiveness.html?_r=0. Accessed October 29, 2015.

Pauly MV, Sloan FA, Sullivan SD. An economic framework for preventive care advice. *Health Affairs*. November 2014: 33(11); 2034–2040.

Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) from a healthy donor has gained much attention as a highly effective treatment for recurrent *Clostridium difficile* infection. *C difficile* is an opportunistic infection that occurs when antibiotic therapy kills off beneficial gut bacteria, allowing *C. difficile* bacteria to flourish. Communities of microbes in the gut and other areas of the body are proving to have important roles in maintaining health. In a healthy person, gut microbiota actively participate in energy metabolism and immune function for the entire body. FMT is the most effective way to supply a dysfunctional gut with the hundreds of microbes that contribute to health.

Some clinicians and researchers, such as Thomas J. Borody and Alexander Khoruts, hypothesize that many conditions associated with the Western lifestyle – including constipation, IBS, IBD, neurological diseases, cardiovascular diseases, metabolic syndrome, obesity, autoimmunity, asthma, and allergies – stem from alterations in the GI microbiome. Widespread antibiotic use in medicine and in farming, a Western diet that relies on processed rather than whole foods, and farming practices that deplete beneficial soil microbes affect the composition of the GI microbiome. The effects of these alterations are just beginning to be investigated.

Because of FMT's success in treating *C. difficile*, the treatment is also being studied as a possible therapy for inflammatory bowel diseases. So far, results are less consistent for irritable bowel disease, ulcerative colitis, and Crohn's disease than for *C. difficile* infection (CDI). Patients with recurrent CDI often respond with just one treatment. "A systematic review of FMT in CDI from 27 countries involving over 300 cases reported excellent cure rates for relapsing CDI of around 90% via colonoscopy and enema with 76.5% cure rates via nasogastric infusion. Consequently, FMT is now a recommended treatment for the third recurrence of CDI," report Borody, Brandt, and Paramsothy in their 2014 review. J. S. Bakken et al. published standard practice guidelines for the use of FMT in treating *C. difficile* infection in 2011 (http://dx.doi.org/10.1016/j.cgh.2011.08.014). Unlike those with CDI, people with other bowel conditions often require multiple treatments, and response rate is not as high. The most effective protocol for these patients still needs to be determined.

In treating patients with GI dysfunctions, researchers have observed unexpected improvements in comorbidities, suggesting that FMT may have widespread benefits. For example, neurological symptoms in three wheelchair-bound patients with multiple sclerosis greatly improved after successful FMT treatment for constipation. Urinary function returned in two patients with catheters, and all three patients regained the ability to walk (Borody TJ, Leis S, Campbell J, et al. Fecal microbiota transplantation [FMT] in multiple sclerosis. *Am J Gastroenterol*. 2011;106:s352). Obese male patients in a small controlled 2012 study, led by A. Vrieze, showed significantly improved insulin sensitivity after FMT from lean donors, suggesting that GI microbiota play a major role in metabolic syndrome. Patients with chronic fatigue syndrome have also reported "persisting relief" after FMT treatment. To define the wider benefits of FMT, Borody and Khoruts say that clinical observations need to be followed by well-designed randomized trials that include systematic study of microbiota composition pre-FMT and post-FMT.

Borody TJ, Khoruts A. Fecal microbiota transplantation and emerging applications. *Nat Rev Gastroenterol Hepatol*. February 2012;9:88–96. Available from www.drperlmutter.com/study/fecal-microbiota-transplantation-emerging-applications. Accessed October 19, 2015.

Borody TJ, Brandt LJ, Paramsothy S. Therapeutic faecal microbiota transplantation: current status and future developments. *Curr Opin Gastroenterol*. 2014;30:97–105. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3868025. Accessed October 19, 2015.

Medical Cannabis Quality

Cannabis is a medicinal herb with numerous therapeutic effects. Cannabinoid compounds relieve pain, reduce nausea and vomiting, suppress muscle spasms, reduce anxiety, reduce blood sugar, promote bone growth, and have antiseizure, anti-inflammatory, neuroprotective, and anticancer effects. Like all botanicals, however, chemical content varies according to the plant's growing, harvesting, and processing conditions as well as genetics.

To help practitioners and consumers identify high-quality medical cannabis, Americans for Safe Access has created Patient Focused Certification (PFC), a third-party certification program for the medical cannabis industry. Products and companies that gain PFC certification meet the quality standards issued by the American Herbal Products Association (AHPA) and published in the American Herbal Pharmacopeia (AHP) Cannabis monograph. Products made by a PFC-certified company have a PFC seal on their labels. PFC also provides support services to companies that cultivate, manufacture, analyze, or distribute medical cannabis products. A list of PFC-certified companies in the US is posted at http://patientfocusedcertification.org.

In addition to the certification program, Americans for Safe Access educates medical cannabis providers about government regulations and informs health care providers about legitimate clinical uses for medical cannabis. For more information, go to www.safeaccessnow.org.

Urinary Porphyrins, Autism

In a chapter for the 2014 book *Comprehensive Guide to Autism* (Springer Media), Janet K. Kern, David A. Geier, Lisa Sykes, and Mark Geier discuss the use of urinary porphyrin levels to assess heavy metal toxicity in children with autism spectrum disorders (ASD). They report that 43 of 58 research articles (74%) observed a significant link between autism and one or more heavy metals, according to a 2010 review. "Moreover, eight recent studies have shown that the greater the toxic metal body burden in a child, the worse the autism," say Kern and colleagues. Mercury, a known neurotoxin, tops the list of implicated metals; but cadmium, lead, arsenic, and aluminum have also been linked to ASD.

Although urinary porphyrins are not a direct measure of toxic metals, they can provide a way to assess body burden. (Blood testing shows only recent or ongoing metal exposure.) Some heavy metals inhibit enzymes needed for heme synthesis. This inhibition produces increased excretion of certain porphyrins (heme precursors). The types and levels of excreted porphyrins form metal-specific patterns that let doctors identify prolonged exposure to mercury, lead, arsenic, and other metals. Studies conducted on four continents have found that many children with ASD, unlike unexposed controls, show increased levels of coproporphyrin (cP) and pentacarboxyporphyrin (5cxP) and precoproporphyrin (prcP; also called keto-isocoproporphyrin) in their urine – a pattern that occurs with prolonged mercury exposure. Kern and colleagues report that chelation therapy reduces prcP and cP levels in children with autism.

"Measuring toxic metal body burden is particularly important in ASD," write Kern et al. Children with ASD tend to have low plasma glutathione (GSH) and sulfate levels and high plasma levels of oxidized glutathione, indicating poor detoxification capacity and an overburdened detoxification system. Children with a decreased ability to remove toxins are more susceptible to damage from heavy metals.

This chapter includes guidelines for the use of urinary porphyrin testing. The authors do not recommend proceeding with detoxification until blood test levels for heavy metals are normal (indicating that ongoing exposures have been eliminated) and urinary porphyrin levels are still elevated. If porphyrin levels do not decrease with detoxification, Kern and colleagues say, "It may be important to consider other environmental/genetic factors contributing to the elevated urinary porphyrins."

Kern JK, Geier DA, Sykes L, Geier M. Chapter 72: Urinary porphyrins in autism spectrum disorders. In: Patel VB et al., eds. *Comprehensive Guide to Autism*. New York: Springer; 2005:1333–1348. Available at www.researchgate.net/publication/258010236. Accessed October 25, 2015.

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Pathways to Healing

by Elaine Zablocki

Understand How Digital Medicine Is Changing Health Care

We've all heard about the many ways that digital medical records will improve our health-care system. They could solve the problem of lost charts. They could eliminate errors due to sloppy physician handwriting.

But over the past few years, I've noticed that electronic health records also have their problems. The last time I saw my primary care physician, she began by checking my personal history, and we found that certain facts had been distorted when the practice switched from paper to digital records. My medication list was slightly inaccurate, because the options in the electronic chart don't exactly match the medications that I'm actually using. Also, I was particularly concerned to notice my doctor doing data entry during our conversation at a fixed-height desk, with her hands in an inappropriate, potentially harmful position for typing.

Recently I read a new book by Robert Wachter, MD, and realized that the small problems which I've noticed in my own experience are just tiny signals about major issues reverberating through the entire health-care system as we transition to electronic health records. While these records certainly have benefits, and eliminate some familiar problems, they also introduce new problems.

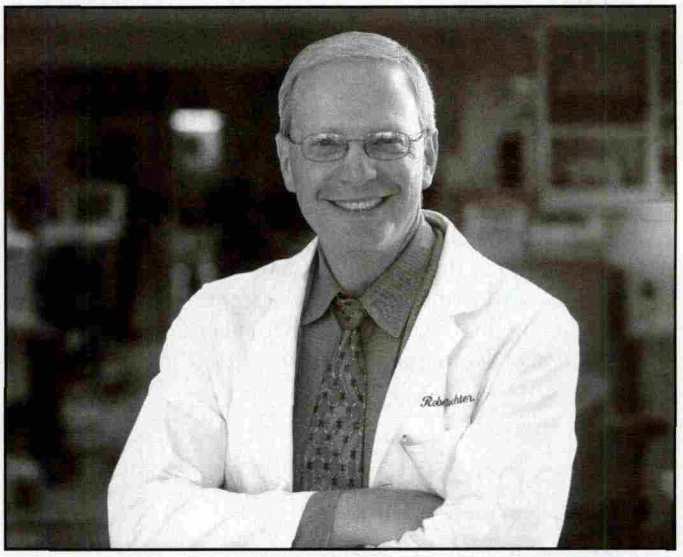
Wachter is a respected academic physician, serving as professor and interim chair of the Department of Medicine at the University of California, San Francisco. He's the author of an important textbook on health-care quality and patient safety. His new book, *The Digital Doctor: Hope, Hype, and Harm at the Dawn of Medicine's Computer Age*, introduces readers to the many different personalities, organizations, and interests shaping digital medicine.

When Wachter first mentioned on his blog that he was working on this book, I expected it to be a valuable but somewhat dry textbook. Months later, when I came across a few chapters while browsing the Internet, I couldn't stop reading.

The Overdose

In 2013, a teenager at Wachter's hospital received 38.5 antibiotic pills. The correct, intended dose was one pill. He went into convulsions and almost died.

In eight chapters, Wachter explores the many different factors that led to this event. The computer ordering system



Robert Wachter, MD

used weight-based dosages for pediatric patients without clearly highlighting this, so it was all too easy for a physician to order "160 mg per kilogram" instead of the total 160 mg that was intended. The computerized system also used an alert system for possible errors, but nowadays there are so many alerts (in the chart and also on every medical device) that practitioners often ignore them. An automated robot actually dispensed the medication, and everyone assumed that the robot would be far more accurate than a human being, so it could not make an error.

When the nurse on the unit received 38½ antibiotic pills to dispense, she paused to wonder if this could possibly be correct. But she was working in an academic institution that often dispenses unusual medications. She was under extra stress that night because she was "floating," working on an unfamiliar unit. "Another factor was her rush to complete her tasks," Wachter writes. "She also didn't want to bother the busy charge nurse. ... As is so often the case with medical mistakes, the human inclination to say 'it must be right' can be powerful."

About 6 hours after ingesting the medication, the patient blacked out, began seizing, and stopped breathing. Fortunately the hospital's Code Blue team was able to

quickly revive him. He spent several days in the ICU, but has not experienced long-term effects from the overdose.

Reading this section of the book is a gripping experience. UCSF Medical Center is one of the best hospitals in the country. It was and is committed to first-class health care, including the best possible digital systems. All of the staffers involved in the overdose were intelligent, committed people trying to do the best work possible under the circumstances. Yet the error still occurred. It makes you stop and think about the unexpected, unintended consequences of the digital transformation.

One important aspect of this story is that it propelled Wachter into writing the book, with full support from the leadership at UCSF. "Being transparent about such a case is an act of individual and institutional bravery," he writes. "The nurse, the physician and the pharmacist all agreed to speak with me about this terrible incident because they knew that doing so could save lives."

In the past, other industries, such as the airlines, have led the way by setting high safety standards and exhaustively exploring the root causes of any disaster. When a book like this can publicly explore the many causes behind one major medication error, it gives us hope for increased transparency and quality improvement in health care.

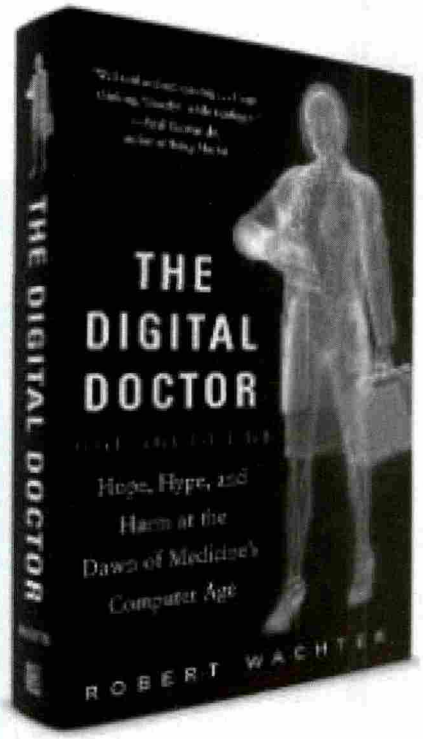
Exploring Digitized Health care from Many Different Angles

The Digital Doctor explores the effects of electronic health records from many different angles. Digitizing records changes the social environment. Physicians are tied to their computer screens, and miss some of the informal social interactions, with patients and with other physicians, that have been so valuable in the past.

The chart used to be the physician's record of information needed to offer appropriate care. Nowadays computerized charts are used for many additional functions, such as research and billing. This means that it can be more difficult for the physician to quickly grasp the most essential information on a patient. Wachter describes one primary care physician's experience: "Because the computer system doesn't allow Sinsky to navigate the patient's record in an intuitive way ... her staff spends hours the day before every clinic session printing out most of the electronic record. It's the only way she can see what she needs to see."

Unfortunately, the current crop of electronic health records often requires physicians to enter information in convoluted, clunky, time-consuming ways. Wachter tells stories that are both funny and horrifying, about physicians who point out major flaws in their hospital's EHR systems, expecting to be thanked for their useful comments. Instead they are often rebuffed and even ostracized.

Wachter describes efforts to make medical records more open and available to patients. Susan Edgman-Levitan, a leader in the field of patient communication, reviewed her own record and found a major error. A radiologist's report left out the word "no," so it said exactly the opposite of the intended meaning. She was concerned because this could affect her care if she found herself unconscious in the ER. It took several months plus a couple of committee meetings to correct her record. In general she finds that when patients review their charts, they often discover significant errors.



Wachter includes a section on the players and policies in digital health care, reviewing incentives for various forms of medical records. He describes meetings with Silicon Valley entrepreneurs brainstorming new technical possibilities. One of the major pleasures of this section, and of the book as a whole, is seeing isolated news stories within a larger context. Suddenly, many specific headlines about changes in payment methods or physician frustration with new charting methods all fit together and make sense.

Throughout the book, Wachter emphasizes that using digital technology requires major changes in work flow – that we are only at the start of a transformational process. "It turns out that new technologies always rearrange social relationships," he writes. "Perhaps it was naïve of us to believe that the first versions of these technologies would be perfect. ... After all, before there was the iPad there was the Newton. ... We're simply not smart enough to make it from A to Z without going through the rest of the alphabet first."

If you are interested in how and why our health-care system works now, and how it may change in the future, read this book.

Resources

Books

Wachter R. *The Digital Doctor: Hope, Hype, and Harm at the Dawn of Medicine's Computer Age* (McGraw-Hill; 2015). Several chapters about the overdose are posted on the Internet, at http://bit.ly/1DHij1W.

———. *Understanding Patient Safety* (McGraw-Hill; 2nd edition 2012). A lively, up-to-date primer on patient safety, full of case vignettes, tools, references, and other key resources.

Blog

Wachter posts occasional comments and sparks interesting discussions on his blog, Wachter's World, at http://community.the-hospitalist.org.

Elaine Zablocki has been a freelance health-care journalist for more than 20 years. She was the editor of *Alternative Medicine Business News* and *CHRF News Files*. She writes regularly for many health-care publications.

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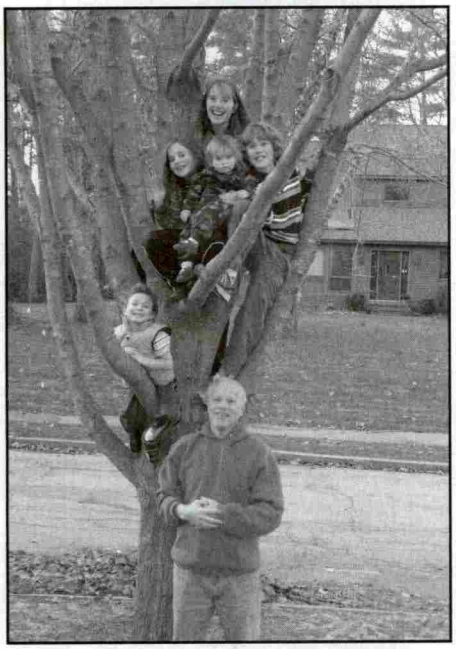

Literature Review & Commentary

by Alan R. Gaby, MD
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Probiotic Prevents Urinary Tract Infections

One hundred twenty-eight infants (aged 1 week to 12 months) with primary vesicoureteral reflux and frequently recurring urinary tract infections (UTIs) were randomly assigned to receive *Lactobacillus acidophilus* ATCC 4356 (Antibio300; Hanwha, Korea; 10^8 colony-forming units per gram; the actual amount given was not clear) twice a day or low-dose trimethoprim/sulfamethoxazole at bedtime for 1 year. The recurrence rate of UTIs was nonsignificantly lower in the probiotic group than in the antibiotic group (32.8% vs. 40.6%; $p = 0.35$). Among infants who had a recurrence, the incidence of antibiotic resistance to causative *E. coli* organisms was significantly lower in the probiotic group than in the antibiotic group.

Comment: In this study, a specific probiotic strain was at least as effective as, and possibly more effective than, low-dose trimethoprim/sulfamethoxazole for preventing recurrent UTIs in infants with primary vesicoureteral reflux. In addition, infections that developed in the probiotic group were less likely to be resistant to antibiotics. In previous research, the combination of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 given daily for 1 year was nearly as effective as prophylactic antibiotic therapy for preventing UTIs in postmenopausal women with a history of recurrent UTIs (Beerepoot MA et al. Lactobacilli vs antibiotics to prevent urinary tract infection. A randomized, double-blind, noninferiority trial in postmenopausal women. *Arch Intern Med*. 2012;172:704–712).

Not all probiotic strains would be expected to be effective for preventing UTIs. For example, *L. rhamnosus* GG, a well-researched strain that is effective against various gastrointestinal conditions, is not capable of colonizing the genitourinary tract. *L. acidophilus* ATCC 4356 (the product used in the new study) does not appear to be commercially available in the US. *L. rhamnosus* GR-1/*L. reuteri* RC-14 (the product used in the earlier study) is sold under the names Pro-Flora Women's Probiotic (Integrative Therapeutics) and Femdophilus (Jarrow Formulas).

Lee SJ, Lee JW. Probiotics prophylaxis in infants with primary vesicoureteral reflux. *Pediatr Nephrol*. 2015;30:609–613.

Delayed Cord Clamping Improves Neurological Development

Four hundred full-term infants born in Sweden after a low-risk pregnancy were randomly assigned to delayed umbilical cord clamping (at least 3 minutes after delivery) or early cord clamping (10 seconds or less after delivery). At 4 months of age, compared with the infants assigned to early cord clamping, those assigned to delayed cord clamping had a 44% higher mean ferritin concentration (117 vs. 81 mcg/L; $p < 0.001$) and a lower prevalence of iron deficiency (0.6% vs. 5.7%; $p = 0.01$). The results of this study were published in 2011. The authors have now conducted a follow-up study of the original cohort of infants. At 4 years of age, delayed cord clamping, as compared with early cord clamping, was found to improve measures of fine-motor and social function, especially in boys.

Comment: Iron plays a crucial role in early brain development, and iron-deficiency anemia during infancy can cause irreversible impairment of cognitive function. At the time of birth, the placenta contains a relatively large amount of blood, much of which is transferred by a natural process to the baby, if the cord is allowed to remain open. The volume of this placental "transfusion" is approximately 40 ml/kg of body weight, which provides about 75 mg of extra iron, an amount sufficient to meet the baby's iron needs for more than 3 months. The results of the present study indicate that delayed cord clamping may improve neurological development in a low-risk population of children born in a high-income country.

Andersson O et al. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. *BMJ*. 2011;343:d7157.
Andersson O et al. Effect of delayed cord clamping on neurodevelopment at 4 years of age: a randomized clinical trial. *JAMA Pediatr*. 2015;169:631–638.

Which Weight-Loss Diet Works Best?

A meta-analysis was conducted on 48 clinical trials (including a total of 7286 participants) that examined the effect of various popular diets on weight loss in overweight and obese adults. The largest mean weight loss was associated with low-carbohydrate diets (8.73 kg at 6 months and 7.25 kg at 12 months) and low-fat diets (7.99 kg at 6 months and 7.27 kg at 12 months). Differences between individual diets (e.g., Atkins diet vs. Zone diet) were minimal.

Comment: This meta-analysis found that significant weight loss can be achieved with any low-carbohydrate or low-fat diet, and that no specific diet program is substantially more effective than other programs. Therefore, for individuals who want to lose weight, it would be reasonable for practitioners to recommend any diet the patient is willing to adhere to.

Johnston BC et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA*. 2014;312:923–933.

Vitamin D and Hypertension

Five hundred thirty-four individuals (aged 18–50 years) living in the US who had a serum 25-hydroxyvitamin D level of 25 ng/ml or lower and prehypertension or stage 1 hypertension (systolic blood pressure of 120–159 mm Hg) were randomly assigned to receive, in double-blind fashion, high-dose (4000 IU/day) or low-dose (400 IU/day) vitamin D3 for 6 months. At the end of the study, compared with baseline, the decrease in mean 24-hour systolic blood pressure (the primary endpoint) was nonsignificantly greater in the low-dose group than in the high-dose group (−1.6 vs. −0.8 mm Hg; $p = 0.71$). Results were consistent among white and black participants.

Comment: Numerous studies have investigated whether vitamin D supplementation can lower blood pressure. The results have been conflicting. A meta-analysis of 46 randomized placebo-controlled trials concluded that vitamin D had no significant effect on systolic or diastolic blood pressure, and subgroup analysis did not reveal any baseline factor predictive of a better response to vitamin D. Some practitioners have argued that the lack of effectiveness in various vitamin D studies was due to an insufficient dose. However, the results of the present study indicate that 4000 IU/day was not more effective, and may have been less effective, than 400 IU/day for reducing blood pressure. The available evidence does not support the use of vitamin D as a treatment for hypertension.

Arora P et al. Vitamin D therapy in individuals with prehypertension or hypertension: the DAYLIGHT trial. *Circulation*. 2015;131:254–262.

Folinic Acid for Schizophrenia

Of 18 patients (aged 11–50 years) with schizophrenia since adolescence that had failed to respond to conventional therapy, 15 (83%) had folate receptor antibodies in their serum. In contrast, only 1 of 30 healthy controls (3.3%) had such antibodies ($p < 0.0001$). Folate receptor antibodies were measured once a week for 5 weeks; the levels fluctuated in 9 patients between positive (sometimes with a high titer) and negative, whereas the levels remained consistently positive in 6 others. The mean concentration of 5-methyltetrahydrofolate (MTHF; the biologically active form of folate) in cerebrospinal fluid (CSF) of patients with folate receptor antibodies was significantly lower by 43% than that in a previously established control group ($p = 0.0002$). Only 6 of 13 patients with folate receptor antibodies had low CSF levels of MTHF, presumably because antibody levels fluctuated in some patients, resulting in intermittently normal MTHF transport. Seven patients with folate receptor antibodies were treated with folinic acid in doses of 0.1 to 0.3 mg/kg of body weight per day for at least 6 months. Six of the 7 patients continued their psychotropic medication, and 3 patients also went on a milk-free diet. In all 7 cases, "positive" symptoms (delusions, hallucinations, and disorders of speech and thought) disappeared, whereas the effect on "negative" symptoms (flat affect, lack of speech, and lack of motivation) was variable. Patients also reported an improvement in concentration and memory.

Comment: Cerebral folate deficiency has been defined as any neuropsychiatric condition in which MTHF levels in the CSF are low, whereas folate status outside the central

nervous system is normal. Manifestations of cerebral folate deficiency include marked irritability, slow head growth, psychomotor retardation, cerebellar ataxia, pyramidal tract signs in the legs, dyskinesias, and, in some children, seizures or autism. Cerebral folate deficiency appears to be caused in most cases by the production of autoantibodies that block the receptor involved in transporting folate across the blood-brain barrier. Folinic acid can bypass autoantibody-blocked folate receptors and enter the CSF by a different mechanism.

In previous case reports, treatment with folinic acid resulted in clinical improvement in several children with autism associated with cerebral folate deficiency. The results of the present study suggest that cerebral folate deficiency is also a contributing factor in some cases of schizophrenia. An Internet search revealed that one commercial laboratory is currently offering the serum folate receptor antibody test for $200 (http://iliadneuro.com). Because of the high frequency of positive antibody tests observed in the present study (15 of 18 patients), a therapeutic trial of folinic acid might be considered even when antibody testing is not feasible.

Ramaekers VT et al. Folinic acid treatment for schizophrenia associated with folate receptor autoantibodies. *Mol Genet Metab*. 2014;113:307–314.

How to Lose the Taste for Sweets

Twenty health-care workers in California agreed to eliminate all added sugars and artificial sweeteners from their diet for 2 weeks. After 2 weeks, 95% of participants found that sweet foods and drinks tasted sweeter or too sweet, 75% found that other foods tasted sweeter, and 95% said they would use less or even no sugar in the future. Eighty-seven percent of the participants stopped craving sugar after 6 days.

Comment: I have long believed that consumption of refined sugar is an important contributing factor to many diseases, and I have advised most patients with chronic illnesses to limit their sugar intake. Many patients ask whether it is OK to use artificial sweeteners instead. I typically reply that there are also concerns about artificial sweeteners, and that the best approach is to "decondition" the taste for sweets by removing all sweet foods from the diet for 3 weeks. I don't recall whether I had read somewhere that it is possible to lose the taste for sweets, or whether I simply made the idea up and hoped that it was true. What I do know is that patients usually reported the same experiences as those of the participants in the new study. It is encouraging to know that we do not have to remain slaves to our sweet tooth.

Bartolotto C. Does consuming sugar and artificial sweeteners change taste preferences? *Perm J*. 2015;19(3):81–84.

Honey Prevents Oral Mucositis In Cancer Patients

A meta-analysis was conducted on 9 randomized controlled trials (including a total of 476 patients) that examined the effect of regular consumption of honey in patients receiving radiation therapy for head and neck cancer. The dosage and frequency of consumption of honey were not specified in the report. In the pooled analysis, ingestion of honey significantly reduced the incidence of radiation-induced moderate or severe mucositis and significantly decreased the mean severity of mucositis during the first 3 weeks of therapy. In addition, the onset of mucositis was significantly later in the honey group than the control group.

Comment: Oral mucositis is a common and sometimes serious complication of radiation therapy and chemotherapy and in some cases necessitates the interruption of treatment. The present meta-analysis found that regular consumption of honey either during or after radiation therapy can prevent moderate to severe mucositis and the associated weight loss. The mechanism of action is not known; it was not related to a reduction in the incidence of bacterial or fungal colonization of the oral cavity.

Cho HK et al. Effects of honey on oral mucositis in patients with head and neck cancer: a meta-analysis. *Laryngoscope*. 2015;125:2085–2092.

Gluten Sensitivity: Real or Imagined?

Thirty-five individuals with self-reported nonceliac gluten sensitivity, who experienced intestinal or extraintestinal symptoms from gluten-containing foods and who had been on a gluten-free diet for at least 6 months, were randomly assigned to consume gluten-containing flour or gluten-free flour for 10 days. After a 2-week washout period, each person consumed the other flour for an additional 10 days. The gluten-containing flour was correctly identified by 12 participants (34%). Seventeen participants (49%) erroneously considered the gluten-free flour to contain gluten. The other 6 participants (17%) were unable to distinguish between the two flours.

Comment: One might conclude from this study that most people who do not have celiac disease but who believe they are sensitive to gluten are not in fact sensitive to gluten. That conclusion contradicts the findings from another double-blind study that I reviewed in this column 2 months ago, which confirmed that gluten can trigger both intestinal and extraintestinal symptoms in patients with self-reported nonceliac gluten sensitivity (Di Sabatino A et al. Small amounts of gluten in subjects with suspected nonceliac gluten sensitivity: a randomized, double-blind, placebo-controlled, cross-over trial. *Clin Gastroenterol Hepatol*. 2015;13:1604–1612.e3.). In the negative study described above, the subjects had been on a gluten-free diet for at least 6 months. Many people lose their sensitivity to allergenic foods after avoiding them for a long period of time. In those cases, 10 days of daily food challenges may not be sufficient to bring the sensitivity back. In the positive study reviewed 2 months ago, the subjects had been on a gluten-free diet for only 1 week before being challenged with gluten.

Zanini B et al. Randomised clinical study: gluten challenge induces symptom recurrence in only a minority of patients who meet clinical criteria for non-coeliac gluten sensitivity. *Aliment Pharmacol Ther*. 2015;42:968–976.

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Innovative Approaches to Obesity and Metabolic Syndrome

by Stephen F. Olmstead, MD

The Scope of the Problem

Obesity and type 2 diabetes mellitus are pandemic metabolic disorders.[1,2] Over 40% of Americans are obese.[3] Over 10% of the world's population is obese.[4] Across the globe, the prevalence of diabetes has soared nearly fourfold, rising to 21.1 million in 2001.[2] Worldwide, diabetes is projected to affect 592 million people by the year 2035, nearly 7% of the earth's population. Metabolic syndrome is the concurrence of central or visceral obesity with insulin resistance, high blood pressure, elevated triglycerides, reduced high density lipoprotein (HDL) cholesterol levels, and a pro-inflammatory, prothrombotic milieu.[5] People with metabolic syndrome have double the risk of developing cardiovascular disease (CVD).[6] They are 3 to 4 times more likely to have a heart attack, while the risk of stroke is 2- to 4-fold higher in metabolic syndrome.[5] When people with metabolic syndrome suffer a myocardial infarction or stroke, they are twice as likely to die.[6] In addition to CVD, people with obesity and metabolic syndrome are at significantly increased risk for cancer of the breast, pancreas, and prostate, as well as a variety of diseases affecting the eyes, liver, kidney, skin, and reproductive system.[6] Obesity and metabolic syndrome are major health challenges yet to be successfully met by the medical community.

Conventional Approaches to Obesity and Metabolic Syndrome

Obesity is the major impetus for the rising prevalence of metabolic disorders.[1] Conventional approaches to obesity and metabolic syndrome have focused on weight loss primarily through diet and exercise.[7] While the merits of low-carbohydrate diets versus low-fat diets are contentiously debated, a daily reduction in calorie intake is essential to successful weight loss.[1,8] The daily energy deficit should be about 500 calories to sustain consistent weight reduction. Even modest weight loss delivers numerous metabolic health benefits such as reduced blood pressure, improved insulin sensitivity, decreased triglyceride levels, and increased HDL-cholesterol.[9] Low-carbohydrate diets favorably affect triglyceride (TG) and HDL-cholesterol levels.[10] There is also evidence that they improve glucose tolerance in people with diabetes. Exercise is vital for initial weight loss and healthful weight maintenance.[11] There is evidence that exercise promotes visceral fat loss.[12] Even without weight loss, exercise can improve insulin sensitivity in people who have been sedentary.[13] Once simplistically considered a disorder caused by an imbalance of caloric intake versus energy expenditure, obesity is now understood to be a complex, multifaceted systemic inflammatory disease.

Eat Less, Exercise More – Easier Said Than Done

Although the approach of an energy-restricted diet and exercise for obesity and metabolic syndrome is simple and straightforward, in clinical practice it is difficult for people to maintain a diet and exercise regimen. Even when people are diligent, modest weight loss is usually the best expected outcome from participation in a structured diet program.[8,14] Commitment and adherence to a change in diet and lifestyle are often insurmountable barriers to successful and sustained weight loss.[15] Even when initial weight loss is accomplished, long-term maintenance of a more healthful weight is usually a major challenge.[8] Clearly additional interventions are needed to make diet and exercise more effective in metabolic disorders. A novel approach to support a healthful weight and metabolism is the use of probiotics and prebiotics to address the gastrointestinal dysbiosis associated with obesity, type 2 diabetes mellitus, and metabolic syndrome. Probiotics and prebiotics are optimally combined with exercise, an energy-reduced diet, and supplements that reduce dietary starch and fat absorption.

Obesity-Associated Gastrointestinal Dysbiosis

The understanding of the pathogenesis of obesity and metabolic syndrome was radically transformed in 2004 when investigators reported that intestinal microorganisms transplanted from normal mice into germ-free mice not only led to weight gain but also promoted body fat accumulation and insulin resistance even with calorie restriction.[16] Transplantation of gut microbes from genetically obese rodents into germ-free animals resulted in significantly greater weight gain than microbiota harvested from lean mice.[17] Human

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studies found that the gut microbiota of obese people contained greater microbial populations in the phylum Firmicutes and fewer in the phylum Bacteroidetes compared with microbiota in lean people.[18] Interestingly, after a carbohydrate- or fat-restricted, low-calorie diet, the ratio of Firmicutes to Bacteroidetes in obese individuals approached that found in lean subjects. The link between diminished Bacteroidetes numbers and obesity is controversial. While some studies confirm reduced gut Bacteroidetes populations in obese humans, others find *increased* numbers of Bacteroidetes in obese people.[17,19] Yet others fail to find any association between Bacteroidetes and obesity.[20,21] The focus on the phyla Bacteroidetes and Firmicutes ignores the important role of other microbes such as *Bifidobacterium* in the phylum Actinobacteria. *Bifidobacterium* populations are much higher during infancy in children who have a normal weight in later childhood than in obese children.[22] Diminished *Bifidobacterium* numbers have also been described in overweight women compared with lean women. Low gut *Bifidobacterium* populations are associated with excessive weight gain during pregnancy and are depressed in people with type 2 diabetes.[23,24] While a definitive link between obesity and relative proportions of Bacteroidetes and Firmicutes has yet to be established and may not exist, it is clear that obesity, type 2 diabetes, and metabolic syndrome are associated with complex gastrointestinal dysbiosis. The important microbiota disturbances appear to be at the genus and species levels and in reduced microbiota diversity.

Probiotics in Obesity and Metabolic Syndrome

While these are early days for the use of probiotics to support a healthful weight, given the current knowledge base, a reasonable approach is to use a formula that combines probiotics species with evidence for weight loss, healthful weight maintenance, and balanced glucose metabolism. These probiotics include *Lactobacillus acidophilus, L. gasseri, L. plantarum, L. rhamnosus,* and a robust mix of *Bifidobacterium* species including *B. bifidum, B. breve,* and *B. lactis*. A clinical trial performed at Stanford University showed that *L. acidophilus* supplementation was associated with significantly more weight loss following Roux-en-Y gastric bypass surgery.[25] People receiving the probiotic had significantly greater weight loss up to 6 months postoperatively. In a randomized, controlled, double-blind study, *L. acidophilus* in yogurt together with *B. lactis* and *L. casei* significantly reduced body mass index (BMI), fat percentage, and leptin levels in overweight and obese adults.[26] *L. acidophilus* has also been shown to improve insulin sensitivity and reduce markers of systemic inflammation in people with both normal and impaired glucose tolerance.[27] And a randomized, double-blind, placebo-controlled study has evaluated the antiobesity effects of *Lactobacillus gasseri*.[28] A fermented milk beverage with or without 100 billion CFU/day of *L. gasseri* was administered to 87 obese men and women. After 12 weeks, participants in the *L. gasseri* group experienced significant reductions in BMI, waist-to-hip ratio, total body fat mass, and abdominal visceral fat area compared with control subjects who experienced mild to moderate increases in each of these metrics. *L. plantarum* consistently reduces gains in total body, liver, and fat pad weight in rodents fed high-cholesterol diets.[29] In mice *L. plantarum* has been shown to reduce obesity through production of active conjugated linoleic acid (CLA) isomers.[30] In a small double-blind, controlled study involving people with obesity and hypertension, *L. plantarum* administered in a probiotic cheese significantly reduced BMI.[31] There was a trend for *L. plantarum* to lower blood pressure. Women who received dietary counseling plus *L. rhamnosus* and *B. lactis* during their first trimester of pregnancy were significantly less likely to develop central adiposity after delivery than women who only received dietary counseling.[32] *L. rhamnosus* and *B. lactis* supplementation in pregnant women has also been shown to reduce the risk of gestational diabetes.[33] Consumption of a symbiotic shake containing *B. bifidum* together with *L. acidophilus* and oligofructans by elderly diabetics significantly reduces blood glucose and increases HDL-cholesterol levels.[34] *B. breve* strains have been shown to reduce weight gain in rats fed a high-fat, adipogenic diet.[35] In a randomized, double-blind, placebo-controlled trial involving people with a tendency to obesity, after 12 weeks *B. breve* significantly reduced fat mass compared with the placebo.[36] Improvements in liver function and diminished inflammation were indicated by reductions in γ-glutamyl-transpeptidase and high-sensitivity C-reactive protein levels.

Prebiotics in Obesity and Metabolic Syndrome

While the data are thin, evidence from animal models suggests prebiotics may be used to modify the gut microbiota and promote a healthful weight. Feeding inulin-type fructans to genetically obese mice significantly elevates cecal *Bifidobacterium and Lactobacillus* populations while decreasing intestinal permeability, plasma lipopolysaccharide (LPS) levels, inflammatory mediators, and fat deposition in visceral, epididymal, and subcutaneous adipose tissues.[37] Rats fed a standard diet enriched with 10% oligofructose for 4 weeks lose significantly more weight than rats fed the same diet alone.[38] There are few human intervention trials studying prebiotics and weight maintenance. In a study of adolescent males, intake of 8 g/day of inulin-type fructans was associated with less weight gain and reduced total fat mass, especially in those with adequate calcium intake.[39] In another study, obese, dyslipidemic,

premenopausal women were given daily doses of a syrup containing 0.14 g/kg of inulin-type fructans, which led to a reduction in weight, body mass index (BMI), fasting insulin levels, and LDL-cholesterol.[40] In a double-blind, randomized, controlled clinical trial examining the effects of prebiotics on weight loss, 21 g/day of oligofructose or an equicaloric control was administered to obese and overweight individuals.[41] After 12 weeks, the group receiving oligofructose lost approximately 1 kg of body weight, most of it fat mass from the trunk region, while slight increases in weight and fat mass were recorded for the placebo group. Additionally, beneficial satiety hormone changes were observed with an increase in peptide-YY and a decrease in ghrelin. Prebiotics represent a vastly underused modality to favorably modulate the gut microbiota to support health. Inulin-type prebiotics, especially in combination with probiotics, are worth consideration in the setting of obesity and metabolic syndrome.

α-Cyclodextrin: A Novel Soluble Dietary Fiber

A viscous soluble dietary fiber called α-cyclodextrin offering significant potential benefits to people with obesity and metabolic syndrome is available as a dietary supplement. α-cyclodextrins are naturally occurring oligosaccharides consisting of 6 D-glucose molecules linked end to end by a-1,4 glycosidic bonds to form a doughnut or truncated cone.[42] It is highly water soluble, its glycosidic bonds are resistant to hydrolysis by human salivary and pancreatic a-amylase, and the hydrophobic interior space of the doughnut or truncated cone complexes with the bi- and triglycerides that constitute most dietary fat.[42] When α-cyclodextrin is ingested with a meal containing fat, it complexes the fat at up to a 1:9 w/w ratio forming microemulsions.[43] Due to its high water solubility and resistance to salivary and pancreatic α-amylase, an ingested dose of acyclodextrin can pass intact and in solution through the stomach and small intestine into the colon.[44] α-cyclodextrin interferes with fat absorption by preventing the hydrolysis of bi- and triglycerides into free fatty acids and glycerol. One gram of α-cyclodextrin can complex up to 9 grams of dietary fat. In human studies, α-cyclodextrin has been shown to stabilize weight in obese people with diabetes mellitus without any change in diet.[45] When weight change was normalized for dietary energy intake, people receiving α-cyclodextrin lost weight. In a double-blind study involving healthy but overweight adults, α-cyclodextrin alone facilitated significant weight loss over 2 months without diet or exercise.[46] If dyslipidemia is present, α-cyclodextrin significantly lowers cholesterol and LDL-cholesterol levels and blunts postprandial hypertriglyceridemia.[45-47] Among healthy but overweight people, α-cyclodextrin reduced insulin levels by nearly 9.5%, indicating improved insulin sensitivity.[46] In people with obesity and diabetes, α-cyclodextrin increases adiponectin levels especially in those not using insulin.[45] Higher adiponectin levels favorably impact insulin tolerance, glucose regulation, and weight reduction.[48] α-cyclodextrin is an effective adjunct to an energy-reduced diet as well as providing support to glucose and lipid metabolism.

α-Amylase Inhibitors from White Bean (*Phaseolus Vulgaris*)

White bean contains a variety of α-amylase inhibitor isoforms.[49] A standardized water extract of non-GMO white kidney beans is available as the branded preparation Phase 2 that has been well documented to inhibit salivary, intraduodenal, and intraileal α-amylase.[49] Human studies document significant reductions in postprandial glucose and insulin levels.[50] In a randomized, double-blind, placebo-controlled trial involving overweight and obese people, those receiving the white bean α-amylase inhibitor lost weight over 12 weeks, while those receiving placebo gained weight.[49] In a study involving mildly overweight people, the white bean α-amylase inhibitor plus 0.5 mg/d of chromium picolinate experienced a significant reduction in body weight, BMI, fat mass, adipose tissue thickness, and waist, hip and thigh circumferences while maintaining lean body mass.[51] In conjunction with a 1200 calorie/day, low-fat diet, white bean α-amylase inhibitor combined with inulin and *Garcinia cambogia* extract resulted in significant drop in weight BMI and percent body fat compared with baseline, while there was no significant change in these parameters in the placebo group.[52]

Conclusion

Conventional approaches to obesity and metabolic syndrome are generally acknowledged to have limited success. The fundamentally moralistic view that obesity is an imbalance between excessive dietary intake and inadequate activity has been demonstrated to be exceedingly simplistic. The appreciation that the pathogenesis of obesity, type 2 diabetes mellitus, and metabolic syndrome involves gastrointestinal dysbiosis and systemic inflammation may well prove transformative to the management of weight and metabolism. While low-carbohydrate and low-fat diets may have similar long-term effects on weight, low-

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carbohydrate diets appear to offer additional benefits for glucose and lipid metabolism. Probiotics and prebiotics offer exciting modalities to favorably modify gut dysbiosis and reduce systemic inflammation, thereby promoting healthful weight and metabolism. α-cyclodextrin and white bean α-amylase inhibitors offer ways to safely reduce absorption of dietary fat and starch, thereby promoting weight loss and healthful glucose and lipid levels.

Notes

1. Nejat EJ, Polotsky AJ, Pal L. Predictors of chronic disease at midlife and beyond – the health risks of obesity. *Maturitas*. 2010;65:106–111.
2. Forouhi NG, Wareham NJ. Epidemiology of diabetes. *Medicine (Abingdon)*. 2014;42:698–702.
3. Wang Y, Beydoun MA. The obesity epidemic in the United States—gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007;29:6–28.
4. Obesity and overweight [online fact sheet]. World Health Organization. January 2015. http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Accessed Sept. 23, 2015.
5. Kaur J. A comprehensive review on metabolic syndrome. *Cardiol Res Pract*. 2014;2014:943162.
6. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.
7. Wong ND. Intensified screening and treatment of the metabolic syndrome for cardiovascular risk reduction. *Prev Cardiol*. 2005;8:47–52.
8. Atallah R, Filion KB, Wakil SM, et al. Long-term effects of 4 popular diets on weight loss and cardiovascular risk factors: a systematic review of randomized controlled trials. *Circ Cardiovasc Qual Outcomes*. 2014;7:815–827.
9. Van Gaal LF, Wauters MA, De Leeuw IH. The beneficial effects of modest weight loss on cardiovascular risk factors. *Int J Obes Relat Metab Disord*. 1997;21 Suppl 1:S5–S9.
10. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:285–293.
11. Hill JO, Wyatt HR. Role of physical activity in preventing and treating obesity. *J Appl Physiol*. 2005;99:765–770.
12. Goedecke JH, Micklesfield LK. The effect of exercise on obesity, body fat distribution and risk for type 2 diabetes. *Med Sport Sci*. 2014;60:82–93.
13. Duncan GE, Perri MG, Theriaque DW, Hutson AD, Eckel RH, Stacpoole PW. Exercise training, without weight loss, increases insulin sensitivity and postheparin plasma lipase activity in previously sedentary adults. *Diabetes Care*. 2003;26:557–562.
14. Terranova CO, Brakenridge CL, Lawler SP, Eakin EG, Reeves MM. Effectiveness of lifestyle-based weight loss interventions for adults with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. Epub 2014 Dec 19.
15. MacLean PS, Wing RR, Davidson T, et al. NIH working group report: Innovative research to improve maintenance of weight loss. *Obesity (Silver Spring)*. 2015;23:7–15.
16. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004;101:15718–15723.
17. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006;444:1027–1031.
18. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006;444:1022–1023.
19. Schwiertz A, Taras D, Schafer K, et al. Microbiota and SCFA in lean and overweight healthy subjects. *Obesity (Silver Spring)*. 2010;18:190–195.
20. Duncan SH, Lobley GE, Holtrop G, et al. Human colonic microbiota associated with diet, obesity and weight loss. *Int J Obes (Lond)*. 2008;32:1720–1724.
21. Jumpertz R, Le DS, Turnbaugh PJ, et al. Energy-balance studies reveal associations between gut microbes, caloric load, and nutrient absorption in humans. *Am J Clin Nutr*. 2011;94:58–65.
22. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr*. 2008;87:534–538.
23. Collado MC, Isolauri E, Laitinen K, Salminen S. Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *Am J Clin Nutr*. 2008;88:894–899.
24. Xu X, Hui H, Cai D. Differences in fecal Bifidobacterium species between patients with type 2 diabetes and healthy individuals. *Nan Fang Yi Ke Da Xue Xue Bao*. 2012;32:531–533,564. [In Chinese, abstract in English.]
25. Woodard GA, Encarnacion B, Downey JR, et al. Probiotics improve outcomes after Roux-en-Y gastric bypass surgery: a prospective randomized trial. *J Gastrointest Surg*. 2009;13:1198–1204.
26. Zarrati M, Salehi E, Nourijelyani K, et al. Effects of probiotic yogurt on fat distribution and gene expression of proinflammatory factors in peripheral blood mononuclear cells in overweight and obese people with or without weight-loss diet. *J Am Coll Nutr*. 2014;33:417–425.
27. Andreasen AS, Larsen N, Pedersen-Skovsgaard T, et al. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. *Br J Nutr*. 2010;104:1831–1838.
28. Kadooka Y, Sato M, Imaizumi K, et al. Regulation of abdominal adiposity by probiotics (Lactobacillus gasseri SBT2055) in adults with obese tendencies in a randomized controlled trial. *Eur J Clin Nutr*. 2010;64:636–643.
29. Xie N, Cui Y, Yin YN, et al. Effects of two Lactobacillus strains on lipid metabolism and intestinal microflora in rats fed a high-cholesterol diet. *BMC Complement Altern Med*. 2011;11:53.
30. Lee K, Paek K, Lee HY, Park JH, Lee Y. Antiobesity effect of trans-10,cis-12-conjugated linoleic acid-producing Lactobacillus plantarum PL62 on diet-induced obese mice. *J Appl Microbiol*. 2007;103:1140–1146.
31. Sharafedtinov KK, Plotnikova OA, Alexeeva RI, et al. Hypocaloric diet supplemented with probiotic cheese improves body mass index and blood pressure indices of obese hypertensive patients – a randomized double-blind placebo-controlled pilot study. *Nutr J*. 2013;12:138.
32. Ilmonen J, Isolauri E, Poussa T, Laitinen K. Impact of dietary counselling and probiotic intervention on maternal anthropometric measurements during and after pregnancy: a randomized placebo-controlled trial. *Clin Nutr*. 2011;30:156–164.
33. Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. *Br J Nutr*. 2010;103:1792–1799.
34. Moroti C, Souza Magri LF, de Rezende Costa M, Cavallini DC, Sivieri K. Effect of the consumption of a new symbiotic shake on glycemia and cholesterol levels in elderly people with type 2 diabetes mellitus. *Lipids Health Dis*. 2012;11:29.
35. Kondo S, Xiao JZ, Satoh T, et al. Antiobesity effects of Bifidobacterium breve strain B-3 supplementation in a mouse model with high-fat diet-induced obesity. *Biosci Biotechnol Biochem*. 2010;74:1656–1661.
36. Minami J, Kondo S, Yanagisawa N, et al. Oral administration of Bifidobacterium breve B-3 modifies metabolic functions in adults with obese tendencies in a randomised controlled trial. *J Nutr Sci*. 2015;4:e17.
37. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*. 2009;58:1091–1103.
38. Delzenne NM, Kok N, Deloyer P, Dandrifosse G. Dietary fructans modulate polyamine concentration in the cecum of rats. *J Nutr*. 2000;130:2456–2460.
39. Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. *J Pediatr*. 2007;151:293–298.
40. Genta S, Cabrera W, Habib N, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. *Clin Nutr*. 2009;28:182–187.
41. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr*. 2009;89:1751–1759.
42. Del Valle EM. Cyclodextrins and their uses: a review. *Process Biochem*. 2004;39:1033–1046.
43. Artiss JD, Brogan K, Brucal M, Moghaddam M, Jen KL. The effects of a new soluble dietary fiber on weight gain and selected blood parameters in rats. *Metabolism*. 2006;55:195–202.
44. Irie T, Uekama K. Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. *J Pharm Sci*. 1997;86:147–162.
45. Grunberger G, Jen KL, Artiss JD. The benefits of early intervention in obese diabetic patients with FBCx: a new dietary fibre. *Diabetes Metab Res Rev*. 2007;23:56–62.
46. Comerford KB, Artiss JD, Jen KL, Karakas SE. The beneficial effects of α-cyclodextrin on blood lipids and weight loss in healthy humans. *Obesity (Silver Spring)*. 2011;19:1200–1204.
47. Jarosz PA, Fletcher E, Elserafy E, Artiss JD, Jen KL. The effect of α-cyclodextrin on postprandial lipid and glycemic responses to a fat-containing meal. *Metabolism*. 2013;62:1443–1447.
48. Waki H, Tontonoz P. Endocrine functions of adipose tissue. *Annu Rev Pathol*. 2007;2:31–56.
49. Barrett ML, Udani JK. A proprietary alpha-amylase inhibitor from white bean (Phaseolus vulgaris): a review of clinical studies on weight loss and glycemic control. *Nutr J*. 2011;10:24.
50. Layer P, Zinsmeister AR, DiMagno EP. Effects of decreasing intraluminal amylase activity on starch digestion and postprandial gastrointestinal function in humans. *Gastroenterology*. 1986;91:41–48.
51. Celleno L, Tolaini MV, D'Amore A, Perricone NV, Preuss HG. A dietary supplement containing standardized Phaseolus vulgaris extract influences body composition of overweight men and women. *Int J Med Sci*. 2007;4:45–52.
52. Thom E. A randomized, double-blind, placebo-controlled trial of a new weight-reducing agent of natural origin. *J Int Med Res*. 2000;28:229–233.

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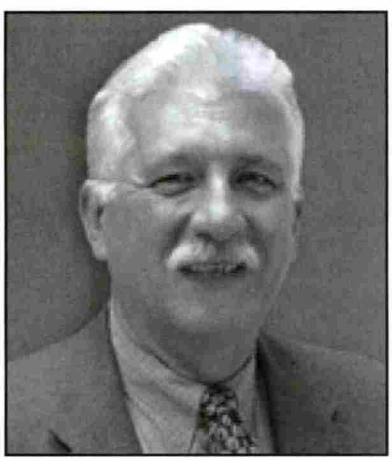

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Three New Biomarkers of Interest for Breast Cancer

by Jacob Schor, ND, FABNO

Three lab tests, though not yet available, may prove useful for menopausal breast cancer patients. Hopefully this article will inspire some laboratory to offer them. The tests are 27-hydroxycholesterol (27-HC), CYP27A1, and CYP7B1.

These tests may help determine prognosis and to advocate for certain treatments.

The most interesting of these three tests is 27-HC. This chemical is a cholesterol metabolite and recently determined to act as a selective estrogen receptor modulator (SERM), stimulating ER+ breast cancer cells to grow. Until recently, estrogen was the only chemical made in the body known to stimulate growth in this way. This changed in 2008 when DuSell reported that 27-HC "... may influence the pathology of breast cancer." Umetani and Shaul confirmed this in 2011 when they reported that 27-HC stimulates growth of ER+ breast cancer tumor cells. [1]

A pair of studies published in November 2013 confirmed these effects in animals and humans. Nelson et al. reported that 27-HC not only stimulates breast cancer growth in petri dishes but also stimulates tumor growth and metastasis in mice.[2] A human study, part of a larger paper by Wu et al., gives us reason to believe that 27-HC influences human tumors as well. [3]

> (27-OHC), a cholesterol metabolite that is different in structure but similar in action to estradiol, could plausibly confer the same benefits and risks as estradiol. On the one hand, it might protect postmenopausal women from osteoporosis and the drying of skin and mucous membranes. On the other, it might increase the risk of breast cancer. Does one role predominate?[4]

Wu et al. compared levels of serum cholesterol, 27-hydroxycholesterol (27-HC), CYP27A1, and CYP7B1 in 66 women with ER-positive breast cancer with levels in 18 cancer-free women matched by age and race.

Remember, 27-hydroxycholesterol (27-HC) is a cholesterol metabolite. The two CYP450 enzymes, CYP27A1 and CYP7B1, regulate 27-HC; CYP27A1 is the enzyme that makes 27-HC while CYP7B1 breaks it down.

Wu found that "Women with cancer had significantly more 27-HC in their normal breast tissue than controls and even more in their tumors." 27-HC levels were 3-fold higher in normal breast tissue of cancer patients and another 2.3 times higher in the actual tumors. Breast cancer patients with low levels of the enzyme CYP7B1, the enzyme that breaks down 27-HC, did not survive as long as women with high levels.[5,6]

While it is tempting to think that testing women for these biomarkers will be useful, this might not be as straightforward as we would wish. In Wu's data, no association was seen between tumor 27-HC levels and serum levels of either 27-HC or total cholesterol, so simply measuring blood serum levels of either might not help; no association was found between serum levels and healthy breast tissue 27-HC levels. So simple blood tests may not be as helpful as we would like. Levels of these enzymes may prove more useful.

This chemical 27-HC may prove to be the missing link between metabolic syndrome, obesity, cholesterol, and estrogen-sensitive cancers.[7] Quite a few cancers are strongly associated with obesity, including "endometrial, esophageal adenocarcinoma, colorectal, postmenopausal breast, prostate, and renal" cancer.[8,9] Elevated cholesterol levels promote formation of larger tumors and enhance metastasis. The increased conversion of cholesterol to 27-HC may be the explanation that links these conditions to cancer.[10] Of these cancers, a few seem to be stimulated by estrogen, and so aromatase inhibitors may be useful to lower estrogen. While this strategy is well established for treating breast cancer, there are suggestions that aromatase inhibition may prove useful for endometrial and ovarian cancers.[11,12] Reducing 27-HC could play a role in more than breast cancer.

In the breast cancer patients tested in Wu's study, the more aggressive tumors had higher levels of CYP27A1, the enzyme that converts cholesterol to 27-HC. Tumors get 27-HC from the blood but also convert cholesterol into 27-HC within their own cells. The enzyme that breaks down 27-HC, CYP7B1, is also important: patients with low tumor levels of CYP7B1 did not survive as long as patients with high levels.

Thus both of these enzymes could become treatment targets; lower the

CYP27A1 and/or increase CYP7B1 if you can.

In a separate animal experiment, Nelson implanted mice bred to have high cholesterol with breast cancer cells. Putting these mice on high-fat diets increased production of 27-HC, and over a period of 15 days, their tumors grew 30% more. (This provides a rationale for menopausal women with ER + BC to avoid high-fat diets.) Treating these mice with statins both lowered their cholesterol levels and slowed tumor growth. Chemically blocking CYP27A also slowed tumor growth.

There is limited information on how 27-HC affects health. Patients with chronic obstructive pulmonary disease (COPD) have high levels, and it is thought that the 27-HC may play a role in the fibrotic changes seen in their lung tissues.[13] 27-HC levels increase with rising cholesterol levels, and one theory is that 27-HC "... may act as a compensatory mechanism in a condition of larger plasma cholesterol pool." That is, as a way to manage excess cholesterol.[14] High levels of 27-HC are markers of neurodegenerative diseases and have been proposed as the link between hypercholesterolemia and Alzheimer's disease.[15,16]

This pair of enzymes, the CYP27A1 enzyme that makes 27-HC and the CYP7B1 enzyme that breaks it down, may in the future provide treatment options. At this point, our understanding of how to influence either is limited. It has been reported that dexamethasone, growth hormone, and IGF-1 stimulate CYP27A1 production. Thus these would potentially be "bad" for breast cancer patients. Well, we kind of already knew that. Thyroid hormone (T4) has the opposite effect, inhibiting CYP27A1.[17] This may be an argument for being more forward in treating subclinical hypothyroidism in breast cancer patients.

Dietary phytosterols may also inhibit 27-HC production.[18] Perhaps some of the natural cholesterol lowering agents will do the same thing as statins? It is clear, though, that statins lower 27-HC levels, and this may be why these drugs appear to sometimes impede breast cancer.

These recent publications should shift how we view breast cancer. At a minimum, we have new biomarkers to follow, 27-HC, CYP27A1, and CYP7B1, biomarkers that could become targets for treatment. Cholesterol can no longer be seen as unrelated to breast cancer.

A number of papers link statin use to improved breast cancer outcomes. In July 2013 Brewer et al. reported that statin use by women with inflammatory breast cancer significantly improved progression-free survival, cutting hazard ratios by half.[19] In November 2012 Nielsen et al. reported that people who take statins had a lower risk of dying

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from cancer than non-statin users. These researchers had analyzed the causes of death from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, and followed them until December 31, 2009. Of patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins. Those Danes who had taken statins had a 15% lower risk of dying from any cause or from cancer. The reduced cancer-related mortality among statin users was observed for each of 13 cancer types.[20]

In 2013, Teemu Murtola associated statin use with a possible 66% reduction in risk of dying from breast cancer. Death rate among statin users was 7.5% while among non-statin users it was 21%. Women with localized disease taking statins were 67% less likely to die than nonusers (hazard ratio, 0.33).[21]

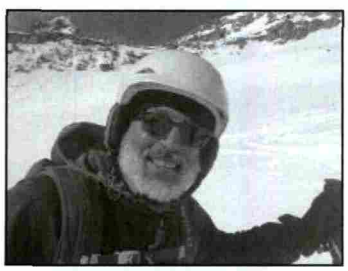
Could the possible benefits from taking statins be the result of lowering 27-HC levels? Could other strategies such as diet and exercise that lower cholesterol have a similar impact on 27-HC and breast cancer? We do not know the answers to these questions.

Information from two recent papers published in August and September 2015 should be added to the considerations that a woman with a history of breast cancer and her oncologist need to ponder in making her choice of adjunctive treatments, whether she takes tamoxifen or an aromatase inhibitor.

Norman Javitt reported in August 2015 in the journal *Steroids* that tamoxifen blocks several steps in the cholesterol metabolic pathway so that, "In genetically disposed women, tamoxifen may increase the amount of 27-hydroxycholesterol in breast tissue."[22] This fact might argue against using tamoxifen in obese women with high cholesterol. Knowing their levels of 27-HC, CYP27A1, and CYP7B1 might help inform a decision.

Last September, Natalia Mast et al. identified half a dozen drugs already on the market that inhibit CYP27A1 and that might thus be useful in lowering 27-HC. Two of them, anastrozole (Arimidex) and fadrozole (Afema), are aromatase inhibitors and are already used to treat breast cancer.[23] When tested in mice, anastrozole lowered plasma 27-HC 2.6-fold in a week. Thus anastrozole, a drug already on offer, might offer dual benefit for certain women over letrozole (Femara), lowering not just estrogen but also 27-HC.[24]

Medical oncologists rarely concern themselves with cholesterol, considering blood lipids to be the province of general practitioners and cardiologists. It is time to change this. High cholesterol levels may be a clear risk for breast cancer progression in ER+ postmenopausal women. Lowering total cholesterol, either through lifestyle or drugs, could reduce a woman's risk of getting breast cancer or slow the cancer's progression. It is tempting to write that all medical practitioners must concern themselves with the whole patient, but doing so would be kind of preaching to the choir when writing for the *Townsend Letter*; yet it is hard to think of a better way to express this. It is certainly high time that we pay attention to and be concerned about cholesterol in breast cancer patients.



Jacob Schor, ND, FABNO, is a naturopathic doctor and a 1991 graduate of NCNM. He has practiced in Denver, Colorado, with his wife Rena Bloom, ND, ever since. Dr. Schor is a past board member of the American Association of Naturopathic Physicians and a current board member of the Oncology Association of Naturopathic Physicians (OncANP). He is a past president of OncANP and also of the Colorado Association of Naturopathic Physicians (CANP). He is a frequent contributor to the *Townsend Letter* and the *Natural Medicine Journal*.

Notes

1. Umetani M, Shaul PW. 27-Hydroxycholesterol: the first identified endogenous SERM. *Trends Endocrinol Metab.* 2011 Apr;22(4):130–135. doi:10.1016/j.tem.2011.01.003. Epub 2011 Feb 23.
2. Nelson ER, Wardell SE, Jasper JS, et al. 27-Hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. *Science.* 2013 Nov 29;342(6162):1094–1098. doi:10.1126/science.1241908.
3. Wu Q, Ishikawa T, Sirianni R, et al. 27-Hydroxycholesterol promotes cell-autonomous, ER-positive breast cancer growth. *Cell Rep.* 2013 Nov 14;5(3):637–645.
4. Warner M, Gustafsson JA. On estrogen, cholesterol metabolism, and breast cancer. *N Engl J Med.* 2014 Feb 6;370(6):572–573. doi:10.1056/NEJMcibr1315176.
5. Kaiser J. Cholesterol forges link between obesity and breast cancer. *Science.* 2013 Nov 29;342(6162):1028. doi:10.1126/science.342.6162.1028.
6. Wu Q, Ishikawa T, Sirianni R, et al. 27-Hydroxycholesterol promotes cell-autonomous, ER-positive breast cancer growth. *Cell Rep.* 2013 Nov 14;5(3):637–645. doi:10.1016/j.celrep.2013.10.006. Epub 2013 Nov 7.
7. Lee WR, Ishikawa T, Umetani M. The interaction between metabolism, cancer and cardiovascular disease, connected by 27-hydroxycholesterol. *Clin Lipidol.* 2014;9(6):617–624.
8. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. *J Obes.* 2013;2013:291546. doi:10.1155/2013/291546. Epub 2013 Aug 29.
9. McDonnell DP, Park S, Goulet MT, et al. Obesity, cholesterol metabolism, and breast cancer pathogenesis. *Cancer Res.* 2014 Sep 15;74(18):4976–4982. doi:10.1158/0008-5472.CAN-14-1756. Epub 2014 Jul 24.
10. Ben-Shmuel S, Rostoker R, Scheinman EJ, LeRoith D. Metabolic syndrome, type 2 diabetes, and cancer: epidemiology and potential mechanisms. *Handb Exp Pharmacol.* Epub 2015 Apr 23.
11. Thangavelu A, Hewitt MJ, Quinton ND, Duffy SR. Neoadjuvant treatment of endometrial cancer using anastrozole: a randomised pilot study. *Gynecol Oncol.* 2013 Dec;131(3):613–618. doi:10.1016/j.ygyno.2013.09.023. Epub 2013 Sep 27.
12. Hirakawa H, Yokoyama Y, Yoshida H, Mizunuma H. Inhibitory effects of aromatase inhibitor on estrogen receptor-alpha positive ovarian cancer in mice. *J Ovarian Res.* 2014 Jan 10;7(1):4. doi:10.1186/1757-2215-7-4.
13. Kikuchi T, Sugiura H, Koarai A, et al. Increase of 27-hydroxycholesterol in the airways of patients with COPD: possible role of 27-hydroxycholesterol in tissue fibrosis. *Chest.* 2012 Aug;142(2):329–337.
14. Bertolotti M, Del Puppo M, Corna F, et al. Increased appearance rate of 27-hydroxycholesterol in vivo in hypercholesterolemia: a possible compensatory mechanism. *Nutr Metab Cardiovasc Dis.* 2012 Oct;22(10):823–830. doi:10.1016/j.numecd.2011.02.009. Epub 2011 May 4.
15. Leoni V, Caccia C. Oxysterols as biomarkers in neurodegenerative diseases. *Chem Phys Lipids.* 2011 Sep;164(6):515–524. doi:10.1016/j.chemphyslip.2011.04.002. Epub 2011 Apr 16.
16. Björkhem I, Heverin M, Leoni V, Meaney S, Diczfalusy U. Oxysterols and Alzheimer's disease. *Acta Neurol Scand Suppl.* 2006;185:43–49.
17. Araya Z, Tang W, Wikvall K. Hormonal regulation of the human sterol 27-hydroxylase gene CYP27A1. *Biochem J.* 2003;372:529–534. doi:10.1042/BJ20021651.
18. Brauner R, Johannes C, Ploessl F, Bracher F, Lorenz RL. Phytosterols reduce cholesterol absorption by inhibition of 27-hydroxycholesterol generation, liver X receptor α activation, and expression of the basolateral sterol exporter ATP-binding cassette A1 in Caco-2 enterocytes. *J Nutr.* 2012 Jun;142(6):981–989. doi:10.3945/jn.111.157198. Epub 2012 Apr 25.
19. Brewer TM, Masuda H, Liu DD, et al. Statin use in primary inflammatory breast cancer: a cohort study. *Br J Cancer.* 2013 Jul 23;109(2):318-24. doi:10.1038/bjc.2013.342. Epub 2013 Jul 2.
20. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med.* 2012 Nov 8;367(19):1792–1802.
21. Murtola TJ, Visvanathan K, Artama M, Vainio H, Pukkala E. Statins and breast cancer mortality. American Association for Cancer Research Annual Meeting; April 7, 2013.
22. Javitt NB. Breast cancer and (25R)-26-hydroxycholesterol. *Steroids.* Epub 2015 Aug 20. pii:S0039-128X(15)00226-3. doi:10.1016/j.steroids.2015.08.012.
23. Fadrozole is licensed for use in Japan but apparently not in the US.
24. Mast N, Lin JB, Pikuleva IA. Marketed drugs can inhibit cytochrome P450 27A1, a potential new target for breast cancer adjuvant therapy. *Mol Pharmacol.* 2015 Sep;88(3):428–436. doi:10.1124/mol.115.099598. Epub 2015 Jun 16.

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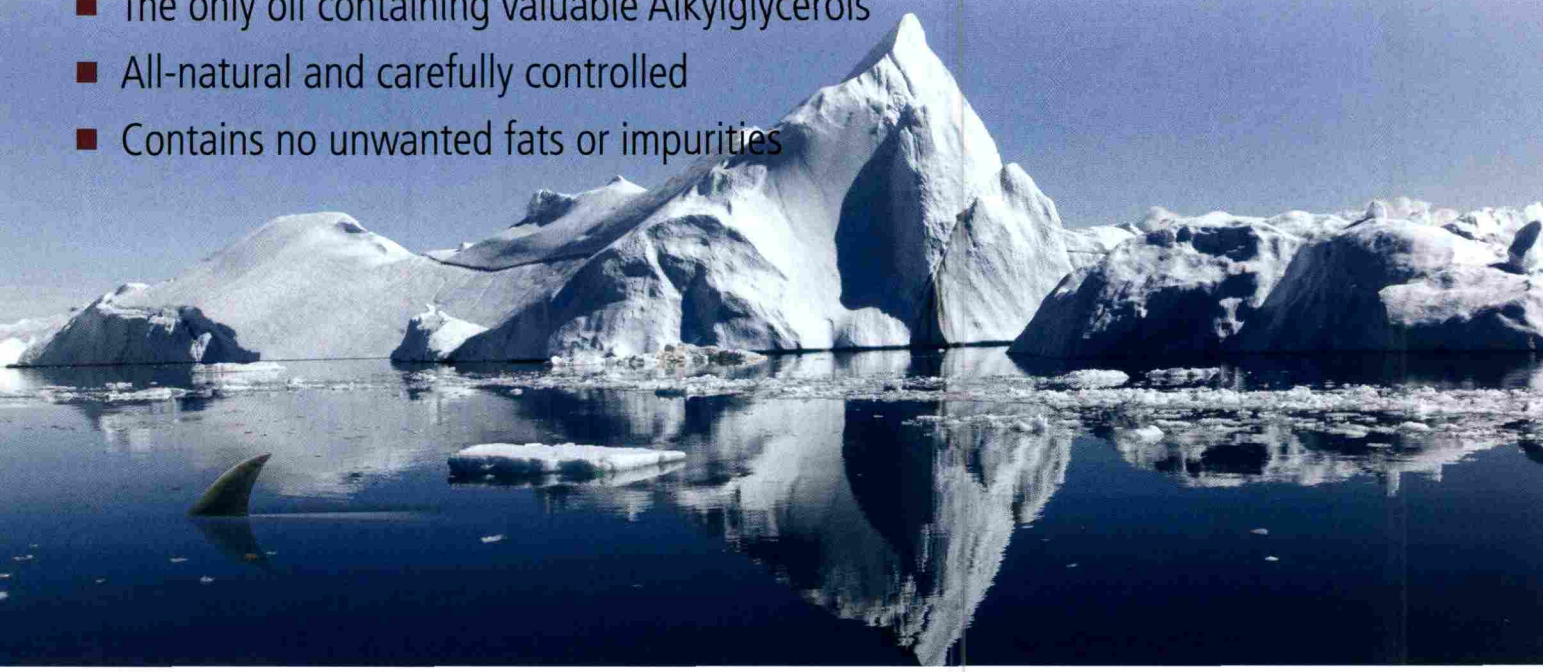

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Toxic Nonmetal Chemicals: New Comprehensive Testing Available

by William Shaw, PhD

Screening for a wide variety of toxic metals has been available for many decades, first by atomic absorption and later by mass spectrometry. The availability of such testing allowed integrative and environmentally oriented physicians to solve clinical problems of their patients who had not experienced adequate resolution of their severe medical symptoms through "conventional" medicine, largely through the use of metal chelating agents.

However, the availability of an economical, accurate, and fast screening tool for a wide range of *nonmetal* toxic chemicals prevalent in the environment lagged considerably behind. Many environmental chemicals could be tested individually, but the vast majority of people are exposed to a wide variety of chemicals in food, water, and air. Since many of the symptoms of nonmetal toxic exposures are similar, what type of testing should a physician order?

If 50 different chemicals were tested at a typical price of $100 each, the total price would be $5000. With insurance companies now notoriously tightfisted about paying for unusual testing, it is to be expected that most or all of this testing would be denied coverage. Another common consideration is that such testing may not give any indication of the overall clinical severity of the total toxic exposure. New testing from the Great Plains Laboratory addresses many of these considerations. First, it screens for 168 toxic chemicals in a single urine sample, using state-of-the-art, high-performance liquid chromatography coupled with triple quadrupole mass spectrometry. This includes screening for over 150 organophosphate pesticides, benzene, styrene, xylene, the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D), monoethylphthalate (a major metabolite of the toxic plasticizer diethyl phthalate), six different pyrethroids, and the common gasoline additives MTBE and ETBE.

Organophosphate pesticides are some of the most common insecticides used worldwide. In 2013, the American Association of Poison Control Centers' National Poison Data System reported 2354 single exposures to organophosphate insecticides alone.[1] Two cases were fatal. There were also 578 single exposures to organophosphate insecticides in combination with other insecticides. Of all those exposures, 715 occurred in children younger than 6 years. Organophosphates are widely used in agriculture. EPA data indicate that 35% of apples tested in 2009 had detectable organophosphate residue.[2] Undoubtedly, many exposures to organophosphates go undetected. Organophosphates react with the hydroxyl group of the amino acid serine that is found in all proteins. Many of the severe clinical effects of organophosphate pesticides are due to the reaction of these compounds with acetylcholinesterase, an enzyme found in both the peripheral parasympathetic nervous system as well as the central nervous system. The initial reaction of organophosphates with acetylcholinesterase is reversible. However, a nonenzymatic reaction between the organophosphate and acetylcholinesterase results in an "aging" reaction such that the enzyme is permanently deactivated. The symptoms of organophosphate poisoning are due to a marked excess of acetylcholine as its receptors are overstimulated leading to diarrhea, sweating, lacrimation, and vomiting. Other symptoms include anxiety, headache, convulsions, ataxia, impaired respiration and circulation, and tremor. Associations between organophosphate exposures have also been made for attention deficit with hyperactivity, autism spectrum disorders, impaired fertility, decreased IQ, brain structure abnormalities, psychosis, and depression.[3–6] An example of the value of such testing is given in Table 1. The patient was a 2-year-old child with autism. Toxic chemical exposure is not usually anticipated in a 2-year-old child. The results in Table 1 indicated abnormally elevated values in the urine for the major metabolite of vinyl chloride as well as the major metabolite of many organophosphates. Organophosphate exposure has been connected with mitochondrial damage.[7,8] In addition, the urine of the child had detectable values for metabolites of the gasoline additives MTBE and ETBE, diethylphthalate, styrene, benzene, and xylene (data not shown). The urine of the child also contained extremely high values for a very sensitive marker for mitochondrial damage called tiglylglycine (TG); elevated values

indicate mitochondrial dysfunction.[9] Organic acid testing on the same urine sample revealed high concentrations of lactic acid and high values of the Krebs cycle metabolites succinic acid, fumaric acid, and aconitic acid, which are also consistent with mitochondrial damage.

Both vinyl chloride and diethylphosphate have been associated with autism spectrum disorders, based on epidemiological studies.[10,11] To my knowledge, this appears to be the first case study confirming the presence of either of these chemicals at high concentrations in a child with autism and associating these toxic chemicals with a high concentration of a biochemical marker, tiglylglycine, that is a marker for mitochondrial dysfunction. Autism has previously been reported to be associated with mitochondrial damage, and both vinyl chloride and organophosphate have been associated with mitochondrial damage.[7,812,13] It is interesting that in one of the cases in which the US Department of Health and Human Services (DHHS) made a substantial vaccine damage award to the parents of a child who developed autism shortly after receiving multiple vaccines, the child was later found to have had substantial mitochondrial dysfunction.[14]

Vinyl chloride is one of the most abundant industrial chemicals on earth, with more than 13 billion kilograms produced annually. Its main industrial use is the production of polyvinyl chloride (PVC), which is used for a variety of plastic products, including pipes, wire and cable coatings, and packaging materials. PVC plastics are somewhat rigid so that plasticizers, predominantly phthalates, are frequently added to PVC to obtain better flexibility. Most phthalates are also toxic. In the study on autism, people who lived in homes with PVC floors were more likely to have a child with autism.[15] It is known that vinyl chloride monomer becomes entrapped in PVC dust and can be released slowly over time, and vinyl chloride exposure is associated with angiosarcoma of the liver in both humans and animals.[16] Other organs for which there is increased cancer risk with vinyl chloride exposure include the liver, brain, and lung, and probably the lymphohematopoietic system. Liver damage, severe neurologic disorder, and angioneuropathy have also been associated with increased vinyl chloride exposure.

Pyrethroids are insecticidal chemicals with similarities to naturally occurring pyrethrins but which possess greater toxicity to insects and mammals. *Pyrethrum* is the term used to describe a crude extract of the chrysanthemum flower, which was used by the Chinese for thousands of years. The term *pyrethrins* refers to at least six insecticidal chemicals isolated from pyrethrum. The Agency for Toxic Substances and Disease Registry (ATSDR), the US federal agency that distributes information about toxic chemicals, lists the symptoms associated with pyrethroid exposure: feelings of numbness, itching, burning, stinging, tingling, or warmth that could last for a few hours, dizziness, headache, and nausea that might last for several hours, muscle twitching, reduced energy, changes in awareness, loss of consciousness, incoordination, tremors, convulsions, allergic reactions, and death.[17]

Müller-Mohnssen and Hahn indicate that exposure to pyrethroids can cause neurological symptoms, locomotory disorders reminiscent of multiple sclerosis or Parkinson's and sensory, motor, and vegetative polyneuropathy, leading, for instance, to cardiovascular regulatory disorder.[18] Nonneurological symptoms include immunosuppression with consecutive opportunistic infections, such as *Candida albicans*, most frequently of the alimentary tract, but also dermal and mucosal swellings, lichen-ruber-like efflorescences, loss of hair, and conjunctivitis. Other symptoms are hypoglycemic crises, inhibition of fertility, disturbances of blood clotting, and, most frequently in children, suspected hematopoietic disorders. Children with pyrethrins metabolite concentration above the limit of detection were twice as likely to have ADHD, and hyperactive-impulsive symptoms increased by 50% for every 10-fold increase in pyrethrin metabolites.[19] The effects of pyrethroids in this study were sex specific: pyrethroid biomarkers were associated with increased odds of an ADHD diagnosis and number of ADHD symptoms for boys but not girls.

The pesticide 2,4-dichlorophenoxyacetic acid (2,4-D) is a common systemic herbicide used in the control of broadleaf weeds. It is one of the most widely used herbicides in the world and is a possible carcinogen.[20] Since 2014, Enlist Duo, a herbicide product which contains a 2,4-D salt and glyphosate, has been approved in Canada and the US for use on soybeans and maize that were genetically modified to be resistant to both 2,4-D and glyphosate. Men who work with 2,4-D are at risk for abnormally shaped sperm and impaired fertility.[21] A cohort study found increased risk of ALS among workers exposed to the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) compared with other company employees and found that 2,4-D interfered with myelination in the brain of animals as the result of lactational exposure.[22–24] There ➤

Table 1: Results of Toxic Chemical Analysis on a Child with Autism

Chemical tested	Patient's value	95th percentile	Ratio*
Vinyl chloride metabolite thiodiglycolic acid	2444 mcg/g creatinine	1380 mcg/g creatinine	1.77
Organophosphate metabolite diethylphosphate	16 mcg/g creatinine	12 mcg/g creatinine	1.33
Mitochondrial function marker tiglylglycine	40 mmol/mol creatinine	11 mmol/mol creatinine	3.64

* Ratio is patient's value divided by the 95th percentile of the reference range.

➤

were changes in behavior patterns of animals that included apathy, reduced social interaction, repetitive movements, tremors, and immobility in pups exposed to 2,4-D.[25] Neuritis, weakness, nausea, abdominal pain, headache, dizziness, peripheral neuropathy, stupor, seizures, brain damage, and impaired reflexes have been associated with dermal or oral exposure.[26] 2,4-D is a known endocrine disruptor and can block hormone distribution and cause glandular breakdown. 2,4-D causes indirect disruption of the mitochondrial transmembrane potential, inhibition of oxidative phosphorylation, and decreasing levels of ATP in mitochondria. It is expected that the mitochondrial marker tiglylglycine would be elevated with mitochondrial damage caused by this chemical. The mutagenicity of 2,4-D is due to homologous recombination, A•G mutation, chromosome aberrations, sister chromatid exchange, and DNA damage, and also an increase in the frequency of DNA strand breaks.[26]

Benzene, xylene, styrene, MTBE, and ETBE are volatile chemicals that are all associated with gasoline usage. MTBE and ETBE are gasoline additives used as replacements for tetraethyllead to improve combustion. These chemicals, however, are water soluble and when they leak from underground storage tanks can follow underground water plumes and contaminate underground wells used for drinking water. For example, the municipal water supply of Santa Monica, California, was contaminated in this way. The water wells were shut down for more than 14 years due to contamination with methyl tert-butyl ether (MTBE), a now-banned gasoline additive that was leaking from gas stations in the area. When this happened, the city was forced to rely on imported water for 85% of its needs. In 2006, Santa Monica reached an agreement with three major oil companies responsible for the MTBE contamination to restore the contaminated wells so that they could once again be a viable drinking water source. The wells and new facilities at the Santa Monica Water Treatment Plant began producing potable water again on December 4, 2010.[27]

Almost all chemicals can be reduced by eliminating the sources of contamination, by eating organic foods, drinking reverse osmosis purified water, and living in areas with low air pollution. Sauna treatment, especially sauna treatment using the Hubbard protocol, was especially useful in the treatment of rescue workers exposed to a variety of toxic chemicals in the September 11 terrorist attack in New York City.[28]

Notes

1. Mowry J, Spyker D, Cantilena, Jr. L , McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clin Toxicol (Phila).* 2014;Dec. 52 (10):1032–283.
2. Environments and contaminants: chemicals in food [Web page]. United States Environmental Protection Agency. http://www2.epa.gov/ace/environments-and-contaminants-chemicals-food. Accessed October 5, 2015.
3. Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ Health Perspect.* 119:2011;1189–1195.
4. Bourchard M, Chevrier J, Harley K, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect.* 119:1999;1189–1195.
5. Rauh V, Perera F, Horton M, et al. Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc Natl Acad Sci USA.* 2012;109:7871–7876.
6. Jokanovic M, Kosanovic M. Neurotoxic effects in patients poisoned with organophosphate pesticides. *Environ Toxicol Pharmacol.* 2010;29:195–201.
7. Salama M, El-Morsy D, El-Gamal M, et al. Mitochondrial complex I inhibition as a possible mechanism of chlorpyrifos induced neurotoxicity. *Ann Neurosci.* 2014;Jul;21(3):85–89.
8. Basha PM, Poojary A. Mitochondrial dysfunction in aging rat brain regions upon chlorpyrifos toxicity and disorders of soleucine cold stress: an interactive study. *Cell Mol Neurobiol.* 2014;Jul;34(5):737–756.
9. Bennett M, Powell J, Daniel J, et al. Tiglylglycine excreted in urine in metabolism and the respiratory chain measured by stable isotope dilution GC–MS. *Clin Chem.* 1994;40(10):1879–1883.
10. Windham G, Zhang L, Gunier R, et al. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the San Francisco bay area. *Environ Health Perspect.* 2006;Sep;114(9):1438–1444.
11. Roberts E, English P, Grether J, et al. Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California central valley. *Environ Health Perspect.* 2007;115(10):1482–1489.
12. Weissman J, Kelley R, Bauman M, et al. Mitochondrial disease in autism spectrum disorder patients: a cohort analysis. *PLoS One.* 2008;3(11) :e3815. doi:10.1371/journal.pone.0003815. Epub 2008 Nov 26.
13. Miller M, Radike M, Andringa A, et al. Mitochondrial changes in hepatocytes of rats chronically exposed to vinyl chloride and ethanol. *Environ Res.* 1982;Dec;29(2):272–279.
14. Poling J, Frye R, Shoffner J, et al. Developmental regression and mitochondrial dysfunction in a child With autism. *J Child Neurol.* 2006;February ;21(2):170–172.
15. Larsson M, Weiss B, Janson S, et al. Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. *Neurotoxicology.* 2009;30:822–831.
16. Wagoner J. Toxicity of vinyl chloride and poly(vinyl chloride): a critical review. *Environ Health Perspect.* 1983;52:61–66.
17. Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Pyrethrins and Pyrethroids* [online document]. http://www.atsdr.cdc.gov/toxprofiles/tp155.pdf. Accessed October 12, 2015.
18. Müller-Mohnssen H, Hahn K. A new method for early detection of neurotoxic diseases exemplified by pyrethroid poisoning. *Gesundheitswesen.* 1995;Apr;57(4):214–222.
19. Wagner-Schuman M, Richardson J, Auinger P, et al. Association of pyrethroid pesticide exposure with attention-deficit/hyperactivity disorder in a nationally representative sample of U.S. children. *Environ Health.* 2015;14:44.
20. Loomis D. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. *Lancet Oncol.* 2015;Aug;16(8):891–892.
21. The National Institute for Occupation Safety and Health. Updated June 2014. The effects of workplace hazards on male reproductive health [online publication]. http://www.cdc.gov/niosh/docs/96-132. Accessed October 8, 2015.
22. Burns C, Beard K, Cartmill J. Mortality in chemical workers potentially exposed to 2,4-dichlorophenoxyacetic acid (2,4-D) 1945-94:an update. *Occup Environ Med.* 2001;58:24–30.
23. Duffard R, Garcia G, Rosso S, et al. Central nervous system myelin deficit in rats exposed to 2,4-dichlorophenoxyacteic acid throughout lactation. *Neurotoxicol Teratol.* 1996;18:691–696.
24. Rosso S, Garcia G, Madariaga M, et al. 2,4-Dichlorophenoxyacetic acid in developing rats alters behaviour, myelination and regions brain gangliosides pattern. *Neurotoxicology.* 2001;21:155–163.
25. Bortolozzi A, Duffard R, Evangelista de Duffard A. Behavioral alterations induced in rats by a pre- and postnatal exposure to 2,4-dichlorophenoxyacetic acid. *Neurotoxicol Teratol.* 1999;21(4):451–465.
26. Bukowska B. Toxicity of 2,4-Dichlorophenoxyacetic acid– molecular mechanisms. *Polish J Environ Stud.* 2006;15(3):365–374.
27. Santa Monica water treatment plant [Web page]. Santa Monica Public Works. http://www.smgov.net/santamonicawatertreatmentplant.aspx. Accessed October 12, 2015.
28. Cecchini M, Root D, Rachunow J, et al. Chemical exposures at the World Trade Center: use of the Hubbard sauna detoxification regimen to improve the health status of New York City rescue workers exposed to toxicants. *Townsend Lett.* April 2006. Available at http://www.townsendletter.com/Dec2006/chemexp1206.htm. Accessed October 13, 2015.

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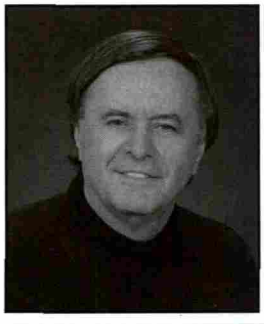

William Shaw, PhD, is board certified in the fields of clinical chemistry and toxicology by the American Board of Clinical Chemistry. Before he founded the Great Plains Laboratory Inc., Dr. Shaw worked for the Centers for Disease Control and Prevention (CDC), Children's Mercy Hospital, University of Missouri at Kansas City School of Medicine, and Smith Kline Laboratories. He is the author of *Biological Treatments for Autism and PDD*, originally published in 1998, and *Autism: Beyond the Basics*, published in 2009. He is also a frequent speaker at conferences worldwide.

He is the stepfather of a child with autism and has helped thousands of patients and medical practitioners to successfully improve the lives of people with autism, AD(H)D, Alzheimer's disease, arthritis, bipolar disorder, chronic fatigue, depression, fibromyalgia, immune deficiencies, multiple sclerosis, OCD, Parkinson's disease, seizure disorders, tic disorders, Tourette syndrome, and other serious conditions.

GPL-TOX

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Every day, we are exposed to hundreds of toxic chemicals through products like pharmaceuticals, pesticides, packaged foods, household products, and environmental pollution. As we have become more accustomed to chemical-laden products, and as our environment has become more contaminated, we have been confronted with an accelerating rate of chronic illnesses.

GPL-TOX tests for 168 toxic chemicals in one urine sample:

- **Organophosphate Pesticides**
- **Phthalates**
- **Vinyl Chloride**
- **Pyrethrin Insecticides**
- **Xylenes**
- **Styrene**
- **MTBE and ETBE**
- **2,4-Dichlorophenoxyacetic Acid** (2,4-D)
- **Tiglyglycine** (marker for mitochondrial dysfunction)

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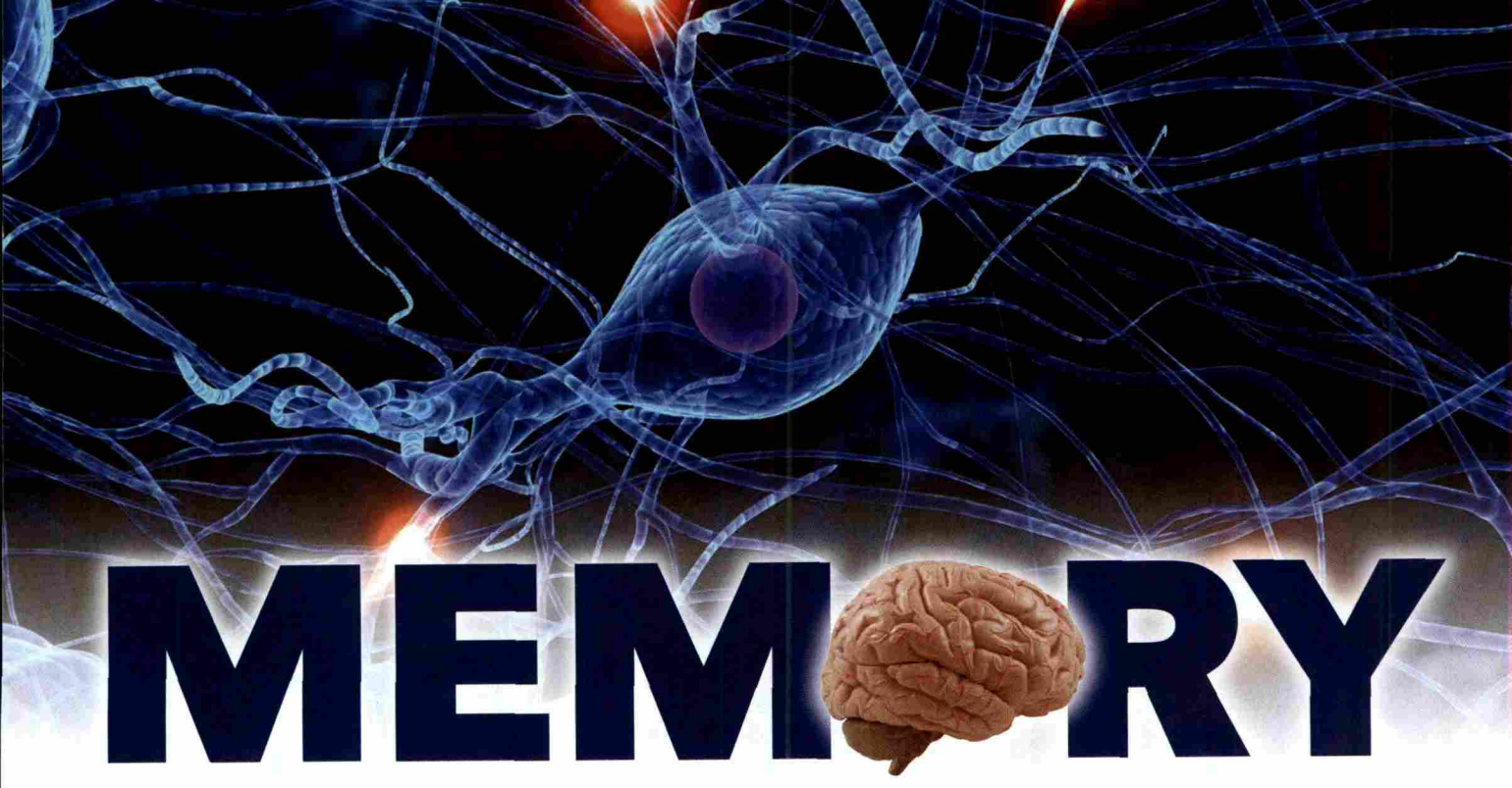

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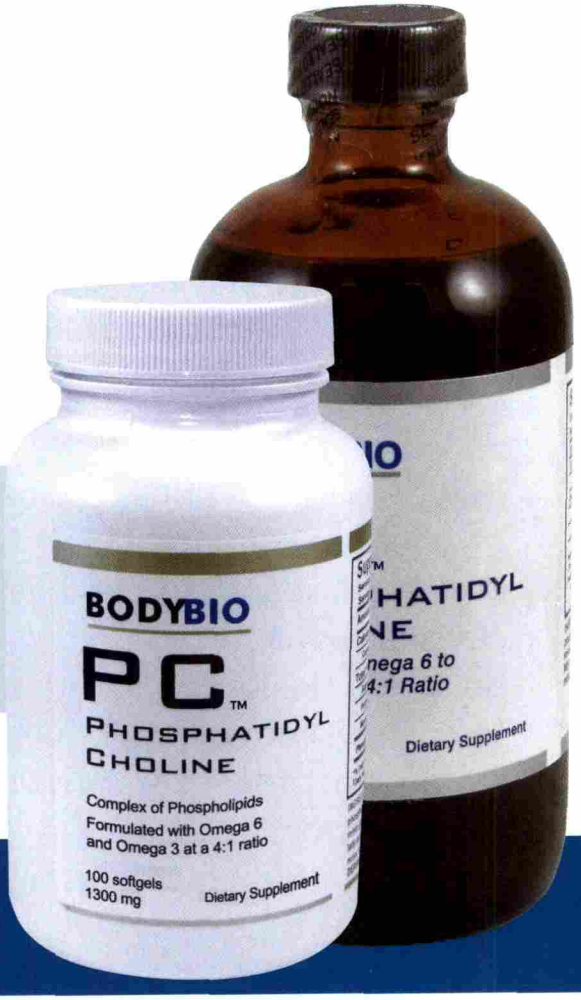

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Diagnosing and Addressing Causes of Chronic Diseases through Bioresonance Testing and Field Control Therapy

by Savely Yurkovsky, MD
SYY Integrated Health Systems Ltd.

> Medicine has failed in the care of chronic diseases. None of the types of research or clinical trials have made a difference because we have not identified a cause.
>
> – Professor Colin J. Alexander, MD

Bioresonance Testing: Why and What It Is?

Since the above quote reflects one of the most important reasons for medical failures in chronic diseases, depth and clinical significance of diagnostic testing in relation to causes of disease hold enormous potential for their cures. Certainly, the latter still requires choosing the right treatment, among the many in conventional and alternative medicine. In this regard the proper diagnostic testing, besides apprehending the very causes of disease, is also indispensable in determining which treatments did or did not fail in addressing the causes. Overall, the importance of high precision diagnostic methods in relation to causes of chronic diseases cannot be overestimated. However before we determine what the right method is, we need to consider the major reason for failure or why "we have not identified a cause." The main reason for this is that the prevailing laboratory or imaging tests cannot identify the pathogens within the very source of chronic diseases – sick internal organs – in the living. This leaves us with the only viable option, which is proficient bioresonance testing. Thanks to the human body's being a macroquantum energetic system with its organs and tissues being electric semiconductors, according to the most fundamental science – physics – such testing becomes medically practical and scientifically sound. It also uses another well-established phenomenon of physics, resonance, which assures energetic resonance communication between the fields of homeopathic vials carrying energetic imprints of the internal organs and potential causative agents of their illness, on one hand and the person's internal organs, on the other for diagnosis.

How Accurate Is Bioresonance Testing?

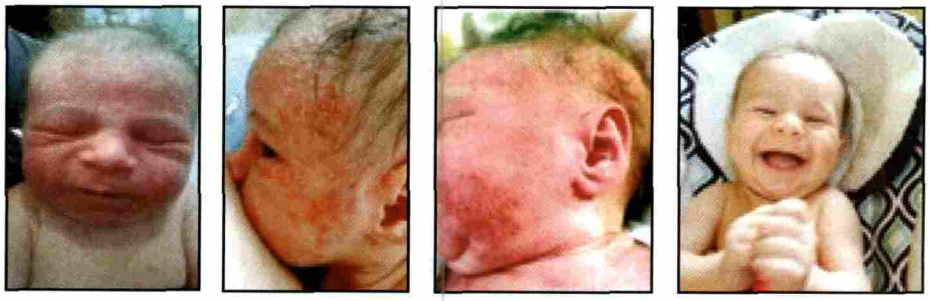
Let us start with the picture that is worth 1000 words.

The photos below are of a 14-day-old boy with a "helluva" rash that was causing him great distress plus lethargy and loss of appetite. Steroid and antifungal ointments prescribed by a dermatologist and his pediatrician, respectively, did not help. Bioresonance testing indicated mercury in his skin and gastrointestinal tract, due to mercury residues in his mom's dental fillings, which were removed before the pregnancy. The test also indicated a double skin infection with candidiasis and staphylococcal bacteria.

Several homeopathic remedies were given to address the findings, as based on the testing, and the house's electromagnetic fields (EMFs) were addressed through the German technology Memon. The rightmost photo below is 10 days later displaying a completely recovered and happy baby.

His pediatrician's feedback: "I have never seen anything like this healing so fast."

The next photo (p. 48, L) reflects some "wildlife," or tapeworms, that exited a woman with head-to-toe ➤



complaints, following only homeopathic treatment. The latter was based on the findings of bioresonance testing that detected tapeworms, which even affected her brain. Each day preceding such exiting sessions she would become extremely irritable and aggressive.

The photo below right is of a similar nature, with the host being a man. This followed only homeopathic treatment based again on the findings of bioresonance testing.

Other convincing cases from my practice on behalf of the accuracy of this testing:

This patient, a medical scientist himself, suffered sudden severe delusional schizophrenia immediately following the insertion of a silver mercury amalgam filling. Yet, following removal of presumably all of his new and old mercury fillings, he remained ill by the time I first saw him.

Bioresonance testing, a special type of applied kinesiology, indicated the ill effects of nickel and mercury on his brain and also concealed a mercury filling in one of his teeth. This could not possibly be visualized, as one can tell from his report.

> Dear Dr. Yurkovsky:
>
> I would personally like to express my gratitude for suggesting to me through your expertise in kinesiology to remove the root canal located at the upper right (maxillary) second bicuspid. You had indicated that this tooth was a primary reason for the presence of nickel in my body. I had the tooth extracted on July 22nd by Dr. B——, an oral surgeon and colleague of mine, and sure enough you were correct.
>
> Upon extraction, Dr. B—— first noted that the tooth had a metal crown. I requested that Dr. B—— crack the tooth open and we discovered not only silver mercury amalgam but also two nickel posts to maintain the crown.
>
> Thank you again.

Another statement indicating similar accuracy of the testing:

Dear Dr. Yurkovsky:

Your evaluation by kinesiology of residual mercury in the lower right 2nd molar area on our patient has been confirmed by an X-ray showing a piece of amalgam filling embedded in the tissue.

Yours truly,
———, DDS

Note that the probability of coming to these conclusions by pure chance is only 1 out of 10,000, yet the bioresonance testing correctly identified this problem.

Another example of bioresonance testing identifying high mercury levels embedded in the body of a tooth that had a mercury filling removed in the past.

8 January 2007
To: ——, DDS
From: Dr. ———
Department of Chemistry
RE: Mercury in extracted tooth devoid of amalgam material.

Dear ———:

We tested the tooth that you sent to our lab for mercury levels. Surprisingly, the tooth spiked to over 5,000 nanograms which maximized out my instrument which was set to measure 0 to 100 nanograms. This means that the tooth most likely contained much more mercury than the amount measured. In the future, we will dissolve the teeth and add just a fraction into the instrument to get a more accurate measure. This tooth was ... #31 and tested as severely toxic in our in vitro toxicity tests, which was not surprising.

A boy with multiple food allergies was fed exclusively organic and allegedly pure foods. However, some of these according to this diagnosis, tested less pure than others and indicated the presence of toxic metals. The subsequent toxicological report below indicated the presence of copper and cadmium (a known carcinogen), which he was consuming regularly.

An environmental inspection of the house for asbestos confirmed its presence after bioresonance testing detected it in the lungs of a boy whom I treated. It is very likely that the testing and following treatment with homeopathic asbestos have prevented the possible future development of the deadly lung cancer mesothelioma.

Another young fella was covered with a disfiguring rash from head to toe without any response to pediatric and dermatological treatments. Bioresonance testing indicated mercury as the culprit. While he responded well to its homeopathic treatment, it was only temporary, as the testing again indicated the presence of mercury in his intestines. The bioresonance testing of his mom's breast milk indicated the presence of mercury, with her mercury fillings being the most likely source. This lab report confirmed high levels of mercury being present in her breast milk.

DATE REPORTED: 09/14/1999
UNITS: MERCURY – BREAST MILK 39 MCG/L
TIME COLLECTED: 4:30 PM
NO REFERENCE DATA IS PROVIDED FOR THE SPECIMEN TYPE SUBMITTED FOR THIS ANALYSIS.
ANALYSIS BY COLD VAPOR ATOMIC ABSORPTION SPECTROSCOPY (CVAAS).

And this, a rather striking example concerns a potentially fatal disease, sarcoidosis, which turns lungs into a web of scars and can do the same to the heart. In the case of this young man, both were getting destroyed by scar tissue, with his heart conduction being affected and his heart rate so slow that it was incompatible with life and necessitated a permanent pacemaker. Among the significant causes related to his disease, bioresonance testing detected fungi, molds from wheat flour (he owned a bakery), and numerous environmental pollutants, including dust, asbestos, and other toxic insulating fibers. Also, he used to carry out housing demolitions. In spite of high doses of prednisone, he was still doing very poorly, experiencing chronic fatigue, difficulty breathing, and other debilitating problems. Almost immediately following just the first treatment based on the aforementioned test's findings, his progress led to the discontinuation of prednisone. To fast-forward his medical course, today and for the last 14 years, this man has lived a normal life without any medications, and only on a FCT maintenance treatment. His pulmonologist states that his breathing tests look better than most other people's, his lung scars could not be detected with chest X-rays

➤

Date: 10/15/2012
Sample particulars:
One sample of LAMB LIVER, as declared by the party was received

TEST RESULTS

S. No.	Test	Results	Limit of Detection
1	Lead (as Pb), ppm	Below detection limit	.01
2	Cadmium (as CD), ppm	0.05	-
3	Copper (as Cu), ppm	115	-
4	Tin (as Sn), ppm	Below detection limit	1.0
5	Arsenic (as As), ppm	Below detection limit	0.05
6	Mercury (as Hg), ppm	Below detection limit	.01

for many years, and his heart barely needs the pacemaker since his severe conduction defect has disappeared.

So, as probable or improbable as his diagnosis was, the end result speaks for itself.

Are There Limitations to Bioresonance Testing?

Since there are limitations to 100% of all human inventions, including space rockets and computers, so too are there limitations to bioresonance testing. The main ones are the scope of understanding what is important to diagnose or ignore in disease and, then deciding on the most effective treatment to address the findings. And the great variety of different techniques and equipment in this field only detracts from these most important issues. Exactly the same holds true for personnel who program computerized bioresonance testing equipment. No matter how much we think that computers are another God, if that were the case, why then have computers failed to find a better energy source than toxic fossil fuels, turn everyone into millionaires by playing the stock market, or prevent and cure all chronic diseases? The simple answer is that people who program computers have failed to find such recipes.

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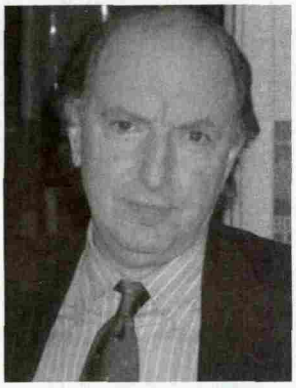

Savely Yurkovsky, MD, has evolved a novel medical model that interfaces important knowledge from biology, medicine, toxicology, and physics. Its primary focus is on the most important aspect of chronic diseases – their causes – along with the most effective diagnostic and therapeutic means to address these. This has transformed the often imprecise medical interventions into a far more effective, exact, and predictable science. He has founded a teaching organization, SYY Integrated Health Systems Ltd., which provides training in this medical system under the concept of FCT (Field Control Therapy). He has presented FCT at many professional symposia in both the US and Europe, including the American College of Advancements in Medicine; American Academy of Environmental Medicine; the annual bioterrorism 2005 conference: Unified Science & Technology for Reducing Biological Threats & Countering Terrorism, affiliated with the Department of Homeland Security; and Harvard Medical School, among others. Dr. Yurkovsky has been nominated for the prestigious Bravewell Leadership Award for "significant contributions to the field of medicine" and "compelling vision for the future of medicine" in 2005. He has authored numerous articles and the book *The Power of Digital Medicine*, which was endorsed by prominent scientists from MIT and Columbia and Stanford Universities, and contributed a chapter on homeopathy to the textbook *Integrative Gastroenterology*, edited by Gerard Mullin, MD, chief of the Integrative Gastroenterology Department at Johns Hopkins University School of Medicine (Oxford University Press; 2011). Dr. Yurkovsky maintains a private practice in Chappaqua, New York.

TAP Integrative Launches Global Membership Initiative

TAP Integrative is globalizing the availability of its peer-reviewed, evidenced educational resource for integrative health-care professionals. The 501(c)(3) nonprofit organization just announced its new international membership opportunity, available to clinicians and practitioners in over 200 countries.

"Clinicians around the world are seeking the latest in integrative health-care approaches and research, and we felt a need to answer their call," said Dr. Lise Alschuler, TAP's executive director. "We are excited we can now offer this opportunity to them."

Headquartered in the US, TAP's membership inquiries sprawl from Ireland to Asia and elsewhere, hence the new membership expansion fulfills an important global demand.

Alschuler notes, "Clinicians aren't the only ones asking for cutting-edge integrative medicine. Patients around the world are increasingly inquisitive about integrative treatments. TAP's new membership options equip global health leaders with the newest, most reputable information they can share with their patients."

Through TAP Integrative membership, professionals in the integrative medicine field gain access to a robust multimedia platform of original, peer-reviewed content from featured TAP clinician experts. New topics, experts, and materials are added regularly, and materials include videos, research reviews, and more. Recent topics include autism spectrum disorder, gluten sensitivity, depression, hypothyroidism, and numerous other issues relevant to millions worldwide.

About TAP

TAP Integrative is an online multimedia nonprofit educational resource for integrative health-care professionals. TAP Integrative's mission is to advance the teaching, advocacy, and practice of integrative medicine. TAP Integrative launched in 2014 as a 501(c)(3) nonprofit educational resource, with Integrative Therapeutics as founding sponsor.

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The Re-emergence of Thallium as a Heavy Metal Contaminant of Human Populations

Michael Rosenbaum, MD, and Ernest Hubbard

Based on an interview with Nancy Faass, MSW, MPH

Thallium is a heavy metal with toxic effects so significant, it was banned for use in American consumer products in 1972, more than two decades before lead was prohibited in gasoline. The toxicity of thallium rivals that of mercury and lead, and the three metals appear consecutively on the periodic table: mercury, atomic number 80; thallium, 81; and lead, 82. Thallium is absorbed readily in all tissues of the body. It can be inhaled, it is absorbed directly through the skin on contact, and it can be consumed in food or liquids. Once thallium is absorbed, it dissolves quickly in liquids and disperses readily into every cell in the body, one of the reasons it is so exceptionally toxic.[1]

Our work in two pilot studies identified the presence of elevated levels of thallium in patient populations, which led to a third pilot project, documenting thallium in the present-day food chain, in cruciferous vegetables such as kale.

Pilot Study 1

EH: The inception of this story dates back to the year 2010. At the Preventative Medical Center of Marin (PMC), we had been asked to test an oral chelation product, a naturally derived detoxification compound made from zeolite by a company out of Cleveland, Life Health Science. They contacted Elson Haas, MD, the Medical Director of PMC, and in a series of conversations asked if he would conduct an independent study of this compound as it related to the removal of toxic heavy metals. My subsequent role involved experimental design, recruitment and coordination of study participants, management and execution of testing and protocols, analysis of lab reports, and reporting of findings. We designed an experiment that was immediately admitted as a pilot study involving 40 people, and the company paid us to perform the research. They provided the chelating agent, and we began submitting lab samples to Doctor's Data, a medical laboratory that Elson had utilized for more than two decades for this type of testing. We found that there was an efficacious response in terms of the removal of certain heavy metals; most notably mercury and lead.

Pilot Study 2

EH: At that time, the company was further refining the chelating product. As the project proceeded they offered us the newer version of the product and asked if we would like to continue with a second phase of the study. Dr. Haas was busy, so Dr. Michael Rosenbaum served as principle investigator on the next phase of the project, which involved setting up another pilot study to test whether or not we found duplication of results, and whether the newer compound was more efficacious. Consequently, we enrolled 10 people from the initial study to provide comparative data and 10 new participants. The data from the two studies provided us a total sample size of 50, which is large enough to be analyzed for statistical significance.

During the second phase of that work I noticed high levels of thallium in a number of the lab reports, and Michael Rosenbaum and I began tracking the thallium levels. We noticed that people who were exhibiting high thallium had

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high thallium in their second lab reports as well. We also noticed that patients with high thallium on the lab results had thallium-related symptoms. One patient, for example, had severe arrhythmia (which later subsided when she stopped eating kale). This raised the question of whether the new, improved version of the chelating product, ORËÁ, is more effectively chelating out thallium, elevating the levels of thallium detected in patients' urine samples. The new product is more highly purified, and has been verified in third-party evaluations in terms of molecular weight, charge profile, and molecular size and is said to be capable of traversing the blood brain barrier.

In retrospect, when I went back and reviewed the results of the first study, there were fairly high thallium levels in that initial study, but compared with the mercury and lead, they did not capture my attention. When I saw thallium emerging as a relatively high toxic metal, reported with frequency in the second study, I started wondering what other issues were involved. Michael and I talked about this a great deal.

Clinical Presentation

Chronic Thallium Exposure

Note: Signs and symptoms of toxicity due to chronic exposure to thallium include fatigue, headaches, depression, hallucinations, psychosis, dementia, poor appetite, leg pain, hair loss, and/or disturbances of vision. Chronic thallium poisoning can occur over a period of months or years, due to absorption through the skin, respiratory tract, or gastrointestinal tract, accumulating to toxic levels. The presentation of chronic thallium toxicity is similar to that of numerous other diseases; consequently, many cases of industrial, environmental, and domestic thallium exposure probably go undetected.[2]

Symptoms of Acute Exposure

MR: We know something about acute exposure because Saddam Hussein put thallium in bread and in birthday cakes and fed it to large numbers of people. They all experienced clinically similar outcomes.[3] The first day involves primarily gastro-intestinal symptoms: nausea, vomiting, and severe abdominal pain. From about day 2 to day 5, thallium primarily affects the nervous system. That begins with ascending neuropathy, starting in the feet and moving up the legs and the thighs. People can experience numbness, tingling, shooting pains, and/or burning sensations in the skin, which can traverse all the way up the body. If the symptoms progress and become more serious, there is a lack of coordination, and ataxia is very common. Of all the heavy metals, thallium is the one that produces ataxia more frequently than any other. People can also develop tremors and seizures, so these are definitely aspects of the clinical picture.[4]

EH: Arrhythmias may be detected even in the absence of physical tremors.

Common Sources of Thallium

According to the US Environmental Protection Agency, sources of thallium pollution include gaseous emission of cement factories, coal-burning power plants, and metal sewers. Thallium has also been associated with petroleum distillation. The US Geological Survey estimates that the annual worldwide production of thallium is approximately 10 metric tons as a by-product of the smelting of copper, zinc, and lead ores. The primary source of elevated thallium concentrations in water is the leaching of thallium from ore-processing operations.

Approximately 60–70% of thallium production is utilized in the electronics industry in superconducting materials, and the remainder in the pharmaceutical industry and optics manufacturing. Thallium is also used in infrared detectors, photo-resistors, and gamma radiation detection equipment. Commercially, thallium was the active ingredient in rat poisons, insecticides, and in marine paint to deter the growth of barnacles on boats.

In medicine, trace amounts of thallium serve as a contrast agent in the visualization of cardiac function and tumors. Thallium is also used in stress testing for risk stratification in patients with coronary artery disease. The amount of thallium utilized is a minute fraction of the toxic doses we have discussed and should pose no health problems.

Physiologic Activity

MR: In addition to effects on the brain, and nervous system, thallium is known to have significant effects on the liver, kidneys, and heart. Approximately 50% of the thallium that goes to the kidney is reabsorbed right back into the kidney rather than being discharged in the urine. That is one of the reasons it takes so long for the body to get rid of this toxin. One of the organs that is most affected by thallium is, therefore, the kidney because the concentration of thallium in the kidney is very high, perhaps five times higher than it is in most other organs.

EH: There is a reverse feedback loop here: the more thallium the body accumulates, the less able it is to rid itself of thallium. So the kidney begins to malfunction, the glutathione detoxification system stops working. The tendency for thallium to stack up in the body increases with every day that goes by, if the source of the exposure is not terminated.

MR: A journal article published in Europe in 2009 reports that thallium bio-accumulates in the body.[5] Thallium binds so tenaciously to sulfur that it persists in hair and in tissue in the body that contains sulfur, released into the body very gradually. In the process of detoxification, toxins are sent to the liver, on to the gall bladder, and on to the small intestine, but 50% of the thallium is reabsorbed right back into the body through the process of enterohepatic recirculation.

Mechanisms of Action

Adverse Effects on Myelin

MR: Thallium is highly toxic to the entire nervous system and more so to that system than perhaps any other system in the body. It upsets the production of myelin, which is responsible for the speed with which nerve impulses are conducted. When myelin is destroyed, that results in lesions that can resemble multiple sclerosis. Thallium de-myelinates nerves and therefore, slows down nerve conduction, in some cases causing symptoms that look like optic nerve neuritis.

EH: From the standpoint of the biochemistry, thallium's atoms, molecules, and ions function like a Jekyll and Hyde phenomenon. Myelin contains both cysteine and methionine, which enable the myelin sheath to retain its structure. It doesn't take much of a breakdown in the myelin sheath to trigger cross firing. In other systems of the body, 10% loss is less of an impairment. You could lose 10% of a muscle and simply feel fatigued. Even 10% of your hair could fall out, and you might not notice it that day. However, with the nervous system, petit mal, grand mal, arrhythmias, tremors, ataxia, these are symptoms that could be triggered in the early stages of myelin degeneration.

MR: The myelin degeneration is consistent with thallium's mechanism of action with respect to sulfur and sulfur-containing bonds, and interference with sulfur metabolism.

Compromised Sulfur Metabolism

MR: Many heavy metals bind to sulfur. Mercury binds to sulfur. Thallium binds tenaciously to both disulfide bonds, which are sulfur-sulfur bonds, and to mercaptans, sulfur-hydrogen bonds. Glutathione contains a mercaptan. Thallium interferes with the synthesis and production of glutathione, which is considered the most important antioxidant in the body. When glutathione is reduced, there is less ability to fight infection, and immune response is diminished. Glutathione is the key detoxifier, and among all the antioxidants, it detoxifies heavy metals. Thallium manages to destroy its nemesis, the very substance that could eliminate the thallium.

Clinically, thallium manifests in the body in hair, nails, and skin – keratin: the protein keratin contains mostly disulfide bonds. When thallium binds to these disulfide bonds they begin to unravel, and their ability to bind to each other becomes disrupted.

EH: Thallium compromises the ability to maintain protein structure and function. To the extent that enzyme function is in direct relationship to the integrity of its structure, enzymes cease to function, and structural proteins lose their ability to function correctly.

MR: The conformation of the proteins is changed. People experience thinning hair and hair loss. That may be one of the first things that people notice and indeed, we have found a few patients who had hair loss that directly correlated with their thallium exposure.

Interruption of Potassium Metabolism

MR: Thallium mimics the structure of potassium. When thallium is expelled in coal-ash, for example, and released into the atmosphere, the thallium content converts into various salts, so it no longer exists as pure organic thallium. It exists as thallium oxide, thallium hydroxide, thallium sulphides, or thallium sulphate, in these ionic forms.[6] The size of the atom of the ion of thallium almost perfectly simulates the size of the atom in the potassium ion. Consequently the body is completely misled, responding as if the thallium were potassium. Thallium, therefore, has the ability to enter into all the metabolic processes that involve potassium. The major biochemical effect of potassium is that it is pumped inside cells, sequestered inside cells, and it exchanges with sodium in order to produce electrical discharges. That is how nerves function.

NF: What about ATP, also?

MR: In substituting for potassium, thallium interferes with the major enzyme in the human body, sodium potassium – ATPase. Although there are over 600 enzymes in the human body, ATPase is so important that it uses about 25% of the total energy in the body. This is especially true in the systems that have high utilization such as the nervous system. Consequently, interference with that enzyme's electrical transmissions through nerves has an impact on all the functions that nerves perform – on sensation, on motor ability, movement, coordination, and cognition (both the ability to think and to remember). All of these functions are at risk.

EH: There is an interesting aspect of the physics here. If you take a very heavy atom that has a strong attraction for electrons, for example thallium, and you compare it with potassium, it becomes apparent that potassium is lighter and has far fewer protons and neutrons in the nucleus. Looking at the atomic diameters of those two atoms when they are fully loaded with electrons, they appear to be quite different. The thallium atom has an electron in its outermost shell that is quite some distance relative to potassium. But when you strip that electron away, it's like taking Pluto out of the solar system. All of a sudden, the size of the remaining ion is so close in diameter to that of potassium, the cell has no way of knowing what it is looking at. It is looking at Dr. Jekyll and doesn't realize that five times the weight of that potassium atom is about to descend on a molecular process in the form of Mr. Hyde. Imagine Dr. Jekyll and Mr. Hyde driving a Ferrari – that's the image.

Compromised Protein Production

MR: One other aspect of the clinical story that we have not discussed involves protein. Thallium exists ionically in two forms – thallium +1 and thallium +3. As thallium +1, the thallium ion mimics potassium. Thallium +3 has the ability to bind to the ribosome of the cell where messenger RNA binds amino acids together to create proteins. Thallium +3 interferes with that process directly. Therefore, it sabotages the production of new proteins, which are used for healing, to make antibodies, to create neurotransmitters.

EH: If you think about nausea as one of the early symptoms, and consider the role of digestive enzymes and of the nervous system in good digestion, those two processes alone could ➤

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explain some of the dramatic effects of thallium. Ribosomes produce digestive enzymes when food is being consumed. If that process is broken down, there is no normal digestion, and there is no normal peristalsis. No wonder people get nauseous. This is one bad atom.

Testing and Clinical Interventions

Clinical Screening

I encourage anyone who is working with patients to put this right on the front of their radar, because there are a great many symptoms being ascribed to other causes that, in fact, may correlate with exposure to thallium or other toxic metals. You will want to put testing in place so that it is available, and it is as affordable as possible. We use a simple questionnaire to determine if patients are a candidate for heavy metal toxicity testing.

Talking Points in Screening Patients

- Are you experiencing symptoms for which there are no other logical explanations?
- Are you exhibiting symptoms of heavy metal toxicity?
- Have you experienced a possible exposure; for example, do you live near a power plant or a refinery? What are your 10 most frequently consumed foods?
- Have you had a toxic heavy metals test in the last 2 or 3 years?

Differential Diagnosis

EH: Metals, including thallium, are important to rule out because of the ubiquitous toxic effects that occur across every major system in the body, including the brain and nervous system. If you have patients with any of the following symptoms, heavy metals testing will be absolutely essential to a good differential diagnosis.

Ruling Out Thallium Toxicity

Thallium toxicity can cause symptoms also associated with a number of other disorders:

- Neurological symptoms including ataxia, tremors, seizure activity (petit mal and grand mal), arrythmia, neuropathies, neuritis, autism
- Neurological disorders: cognitive disruption, amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, and other dementias
- Conditions involving demyelination, which is the hallmark of certain neurodegenerative diseases that include multiple sclerosis and Guillain-Barre syndrome
- Liver toxicity, renal dysfunction or failure
- Energy-related conditions such as fatigue, chronic fatigue syndrome (CFS), and chronic fatigue immune dysfunction syndrome (CFIDS)
- Alopecia
- Idiopathic disorders

Testing

MR: To date, the gold standard in laboratory evaluation is a 24-hour urine collection, with provocation. The provocation agents (EDTA and DMSA) that work well for lead, mercury, and cadmium do not work for thallium. Although, provocation does not appear to be necessary, our testing found that the zeolite supplement ORËÁ appears to increase thallium excretion. The normal range is considered to be below 5 mcg/liter/24 hr, although different reference ranges are sometimes seen. Of all the integrative labs, I think Doctor's Data is best suited to this test. However, even Quest and LabCorp can perform it and may send the sample to a reference lab.

Chemical Analysis of ORËÁ™

ORËÁ™ is a colorless, odorless liquid containing nanoparticles solubilized from clinoptilolite, a naturally occurring zeolite, utilizing a unique proprietary process. Clinoptilolite is federally classified as GRAS (Generally Recognized As Safe). Chemically, it is characterized as a "calcium-sodium-potassium aluminosilicate." Chemical analysis of the initial clinoptilolite material from which ORËÁ™ is produced, performed by a third-party analytical chemical company, shows the following composition: potassium 2.85%, sodium 1.15%, calcium 1.77%, magnesium 0.33%, aluminum 12.22%, silicon 66.73%. As a soluble nanoparticle, ORËÁ™ can be absorbed by the body through the digestive process and carried to the cells through the circulation. The testing of numerous individuals who have used ORËÁ™ confirms that it removes aluminum and other heavy metals from the body.[7]

Hair analysis is used less frequently because the quantitative relationship between exposures, internal levels, and relative concentrations has not been clearly established. "Among poisoning victims, hair concentrations range from 48 ppb to 35,000 ppb with most between 150 and 1500 ppb... With regard to timing, elevated thallium concentrations have been found in hair as early as 2–3 weeks after ingestion in poisonings and as late as 13 months after the cessation of... occupational exposures."[8]

Treatment

MR: The most effective approach to removing thallium from the body is utilizing a substance called "Prussian blue."[9] Prussian blue contains a potassium ion that is replaceable. Thallium displaces the potassium from the Prussian blue, and it occupies the Prussian blue instead. That is how the body gets rid of it.[10] For some reason, the same treatments that typically are used for lead and mercury may not work for thallium. For instance, I often use DMSA to treat mercury poisoning. I use it for lead poisoning. It does not work for thallium. In fact, if you look at the literature, they say that aside from Prussian blue we do not know of much of anything else that really does work. Activated charcoal also helps, and now we know that ORËÁ, a form of zeolite, is helpful. There is also evidence that chlorella binds thallium. It is harder for a clinician to detoxify thallium than it is to detoxify any other heavy metal known.

Prussian blue is a crystal blue lattice of potassium ferric ferrocyanide that exchanges potassium ions from its lattice with thallium ions in the gut lumen, interrupting enterohepatic

recirculation. The Prussian blue releases a negligible amount of cyanide (< 1.6 mg), the minimal lethal dose of cyanide in humans is indicated to be approximately 50 mg.[11]

Thallium in the Food Chain: Connecting the Dots

EH: On July 3rd of 2014 in an otherwise random internet search on what might be the source of the thallium, I stumbled across a Czechoslovakian paper from 2006: "Uptake of Thallium from Artificially Contaminated Soils by Kale."[12] In our attempts to identify the source of the thallium we had ruled out cement manufacturing in Marin County, petroleum distillation, coal-powered plants, and fire-generated electrical plants.

MR: In this Czechoslovakian article they stated directly in the abstract, "It can be concluded that the ability of some plants of the brassica family that are planted as common vegetables to accumulate thallium is very high and can be a serious danger for food chains."[13]

NF: This seems hugely important because currently the green drink du jour is that kale-based green drink...

MR: Kale has become the icon of the green movement.

EH: I had studied enough and talked to Michael enough about the symptom progression and the symptom profile to know that there was a high correlation between the clinical presentation of some of the study participants and high levels of thallium. When the dots got connected to the possibility that it was coming from kale consumption, I emailed everyone in the study with a blinded survey.

Correlating Exposure and Symptoms

EH: When we surveyed participants, we simply asked them to list their top ten favorite vegetables, whether they were organic or not, and approximately how much they ate. People with very low levels of thallium did not eat a lot of crucifers, if any, and people with very high urine thallium were eating kale, cabbage, and broccoli three to ten times a week. There was a fairly strong correlation. So I immediately sat down with Michael, and we began designing the next phase of the study. Within a month Michael and I knew we were onto something.

When we realized that there was a strong correlation between high thallium in the urine, high kale consumption, and thallium-like symptoms, the very first thing that we did was discuss with each of the people who were exhibiting high thallium and eating a lot of crucifers whether or not they would be willing to change their diet, and they were. They also continued taking ORËÁ. We noticed within 60 to 90 days a substantial decline, especially in the case of three people who had all showed significant symptoms and thallium in their urine.

Pilot Study 3

EH: Based on this information, we designed our third pilot study, submitting 121 samples of various foods for testing by two different laboratories for the presence of thallium and other metals.[14] This led to the identification of thallium in the present-day food chain, in approximately 20% of samples, and notably in cruciferous vegetables such as kale.

Outreach

EH: Over the course of the past year, we personally reached out to the local organic community, to growers, and retailers. However, in terms of interviews and publishing, we sat on this data for a year, because we wanted to be sure that this information was going to get out to the public in a productive and conscientious way. On July 7, 2015 an article entitled *Vegetable Detectives* was published on a blog that serves about 150,000 readers (see www.Craftsmanship.com). Since then, the issue has been featured on Salon.com, Huffington Post, at least 10 other blogs, and on the Dr. Oz show (in a segment aired on 10/09/15).

As an interesting update, once our research went public I started receiving calls from people all over the world who had high thallium, from as far away as Tel Aviv and Ireland. I have been Skyping with them and they are showing me their Doctor's Data thallium reports, saying: "Everybody I've been to has put me on a super food-juice diet." I have suggested that they stop their exposure, and I've gotten emails from them indicating that they are actually starting to feel better.

Conclusion

EH: In these pilot projects, we were able to demonstrate on a small scale that both thallium in the urine and symptoms started to abate with a reduction in the intake of cruciferous veggies. This is an important finding, because if patients continue to replenish the source of the thallium every day with kale green drinks or stir-fried vegetables, even the best chelation of thallium is going to be hampered by a continual replenishment.

A second article will be published in a forthcoming issue of *Townsend Letter* with additional (and surprising) information on potential sources of thallium in the food chain, including organic baby food, and updates on (equally surprising) responses from the organic food industry.

Financial Disclosure

The company that produces ORËÁ, the chelating agent, was a financial contributor to the first study, but was not a financial contributor in any way to the second pilot study or the third study, which consisted of vegetable assays. Michael and I did this on our own time and our own money, to buy the

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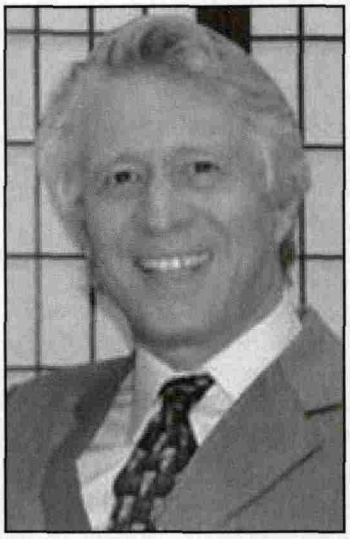
equipment and to gear up to obtain and prepare the samples for the labs. We paid thousands of dollars for heavy metal assays on vegetable samples. The company that produces ORËÁ was not involved in the third study in any way, so there has been no conflict of interest.

Michael Rosenbaum, MD



Dr. Rosenbaum holds a medical degree from Albert Einstein College of Medicine in New York, and a master's degree in biochemistry and metabolic medicine from Hebrew University in Jerusalem, with residence in psychiatry at UCSF and certification in medical acupuncture. His practice, located in the San Francisco Bay Area, emphasizes clinical nutrition, environmental medicine, allergy and immunology, antiaging medicine, and the treatment of chronic health conditions such as Lyme disease. Within integrative medicine, he has served as President and Vice President of the Orthomolecular Medical Society (OMS); editor of the Society's journal; Director and Vice President of the Orthomolecular Health Medicine Organization (OHM); and President and Board member for The Healthy Foundation. Additionally, Dr. Rosenbaum is the author of two successful books, *SuperSupplements*, and *Solving the Puzzle of Chronic Fatigue Syndrome*.

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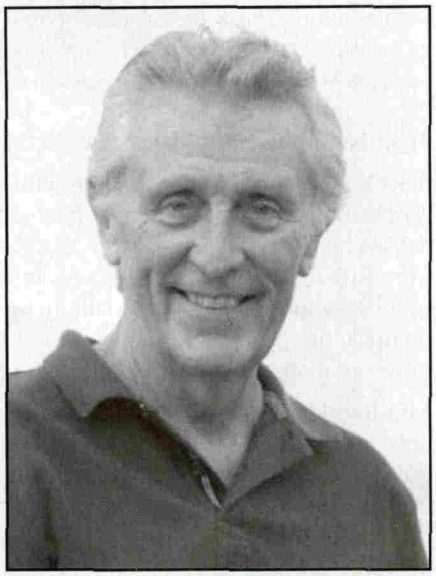
Working collaboratively with clients, Ms. Faass has been active in the development, research, writing, and editing of more than 45 books on functional and integrative medicine by publishers that include Elsevier, Harper, McGraw-Hill, and a dozen other imprints. Director of Writers' Group Inc. for the past 20 years, she also develops articles, white papers, lab manuals, blogs, and Web content. To obtain a 20-minute phone consult at no charge, email info@HealthWritersGroup.com, or call 415-922-6234.

E. Hubbard



Hubbard's academic background includes a Bachelor of Science in genetics/biochemistry from Oregon State University and two years of work toward a PhD in molecular biology and developmental genetics at the University of Minnesota. He has more than three decades of hands-on scientific experience, including research manager of multi-million dollar programs with major corporations such as Eli Lilly and Mitsubishi. He was co-founder and VP of research at Sungene Technologies Corp., and CEO of BioSource Technologies Corp. Within the field of organics, Hubbard has been consultant to a number of food companies and was founder and manager of PureHarvest Corp, a company that developed patented technology for growing crops such as rice without the use of herbicides and pesticides. Within integrative healthcare, he has conducted more than 10 years of research in the field of human aging, and he has served as a health coach to several thousand people.

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References

1. Li JM, Wang W, Lei S, Zhao LL, Zhou D, Xiong H. Misdiagnosis and long-term outcome of 13 patients with acute thallium poisoning in China. *Clin Toxicol (Phila)*. 2014;52(3):181-186.
2. McMillan TM, Jacobson RR, Gross M. Neuropsychology of thallium poisoning. *J Neurol Neurosurg Psychiatry*. 1997;63(2):247-250.
3. Al Hammouri F, Darwazeh G, Said A, Ghosh RA. Acute thallium poisoning: series of ten cases. *J Med Toxicol*. Dec 2011;7(4):306-311.
4. Liu CH, Lin KJ, Wang HM, Kuo HC, Chuang WL, Weng YH, et al. Brain fluorodeoxyglucose positron emission tomography (18FDG PET) in patients with acute thallium intoxication. *Clin Toxicol (Phila)*. 2013;51(3):167-173.
5. Cvjetko P, Cvjetko I, Pavlica M. Thallium toxicity in humans. *Arh Hig Rada Toksikol*. Mar 2010;61(1):111-119.
6. Peter A, Viraraghavan T. Thallium: a review of public health and environmental concerns. *Environment International*. 2005;31(4):493–501.
7. Moyar B. Chemical Analysis of ORËÁ™. Personal communication 10/27/15.
8. Tobin DJ. Hair in Toxicology: An Important Bio-monitor. Cambridge, UK: RSC Publishing. 2005:147.
9. Miller MA, Patel MM, Coon T. Prussian blue for treatment of thallium overdose in the US. *Hosp Pharm*. 2005;40:796-797.
10. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev*. 2003;22(1):29-40.
11. Yang Y, Brownell C, Sadrieh N, et al. Quantitative measurement of cyanide released from Prussian Blue.*Clin Toxicol (Phila)*. 2007;45(7):776-781.
12. Pavlickova J, Abiral J, Smatanova M, et al. Uptake of thallium from artificially contaminated soils by kale (*Brassica oleracea* L. var. *acephala*). *Plant Soil Environ*. 2006;52(12):544-549.
13. Cvjetko P, Cvjetko I, Pavlica M. *Thallium toxicity in humans*. *Arh Hig Rada Toksikol*. Mar 2010;61(1):111-119.
14. Hubbard E. Sage Center Technical Publication 7.3 – 09-11-15. Mill Valley, CA: The Sage Center. 2015:1–45.

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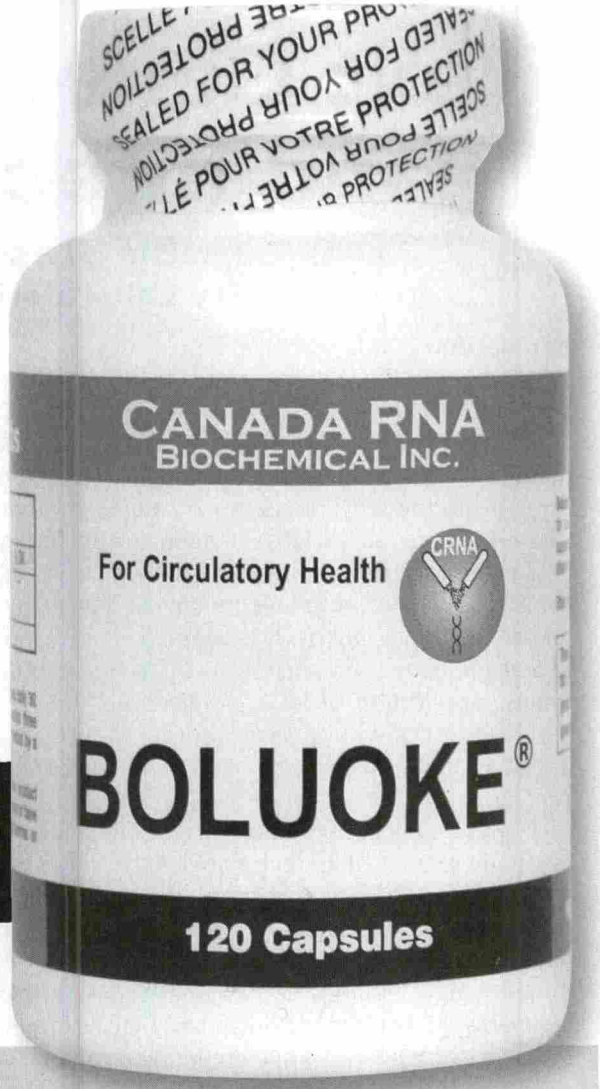

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Next-Generation Sequencing and Infectious Diseases

by Stephen E. Fry, MS, MD
Fry Laboratories, LLC, Scottsdale, Arizona

Introduction

Next-generation DNA sequencing: what does that mean and why would we use it?

Next-generation DNA sequencing (NGS) is a fairly new method for sequencing DNA segments in large numbers at a relatively low cost. NGS is considered by many as the second generation of DNA sequencing technologies and is sometimes referred to as massively parallel sequencing (MPS) due to the central technological advantage over the first-generation methods. It is useful for rapid and accurate characterization of nucleic acid sequences in living things. Application of NGS to infectious disease research and diagnostics will be significant for its use in rapid and accurate pathogen determination in viruses, bacteria, and protozoa.

Current clinical microbiological identification strategies generally rely on older technologies that have been in use for decades. One such technology is microbial culture, often used as a primary enrichment step that may take days. Culture, and by extension the majority of medical microbiology, assumes that a disease-causing bacterium is cultivable. Nonculturable organisms may be entirely missed as an etiologic agent, while emerging or unique organisms could easily be misidentified.[1–4] Traditional alternative technologies include microscopy, serology, and, more recently, molecular-based assays. Molecular technologies commonly rely upon the amplification of pathogen specific DNA for detection. These tests are exceptionally sensitive; however, they can only detect a limited number of organisms or genetic variants. Recently, it is becoming increasingly clear that the majority of bacteria are fastidious (i.e., uncultivable) and present in polymicrobial communities. The true impact of uncultivable bacteria in medicine is likely significantly underestimated in addition to the ever-increasing need for more rapid diagnostic methods. These concepts have not gone unrecognized, and use of rapid culture-independent diagnostics has recently gained scientific and medical attention.

To address these challenges, a number of rapid microbial detection and identification systems have or are being developed. For cultured isolates, new protein based diagnostics such as matrix-assisted laser desorption/ionization time-of-flight (MALDI TOF) mass spectroscopy systems have been approved in Europe, with approval pending in the US. Bruker and BioMérieux have MALDI TOF systems that show promise. The IRIDICA system (previously named IBIS 5000) by Abbott is a rapid MALDI TOF mass spectroscopy PCR system and has been approved for use in Europe. Lastly, a number of point-of-care PCR based systems are available, with the BioFire system representing one of the most recent obtaining FDA approval. Generally, these systems require an initial culture step, rely on a limited reductionist approach, or have limited throughput.

Application

The diagnostic "holy grail" for both microbiologists and clinicians is an all-inclusive molecular approach that can be used in both acute and chronic infectious diseases. This perspective was reinforced at both the American Society of Microbiology and American Association of Clinical Chemistry conference meetings last summer. This view was again reiterated at the First ASM Conference on Rapid Next-Generation Sequencing and Bioinformatic Pipelines for Enhanced Molecular Epidemiologic Investigation of Pathogens last September. These emerging technologies and systems for infectious disease detection are rapidly becoming a reality.

Chronic diseases are also of great interest and represent an immense region of investigation. Examples of such diseases include chronic Lyme disease, chronic wounds, irritable bowel syndrome (IBS), sepsis, dental abscesses, chronic inflammatory disease, and fevers of unknown origin (FUO). Microbial involvement in these illnesses has been established or are suspected. Additionally, research suggests that these systems could have great relevance in the chronic inflammatory disease arena.

The application of molecular-based technology was well represented in recent Lyme disease research.[5] This epidemiologic study of ticks in the San Francisco Bay Area utilized molecular-based approaches to assay for *Borrelia* species. This study demonstrated that 8.1% of the adult ticks harbor a *Borrelia* species and 1.8% have an emerging species, *B. miyamotoi*. This identification was made based on comparative sequence analysis and not by a matching control standard. In other words, the sequenced organism matched that of the textbook *B. miyamotoi* strain. Historically the "gold standard" for *Borrelia* detection has been antibody detection. Of course, these serologic techniques have limitations, such as antigenic cross-reactivity of a related, or sometimes distantly related, species. In sum, identification based on sequence identity in most cases is now considered a gold standard and is sufficient for detection and identification purposes.

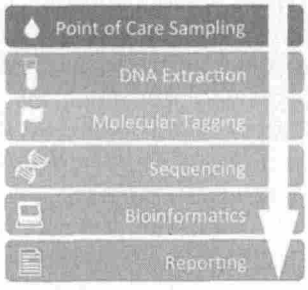
Another rapidly expanding application of NGS-based methods is in stool microbiome analysis. NGS can allow for a comprehensive sequence based approach to studying and characterizing the plethora of bacteria in a patient's digestive system. Few systems currently exist that can accurately process samples and generate true enterotype results as most use culture or multiplex PCR, which can miss a number of important organisms. Furthermore, current methods suffer from severe limitations for the detection and identification of eukaryotic organisms including both protozoa and fungi.

Future iterations of diagnostics will rely heavily on molecular based technologies as they offer speed, inclusivity, and unparalleled accuracy. It is fortunate that these advantages are now being applied to infectious diseases enabling culture independent methods.[3,4,6–34] These emerging diagnostic systems will share certain analysis methods that combine shared processing and bioinformatics processing pipelines.

System

The majority of NGS-based approaches will likely include similar steps:

1. **Point of Care Sampling**: Infected tissues, material, and/or fluid samples may be submitted for analysis. Proper collection techniques should be used to minimize contamination of the sample by nontargeted microbial populations. Blood draw sites should be cleaned thoroughly with disinfectants to remove potentially contaminating microbial DNA and cells. Tissue samples should be collected using aseptic techniques.



2. **Nucleic Acid Extraction**: Nucleic acid (DNA or RNA) content is then purified from the samples believed to contain the microbes. In the case of RNA it is converted into cDNA prior to sequencing.
3. **Molecular Tagging and Amplification**: The patient-derived DNA/cDNA is then prepared by fragmenting the full-length DNA into shorter segments compatible with sequencing. These fragments are often tagged with identifying sequences to allow for multiple samples to be pooled together. The subsequent DNA pool is then ready for NGS.
4. **Next-Generation DNA Sequencing**: Millions of digital DNA reads are produced by the NGS. The main NGS platforms include Illumina, Oxford-Nanopore, Thermo Fisher's Ion Torrent, and PacBio systems.
5. **Bioinformatics Analysis**: Software is used to sort and categorize the sequences depending on the intended downstream use. Human DNA sequences are often removed from analysis to allow for focused processing of possible infectious agents. Analysis often utilizes heavy computational analysis to identify or recreate the genetic material of nonhuman organisms in the sample.

RIDI (Rapid Infectious Disease Identification)

Our laboratory has developed a metagenomic testing method that uses *direct* DNA sequencing and computational analysis to enable the detection, identification, and in the case of novel or divergent organisms, the identification of the nearest characterized microbial species. According to experts at the recent American Association of Clinical Chemistry (AACC) meetings, we are the first to enter the commercial marketplace of rapid NGS infectious disease diagnostics. This stands in stark contrast to the myriad of current indirect testing technologies, including serology, T-cell stimulation assays, and ELISA. Furthermore, this method allows us to provide a relative measure of the bacterial, protozoal, or fungal contribution and diversity within a given sample. In summary, this method aims to identify the genetic composition and diversity across all microbes in a sample, simultaneously.

Our laboratory uses the Ion Torrent PGM system, clinically regulated methods, proprietary reagents, and in-house bioinformatics analysis to identify and survey the organisms of an unknown or polymicrobial infection. We call this system the Rapid Infectious Disease Identification system, or RIDI. It is important to note that the RIDI bioinformatics system has proven compatibility across other NGS systems, including the Illumina and PacBio platforms. By using direct DNA sequencing from the Ion Torrent PGM coupled with computational analysis, we can identify or match a detected organism to the nearest microbial relative in a given clinical sample. Furthermore, this method allows us to provide a relative measure of the microbial contribution and diversity within a given sample. Fry Laboratories believes that wider adoption of this test in clinical use will have far-reaching implications by not only providing superior, unbiased, sequence-based diagnosis, but also reducing patient mortality, morbidity, length of stay, and associated hospital and health care costs. This test is currently offered worldwide and is performed as a Laboratory Developed Test (LDT) in our CLIA regulated diagnostics laboratory.

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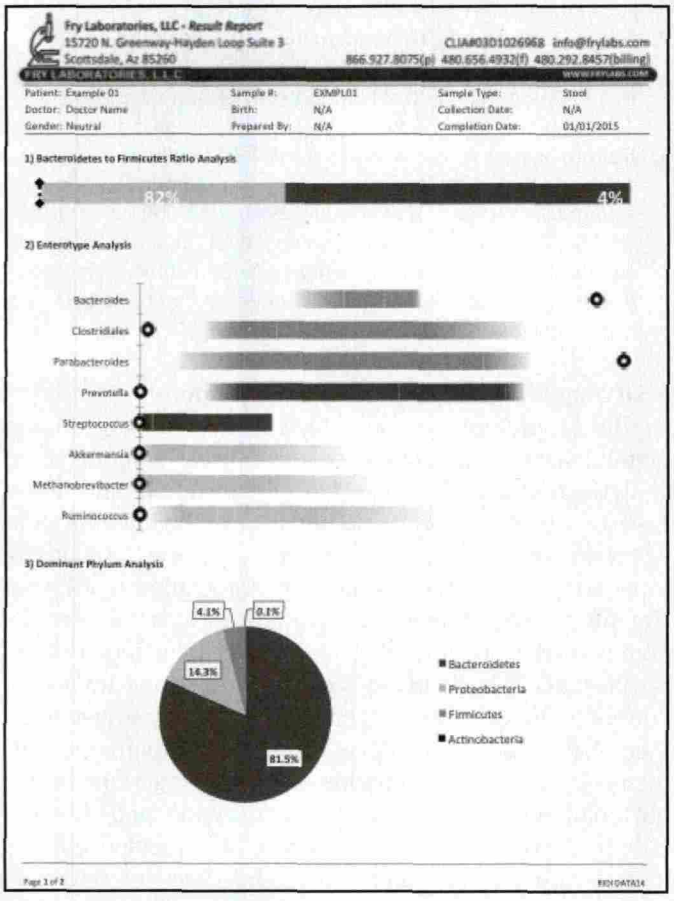
Example Reports

Figure 1: Photo Stool RIDI-IBS

An example of an application is rapid stool metagenomics here showing the enterotype distribution and the actual breakdown of bacteria present. This is by technique more comprehensive than multiplex PCR.



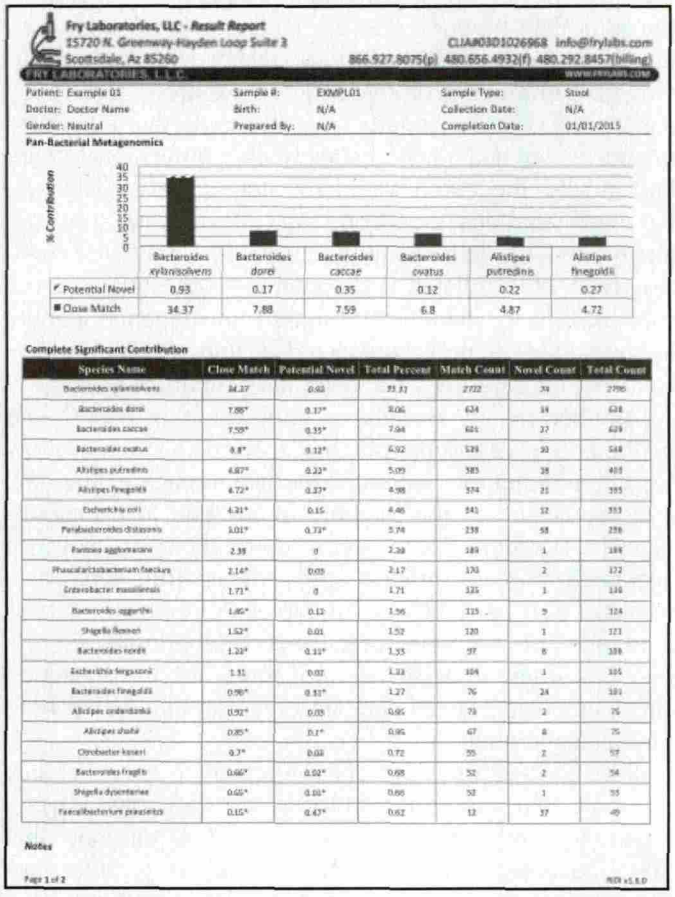
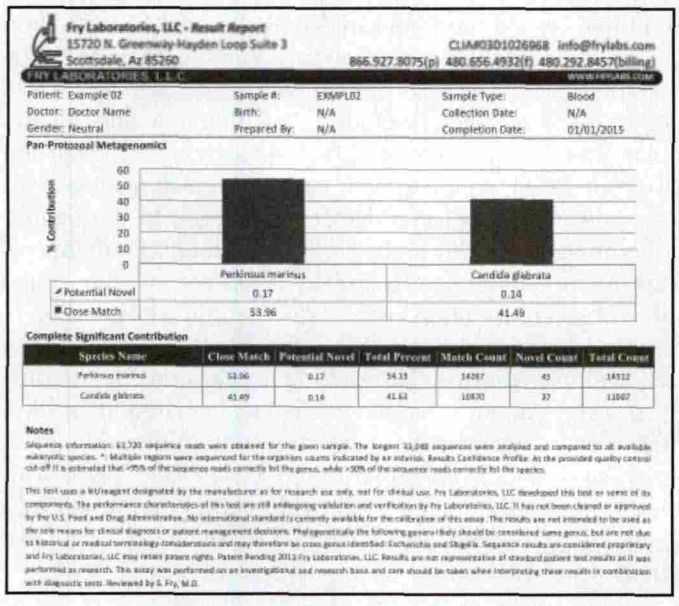


Figure 2: Photo Blood RIDI CFS

An example is a report on a patient with CFs showing the results of eukaryotic (protozoal and fungal) assessment.



Validation of Next-Gen Systems, or, How Well Do These Systems Work?

NGS manufactures and industry experts agree that there is need for comprehensive validation and standardized control procedures in the NGS diagnostics field. Our Pan-Bacterial Metagenomics assay by RIDI has successfully and repeatedly sequenced *Borrelia burgdorferi* and several *Bartonella* species standards from the American Type Culture Collection (ATCC). Additionally, this assay has an ever-increasing list of validated and control ATCC species and taxonomic groups that include *Acholeplasma laidlawii*, *Acinetobacter baumannii*, *Bacillus cereus*, *Bartonella bacilliformis*, *Bartonella henselae*, *Bordetella pertussis*, *Borrelia burgdorferi*, *Capnocytophaga gingivalis*, *Clostridium difficile*, *Enterococcus faecalis*, *Escherichia coli*, *Gemella haemolysans*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Legionella pneumophila*, *Mycoplasma arthritidis*, *Mycoplasma fermentans*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Mycoplasma pneumoniae*, *Ralstonia solanacearum*, and others.

Our laboratory has undertaken the mapping of bacterial, protozoa, fungi, and simple eukaryotic populations in a variety of sample types, including stool, blood, joint fluid, abscess, cerebrospinal fluid, bone, and tissues. This is especially true in certain disease states such as IBS, chronic fatigue syndrome (CFS), Lou Gehrig's disease, multiple sclerosis, atherosclerosis, and prostate cancer. Figure 1 displays a typical report in a patient with IBS. Of note is the identification of pathogenic *Shigella* spp. when simple multiplex PCR and culture techniques had failed. Our ongoing research with next-gen detection systems has allowed us to verify a variety of aquatic "parasites" in humans. Figure 2 displays a typical result in a patient with CFS. We currently are developing a collaborative relationship with the Los Alamos National Research Laboratory investigating and documenting the presence of advanced microbes in chronic disease.

Summary

NGS systems will not replace culture systems in the near term, but it is likely that this technology will become a mainstay in the clinical microbiology arena with culture, microscopy, and serology serving as an adjunct. Eventually NGS systems will most likely replace both standard and quantitative PCR. Microscopy, serology, and emerging metabolomics will play a role in organism detection and identification; however, there is general agreement that NGS systems will dominate the infectious disease arena this decade.

Declarations

Dr. Fry owns and directs Fry Laboratories LLC, a clinical diagnostics laboratory, and is a central developer of the RIDI system.

Acknowledgements

I would like to thank Dr. Jeremy Ellis for review of this manuscript.

Notes

1. Brouqui P, Raoult D. Endocarditis due to rare and fastidious bacteria. *Clin Microbiol Rev*. 2001;14(1):177–207.
2. Singh S et al. Axenic culture of fastidious and intracellular bacteria. *Trends Microbiol*. 2012;21(2):92–99.
3. Bruneval P et al. Detection of fastidious bacteria in cardiac valves in cases of blood culture negative endocarditis. *J Clin Pathol*. 2001;54(3):238–240.
4. Levy PY, Fenollar F. The role of molecular diagnostics in implant-associated bone and joint infection. *Clin Microbiol Infect*. 2012;18(12):1168–1175.
5. Salkeld DJ et al. Disease risk & landscape attributes of tick-borne Borrelia pathogens in the San Francisco Bay Area, California. *PLoS One*. 2015;10(8):e0134812.
6. Biswas S, Rolain JM. Use of MALDI-TOF mass spectrometry for identification of bacteria that are difficult to culture. *J Microbiol Methods*. 2012;92(1):14–24.
7. Claesson MJ et al. Comparison of two next-generation sequencing technologies for resolving highly complex microbiota composition using tandem variable 16S rRNA gene regions. *Nucleic Acids Res*. 2012;38(22):e200.
8. Junemann, S et al. Bacterial community shift in treated periodontitis patients revealed by ion torrent 16S rRNA gene amplicon sequencing. *PLoS One*. 2012;7(8):e41606.
9. Pattison SH et al. Molecular detection of CF lung pathogens: Current status and future potential. *J Cyst Fibros*. 2012.
10. Whiteley AS et al. Microbial 16S rRNA Ion Tag and community metagenome sequencing using the Ion Torrent (PGM) Platform. *J Microbiol Methods*. 2012;91(1):80–88.
11. Yergeau E et al. Next-generation sequencing of microbial communities in the athabasca river and its tributaries in relation to oil sands mining activities. *Appl Environ Microbiol*. 2012;78(21):7626–7637.
12. Johnson G, Nolan T, Bustin SA. Real-time quantitative PCR, pathogen detection and MIQE. *Methods Mol Biol*. 2013;943:1–16.
13. Hedman J, Rådström P. Overcoming inhibition in real-time diagnostic PCR. *Methods Mol Biol*. 2013;943:17–48.
14. Wallace PS, MacKay WG. Quality in the molecular microbiology laboratory. *Methods Mol Biol*. 2013;943:49–79.
15. Hansen WL, Bruggeman CA, Wolffs PF. Evaluation of new preanalysis sample treatment tools and DNA isolation protocols to improve bacterial pathogen detection in whole blood. *J Clin Microbiol*. 2009;47(8):2629–2631.
16. Hansen WL, Bruggeman CA, Wolffs PF. Pre-analytical sample treatment and DNA extraction protocols for the detection of bacterial pathogens from whole blood. *Methods Mol Biol*. 2013;943:81–90.
17. Vollmer T, Kleesiek K, Dreier J. Detection of bacterial contamination in platelet concentrates using flow cytometry and real-time PCR methods. *Methods Mol Biol*. 2013;943:91–103.
18. Renwick L, Holmes A, Templeton K. Multiplex real-time PCR assay for the detection of meticillin-resistant Staphylococcus aureus and Panton-Valentine leukocidin from clinical samples. *Methods Mol Biol*. 2013;943:105–113.
19. Abdeldaim GM, Herrmann B. PCR detection of Haemophilus influenzae from respiratory specimens. *Methods Mol Biol*. 2013;943:115–123.
20. Abdeldaim GM et al. Detection of Haemophilus influenzae in respiratory secretions from pneumonia patients by quantitative real-time polymerase chain reaction. *Diagn Microbiol Infect Dis*. 2009;64(4):366–373.
21. Ling CL, McHugh TD. Rapid detection of atypical respiratory bacterial pathogens by real-time PCR. *Methods Mol Biol*. 2013;943:125–133.
22. Tatti, K.M. and M.L. Tondella, Utilization of multiple real-time PCR assays for the diagnosis of Bordetella spp. in clinical specimens. *Methods Mol Biol*. 2013;943:135–147.
23. Winchell JM, Mitchell SL. Detection of Mycoplasma pneumoniae by real-time PCR. *Methods Mol Biol*. 2013;943:149–158.
24. Fillaux J, Berry A. Real-time PCR assay for the diagnosis of Pneumocystis jirovecii pneumonia. *Methods Mol Biol*. 2013;943:159–170.
25. Yam WC, Siu KH. Rapid identification of mycobacteria and rapid detection of drug resistance in Mycobacterium tuberculosis in cultured isolates and in respiratory specimens. *Methods Mol Biol*. 2013;943:171–199.
26. Lavender CJ, Fyfe JA. Direct detection of Mycobacterium ulcerans in clinical specimens and environmental samples. *Methods Mol Biol*. 2013;943:201–216.
27. Bergmans AM, Rossen JW. Detection of Bartonella spp. DNA in clinical specimens using an internally controlled real-time PCR assay. *Methods Mol Biol*. 2013;943:217–228.
28. McKechnie ML, Kong F, Gilbert GL. Simultaneous direct identification of genital microorganisms in voided urine using multiplex PCR-based reverse line blot assays. *Methods Mol Biol*. 2013;943:229–245.
29. Van den Berg RJ, Bakker D, Kuijper EJ. Diagnosis of Clostridium difficile infection using real-time PCR. *Methods Mol Biol*. 2013;943:247–256.
30. Stoddard RA. Detection of pathogenic Leptospira spp. through real-time PCR (qPCR) targeting the LipL32 gene. *Methods Mol Biol*. 2013;943:257–266.
31. Yamazaki W. Sensitive and rapid detection of Campylobacter jejuni and Campylobacter coli using loop-mediated isothermal amplification. *Methods Mol Biol*. 2013;943:267–277.
32. Rimbara E, Sasatsu M, Graham DY. PCR detection of Helicobacter pylori in clinical samples. *Methods Mol Biol*. 2013;943:279–287.
33. Maheux AF, Bissonnette L, Bergeron MG. Rapid detection of the Escherichia coli genospecies in water by conventional and real-time PCR. *Methods Mol Biol*. 2013;943:289–305.
34. Barletta F, Ochoa TJ, Cleary TG. Multiplex real-time PCR (MRT-PCR) for diarrheagenic. *Methods Mol Biol*. 2013;943:307–314.

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Bovine Colostrum: The Anti-Aging Revolution: What Athletes Can Teach Us About Staying Young

Part 2

by Douglas A. Wyatt
Director, Center for Nutritional Research

Aging is generally accepted as a normal and inevitable part of the human experience, and as discussed previously, bovine colostrum is the only medicinal food that can offer Fountain of Youth benefits without the financial and health costs of synthetic growth hormone. Practitioners in the field of anti-aging medicine need to understand the benefits that bovine colostrum can offer their patients in terms of avoiding the physical and mental ravages of modern diseases and enhancing quality of life. Early research with colostrum supplementation in highly trained ("super") athletes gave us a significant clue as to how these findings are applicable to aging well. It's important to note that with more effective colostrum processing, resulting in better preservation of naturally occurring growth hormones and more effective liposomal delivery methods, health benefits could be achieved at lower doses than 20 years ago (20 grams/day vs. 60 grams/day).

Improved Recovery After Exercise

Early research with elite Australian athletes showed that supplementing with bovine colostrum was advantageous. After four weeks of supplementation (60 grams/day), athletes had up to a 20% increase in strength, stamina, and endurance, and recovery time after intense exercise was reduced by nearly half. These benefits, in turn, allowed them to train harder and improve performance.[1] Oxidative stress due to intense exercise contributes to muscle fatigue, but glutathione (and its precursors, cysteine, glycine, and glutamic acid) can increase an athlete's exercise capacity before fatigue sets in by neutralizing free radicals that otherwise cause inflammation and damage muscle tissue. Glutathione and its antecedents are abundant in colostrum.[2] Physical activity is important at all ages, and so colostrum can help adults be more productive in their exercise regimes and more likely to stay motivated with less pain and more gain. Added benefits of glutathione include regulation of other less effective antioxidants, antiviral and antibacterial activity, immune system enhancement, enhanced functioning of lymphocytes, and carcinogen neutralization.

Tissue Repair and Accelerated Healing

The super athlete experiences injury at a high rate, and although skeletal muscle does repair itself through regeneration, injured muscle does not fully recover its strength.[3] The natural growth hormones in colostrum are significant to healing. IGF-1, highly expressed during the early inflammatory phase of an injury, appears to aid in fibroblast proliferation and migration and subsequently increases collagen production.[4] Platelet-derived growth factor (PDGF) in colostrum helps stimulate IGF-1 production as well as other growth hormones. Growth hormone has been shown to accelerate bone regeneration.[5] Additionally, transforming growth factor in colostrum stimulates the production and repair of DNA and RNA. Heavy exercise damages muscle fibers, tendons, and ligaments, but TGF along with fibroblast growth factor (FGF) and epithelial growth factor (EGF) repairs them. FGF is a powerful stimulator of angiogenesis and a regulator of cellular migration and proliferation. Accelerated repair means that athletes recover more quickly from injuries and can resume training. Less downtime keeps athletes competitive and less likely to miss competitive events. Likewise, adults who heal more quickly from skeletal muscle injuries can resume normal activity faster and minimize any ill health effects caused by inactivity or immobility.

Colostrum also promotes bone formation and suppresses bone resorption, which counteracts the normal loss in bone density associated

with aging. Osteopontin, lactoferrin, EGF, and IGF-2 are the dominant proteins in bovine colostrum affecting bone density in a dose-dependent manner.[6,7] Aging changes the balance of osteoblasts and osteoclasts such that more bone is degraded than built up, leading to increased bone porosity, loss of bone strength, and acceleration of osteoporosis. TGF-β (found in nature only in colostrum) is naturally produced by osteoblasts, and TGF-β dramatically increases apoptosis among the osteoclasts.

Improved Immune System Function

Following intense exercise, the immune system temporarily shuts down so that the body can recover from the physical stress. The normal production of T-cells and natural killer (NK) cells is suppressed. During training, athletes are consistently in an immune-compromised state which opens them up to opportunistic bacteria and viruses, particularly those that cause upper respiratory infections. Colostrum transmits immunity for common pathogens via antibodies, thereby effectively terminating the immune system shutdown. Bovine colostrum contains natural antibodies against *Enterococcus*, *E. coli*, *Campylobacter*, *Salmonella*, *Staphylococcus aureus*, and *Klebsiella pneumoniae*, among hundreds of others. Athletes self-report a lower incidence of upper respiratory infections while taking bovine colostrum.[8,9] The natural antibodies in colostrum can provide a significant benefit in aging, particularly in anyone with a compromised immune system.

A second method of combating infectious pathogens is by the proline-rich polypeptides (PRPs) in colostrum. PRPs are powerful immune system modulators that act by either stimulating an underactive immune system or suppressing an overactive immune system. They do this by helping regulate the thymus gland and stimulate the production of either helper or suppressor T lymphocytes.[10] PRP-2s primarily function as antimicrobials and, along with lactoferrin and lactoperoxidase, destroy viruses and bacteria on contact.[11] Lactoferrin can also increase the production of NK cells. The PRP-3s primarily have an anti-inflammatory effect and help quell the immune system when it overreacts to an otherwise harmless substance, as in the case of allergies.[12] PRPs are not species specific, which makes bovine colostrum an excellent and abundant source. PRPs are vital to returning the immune system to a state of balance, particularly when it has been overtaxed by strenuous exercise or an autoimmune condition.

Prevention of Leaky Gut

Colostrum can also benefit the tendency for "leaky gut" that occurs with heavy exercise, thereby preventing heat stroke.[13] Gut disorders are common in long-distance runners. The physiological response to increased gut permeability is to expel gut contents, usually by diarrhea, which may diminish performance. Research showed that highly trained runners could experience a 250% increase in gut leakage accompanied by a 2° body temperature increase. With daily colostrum supplementation for 2 weeks, that initial amount of gut leakage decreased by 80%, despite the same temperature increase.

To some extent, most people have some degree of leaky gut syndrome (LGS), which makes the intestinal lining more permeable to macromolecules, pathogens, and toxins. Frequently used antibiotics and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) and prescription analgesics are three primary causes of LGS. Not only is LGS a consequence of high intensity training, but perhaps as much as 85% of the general population has this syndrome by virtue of lifestyle, antibiotic-contaminated foods, GMOs, pesticides, and environmental pollution. The damage from LGS may not be obvious at first and may take many years to develop, yet the major health consequences outside of GI pathogens are allergies and autoimmune conditions. Bovine colostrum has been shown to reduce NSAID-induced intestinal permeability.[14] The EGF in colostrum repairs the gut ulcerations, thereby preventing the crossover of pathogens and toxins into the bloodstream and increasing the efficiency of nutrient uptake. In athletes, colostrum allows more of the carbohydrates and amino acids from food to be utilized as fuel during exercise. Similarly, as one ages, the body can more effectively obtain nutrients from the food eaten, and the tendency for malabsorption and malnutrition are greatly reduced with consistent colostrum use.

Colostrum Dosing and Safety

Because the benefits observed in athletic performance are the desired benefits in anti-aging, the recommended dosing is the same. Two to four tablespoons, or 10 to 20 grams, twice daily is ideal. Colostrum should be taken on an empty stomach, 30 minutes prior to a meal or 2 hours after a meal. At least one dose should be taken before bedtime, because the growth hormones work optimally during sleep.

There are no known contra-indications for colostrum supplementation in athletes or the general public. Colostrum supplementation is generally regarded as a noninvasive intervention, and therefore, safe. As a basic precaution, pregnant or lactating women should check with their physicians before taking colostrum.

Efficacy and Quality Colostrum

Bovine colostrum for human consumption is essentially worthless if the active components have been destroyed during processing. Not only must it must contain high levels of the active components, the active components must be able to reach the target cells with no compromise in bioactivity. Therefore, the quality and in turn the effectiveness of any colostrum supplement depends on four factors – the colostrum source, the processing methods, testing and

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verification of active components, and a liposomal delivery (LD) system.[15] Colostrum should be sourced from pasture-fed dairy cows that are certified to be healthy and BST, BSE, and antibiotic free, and gently processed using flash pasteurization and low-heat drying. A phospholipid coating, such as liposomal delivery, protects the colostrum from digestion and ensures that it can deliver the nutrients, growth hormones, and antipathogenic action of colostrum to the cells. Raw fresh colostrum has a liposomal surrounding of the active, sensitive molecules, and so we know that this is critical for processed supplements. Trainers and physicians who recommend colostrum supplements to athletes and patients wanting to age well must recommend a high-quality, efficacious product if they expect to see results.

An added benefit of liposomal delivery and improvements in colostrum processing over the last two decades is that a smaller quantity of powdered colostrum can now produce the same results. The early research with Australian athletes entailed supplementing with 60 grams, whereas today only 10 to 20 grams is required.[16] Not only is it more economical but certainly easier to consume.

Conclusion

We know that athletes will go to great lengths to achieve superior performance, as evidenced by seemingly pervasive doping and illegal growth hormone use in professional sports. Even nonathletes turn to synthetic growth hormone injections in the hopes of staying young and vibrant. We also know that the financial and health cost of HGH isn't worth it, especially when there's an all-natural and safe alternative. Bovine colostrum can help build lean muscle mass; burn adipose tissue; maintain ideal blood glucose levels; improve recovery after exercise; accelerate healing of injuries; preserve and boost immune function; and heal leaky gut syndrome. Colostrum's ability to enhance health, maintain an optimally functioning body, and help heal chronic conditions gives it the power to halt the deleterious and dreaded effects that we associate with human aging. And, unlike isolated hormones, colostrum works naturally to help replace the body's own growth hormones and stimulates the endocrine system to continue producing these anti-aging hormones. From professional athletes to those of us just trying to age well, the search for the Fountain of Youth may have finally come to a jubilant end.

Douglas Wyatt is the founder of Sovereign Laboratories LLC, a Sedona-based company dedicated to developing natural products that provide the public with the best solutions for optimal health. He is honored to be listed as the leading expert in colostrum and is credited with reintroducing bovine colostrum into human use. Additionally, he serves as the research director of the International Center of Nutritional Research, a not-for-profit institute dedicated to nutritional health, and is one of the leading figures in the natural products Industry. Doug is a leader in the research and a proponent of colostrum's unique and powerful healing components that show incredible promise for turning the tide on the prevention and treatment of the world's increasing chronic disease endemic. As a publisher, author, writer, scientist, and public speaker, Doug has appeared nationwide on television and radio shows and at health conventions worldwide. He is dedicated to the prevention of chronic disease through natural nutritional intervention and is working with the WHO (World Health Organization) and other internationally recognized research organizations on clinical trials on HIV/AIDS and other infectious diseases, autoimmune disease, and bowel health issues.

Notes

1. Buckley JD et al. Bovine colostrum supplementation during endurance running training improves recovery, but not performance. *J Sci Med Sport*. 2002 Jun;5(2):65–79.
2. Borissenko M. Glutathione: a powerful anti-oxidant found in colostrum. New Zealand Milk Products. August 2002.
3. Sato K et al. Improvement of muscle healing through enhancement of muscle regeneration and prevention of fibrosis. *Muscle Nerve*. 2003 Sep;28(3):365–372.
4. Molloy T et al. The roles of growth factors in tendon and ligament healing. *Sports Med*. 2003;33(5):381–394.
5. Schmidmaier G et al. Improvement of fracture healing by systemic administration of growth hormone and local application of insulin-like growth factor-1 and transforming growth factor-beta1. *Bone*. 2002;31(1):165–172.
6. Du M et al. Protective effects of bovine colostrum acid proteins on bone loss of ovariectomized rats and the ingredients identification. *Mol Nutr Food Res*. 2011 55(2):220–228.
7. Hou JM et al. Bovine lactoferrin improves bone mass and microstructure in ovariectomized rats via OPG/RANKL/RANK pathway. *Acta Pharmacol Sin*. 2012 33(10):1277–1284.
8. Brinkworth GD, Buckley JD. Concentrated bovine colostrum supplementation reduces the incidence of self-reported symptoms of upper respiratory tract infection in adult males. *Eur J Nutr*. 2004;42(4):228–232.
9. Crooks C et al. Effect of bovine colostrum supplementation on respiratory tract mucosal defenses in swimmers. *Int J Sport Nutr Exerc Metab*. 2010 Jun;20(3):224–235.
10. Shau H, Kim A, Golub SH. Modulation of natural killer cell and lymphokine-activated killer cell cytotoxicity by lactoferrin. *J Leukoc Biol*. 1992;51(4):343–349.
11. See DM et al. An in vitro screening study of 196 natural products for toxicity and efficacy. *J Am Nutraceutical Assoc*. 1999;2(1):25–39.
12. Keech A. Unpublished research. 2007.
13. Marchbank T et al. The nutriceutical bovine colostrum truncates the increase in gut permeability caused by heavy exercise in athletes. *Am J Physiol Gastrointestin Liver Physiol*. 2011;300(3):G477–G484.
14. Playford RJ et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. *Clin Sci (Lond)*. 2001 Jun;100(6):627–633.
15. Chrai SS et al. Liposomes (a review) part two: drug delivery systems. *BioPharm*. 2002 Jan:40–43.
16. Antonio J et al. The effects of bovine colostrum supplementation on body composition and exercise performance in active men and women. *Nutrition*. 2001;17:243–247.

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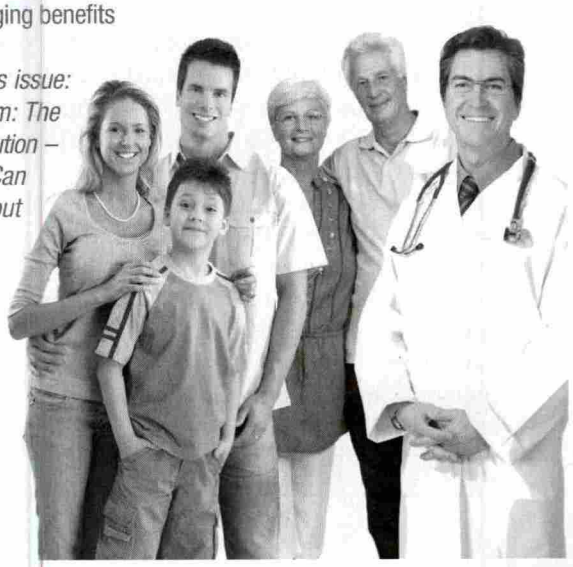

Applied Kinesiology Essentials

by Scott C. Cuthbert, BA, DC

During the past 3000 years, many diagnostic methods have been developed to discover the causes of human pain and dysfunction. In 1964, a significant step forward in the evaluation of neurological disturbances related to functional-structural impairments was made by the chiropractor Dr. George J. Goodheart Jr. and his development of applied kinesiology (AK).[1–4]

The manual muscle testing (MMT) applications that Goodheart delineated have been taken up by practitioners in a broad cross-section of the healing arts, including chiropractors, osteopaths, psychologists and psychiatrists, acupuncturists, nutritionists, naturopaths, bodyworkers, and kinesiologists. AK's approach to specific health problems has been presented in the *Townsend Letter*; however, a broad overview of the neurophysiology underlying this unifying concept of health-care diagnosis has not been published before.[5–7]

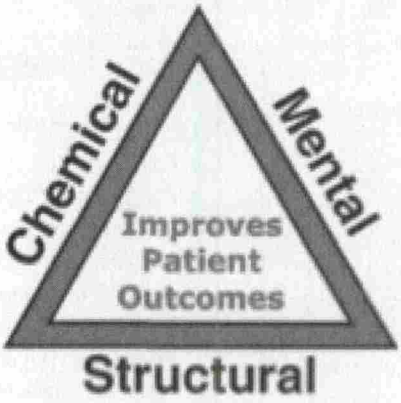

Figure 1: The "Triad of Health" suggests that structural, biochemical, and psychosocial factors are components in functional disorders that are amenable to manual muscle testing assessment and treatment.

Influence of AK Worldwide

Goodheart's work drew a large following of doctors and recognition. He was the first chiropractor officially appointed to the US Olympic Sports Medicine team.[8] In 1976 the International College of Applied Kinesiology was founded to promote the research and teaching of AK.[9] In Europe, some 3000 MDs and osteopaths now use AK as part of their diagnostic regimen.

The first book to describe the value of AK to other professions, *AK and the Stomatognathic System*, was authored by Harold Gelb, a dentist, and Goodheart in 1977.[10] Gelb founded the Craniomandibular Pain Center at Tufts University College of Dental Medicine in Boston, Massachusetts. He and his team have been using MMT and the methods developed by Goodheart and the International College of Applied Kinesiology in the evaluation of patients with TMD ever since, and have published a substantial body of research on the relationship between muscle imbalances and TMD.[11,12] Significant inroads into the dental profession have been made by AK.[13–15]

Many other "name techniques" have evolved from AK that also incorporate many of the same MMTs and neurological reflexes and procedures as part of their diagnostic systems, including Neuro Emotional Technique (NET), Neural Organization Technique (NOT), clinical kinesiology, Contact Reflex Analysis (CRA), Total Body Modification (TBM), Thought Field Therapy (TFT), behavioral kinesiology (BK), and Ulan Nutritional Systems, in addition to nearly 100 systems of "kinesiology" around the world.[16–22] Emotional Freedom Technique, commonly known as EFT, is a popular form of "energy psychology" and has been described in the *Townsend Letter*. Its founder, Gary Craig (an engineer from Stanford), gives Goodheart credit for its development. Goodheart demonstrated the effect of the meridian system upon human muscle function for Craig and his teacher Dr. Roger Callahan (the founder of TFT) and, from their use of these insights, developed methods that have spread around the world.[23] The ability to improve mental health problems with applied kinesiology techniques is now beginning to emerge, with much credit going to the innovative techniques of the chiropractors Goodheart and Walker, the psychiatrist John Diamond, the psychologists Roger Callahan and Fred Gallo, and many others.

In 1970, Dr. John Thie (the first chairman of the International College of Applied Kinesiology USA) wanted "kinesiology" to be available for the general public, while Goodheart wanted to continue teaching AK only to professionals licensed to diagnose and treat patients. Goodheart challenged Thie to write a book for the public. Thie's book *Touch for Health* is a best-seller in the self-help domain.[24]

Before AK's expansion of the applications to which the MMT could be put, the actual testing of muscles had been firmly established by Kendall and Kendall, who held that a muscle from a contracted position against increasing applied pressure could either maintain its position (rated as "facilitated" or "strong") or break away and thus be rated as "inhibited" or "weak."[25] The testing of muscle strength itself has been widely practiced in manual medicine for almost a century, whose reliability and validity have recently been shown.[26–30]

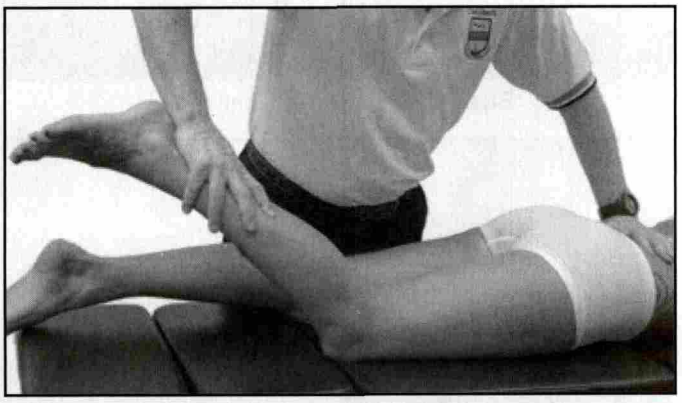

Figure 2: Hamstring Manual Muscle Test

Since the original discovery that muscle inhibition related to neurological disturbances and could be used to diagnose neuromuscular problems, the AK examination system has broadened to include evaluation of nutritional, acupuncture, cerebrospinal fluid, lymphatic and vascular function, and many other controlling or disturbing factors that influence health and neurological function.[1–4] The investigation of these other causes of muscle weakness and their correction developed into the current practice of AK for the broad number of different professions that use it for their own purposes. Each of these areas of human function has been shown to affect the muscular system, and AK and allied health systems' research evidence in this regard is constantly growing.[9,31] Even the American Medical Association has accepted that the standard method of MMT used and taught in AK is a reliable tool and advocates its use for the evaluation of disability impairments.[32]

Knowing precisely what a specific malfunctioning factor in patients' functional ensemble does to muscle strength can greatly enhance their understanding of their health problem. As is well known in modern therapeutics, the location of a primary complaint does not necessarily correlate with the symptoms for which the patient seeks care. Take for example the patient whose low back "slips out" when he bends over to pick up a pencil. He thinks that bending over caused the incident; the doctor knows that the spine does not usually develop a problem from such simple activity. There probably was a subclinical and preexisting condition in the area in the form of muscular imbalance or pathology. This may be why the MMT has the predictive capacity to diagnose problems before they emerge.[30,33]

Principles and Theories

When muscle dysfunction is found, the clinician proceeds with examination to find what therapy restores proper function. Application of the therapy, if successful, *immediately* improves muscle function. Reexamination at a later time determines if the correction is maintained. Thus the system (1) finds disturbance, (2) determines how to fix it, (3) determines if the corrective effort is successful, and, most importantly, (4) determines if the correction is stable. If the correction is not stable, further examination is done to find the reason so it can be eliminated.

But what distinguishes AK is its emphasis upon proprioceptive responses of the muscle rather than the strength of the muscle itself. It essentially sees muscle function as a transcript of the central integrative state of the anterior horn motor neurons, summing all excitatory and inhibitory inputs from the entire organism.[31] In other words, the locus of muscle dysfunction ultimately rests with the nervous system.

Diagnostic Tools: 'Challenge' and 'Therapy Localization'

Sensorimotor "challenge" is a diagnostic procedure unique to AK that is used to determine the body's ability to cope with external stimuli, which can be physical, chemical, or emotional. Challenge defines a mechanism to test the body's ability to cope with external stimuli, again assessed by muscle testing.[34] The use of challenge assessments gives the clinician important clues as to what removes the inhibitions of muscles associated with functional pain syndromes and health problems. The appropriate "challenge" will also remove synergist substitution employed by the patient, particularly during the MMT, because of pain.[35,36]

After an external stimulus is applied, muscle-testing procedures are done to determine a change in the muscle strength as a result of the stimulus. Through this approach, ineffective therapies that produced no improvements in muscle strength are rejected and only those that elicit a positive muscle response are used. This guides the treatment given to a patient.

Nutritional challenge as used in AK was explored and a literature review given in a recent issue of the *Townsend Letter*.[5] Structural (or joint challenge) has been described in the AK outcomes research literature from the beginning, and all of the evidence for this approach was recently offered.[2,3] Cranial challenge has been described in the literature previously.[37,38]

Psychological challenge has been described by Mollon and Monti and many others.[39,40] Monti et al. have shown that if the emotional stress is strong enough, almost any muscle in the body will show the inhibition.[40] A review of the published outcomes research in this area offered by Walker, Callahan, and Mollon elaborates on these ideas.[16,21,39] Mollon's history of AK's contributions in this area is exhaustive.[39]

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Another procedure unique to AK and allied schools of therapeutics is called *therapy localization* (TL).[41] TL seeks a change of muscle strength when the patient's hand is placed over an area of suspected involvement. The neurophysiology of therapy localization has been updated in two recent textbooks and at the 3rd International Association of Functional Neurology and Rehabilitation Conference.[2,3,42] This method is hypothesized to assist the doctor in finding areas that are involved with the muscle dysfunction found on MMT. Pollard et al. in a recent literature review presented some of the research about the AK concept of therapy localization.[43] Collectively these data suggest that stimulating the skin and the cutaneomotor reflexes can produce changes in muscle function.

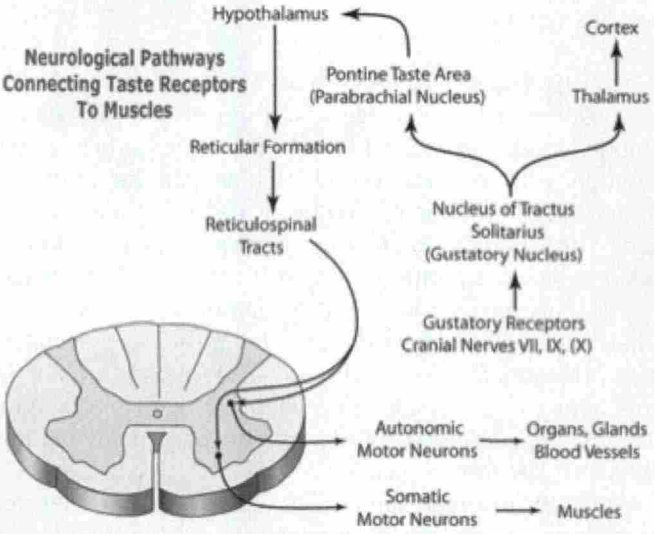

Figure 3: AK Nutritional Challenge

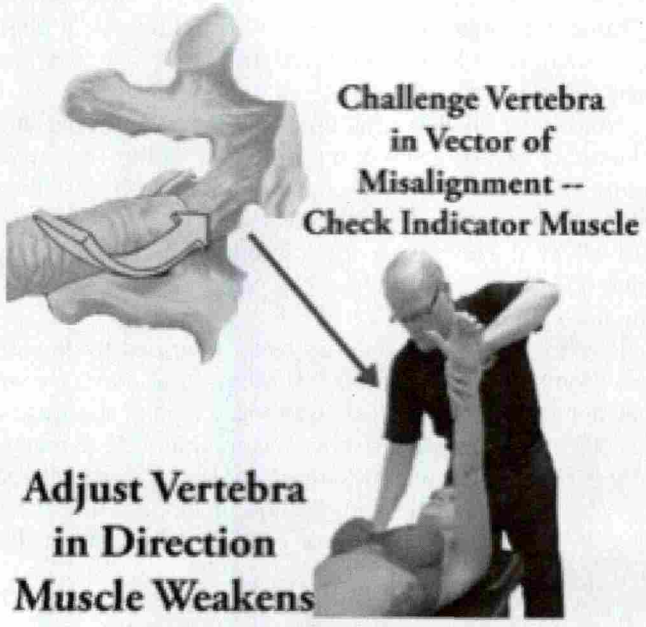

Figure 4: AK Vertebral Challenge

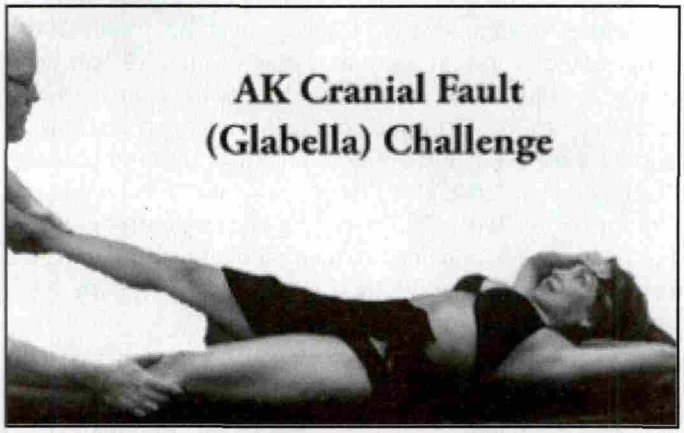

Figure 5: AK Cranial Challenge

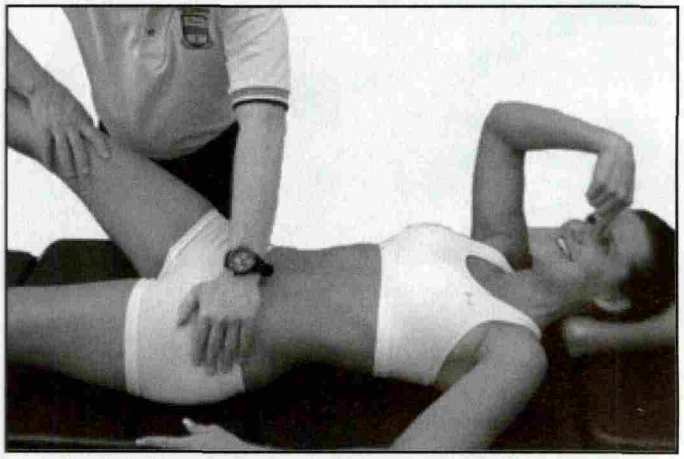

Figure 6: AK and Acupuncture Point (Bladder-1) Therapy Localization

It is also characteristic of AK assessment procedures to move from the examination of the patient into the treatment almost immediately.[44] As a clinician searches for information through the manual muscle test, the appropriate challenge or therapy localization to the responsible tissue or remedy will turn "finding" into "fixing." One treatment modality accompanies another as a rather "custom made" application is created that not only varies from patient to patient but should vary from one session to the next for a particular individual as a condition improves.

Applied Kinesiology's Future in the Management of Stress-Related Illness

Since 1964, the AK model has aimed to integrate the physical, biochemical, and psychosocial manifestations of musculoskeletal pain. This integrative model is overdue in the conceptualization and investigation of neuromusculoskeletal pain and psychological and biochemical imbalances. This model may also provide an evidence-based rationale for the integration and appropriate timing of complementary and alternative medicine (CAM) treatments directed toward physical (biological) impairments, and biochemical and psychological factors. It is suggested that this integrated approach will be the way forward in the management of pain as well as stress-

related and lifestyle illnesses, rather than the dichotomous separation of physical, biochemical, and psychological factors that so often occurs in research and practice.

There are now over 100 papers published in peer-reviewed journals on the methods and outcomes of AK.[2-4,45] Few CAM therapeutic methods have been investigated or written about as extensively as AK. There have been 38 separate books published about AK methods since 1964.

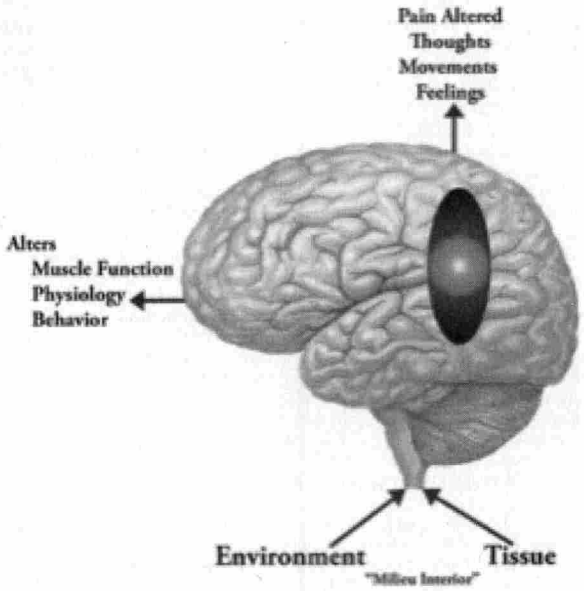

Figure 7:
Applied Kinesiology's Integrative Model of Health Care

Further research and reviews of applied kinesiology are listed at the National Library of Medicine, where AK research has now been given its own MESH heading. It must be cautioned, however, that several muscle testing protocols which have appeared have not adhered to AK protocols and should never be confused with the methods employed in AK.[46-49]

Gifford's mature organism model demonstrates the importance of a multifactorial understanding of health, showing that physical, environmental, and emotional aspects interrelate.[50] Critically, a method of assessment for these interweaving factors is vital.

The Cochrane Collaboration defined CAM as follows:

> CAM is a broad domain of healing resource that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideals self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and that of the dominant system are not always sharp or fixed.[51]

Applied Kinesiology

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Applied kinesiology offers an important diagnostic tool to supplement those already in place because it unifies within one diagnostic modality – the manual muscle test – the approaches commonly used throughout CAM. In considering how acupuncturists focus upon meridians, physiotherapists upon rehabilitative exercise, naturopaths upon nutrition, and chiropractors upon the joints, AK does not overrule the tenets of any of these approaches, but rather implies that human ailments may be attributed to multiple systems and that the MMT may identify these for the muscle tester educated in its use. This allows for an integrative and interprofessional model of health care to be developed.

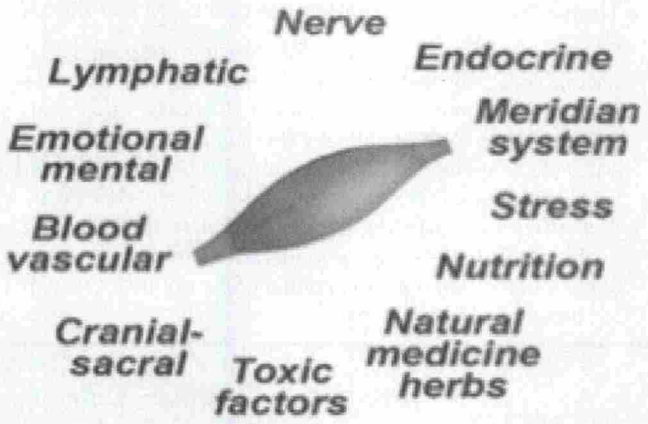

Figure 8: Abnormal results of the manual muscle test may indicate abnormal involvement of any of the factors surrounding it. A change in muscle function when specific stimulation is applied to one of these elements also indicates dysfunction of the surrounding factors.

Notes

1. Goodheart GJ. *Applied Kinesiology Research Manuals*. Detroit; 1964–1995.
2. Cuthbert S. *Applied Kinesiology Essentials: The Missing Link in Health Care*. Pueblo, CO: Gangasas Press; 2014.
3. Cuthbert S. *Applied Kinesiology: Clinical Techniques for Lower Body Dysfunctions*. Pueblo, CO: Gangasas Press; 2014.
4. Walther DS. *Applied Kinesiology Synopsis*. 2nd ed. Shawnee Mission, KS; 2000.
5. Cuthbert S, Rosner AL, Chetcuti T, Gangemi S. Correlation of manual muscle tests and salivary hormone tests in adrenal stress disorder: a retrospective case series report. *Townsend Lett*. 2015 January.
6. Cuthbert S. Applied kinesiology: An effective complementary treatment for children with Down syndrome. *Townsend Lett*. 2007 July;288:94–107.
7. Rochlitz S. On the balancing of candida albicans and progenitor cryptocides: a triumph of the science of applied kinesiology. *Townsend Lett*. 1986;37:113–152.
8. Green BN, Gin, RH. George Goodheart, Jr., D.C., and a history of applied kinesiology. *J Manipulative Physiol Ther*. 1997;20(5):331–337.

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9. ICAK USA research; ICAK published articles [websites]. http://www.icakusa.com/research; http://www.icak.com/index.php/research/published-papers. Accessed January 11, 2015.
10. Gelb H. Clinical management of head, neck and TMJ pain and dysfunction. Philadelphia: W.B. Saunders; 1977.
11. Sakaguchi K, Mehta NR, Abdallah EF, et al. Examination of the relationship between mandibular position and body posture. *Cranio*. 2007;25(4):237–249. Research conducted at Tufts Craniofacial Pain Center.
12. Gelb H, Mehta NR, Forgione AG. The relationship between jaw posture and muscular strength in sports dentistry: a reappraisal. *Cranio*. 1996 Oct;14(4):320–325.
13. Gelb H, Ed. *The Dental Clinics of North America: Symposium on Temporomandibular Joint Dysfunction and Treatment*. Chapter 13. Philadelphia: WB Saunders Company; 1983:613–630.
14. Gelb H, Ed. *New Concepts in Craniomandibular and Chronic Pain Management*. Chapter 15. London: Mosby-Wolfe; 1994:349–368.
15. Smith G. *Cranial-Dental-Sacral Complex*. Newtown, PA; 1983.
16. NET Mind Body [website]. https://www.netmindbody.com.
17. Neural Organization Technique – International *Professional* [website]. http://www.neuralorganizationtechnique.net.
18. Clinical Kinesiology [website]. http://www.clinicalkinesiology.com.
19. Contact Reflex Analysis [website]. https://www.crawellnessartists.com/about.
20. Total Body Modification [website]. http://www.tbmseminars.com.
21. Thought Field Therapy [website]. http://www.rogercallahan.com/index.php.
22. Kinesiology Network [website]. http://www.kinesiology.net.
23. Emotional Freedom Techniques [website]. http://www.emofree.com.
24. Thie J, Thie M. *Touch for Health*. Devorss & Co.; 2012. Available at http://stores.tfhka.com.
25. Kendall HO, Kendall FP. *Posture and Pain*. Baltimore; Williams & Wilkins; 1952.
26. Janda V. *Muscle Function Testing*. London: Butterworths; 1983.
27. Liebenson C, ed. *Rehabilitation of the Spine: A Practitioner's Manual*. 2nd ed. Philadelphia: Lippincott, Williams & Wilkins; 2007.
28. Lewit K. *Manipulative Therapy in Rehabilitation of the Locomotor System*. 3rd ed. London: Butterworths; 1999.
29. Sahrmann S. *Diagnosis and Treatment of Movement Impairment Syndromes*. St. Louis: Mosby Inc.; 2001.
30. Cuthbert SC, Goodheart GJ Jr. On the reliability and validity of manual muscle testing: a literature review. *Chiropr Osteopat*. 2007 Mar 6;15(1):4.
31. Schmitt WH Jr, Yanuck SF. Expanding the neurological examination using functional neurological assessment. Part II: Neurological basis of applied kinesiology. *Int J Neurosci*. 1998;97(1–2).
32. American Medical Association. *Guides to the Evaluation of Permanent Impairment*. 5th ed. 2001:510.
33. Jepsen JR et al. Diagnostic accuracy of the neurological upper limb examination I: inter-rater reproducibility of selected findings and patterns. *BMC Neurol*. 2006 Feb 16;6:8.
34. AK Challenge Procedure: "A mechanism used as a testing procedure to determine the body's ability to cope with external stimuli, which can be physical, chemical, or mental."
35. Mense S, Simons DG. *Muscle Pain: Understanding Its Nature, Diagnosis, and Treatment*. Lippincott Williams & Wilkins: Philadelphia; 2001.
36. Lund JP, Donga R, Widmer CG, Stohler CS. The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol*. 1991;69(5):683–694.
37. Cuthbert SC, Barras M. Developmental delay syndromes: psychometric testing before and after chiropractic treatment of 157 children. *J Manipulative Physiol Ther*. 2009 Oct;32(8):660–669
38. Cuthbert S, Blum C. Symptomatic Arnold-Chiari malformation and cranial nerve dysfunction: a case study of applied kinesiology cranial evaluation and treatment. *J Manipulative Physiol Ther*. 2005 May;28(4):e1–e6.
39. Mollon P. *Psychoanalytic Energy Psychotherapy*. London: Karnac Books Ltd.; 2008.
40. Monti D et al. Muscle Test Comparisons of Congruent and Incongruent Self-Referential Statements. *Percept Mot Skills*. 1999, 88:1019–1028.
41. AK Therapy Localization procedure: "A procedure of placing the patient's hand over areas of suspected involvement, then using muscle testing procedures to determine any change in strength."
42. Rosner A, Leisman G, Gilchriest J, Charles E, Keschner M, Minond M. Therapy localization in applied kinesiology: reliability and validity. *J Funct Neurol Rehab Ergon*. 2012;2(4):390–391.
43. Pollard HP, Bablis P, Bonello R: The ileocecal valve point and muscle testing: A possible mechanism of action. *Chiropr J Aust*. 2006;36(4):122–126.
44. Motyka TM, Yanuck SF. Expanding the neurological examination using functional neurologic assessment part I: methodological considerations. *Int J Neurosci*. 1999 Mar;97(1–2):61–76.
45. Applied Kinesiology research page [Web page]. http://appliedkinesiologyresearch.blogspot.com. Full access to research papers.
46. Hall S, Lewith G, Brien S, Little P. A review of the literature in applied and specialised kinesiology. *Forsch Komplementarmed*. 2008;15:40–46.
47. Haas M, Cooperstein R, Peterson D. Disentangling manual muscle testing and Applied Kinesiology: Critique and reinterpretation of a literature review. *Chiropr Osteo*. 2007;15:11.
48. Kenney JJ, Clemens R, Forsyth KD. Applied kinesiology unreliable for assessing nutrient status. *J Am Diet Assoc*. 1988;88:698–704.
49. Tschernitschek H, Fink M. Applied kinesiology in medicine and dentistry: a critical review. *Wien Med Wochemsthr*. 2005;155:59–64.
50. Jones M, Edwards I, Gifford L. Conceptual models for implementing biopsychosocial theory in clinical practice. *Man Ther*. 2002;7(1):2–9.
51. Zollman C, Vickers A. ABC of complementary medicine: what is complementary medicine? *BMJ*. 1999 Sep 11;319(7211):693–696.

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Phytotherapeutic Alternatives or Adjuvants to Testosterone Replacement Therapies in Men

by Joseph J. Collins, RN, ND

The benefits of testosterone replacement therapy (TRT) in men, the possible risks of TRT, and the contraindications of TRT are well discussed in published literature, with most authors agreeing that more research is still required.[1–4] One author concluded with a call for TRT research to also take into account other variables such as diet, exercise, nutraceutical supplementation, sleep, and obesity, in that these factors influence assessments of risk and benefits associated with TRT.[2]

Parallel to the research being done regarding the replacement of hormones, there is a growing body of study which proposes that there are phytotherapeutic agents that may be used as an alternative to testosterone replacement therapies in men. A review of the literature shows that a number of plants are able to increase testosterone production through gonadotrophic action or by other actions. In addition, many of these herbs improve sexual function through mechanisms beyond the actions of testosterone. Some may actually improve fertility in men, which is contrary to the infertility that results from testosterone replacement therapies. The anabolic activity of the herbs is in many cases enhanced by anticatabolic activity. In contrast to the putative increased risks of prostate cancers, many of these phytotherapeutic agents have anticancer properties.

To be fully informed of the choices available, clinicians and patients may both be interested in learning more about how phytotherapeutic agents increase testosterone production, improve sexual function, improve fertility in men, increase anabolic activity, and contain anticancer properties.

Herbs Increase Testosterone Production

An alternative to testosterone replacement therapy (TRT) is the use of phytotherapeutic agents that can increase the endogenous production of testosterone. A number of herbs have been shown to increase endogenous production of testosterone, some of which actually maintain or increase the gonadotrophic hormones follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This is in contrast to TRT, which can suppress pituitary secretion of the gonadotrophic hormones, resulting in testicular atrophy and infertility.

Epimedium sagittatum (horny goat weed extract) promotes testosterone production through the action of icariin, a flavonol that improves the condition of reproductive organs and increases the circulating levels of testosterone in animal studies.[5] *Mucuna pruriens* (velvet bean extract) promotes testosterone production in humans by its action on the hypothalamus-pituitary-gonadal axis, and raises serum levels of both testosterone and LH.[6] *Tribulus terrestris* (gokhru fruit extract) promotes testosterone production. A previous study showed the concentration of blood testosterone increased statistically within 10 days in athletes consuming *Tribulus*.[7] Primates also experienced positive outcomes during studies. *Tribulus terrestris* increases testosterone, dihydrotestosterone (DHT) and dehydroepiandrosterone sulphate.[8] In fact, chronic administration of *Tribulus terrestris* produced a significant increase in serum testosterone levels and sexual behavior with no significant effect on the sperm count. In addition no overt body system dysfunctions were observed in the 28-day oral toxicity animal study published in January 2012.[9] *Eurycoma longifolia* (Tongkat Ali 100:1 extract) promotes testosterone production with a significant increase of plasma testosterone level in human studies as well as animal studies.[10,11] It has been postulated that *Eurycoma longifolia* should be considered as a natural alternative to TRT and has been shown to restore serum testosterone levels.[12] *Panax ginseng* (root extract) may also promote testosterone production. Male patients treated with *Panax ginseng* showed an increase in spermatozoa number/ml and progressive oscillating motility, an increase in plasma total and free testosterone, DHT, FSH, and LH levels, and a decrease in PRL.[13] *Withania somnifera* (Ashwagandha

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root extract) promotes testosterone production and caused significant increases in serum testosterone and luteinizing hormone in men with a history of infertility.[14]

Improved Sexual Function

Of the aforementioned herbs, many but not all of them have been reported to improve sexual function. Some of these properties are independent of testosterone, such as PDE5 inhibition, prolactin inhibition, or nitric oxide upregulation independent of PDE5 inhibition. *Epimedium sagittatum* contains icariin, which has phosphodiesterase-5 (PDE5) inhibitor action affecting all three PDE5 isoforms.[15] The long history of use for treating erectile dysfunction in Traditional Chinese Medicine (TCM) may be attributed to the PDE5 inhibitor actions.[16,17] PDE5 inhibitors can potentiate the sexual response in both men and women.[18] The sexual potentiation effect and improved quality of life due to *Epimedium sagittatum* use was even seen in patients with chronic disease.[19] *Mucuna pruriens* causes a significant improvement in sexual behavior, libido and potency, sperm parameters, and testosterone and LH levels, as well as reproductive organs in females, based on various animal studies.[20–23] *Mucuna* also decreases prolactin levels in men, which is significant because hyperprolactinemia is a major neuroendocrine-related cause of reproductive disturbances in both men and women.[24,25] Significant increase of sexual behavior through enhanced libido has been attributed to L-dopa, the constituent in *Mucuna* that suppresses excessive prolactin.[26,27] *Tribulus terrestris* may improve erectile dysfunction, based on in vivo and in vitro animal studies on relaxation of the smooth muscle of the corpus cavernosum.[28] *Tribulus terrestris* may also help with desire disorder in women experiencing female sexual dysfunction.[29] The ability of *Tribulus terrestris* to increase the release of nitric oxide from the endothelium and nitrergic nerve endings may account for its claims as an aphrodisiac in both sexes.[30]

Eurycoma longifolia improved testosterone levels and symptoms of hypogonadism in men suffering from late-onset hypogonadism, and significantly improving sexual health.[31,32] *Panax ginseng* can mimic actions of testosterone associated with the increase in both sexual desire and sexual function.[33] Various human studies demonstrate that *Panax ginseng* is effective for treating male erectile dysfunction.[34,35] *Panax ginseng* also improved sexual arousal in menopausal women and caused significant improvement in the Kupperman index and the Menopause Rating Scale, indicating that *Panax ginseng* might be used in menopausal women to improve their sexual lives.[37,36] *Panax ginseng* can increase in plasma total and free testosterone, DHT, FSH, and LH levels, and a decrease in PRL.[38]

Even though *Withania somnifera* can increase testosterone production and decrease prolactin levels, it has not been demonstrated as having any direct effect on libido or sexual function.[39]

Herbs that support sexual function, but do not actually raise serum testosterone, appear to have direct effect on sexual function beyond the properties and action of testosterone. *Lepidium meyenii* improves sexual desire in both genders independent of testosterone or estrogen activity.[40,41] *Turnera diffusa* acts as a sexual stimulant, by enhancing engorgement of erectile tissue due to its vasodilatory abilities, though it does not raise testosterone levels.[42,43] *Ptychopetalum olacoides* can enhance erectile function and orgasm in aging men suffering the effects of fatigue or age-related complaints.[44] *Eleutherococcus senticosus* can increase endothelial nitric oxide, which can contribute to improved sexual function in both sexes.[45]

Improved Fertility in Men

In contrast to TRT, which can cause infertility by decreasing spermatogenesis as a consequence of suppression of FSH, a number of herbs can enhance or preserve spermatogenesis and reproductive ability. *Mucuna pruriens* improved semen quality and sperm concentrations in infertile men.[46–48] *Lepidium meyenii* improved sperm production and sperm motility by mechanisms in men, via mechanisms not related to LH, FSH, PRL, T, or E2.[49] *Eleutherococcus senticosus* can also improve sperm motility in men.[50] Rats that were treated with *Eurycoma longifolia* exhibited significantly higher sperm counts and sperm motility when compared with the control group.[51] In patients with oligoastenospermia, *Panax ginseng* showed an increase in spermatozoa number/ml and progressive oscillating motility.[52] Men treated with *Withania somnifera* had improved sperm count and motility.[53]

Increased Anabolic Activity

The aging process is accompanied by hormonal changes characterized by an imbalance between catabolic hormones such as cortisol, which remains relatively stable with aging, and anabolic hormones such as testosterone, which decreases with aging.[54] In fact, decrease in muscular mass and strength is one of the principle signs of hypogonadism in males.[4] This decreased anabolic/catabolic relationship can be remediated with TRT, which decreases fat mass and increases muscle mass.[55] However, a number of herbs may be used to improve the anabolic/catabolic relationship by not only increasing endogenous testosterone production, as noted, but also controlling excessive cortisol activity.

Epimedium sagittatum has glucocorticoid antagonist properties, which may contribute to a relative increase in anabolic function.[56–58] *Mucuna pruriens* returned elevated cortisol levels to normal and improved sperm count and motility in infertile men.[59] *Tribulus terrestris*

also decreased the stress induced rise of cortisol in animal studies.[60] *Lepidium meyenii* also caused a substantial decrease in stress induced in blood cortisol levels in animal studies.[61] *Ptychopetalum olacoides* prevents stress induced increase of corticosterone in animal studies, indicating that glucocorticoid antagonist properties may contribute to a relative increase in anabolic function.[62] *Eleutherococcus senticosus* produced a protective effect during experimental steroid-induced osteoporosis, revealing some anticatabolic property.[63] *Eurycoma longifolia* decreased cortisol levels and increased testosterone levels in both men and women.[64] *Panax ginseng* has been shown to decrease catabolic activity by decreasing the cortisol to DHEA-s ratio in women.[65] *Withania somnifera* improves an individual's resistance towards stress and substantially reduced serum cortisol levels in adults taking it for 60 days.[66]

Anticancer Properties of Androgenic Herbs

The association of TRT with increased risk of prostate cancer has been debated by authors, with one researcher noting no increase in the incidence of prostate cancer in a cohort of 2247 men treated with various forms of TRT.[67–69] Nonetheless, prostate cancer as well as male breast cancer are still considered both risks of TRT and contraindications for TRT by those researchers and others.[70] With the putative risks and contraindications in mind, it may be valuable to review the anticancer properties of androgenic herbs. While many of the herbs mentioned have anticancer activity against prostate cancer or other hormone sensitive cancer such as breast or ovarian cancer, some of those herbs only have generalized anticancer properties recognized at this time. At the time of this writing, no anticancer properties have been attributed to *Ptychopetalum olacoides*.

Epimedium sagittatum is purported to have antitumor activity, which may be due to icariin, which exhibits an anticancer curative effect on ovarian cancer cells.[71,72] The action may also be due to icaritin, an intestinal metabolite of epimedium-derived flavonoids that has an anticancer effect that is mediated by induction of cell cycle arrest which is not associated with estrogen receptors in human prostate carcinoma PC-3 cells.[73,74] A *Mucuna pruriens* compound shows activity against human hepatic carcinoma cell line and may be useful for future hepatic cancer treatment.[75] Terrestrosin D from *Tribulus terrestris* strongly suppressed the growth of prostate cancer cells in a dose-dependent manner.[76] *Tribulus terrestris* affects the processes of apoptosis and metastasizing cancer cells in breast carcinoma cell lines.[77] *Lepidium meyenii* can induce apoptosis in the human breast cancer cell line MCF-7, and has anticancer activity against other human cancer cell lines.[78,79] *Turnera diffusa* has a cytotoxic effect on MDA-MB-231 breast cancer cells.[80] *Eleutherococcus senticosus* may inhibit cell growth in a number of human cancer cell lines and may boost the suppressed immunity in ovarian cancer patients who are subject to chemotherapy.[81–83]

Eurycoma longifolia has anticancer activity against LNCaP human prostate cancer cells and is believed to have anticancer properties due to antiproliferative actions and growth inhibition on MCF-7 breast cells through apoptosis induction.[84–86] It also has moderate cytotoxicity toward numerous cancer cell lines.[87–93] *Panax ginseng* WKRG inhibited testosterone-induced cell proliferation, arrested cell cycle by inducing p21 and p27, and induced apoptosis in human prostate cells.[94,95]

Specific ginseng fractions showed proliferation inhibition on androgen-dependent and -independent prostate cancer cells; effectively inhibited prostate cancer cell proliferation, growth, and proliferation; induced apoptosis; and led to arrest in the G1 phase of the cell cycle.[96–98] *Withania somnifera* has compounds that are cytotoxic toward human prostate cancer cells lines as well as pancreatic and breast cancer cells.[99] *Withania somnifera* compounds possess strong cytotoxic activity against liver and breast cancer with moderate activity against colon and prostate cancer cells.[100] Other studies showed that *Withania somnifera* induced apoptosis in prostate cancer cell lines and inhibited survival of both androgen-responsive and androgen-refractory prostate cancer cells, making it an effective chemopreventive agent relevant to prostate cancer progression.[101–103]

Adjuvant Therapy

Androgenic herbs may be considered an alternative to TRT in men due to their collective ability to increase testosterone production through gonadotrophic action, improve sexual function, ➤

improve fertility in men, and increase anabolic activity, and their anticancer properties. In addition, these androgenic herbs may be used as an adjuvants to improve the functions of TRT in patients who still have symptoms of poor testosterone function even after TRT has been given adequate time to work.

Notes

1. Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. *Indian J Urol.* 2014 Jan;30(1):2–7. Review. PubMed PMID: 24497673.
2. Jia H, Sullivan CT, McCoy SC, Yarrow JF, Morrow M, Borst SE. Review of health risks of low testosterone and testosterone administration. *World J Clin Cases.* 2015 Apr 16;3(4):338–44. Review. PubMed PMID: 25879005.
3. Carruthers M, Cathcart P, Feneley MR. Evolution of testosterone treatment over 25 years: symptom responses, endocrine profiles and cardiovascular changes. *Aging Male.* 2015 Jul 28:1–11. PubMed PMID: 26218766.
4. Üçer O, Gümüş B. The treatment of late-onset hypogonadism. *Turk J Urol.* 2014 Sep;40(3):170–9. Review. PubMed PMID: 26328172.
5. Zhang ZB, Yang QT. The testosterone mimetic properties of icariin. *Asian J Androl.* 2006 Sep;8(5):601–5. PubMed PMID: 16751992.
6. Shukla KK, Mahdi AA, Ahmad MK, Shankhwar SN, Rajender S, Jaiswar SP. Mucuna pruriens improves male fertility by its action on the hypothalamus-pituitary-gonadal axis. *Fertil Steril.* 2009 Dec;92(6):1934–1940. PubMed PMID: 18973898.
7. Milasius K, Dadeliene R, Skernevicius J. The influence of the Tribulus terrestris extract on the parameters of the functional preparedness and athletes' organism homeostasis. *Fiziol Zh.* 2009;55(5):89–96. PubMed PMID: 20095389.
8. Gauthaman K, Ganesan AP. The hormonal effects of Tribulus terrestris and its role in the management of male erectile dysfunction—an evaluation using primates, rabbit and rat. *Phytomedicine.* 2008 Jan;15(1–2):44–54. PubMed PMID: 18068966.
9. Singh S, Nair V, Gupta YK. Evaluation of the aphrodisiac activity of Tribulus terrestris Linn. in sexually sluggish male albino rats. *J Pharmacol Pharmacother.* 2012 Jan;3(1):43–47. PubMed PMID: 22368416.
10. Chan KL, Low BS, Teh CH, Das PK. The effect of Eurycoma longifolia on sperm quality of male rats. *Nat Prod Commun.* 2009 Oct;4(10):1331–1336. PubMed PMID: 19911566.
11. Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? *Andrologia.* 2012 May;44 Suppl 1:226–230. PubMed PMID: 21671978.

Dr. Collins has been a licensed health-care practitioner since 1979, beginning as a nurse and then naturopathic physician. He graduated in 1993 with a doctor of naturopathic medicine degree from the National College of Naturopathic Medicine in Portland. Dr. Collins's practice has always focused on an integrative and functional approach to health care, with an emphasis on endocrinology and cellular signaling, which encompasses women's hormone health and men's hormone health, as well as thyroid health, adrenal function and stress adaptation, and glycemic function. Dr. Collins is a medical educator, author, and speaker who has dedicated over 1000 hours of advanced clinical education to promote growth of integrative health care by teaching at medical conferences, seminars, and webinars. Dr. Collins has also provided over 5000 hours of clinical consultation services and training to physicians, nurse practitioners, pharmacists, and other health-care professionals to promote growth of integrative health care. He also has extensive experience in advancing the development and clinical interpretation of laboratory tests and has worked with or been an adviser to a number of diagnostic laboratories.

12. George A, Henkel R. Phytoandrogenic properties of Eurycoma longifolia as natural alternative to testosterone replacement therapy. *Andrologia.* 2014 Sep;46(7):708–721. Review. PubMed PMID: 24386995.
13. Salvati G, Genovesi G, Marcellini L, et al. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. *Panminerva Med.* 1996 Dec;38(4):249–254. PubMed PMID: 9063034.
14. Ahmad MK, Mahdi AA, Shukla KK, et al. Withania somnifera improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. *Fertil Steril.* 2010 Aug;94(3):989–996. PubMed PMID: 19501822.
15. Ning H, Xin ZC, Lin G, Banie L, Lue TF, Lin CS. Effects of icariin on phosphodiesterase-5 activity in vitro and cyclic guanosine monophosphate level in cavernous smooth muscle cells. *Urology.* 2006 Dec;68(6):1350–4. PubMed PMID: 17169663.
16. Chen CY. Virtual screening and drug design for PDE-5 receptor from traditional Chinese medicine database. *J Biomol Struct Dyn.* 2010 Apr;27(5):627–640. PubMed PMID: 20085380.
17. Chen CY. Computational screening and design of traditional Chinese medicine (TCM) to block phosphodiesterase-5. *J Mol Graph Model.* 2009 Oct;28(3):261–9. PubMed PMID: 19747866.
18. D'Amati G, di Gioia CR, Bologna M, et al. Type 5 phosphodiesterase expression in the human vagina. *Urology.* 2002 Jul;60(1):191–5. PubMed PMID: 12100961.
19. Liao HJ, Chen XM, Li WG. Effect of Epimedium sagittatum on quality of life and cellular immunity in patients of hemodialysis maintenance. *Zhongguo Zhong Xi Yi Jie He Za Zhi.* 1995 Apr;15(4):202–204. PubMed PMID: 7647539.
20. Suresh S, Prakash S. Effect of Mucuna pruriens (Linn.) on sexual behavior and sperm parameters in streptozotocin-induced diabetic male rat. *J Sex Med.* 2012 Dec;9(12):3066–3078. PubMed PMID: 20456630.
21. Suresh S, Prithiviraj E, Prakash S. Effect of Mucuna pruriens on oxidative stress mediated damage in aged rat sperm. *Int J Androl.* 2010 Feb;33(1):22–32. PubMed PMID: 19207619.
22. Suresh S, Prithiviraj E, Prakash S. Dose- and time-dependent effects of ethanolic extract of Mucuna pruriens Linn. seed on sexual behaviour of normal male rats. *J Ethnopharmacol.* 2009 Apr 21;122(3):497–501. PubMed PMID: 19429319.
23. Prasad SK, Qureshi TN, Qureshi S. Mucuna pruriens seed powder feeding influences reproductive conditions and development in Japanese quail Coturnix coturnix japonica. *Animal.* 2009 Feb;3(2):261–8. PubMed PMID: 22444229.
24. Shukla KK, Mahdi AA, Ahmad MK, Shankhwar SN, Rajender S, Jaiswar SP. Mucuna pruriens improves male fertility by its action on the hypothalamus-pituitary-gonadal axis. *Fertil Steril.* 2009 Dec;92(6):1934–40. PubMed PMID: 18973898.
25. Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. *Endocr Rev.* 2001 Dec;22(6):724–763. Review. PubMed PMID: 11739329.
26. Horita H, Sato Y, Adachi H, Suzuki N, Kato R, Hisasue S, Suzuki K, Tsukamoto T. Effects of levodopa on nocturnal penile tumescence: a preliminary study. *J Androl.* 1998 Sep–Oct;19(5):619–624. PubMed PMID: 9796623.
27. Harvey NS. Serial cognitive profiles in levodopa-induced hypersexuality. *Br J Psychiatry.* 1988 Dec;153:833–836. PubMed PMID: 3256388.
28. Kam SC, Do JM, Choi JH, Jeon BT, Roh GS, Hyun JS. In vivo and in vitro animal investigation of the effect of a mixture of herbal extracts from Tribulus terrestris and Cornus officinalis on penile erection. *J Sex Med.* 2012 Oct;9(10):2544–2551. PubMed PMID: 22906304.
29. Mazaro-Costa R, Andersen ML, Hachul H, Tufik S. Medicinal plants as alternative treatments for female sexual dysfunction: utopian vision or possible treatment in climacteric women? *J Sex Med.* 2010 Nov;7(11):3695–3714. PubMed PMID: 20722793 .
30. Adaikan PG, Gauthaman K, Prasad RN, Ng SC. Proerectile pharmacological effects of Tribulus terrestris extract on the rabbit corpus cavernosum. *Ann Acad Med Singapore.* 2000 Jan;29(1):22–26. PubMed PMID: 10748960.
31. Tambi MI, Imran MK, Henkel RR. Standardised water-soluble extract of Eurycoma longifolia, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism? *Andrologia.* 2012 May;44 Suppl 1:226–230. PubMed PMID: 21671978.
32. George A, Henkel R. Phytoandrogenic properties of Eurycoma longifolia as natural alternative to testosterone replacement therapy. *Andrologia.* 2014 Sep;46(7):708–721. PubMed PMID: 24386995.
33. Kim TH, Jeon SH, Hahn EJ, et al. Effects of tissue-cultured mountain ginseng (Panax ginseng CA Meyer) extract on male patients with erectile dysfunction. *Asian J Androl.* 2009 May;11(3):356–361. PubMed PMID: 19234482 .
34. De Andrade E, de Mesquita AA, Claro Jde A, et al. Study of the efficacy of Korean Red Ginseng in the treatment of erectile dysfunction. *Asian J Androl.* 2007 Mar;9(2):241–244. PubMed PMID: 16855773.
35. Hong B, Ji YH, Hong JH, Nam KY, Ahn TY. A double-blind crossover study evaluating the efficacy of Korean red ginseng in patients with erectile dysfunction: a preliminary report. *J Urol.* 2002 Nov;168(5):2070–2073. PubMed PMID: 12394711.
36. Oh KJ, Chae MJ, Lee HS, Hong HD, Park K. Effects of Korean red ginseng on sexual arousal in menopausal women: placebo-controlled, double-blind crossover clinical study. *J Sex Med.* 2010 Apr;7(4 Pt 1):1469–1477. PubMed PMID: 20141583.
37. Kim SY, Seo SK, Choi YM, et al. Effects of red ginseng supplementation on menopausal symptoms and cardiovascular risk factors in postmenopausal women: a double-blind randomized controlled trial. *Menopause.* 2012 Apr;19(4):461–466. PubMed PMID: 22027944.
38. Salvati G, Genovesi G, Marcellini L, et al. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. *Panminerva Med.* 1996 Dec;38(4):249–254. PubMed PMID: 9063034.
39. Ahmad MK, Mahdi AA, Shukla KK, et al. Withania somnifera improves semen quality by regulating reproductive hormone levels and oxidative stress in seminal plasma of infertile males. *Fertil Steril.* 2010 Aug;94(3):989–996. PubMed PMID: 19501822.
40. Brooks NA, Wilcox G, Walker KZ, Ashton JF, Cox MB, Stojanovska L. Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. *Menopause.* 2008 Nov–Dec;15(6):1157–1162. PubMed PMID: 18784609.
41. Gonzales GF, Córdova A, Vega K, et al. Effect of Lepidium meyenii (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia.* 2002 Dec;34(6):367–372. PubMed PMID: 12472620.
42. Arletti R, Benelli A, Cavazzuti E, Scarpetta G, Bertolini A. Stimulating property of Turnera diffusa and Pfaffia paniculata extracts on the sexual-behavior of male rats. *Psychopharmacology (Berl).* 1999 Mar;143(1):15–19. PubMed PMID: 10227074.
43. Hnatyszyn O, Moscatelli V, Garcia J, et al. Argentinian plant extracts with relaxant effect on the smooth muscle of the corpus cavernosum of guinea pig. *Phytomedicine.* 2003 Nov;10(8):669–674. PubMed PMID: 14692728.
44. Rowland D, Tai W. A review of plant-derived and herbal approaches to the treatment of sexual dysfunctions. *J Sex Marital Ther.* 2003 May–Jun;29(3):185–205. Review. PubMed PMID: 12851124.
45. Kwan CY, Zhang WB, Sim SM, Deyama T, Nishibe S. Vascular effects of Siberian ginseng (Eleutherococcus senticosus): endothelium-dependent NO- and EDHF-mediated relaxation depending on vessel size. *Naunyn Schmiedebergs Arch Pharmacol.* 2004 May;369(5):473–480. PubMed PMID: 15095033.
46. Gupta A, Mahdi AA, Ahmad MK, et al. A proton NMR study of the effect of Mucuna pruriens on seminal plasma metabolites of infertile males. *J Pharm Biomed Anal.* 2011 Jul 15;55(5):1060–1066. PubMed PMID: 21459537.
47. Ahmad MK, Mahdi AA, Shukla KK, Islam N, Jaiswar SP, Ahmad S. Effect of Mucuna pruriens on semen profile and biochemical parameters in seminal plasma of infertile men. *Fertil Steril.* 2008 Sep;90(3):627–635. PubMed PMID: 18001713.
48. Shukla KK, Mahdi AA, Ahmad MK, Jaiswar SP, Shankwar SN, Tiwari SC. Mucuna pruriens reduces stress and improves the quality of semen in infertile men. *Evid Based Complement Alternat Med.* 2010 Mar;7(1):137–144. PubMed PMID: 18955292.
49. Gonzales GF, Cordova A, Gonzales C, Chung A, Vega K, Villena A. Lepidium meyenii (Maca) improved semen parameters in adult men. *Asian J Androl.* 2001 Dec;3(4):301–303. PubMed PMID: 11753476.
50. Chen Z, Yin CP, Liu JH, Fang JG, Wang WQ, Shi CY. Extract of acanthopanacis senticosus improves sperm motility of asthenospermia patients in vitro. *Zhonghua Nan Ke Xue.* 2007 Jan;13(1):21–23. PubMed PMID: 17302028.
51. Wahab NA, Mokhtar NM, Halim WN, Das S. The effect of Eurycoma longifolia Jack on spermatogenesis in estrogen-treated rats. *Clinics (Sao Paulo).* 2010;65(1):93–98. PubMed PMID: 20126351.
52. Salvati G, Genovesi G, Marcellini L, et al. Effects of Panax Ginseng C.A. Meyer saponins on male fertility. *Panminerva Med.* 1996 Dec;38(4):249–254. PubMed PMID: 9063034.
53. Ahmad MK, Mahdi AA, Shukla KK, et al. Withania somnifera improves semen quality by regulating reproductive hormone levels and oxidative stress in

seminal plasma of infertile males. *Fertil Steril.* 2010 Aug;94(3):989–996. PubMed PMID: 19501822.
54. Calabrese V, Scapagnini G, Davinelli S, et al. Sex hormonal regulation and hormesis in aging and longevity: role of vitagenes. *J Cell Commun Signal.* 2014 Dec;8(4):369–384. PubMed PMID: 25381162.
55. Neto WK, Gama EF, Rocha LY, et al. Effects of testosterone on lean mass gain in elderly men: systematic review with meta-analysis of controlled and randomized studies. *Age (Dordr).* 2015 Feb;37(1):9742. PubMed PMID: 25637335.
56. Zhang H, Liu B, Wu J, et al. Icariin inhibits corticosterone-induced apoptosis in hypothalamic neurons via the PI3-K/Akt signaling pathway. *Mol Med Rep.* 2012 Nov;6(5):967–972. PubMed PMID: 22923091.
57. Liu B, Zhang H, Xu C, et al. Neuroprotective effects of icariin on corticosterone-induced apoptosis in primary cultured rat hippocampal neurons. *Brain Res.* 2011 Feb 23;1375:59–67. PubMed PMID: 21182828.
58. Wu T, Cui L, Zhang Z, et al. Experimental study on antagonizing action of herba Epimedii on side effects induced by glucocorticoids. *Zhongguo Zhong Yao Za Zhi.* 1996 Dec;21(12):748–751,763. PubMed PMID: 9812684.
59. Shukla KK, Madhi AA, Ahmad MK, Jaiswar SP, Shankwar SN, Tiwari SC. *Mucuna pruriens* reduces stress and improves the quality of semen in infertile men. *Evid Based Complement Alternat Med.* 2010 Mar;7(1):137–144. PubMed PMID: 18955292.
60. Wang Z, Zhang D, Hui S, Zhang Y, Hu S. Effect of Tribulus terrestris saponins on behavior and neuroendocrine in chronic mild stress depression rats. *J Tradit Chin Med.* 2013 Apr;33(2):228–232. PubMed PMID: 23789222.
61. Meissner HO, Kedzia B, Mrozikiewicz PM, Mscisz A. Short and long-term physiological responses of male and female rats to two dietary levels of pre-gelatinized maca (Lepidium peruvianum chacon). *Int J Biomed Sci.* 2006 Feb;2(1):13–28. PubMed PMID: 23674962 .
62. Piato AL, Detanico BC, Jesus JF, Lhullier FL, Nunes DS, Elisabetsky E. Effects of Marapuama in the chronic mild stress model: further indication of antidepressant properties. *J Ethnopharmacol.* 2008 Jul 23;118(2):300–304. PubMed PMID: 18513902..
63. Kimura Y, Sumiyoshi M. Effects of various Eleutherococcus senticosus cortex on swimming time, natural killer activity and corticosterone level in forced swimming stressed mice. *J Ethnopharmacol.* 2004 Dec;95(2–3):447–453. PubMed PMID: 15507373.
64. Talbott SM, Talbott JA, George A, Pugh M. Effect of Tongkat Ali on stress hormones and psychological mood state in moderately stressed subjects. *J Int Soc Sports Nutr.* 2013 May 26;10(1):28. PubMed PMID: 23705671.
65. Tode T, Kikuchi Y, Hirata J, Kita T, Nakata H, Nagata I. Effect of Korean red ginseng on psychological functions in patients with severe climacteric syndromes. *Int J Gynaecol Obstet.* 1999 Dec;67(3):169–174. PubMed PMID: 10659900.
66. Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. *Indian J Psychol Med.* 2012 Jul;34(3):255–262. PubMed PMID: 23439798.
67. Osterberg EC, Bernie AM, Ramasamy R. Risks of testosterone replacement therapy in men. *Indian J Urol.* 2014 Jan;30(1):2–7. Review. PubMed PMID: 24497673.
68. Jia H, Sullivan CT, McCoy SC, Yarrow JF, Morrow M, Borst SE. Review of health risks of low testosterone and testosterone administration. *World J Clin Cases.* 2015 Apr 16;3(4):338–344. Review. PubMed PMID: 25879005.
69. Carruthers M, Cathcart P, Feneley MR. Evolution of testosterone treatment over 25 years: symptom responses, endocrine profiles and cardiovascular changes. *Aging Male.* 2015 Jul 28:1–11. PubMed PMID: 26218766.
70. Üçer O, Gümüş B. The treatment of late-onset hypogonadism. *Turk J Urol.* 2014 Sep;40(3):170–179. Review. PubMed PMID: 26328172.
71. Liu TZ, Chen CY, Yiin SJ, et al. Molecular mechanism of cell cycle blockage of hepatoma SK-Hep-1 cells by Epimedin C through suppression of mitogen-activated protein kinase activation and increased expression of CDK inhibitors p21(Cip1) and p27(Kip1). *Food Chem Toxicol.* 2006 Feb;44(2):227–235. PubMed PMID: 16112786..
72. Li J, Jiang K, Zhao F. Icariin regulates the proliferation and apoptosis of human ovarian cancer cells through microRNA-21 by targeting PTEN, RECK and Bcl-2. *Oncol Rep.* 2015 Jun;33(6):2829–2836. PubMed PMID: 25845681.
73. Yao D, Xie XH, Wang XL, et al. Icaritin, an exogenous phytomolecule, enhances osteogenesis but not angiogenesis—an in vitro efficacy study. *PLoS One.* 2012;7(8):e41264. PubMed PMID: 22952579.
74. Huang X, Zhu D, Lou Y. A novel anticancer agent, icaritin, induced cell growth inhibition, G1 arrest and mitochondrial transmembrane potential drop in human prostate carcinoma PC-3 cells. *Eur J Pharmacol.* 2007 Jun 14;564(1–3):26–36. PubMed PMID: 17382317.
75. Kumar P, Rawat A, Keshari AK, et al. Antiproliferative effect of isolated isoquinoline alkaloid from Mucuna pruriens seeds in hepatic carcinoma cells. *Nat Prod Res.* 2015 Mar 16:1–4. PubMed PMID: 25774560.
76. Wei S, Fukuhara H, Chen G, et al. Terrestrosin D, a steroidal saponin from Tribulus terrestris L., inhibits growth and angiogenesis of human prostate cancer in vitro and in vivo. *Pathobiology.* 2014;81(3):123–132. PubMed PMID: 24642631.
77. Goranova TE, Bozhanov SS, Lozanov VS, Mitev VI, Kaneva RP, Georgieva EI. Changes in gene expression of CXCR4, CCR7 and BCL2 after treatment of breast cancer cells with saponin extract from Tribulus terrestris. *Neoplasma.* 2015;62(1):27–33. PubMed PMID: 25563364.
78. Mahassni SH, Al-Reemi RM. Apoptosis and necrosis of human breast cancer cells by an aqueous extract of garden cress (Lepidium sativum) seeds. *Saudi J Biol Sci.* 2013 Apr;20(2):131–139. PubMed PMID: 23961228.
79. Bai N, He K, Roller M, Lai CS, Bai L, Pan MH. Flavonolignans and other constituents from Lepidium meyenii with activities in anti-inflammation and human cancer cell lines. *J Agric Food Chem.* 2015 Mar 11;63(9):2458–2463. PubMed PMID: 25667964.
80. Avelino-Flores Mdel C, Cruz-López Mdel C, Jiménez-Montejo FE, Reyes-Leyva J. Cytotoxic activity of the methanolic extract of Turnera diffusa Willd on breast cancer cells. *J Med Food.* 2015 Mar;18(3):299–305. PubMed PMID: 25299247.
81. Yu CY, Kim SH, Lim JD, Kim MJ, Chung IM. Intraspecific relationship analysis by DNA markers and in vitro cytotoxic and antioxidant activity in Eleutherococcus senticosus. *Toxicol In Vitro.* 2003 Apr;17(2):229–36. PubMed PMID: 12650677.
82. Cichello SA, Yao Q, Dowell A, Leury B, He XQ. proliferative and inhibitory activity of Siberian ginseng (Eleutherococcus senticosus) extract on cancer cell lines; A-549, XWLC-05, HCT-116, CNE and Beas-2b. *Asian Pac J Cancer Prev.* 2015;16(11):4781–4786. PubMed PMID: 26107240.
83. Kormosh N, Laktionov K, Antoshechkina M. Effect of a combination of extract from several plants on cell-mediated and humoral immunity of patients with advanced ovarian cancer. *Phytother Res.* 2006 May;20(5):424–425. PubMed PMID: 16619374.
84. Tong KL, Chan KL, AbuBakar S, Low BS, Ma HQ, Wong PF. The in vitro and in vivo anti-cancer activities of a standardized quassinoids composition from Eurycoma longifolia on LNCaP human prostate cancer cells. *PLoS One.* 2015 Mar 31;10(3):e0121752. PubMed PMID: 25826409.
85. Tee TT, Cheah YH, Hawariah LP. F16, a fraction from Eurycoma longifolia jack extract, induces apoptosis via a caspase-9-independent manner in MCF-7 cells. *Anticancer Res.* 2007 Sep–Oct;27(5A):3425–3430. PubMed PMID: 17970090.
86. Tee TT, Azimahtol HL. Induction of apoptosis by Eurycoma longifolia jack extracts. *Anticancer Res.* 2005 May–Jun;25(3B):2205–2213. PubMed PMID: 16158965.
87. Meng D, Li X, Han L, Zhang L, An W, Li X. Four new quassinoids from the roots of Eurycoma longifolia Jack. *Fitoterapia.* 2014 Jan;92:105–110. PubMed PMID: 24513570..
88. Wong PF, Cheong WF, Shu MH, Teh CH, Chan KL, AbuBakar S. Eurycomanone suppresses expression of lung cancer cell tumor markers, prohibitin, annexin 1 and endoplasmic reticulum protein 28. *Phytomedicine.* 2012 Jan 15;19(2):138–144. PubMed PMID: 21903368.
89. Miyake K, Li F, Tezuka Y, Awale S, Kadota S. Cytotoxic activity of quassinoids from Eurycoma longifolia. *Nat Prod Commun.* 2010 Jul;5(7):1009–1012. PubMed PMID: 20734929.
90. Zakaria Y, Rahmat A, Pihie AH, Abdullah NR, Houghton PJ. Eurycomanone induce apoptosis in HepG2 cells via up-regulation of p53. *Cancer Cell Int.* 2009 Jun 10;9:16. PubMed PMID: 19508737.
91. Kuo PC, Damu AG, Lee KH, Wu TS. Cytotoxic and antimalarial constituents from the roots of Eurycoma longifolia. *Bioorg Med Chem.* 2004 Feb 1;12(3):537–544. PubMed PMID: 14738962.
92. Kuo PC, Shi LS, Damu AG, et al. Cytotoxic and antimalarial beta-carboline alkaloids from the roots of Eurycoma longifolia. *J Nat Prod.* 2003 Oct;66(10):1324–1327. PubMed PMID: 14575431.
93. Kardono LB, Angerhofer CK, Tsauri S, Padmawinata K, Pezzuto JM, Kinghorn AD. Cytotoxic and antimalarial constituents of the roots of Eurycoma longifolia. *J Nat Prod.* 1991 Sep–Oct;54(5):1360–1367. PubMed PMID: 1800638.
94. Bae JS, Park HS, Park JW, Li SH, Chun YS. Red ginseng and 20(S)-Rg3 control testosterone-induced prostate hyperplasia by deregulating androgen receptor signaling. *J Nat Med.* 2012 Jul;66(3):476–485. PubMed PMID: 22101440.
95. Liu WK, Xu SX, Che CT. Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. *Life Sci.* 2000 Aug 4;67(11):1297–1306. PubMed PMID: 10972198.
96. Liu J, Shimizu K, Yu H, Zhang C, Jin F, Kondo R. Stereospecificity of hydroxyl group at C-20 in antiproliferative action of ginsenoside Rh2 on prostate cancer cells. *Fitoterapia.* 2010 Oct;81(7):902–905. PubMed PMID: 20554003.
97. Yoo JH, Kwon HC, Kim YJ, Park JH, Yang HO. KG-135, enriched with selected ginsenosides, inhibits the proliferation of human prostate cancer cells in culture and inhibits xenograft growth in athymic mice. *Cancer Lett.* 2010 Mar 1;289(1):99–110. PubMed PMID: 19765891.
98. Wang W, Rayburn ER, Hao M, et al. Experimental therapy of prostate cancer with novel natural product anti-cancer ginsenosides. *Prostate.* 2008 Jun 1;68(8):809–819. PubMed PMID: 18324646.
99. Yoneyama T, Arai MA, Sadhu SK, Ahmed F, Ishibashi M. Hedgehog inhibitors from Withania somnifera. *Bioorg Med Chem Lett.* 2015 Sep 1;25(17):3541–3544. PubMed PMID: 26169123.
100. Siddique AA, Joshi P, Misra L, Sangwan NS, Darokar MP. 5,6-de-epoxy-5-en-7-one-17-hydroxy withaferin A, a new cytotoxic steroid from Withania somnifera L. Dunal leaves. *Nat Prod Res.* 2014;28(6):392–398. PubMed PMID: 24422976.
101. Roy RV, Suman S, Das TP, Luevano JE, Damodaran C. Withaferin A, a steroidal lactone from Withania somnifera, induces mitotic catastrophe and growth arrest in prostate cancer cells. *J Nat Prod.* 2013 Oct 25;76(10):1909–1915. PubMed PMID: 24079846.
102. Srinivasan S, Ranga RS, Burikhanov R, Han SS, Chendil D. Par-4-dependent apoptosis by the dietary compound withaferin A in prostate cancer cells. *Cancer Res.* 2007 Jan 1;67(1):246–253. PubMed PMID: 17185378.
103. Aalinkeel R, Hu Z, Nair BB, et al. Genomic analysis highlights the role of the JAK-STAT signaling in the anti-proliferative effects of dietary flavonoid-'Ashwagandha' in prostate cancer cells. *Evid Based Complement Alternat Med.* 2010 Jun;7(2):177–187. PubMed PMID: 18955307.

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Effective Use of Probiotics

review by Katherine Duff

The Probiotic Promise: Simple Steps to Heal Your Body from the Inside Out, by Michelle Schoffro Cook, PhD, DNM
Da Capo Press, 44 Farnsworth Street, 3rd Floor; Boston, Massachusetts 02210
© 2015; hardcover; $25.99; 292 pp.

The marketing of probiotics can be found everywhere in popular media now. But as people self-administer based on marketing, their efforts may very well be wasted. *The Probiotic Promise*, by Michelle Schoffro Cook provides the background in this emerging field of research and how to use probiotics effectively and target various health conditions based on current research.

The statistics of the bacteria that make up our microbiome are quite amazing. We harbor about 100 trillion bacteria in our bodies, compared with 50 to 100 trillion human cells. And though we have historically regarded bacteria as invaders, we now know that some are essential to the proper functioning of the human body. Presently, the Human Microbiome Project is cataloguing the bacteria found in the nasal passages, oral cavities, skin, gastrointestinal tract, and urogenital tract in an effort to determine what is normal. An example of what the project has found to be normal is that the microorganisms on one's left hand are different than those found on the right hand.

For how the bacteria can affect human health, the author looks to the gut, where an imbalance of good and bad bacteria can be addressed. She notes that the environment of the intestines is usually 20% beneficial bacteria, 30% harmful bacteria, and 50% that is considered intermediate. Depending upon one's health status as determined by diet and lifestyle choices, the intermediate bacteria can swing to become beneficial or harmful. Especially problematic is a diet high in sugar, which feeds the harmful bacteria and yeasts, and consumption of animal protein, which causes growth of microorganisms that promote inflammation. The overgrowth of harmful yeasts such as *Candida albicans* can show up as any of the symptoms in a long list included in the book. Inflammation plays a role in heart disease, autoimmune illnesses, and allergies, to name just a few.

Besides consuming a diet lower in sugars and animal proteins, the key to reestablishing balance in the gut is through probiotics. These are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." Probiotics can be found in supplements and fermented foods. Whether in food or pill form, the main beneficial bacteria are in the Lactobacillacea and Bifidobacteriacea families. Within these families are strains that accomplish different tasks in the gut. In general, they can kill harmful bacteria, viruses, and fungi and reduce cytokines in the blood. In particular for example, *Lactobacillus brevis* is known as a booster of anticancer compounds in the intestines, and *Lactobacillus rhamnosus* manufactures enzymes that are anti-inflammatory.

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."

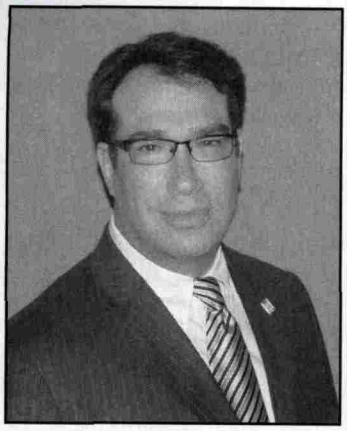
Cook has combed the research for studies that have used bacteria to treat specific health problems. She lists those conditions and the bacteria used to treat them. Many of these entries, though, note that the research is still young and the possible treatments show promise at this point.

Purchasing probiotics presents unique problems compared with other supplements, which the author addresses very well. One must be sure that they have been refrigerated from point of production. Probiotics are inert until mixed with water, so they should be taken with adequate water. Cook lists the brand names of probiotics that contained much less than the label claimed, as well as those that did contain the amounts listed on the label. And while many people assume that they are getting their probiotics from yogurt, Cook lists types that have high sugar content and includes a method for testing whether your yogurt actually contains live cultures: by making a batch using the commercial product as the starter.

Her example of a marketing gimmick concerns a yogurt company that claimed exclusive use of bacterium called *Bifidus regularis* in its product. In truth, this is just a trademarked name for *Bifidobacterium animalis* DN-173010, which is not exclusive to anyone.

To be sure that you are actually getting probiotics in yogurt, Cook recommends making it yourself. A better choice, though, may be to add other fermented foods to the diet, such as unpasteurized sauerkraut, kimchi, miso, kombucha, and kefir. Included are recipes and advice for purchasing.

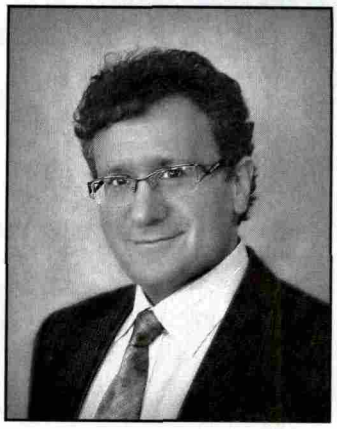
Research into the role of bacteria in human health is a hot area of study now, and so too is the marketing of the probiotic solution to health problems. As this book explains, there is much more to it than taking a one-size-fits-all supplement or believing the advertising. Cook teaches us how to use these microorganisms effectively, with valuable advice for the consumer and prescribing physician alike. ◆



Anti-Aging Medicine

by Ronald Klatz, MD, DO, and Robert Goldman, MD, PhD, DO, FAASP

www.worldhealth.net



Advancements in Anti-Aging Diagnostics

To achieve the triple-digit lifespan, science will harness the Biotech Singularity, whereby we leverage cutting-edge technologies to bridge the gap between the medical knowledge of today and the medical knowledge that we will have in our grasp by the year 2029. As a result, it is not impracticable nor improbable to expect that humankind will reach the point where we'll know how to substantially slow or perhaps even stop aging, and even eventually reset the clock mechanism of life itself.

A key element for achieving the Biotech Singularity is diagnostic medical technologies, which will enable earlier and accurate assessment of diseases. This column shares some of the latest and promising advancements in anti-aging diagnostics that may enable this goal.

Saliva Suggests Cognitive Changes

Cortisol is a hormone that when produced at high levels (often in response to emotional stress) can have a toxic effect on the hippocampus area of the brain – a region with an important role in memory. Lenore J. Launer and colleagues from the National Institute on Aging (Maryland, US) assessed 4244 people, average age of 76 years and without dementia, enrolled in the Agee, Gene/Environment Susceptibility (AGES)-Reykjavik Study. Subjects were assessed via MRI for brain volume, and their saliva was collected at home 45 minutes after awakening and at night. Higher evening cortisol associated with smaller total brain volume, with the smaller volumes observed in all brain regions, but significantly smaller in gray matter than in white matter regions. Further, higher evening cortisol associated with poorer cognitive functioning. In contrast, higher levels of morning cortisol associated with slightly greater normal white matter volume and better processing speed and executive functioning. The study authors submit: "In older persons, evening and morning cortisol levels may be differentially associated with tissue volume in gray and white matter structures and cognitive function."

Geerlings MI, Sigurdsson S, Eiriksdottir G, et al. Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia. *Neurology*. 2015 Aug 19. pii:10.1212/WNL.0000000000001931.

Protein Patterns May Signal Alzheimer's

Changes in the spinal fluid during middle age may identify people at risk of developing Alzheimer's disease later in life. Anne Fagan and colleagues from the Washington University School of Medicine (Missouri, US) studied a group of 169 cognitively normal men and women, ages 45 to 75 years when they entered the study – and followed them for 10 years. Each subject received a complete clinical, cognitive imaging, and cerebrospinal fluid biomarker analysis every 3 years, with a minimum of two evaluations. At the participants' initial assessments, researchers divided them into three age groups: early middle age (45–54); mid-middle age (55–64), and late middle age (65–74). The researchers tracked changes in amyloid beta 42, a protein that is the principal ingredient of Alzheimer's plaques; tau, a structural component of brain cells that increases in the cerebrospinal fluid as Alzheimer's disease damages brain cells; YKL-40, a newly recognized protein that is indicative of inflammation and is produced by brain cells; and the presence of amyloid plaques in the brain, as seen via amyloid PET scans. Observing drops in amyloid beta 42 levels in the cerebrospinal fluid, then the appearance of plaques in brain scans years later among cognitively normal participants ages 45 to 54, the researchers say that the data suggest that patterns of amyloid levels in cerebrospinal fluid in midlife may presage Alzheimer's disease in later years. They also found that tau and other biomarkers of brain-cell injury increase sharply in some individuals as they reach their mid-50s to mid-70s, and YKL-40 rises throughout the age groups focused on in the study. Writing, "Longitudinal [cerebrospinal fluid] biomarker patterns consistent with [Alzheimer's disease] are first detectable during early middle age and are associated with later amyloid positivity and cognitive decline," the study authors submit: "Such measures may be useful for targeting middle-aged, asymptomatic individuals for therapeutic trials designed to prevent cognitive decline."

Sutphen CL, Jasielec MS, Shah AR, et al. Longitudinal cerebrospinal fluid biomarker changes in preclinical Alzheimer disease during middle age. *JAMA Neurol*. 2015 Jul 6.

Listen for Cancer

In that existing methods of separation use tumor-specific antibodies to bind with the cancer cells and isolate them – requiring that the appropriate antibodies be known in advance – and other methods rely on specific molecular properties, Peng Li and colleagues from the Pennsylvania State University (US) have innovated a novel acoustic tweezers device about

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twice the size of a penny, with two sound transducers that separate cells by detecting the differential sizes and weights to push the circulating cancer cells out of the fluid stream and into a separate channel for collection. The power, intensity, and frequency used in this study are similar to those used in ultrasonic imaging, and each cell experiences the acoustic wave for only a fraction of a second. The researchers used two types of human cancer cells to optimize the acoustic separation – HELA cells and MCF7 cells, which are similar in size. Their separation experiment yielded a separation rate of more than 83%. Writing, "We report the development of an acoustic-based device that successfully demonstrates the isolation of rare [circulating tumor cells] from the clinical blood samples of cancer patients. Our work thus provides a unique means to obtain viable and undamaged [circulating tumor cells]," the study authors submit: "The results presented here offer unique pathways for better cancer diagnosis, prognosis, therapy monitoring, and metastasis research."

Li P, Mao Z, Peng Z, et al. Acoustic separation of circulating tumor cells. *PNAS*. 2015;112(16):4970–4975.

Telomeres Tell of Cancer

Telomeres are the end caps of chromosomes, protecting the DNA complexes from deterioration during cell division. Telomere shortening is considered a marker of cellular aging, and prematurely shortened telomeres have been linked to increased risk of cancers, heart disease, dementia, and death. Lifang Hou and colleagues from Northwestern University (Illinois, US) took multiple measurements of telomeres over a 13-year period in 792 persons, 135 of whom were eventually diagnosed with different types of cancer, including prostate, skin, lung, leukemia, and others. The team found that initially telomeres aged much faster (indicated by a more rapid loss of length) in individuals who were developing but not yet diagnosed with cancer: telomeres in persons developing cancer looked as much as 15 years chronologically older than those of people who were not developing the disease. Then the researchers observed that the accelerated aging process stopped 3 to 4 years before the cancer diagnosis. The lead investigator comments: "This pattern of telomere growth may mean it can be a predictive biomarker for cancer."

Gu J. Leukocyte telomere length and cancer risk: a dynamic problem. *EbioMedicine*. May 20, 2015.

Holograms for Health

Responsive holograms that change color in the presence of certain compounds are being developed into portable medical tests and devices, which could be used to monitor conditions such as diabetes, cardiac function, infections, and electrolyte or hormone imbalance easily and inexpensively to test blood, breath, urine, saliva, or tear fluid for a wide range of compounds, such as glucose, alcohol, hormones, drugs, or bacteria. When one of these compounds is present, the hologram changes color, potentially making the monitoring of various conditions as simple as checking the color of the hologram against a color gradient. Researchers from the University of Cambridge (UK) use a highly absorbent material known as a hydrogel, similar to contact lenses, impregnated with tiny particles of silver. Using a single laser pulse, the silver nanoparticles are formed into three-dimensional holograms of predetermined shapes in a fraction of a second. When in the presence of certain compounds, the hydrogels either shrink or swell, causing the color of the hologram to change to any other color in the entire visible spectrum, the first time that this has been achieved in any hydrogel-based sensor. A major advantage of the technology is that the holograms can be constructed in a fraction of a second, making the technology highly suitable for mass production. While these sorts of inexpensive, portable tests aren't meant to replace a doctor, holograms could enable people to easily monitor their own health.

Yetisen AK, Butt H, da Cruz Vasconcellos F, et al. Light-directed writing of chemically tunable narrow-band holographic sensors. *Adv Opt Mater*. 2 Jan. 2014.

Disease Detection by Smartphone

Indeed, technology is a cornerstone in the evolution of medical diagnostics. Researchers around the world are developing smartphone applications to enable fast, inexpensive, accessible, noninvasive detection for a wide range of diseases. A consortium led by Hossam Haick from the Technion-Israel Institute of Technology (Israel) is developing a product that, when coupled with a smartphone, will be able to screen the user's breath for early detection of life-threatening diseases. The SNIFFPHONE project links breathalyzer screening technology to the smartphone, utilizing micro- and nanosensors to read exhaled breath and transfer the information through the attached mobile phone to an information-processing system for interpretation. The data are then assessed, and disease diagnosis and other details are ascertained. Separately, Samuel K. Sia and colleagues from Columbia University (New York, US) have devised a low-cost smartphone accessory that can perform a point-of-care test that simultaneously detects three infectious disease markers from a finger prick of blood in just 15 minutes. The device replicates, for the first time, all mechanical, optical, and electronic functions of a lab-based blood test. Specifically, it performs an enzyme-linked immunosorbent assay (ELISA) without requiring any stored energy: all necessary power is drawn from the smartphone. It performs a triplexed immunoassay not currently available in a single test format: HIV antibody, treponemal-specific antibody for syphilis, and nontreponemal antibody for active syphilis infection. The study authors submit: "The overall system aims to be portable, robust, low-power, and fully utilize the ability of mobile devices for bringing better health care to resource poor areas."

Sia et al.: Guo TW, Laksanasopin T, Sridhara AA, Nayak S, Sia SK. Mobile device for disease diagnosis and data tracking in resource-limited settings. *Methods Mol Biol*. 2015;1256:3–14.

To stay updated on the latest advancements in anti-aging diagnostic medical technologies, visit the World Health Network (www.worldhealth.net), the official educational website of the A4M and your one-stop resource for authoritative anti-aging information. Be sure to sign up for the free Longevity Magazine e-journal, your weekly health newsletter featuring wellness, prevention, and biotech advancements in longevity. ◆

Calendar

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

JANUARY 22-24: INTEGRATIVE THERAPIES INSTITUTE presents GENOMICS, NEUROPSYCHIATRIC THERAPIES, AND CHRONIC ILLNESS, IMMUNE & AUTOIMMUNE CONDITIONS & ADVANCED INTEGRATIVE THERAPIES IN CLINICAL PRACTICE in Irvine, California. CONTACT: www.iti2016.com

JANUARY 22-24: SW COLLEGE OF NATUROPATHIC MEDICINE presents REGENERATIVE INJECTION THERAPY WORKSHOPS (Module 2): Upper Extremity in Tempe, Arizona. CONTACT: www.scnm.edu/RIT-WORKSHOPS

JANUARY 23-26: WALSH RESEARCH INSTITUTE presents PHYSICIAN EDUCATION WORKSHOP: MASTERING BRAIN CHEMISTRY (nutrient protocols for autism, behavioral/learning and mental disorders) in Irvine, California. CONTACT: Sue at 630-400-3400; www.walshinstitute.org/practitioner-education.html

JANUARY 29-31: 13th ANNUAL NATURAL SUPPLEMENTS: AN EVIDENCE-BASED UPDATE in San Diego, California. CONTACT: www.Scripps.org/NaturalSupplements

JANUARY 29-31: WORLD CONGRESS ON NATURAL MEDICINES in Tampa, Florida. CONTACT: www.smoch.org/world_congress_tampa.php

JANUARY 29-31: PHYSICIAN'S ROUND TABLE CONFERENCE in Tampa, Florida. CONTACT: 352-687-2399; www.suevogan.net

JANUARY 29-31: BASTYR UNIVERSITY presents AYURVEDIC NUTRITION in Kenmore, Washington (near Seattle). CONTACT: www.bastyr.edu/civicrm/event/info?id=1786&reset=1

JANUARY 30: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Tampa, Florida. CONTACT: www.organicacidworkshop.com

FEBRUARY 3-5: 1st INTERNATIONAL SYMPOSIUM OF THE CANCER RESEARCH CENTER in Toulouse, France. CONTACT: www.toulouse-onco-week.org.

FEBRUARY 4-6: CARDIOMETABOLIC ADVANCED PRACTICE MODULE – Prevention of Chronic Metabolic and Cardiovascular Disorders in Atlanta, Georgia. CONTACT: www.functionalmedicine.org/Cardiometabolic

FEBRUARY 7-9: IMMUNE ADVANCED PRACTICE MODULE - The Many Faces of Immune Dysregulation and Chronic Inflammation in Atlanta, Georgia CONTACT: www.functionalmedicine.org/Immune

FEBRUARY 13-14: 2016 NWNPC CONVENTION: Food as Medicine in Portland, Oregon. CONTACT: foodasmedicineinstitute.com/2016-symposium-ce/

FEBRUARY 19-21: LDN 2016 CONFERENCE in Orlando, Florida. CONTACT: www.ldn2016.com/townsend/

FEBRUARY 24-27: INTEGRATIVE HEALTHCARE SYMPOSIUM ANNUAL CONFERENCE in Midtown, New York. CONTACT: ihsymposium.com/annual-conference/

MARCH 4-6: ENVIRONMENTAL HEALTH SYMPOSIUM ANNUAL CONFERENCE in San Diego, California. CONTACT: www.EnvironmentalHealthSymposium.com

MARCH 5-6: 4th ANNUAL WOMEN IN BALANCE SYMPOSIUM in Portland, Oregon. CONTACT: womeninbalance.org/4th-annual-women-in-balance-conference/

MARCH 12: ORGANIC ACIDS WORKSHOP FOR DISCOVERING UNDERLYING CAUSES OF CHRONIC ILLNESS with Kurt Woeller in Atlanta, Georgia. CONTACT: www.organicacidworkshop.com

MARCH 14-18: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE – 5 day foundational course in Phoenix, Arizona. CONTACT: www.functionalmedicine.org/AFMCP

MARCH 16: WISDOM DAY 2016 in Washington, D.C. Precedes **39th Annual Psychotherapy Networker Symposium**. CONTACT: www.dcnn.pro/WisdomDay2016.en.html

MARCH 19-20: 2016 HOMEOPATHY SYMPOSIUM @ National College of Natural Medicine in Portland, Oregon. CONTACT: career-alumni.ncnm.edu/homeopathy/

MARCH 21-23: AMERCIAN CENTER FOR INTEGRATIVE MEDICINE presents 13th ANNUAL NUTRITION & HEALTH CONFERENCE in Denver, Colorado. CONTACT: www.nutritionandhealthconf.org/

MARCH 31-APRIL 3: ADVANCED TOPICS IN ENVIRONMENTAL MEDICINE in Dallas, Texas. Includes Dr. Alan McDaniel's 2-day Endocrinology course. CONTACT: American Academy of Environmental Medicine, 316-684-5500; www.aaemconference.com

APRIL 8-10: 11th ANNUAL JOINT AMERICAN HOMEOPATHIC CONFERENCE – Ascending to New Heights: Reaching the Summit with Homeopathy in Westminster, Colorado (near Denver). CONTACT: www.homeopathycenter.org/2016-joint-american-homeopathic-conference

APRIL 14-16: 14th ANNUAL INTEGRATIVE ONCOLOGY CONFERENCE @ Town & Country Resort in San Diego, California. CONTACT: www.bestanswerforcancer.org/annual-conference/2016-conference/

APRIL 14-17: 12th NATIONAL AYURVEDA MEDICAL ASSOCIATION CONFERENCE in Warwick, Rhode Island. CONTACT: www.ayurvedanama.org/?page=2016ConfOverview

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Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

Ingrained: A Novel Look at Gluten Digestion During Premodern Times

Scientists agree that celiac disease rates are rapidly rising and that these rates are not a mere effect of reclassification or new diagnostic methods. Rather, they reflect that gluten intolerance stands in the epicenter of the exploding rates of chronic diseases.

Great strides are being made in understanding what goes awry with digesting gluten. Among the findings are inconvenient truths that modern agricultural practices and food traditions accelerate digestive disorders. But how big a factor is modern living, and what might we change in our modern lives to be proactive in reducing digestive disorders? In this *Townsend Letter* themed on diagnostics, I probe these huge questions in an off-road manner, by going back to a time when salt was the only food preservative, all crops were heirloom, no grains were refined, and chemical manufacturers didn't define agriculture.

Background

Gluten protein is one of the most difficult proteins to digest, especially when it is in the form of baked bread. Gluten intolerance and celiac disease appear to have occurred here and there among wheat-eating communities for a long time. International travel has long been known to trigger a problem with gluten digestion, and it was called tropical sprue before medical scientists recognized it as the same thing as celiac disease. Yet, at no time in history is celiac disease or poor digestion of gluten known to be as common as it is in affluent countries today.

In theory, anything that reduces optimal digestion can contribute to gluten intolerance. The list would include dental problems, infection, inflammation, and emotional stress, and digestion is the rationale by which health professionals may instruct their patients to:

- improve digestion by reducing chronic and acute stress;
- avoid gluten by eating more nutrient-rich seeds, nuts, and spices;
- choose grains that have sprouted, when possible;
- eat more slowly to prevent overeating, especially filling up on bread.

Here the same advice given across modern medical clinics is applied to ancient communities whose well-known narratives are recorded in the Bible. While biblical anthropologists may find modern medicine to be a useful way to study the ancient

texts, modern health-care professionals may find the accounts valuable since they reflect a time without the modern causes of digestive disorders.

Taking Away the Bread of Strife and Reinstating the Bread of Life

Chronic conflict is an underlying cause of poor digestion and immune system problems such as gluten intolerance. If there is strife among people who break bread together, this makes gluten harder to digest.

Chronic conflict among brothers and their families recurs in the Bible. The first account ends in murder as Cain kills Abel. Later in the book of Genesis, chronic conflict among siblings again approaches murder. But instead of leaving him for dead, Joseph's brothers instead sell him off. The conflict was unresolved for decades, as Joseph becomes an Egyptian ruler who organizes grain storage for a famine he anticipates. Not recognizing Joseph as the brother whom they tried to murder, Joseph's brothers bow to him asking for grain. When they learn of his identity, they are reconciled.

In the New Testament, Jesus tells a parable of reconciliation among brothers. A son leaves home with his share of the inheritance mostly because of his brother's arrogance. The combination of a spent inheritance and the famine in a distant land drives the estranged brother back home to unexpected reconciliation.

In both accounts, gluten is removed from the diet through famine. The famine forces reunion of estranged brothers and reconciliation takes place. Once chronic conflict is resolved, grain is reintroduced to the diet.

Not Enough Time: The Passover Story

Passover recounts the Israelites' flight to freedom, leaving their slavery in Egypt behind. When I was a child, my family would join another family for an annual dinner commemorating this freedom. Because I was the youngest, I got to ask the four questions about what makes Passover different from all other nights. "On all other nights we eat bread with leaven. On this night, why do we eat unleavened bread?" The answer was always the same: not enough time for leavened bread. As a child I was puzzled by this answer, because I had reasoned differently. Bread wouldn't take longer to prepare than the roasted lamb. Since bread was prepared daily, some yeast dough was presumably ready for baking. But even if it weren't ready, with a yeast starter bread can rise and be out of the oven in the same time frame needed for the lamb.

I found the answer to my childhood question years later while studying medicine. The Israelites were fleeing in fear that Pharaoh would change his mind again. They were experiencing the fight-or-flight response to the max. The Passover narrative was correct that there was not enough time to eat leavened bread. Even if there was enough time to prepare it as I had reasoned, there was not enough time to digest it.

Unleavened bread would have been easier to digest because it was prepared with less wheat and more barley. ➤

Barley has only about a third as much gluten as does wheat. Additionally, leavened bread forms air pockets with the gluten, which reduces its digestibility. In sum, leavened bread would have been digested about as well as rocks.

Manna Avoids Gluten and Promotes a Suitable Microbiome

After their flight from Egypt, the Israelites experienced a dramatically different way of life. They went from being part of a highly advanced civilization to simple nomads. When people groups make demographic shifts, it's almost always in the opposite direction – from rural to urban.

One reason that it is all but impossible for a people group to transition from urban to nomadic living: the human microbiome. The microbiome is the bacteria and other microorganisms that live in us and on us and hold sway over aspects of our health, especially our immune system and digestion. Nomadic people have manyfold more bacteria than urban dwellers. The microbiome is formed mostly in the first year of life. Adults can change their microbiome somewhat, mostly through diet. So in adulthood it would be unlikely to be able to achieve the optimally large and diverse microbiome.

For the desert-dwelling Israelites to eat foods high in gluten would get in the way of cultivating a healthful microbiome. While they would not have suffered modern-day chronic diseases from eating gluten, this is only because infections and malnutrition would have been more immediate threats to their health.

The background knowledge that modern medicine provides makes the diet of manna, rather than bread, especially intriguing. Manna is described as coriander seed. I take that to mean as coriander seed in taste, aroma, and nutritional properties. However, most scholars assume that the comparison is one of appearance. Yet that doesn't match, because coriander seed is light brown, spherical, and the size of peppercorns. Manna is said to look like white resin flakes, which don't look at all like coriander seeds. I therefore reason that coriander seed is the food which most closely matched manna.

Coriander does not contain gluten, nor is it a grain. Most interestingly, it is the seed of the widely cultivated cilantro plant now renowned as a super food because it cultivates a very healthful microbiome. It was also free of mold spores and leaven to further support a healthful microbiome.

Rituals That Made Grain Easier to Digest: Pilgrim Feasts of the Ancient Hebrews

When grain is cut and left in the field it undergoes changes significant for human digestion. Natural enzymes break down the plant's proteins such as gluten.

The ancient Hebrew people observed the first barley harvest (feast of First Fruits) and the first wheat harvest (*Shavuot*) as pilgrim holidays. The newly harvested grain was eaten only after the men returned from the temple. In order to observe these rituals, both the barley and wheat were cut and laid in the fields for approximately a week. As the grain sat during those warm spring days, it became easier for the people to digest it.

Nutrients Chaperone Gluten: The Practice of the *Shemitah*

As grain grows, it takes in nutrients and microbes from the soil. These same nutrients and microbes promote human digestion of the gluten-containing grains. The nutrients and microbes become less plentiful in the soil as the land is repeatedly farmed.

When the Israelites lived in Egypt, they ate grain grown on the banks of the Nile. Water hauled from the Nile was a pipeline of rich nutrients and microbes. And each rainy season, the Nile flooded and made the soil black with nutrients.

But where the ancient Hebrew people settled, there was no Nile nutrient pipeline for their crops. They approached the challenge of nutrient- and microbe-rich food differently. They were the first to use a crop rotation that left the land fallow every seventh year. During this year, called *shemitah*, wild plants and cover crops would grow and give the soil different nutrients. Livestock would graze freely on the land, further enriching the soil with minerals and microbes. In this way, *shemitah* played an important role in safe digestion of gluten, by promoting the presence of the antioxidant nutrients that chaperone gluten through the gastrointestinal tract.

Mindful Eating: The Blessing over the Bread

"Slow down and chew your food." Medical science calls this common advice mindful eating. It helps us smell and taste our food more fully, so that the brain has the time that it needs to signal when we've eaten enough. In other words, we are less likely to overeat when we slow down and use our senses. With mindful eating, our food is better digested to get the tiny nutrients out of it, not just the calories. It also reduces the chance of developing food allergies at a later time. Mindful eating is so important that some dieters use an invention called the HAPIfork. An electronic sensor inside the fork causes it to vibrate if you eat too fast.

But long before the HAPIfork, people of faith have said a blessing over their bread. A blessing is a form of mindful eating.

Application

Ongoing research into the causes and treatments of gluten disorders form an anthropologist's toolbox. Here the tools have been applied to a well-known ancient text, which suggests that digesting gluten might possibly be a longstanding health challenge. Prevention may have benefited communities long before the added risks imposed by modern agriculture. As health-care practitioners, we can apply the anthropologic tools to helping our patients overcome digestive diseases, despite the added challenges imposed by modern living.

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Faculty Associate, Johns Hopkins Bloomberg School of Public Health
Executive Director, NutriBee National Nutrition Competition Inc.
Editor, *Advancing Medicine with Food and Nutrients* (CRC Press; 2013)

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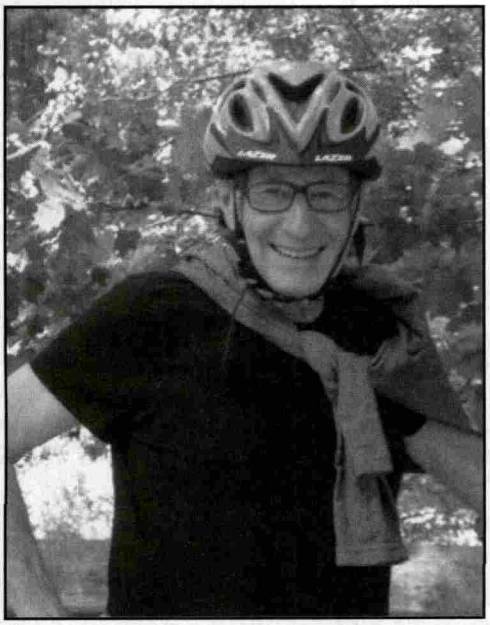

War on Cancer

by Ralph Moss, PhD
www.cancerdecisions.com

More Clinical Trials of Green Tea?

The outstanding work of Prof. D. James Morré and Prof. Dorothy Morré of Purdue University, Indiana, has focused renewed attention on green tea. The Morrés discovered a very important cell surface protein called ENOX2. Green tea is one of the compounds that inhibits ENOX2, an undesirable product of the X chromosome that enables immature cancer cells to increase in size in preparation for renewed cell division.

Green tea is not the only thing that can inhibit ENOX2. There are several well-known anticancer agents that do so, including two jack-of-all-trade drugs, cisplatin and doxorubicin (better known by its trade name, Adriamycin). Almost as powerful, and far less toxic, is a specific combination of concentrated green tea and pure chili pepper, which is sold as "Capsol-T." It combines these two ingredients in a particular ratio, which is determined experimentally for each product lot. (It can vary from 20:1 to 50:1 tea to pepper, depending on the sources.) This has the effect of blocking the dangerous ENOX2, which functions on the surface of cancer cells. ENOX2 also enables cells to exhibit uncontrolled growth and the ability to invade neighboring tissues. When cancer cells are blocked in an immature stage, they cannot divide and within 72 to 96 hours will self-destruct in a process called apoptosis (a form of programmed cell death).

There are currently 6000 scientific publications indexed in PubMed on the topic of green tea. Over 2000 of these contain references to the main medicinal substance found in tea, the polyphenol (or catechin) dubbed epigallocatechin gallate (EGCG). There are 1300 articles referencing both EGCG and cancer.

This is an unusually large amount of research on a natural product. Complementary and alternative medicine (CAM) subjects are usually deficient in solid research, and often scientific research lags behind popular interest. But you can see that green tea is among the best-researched subjects in the nutritional universe.

Unfortunately, the clinical investigation of green tea in human cancer patients has lagged behind the easier-to-perform laboratory studies. However, in the April 2015 issue of the journal *Prostate*, there was a very interesting article on the effects of brewed green tea compared with brewed black tea (and plain water) on various blood markers associated with prostate cancer development and progression.

Dr. Suzanne M. Henning and colleagues at the David Geffen School of Medicine, University of California, Los Angeles, conducted the study. In this phase II trial, 113 men who had been diagnosed with prostate cancer were randomized to consume 6 cups daily of brewed green tea, brewed black tea, or water prior to undergoing a radical prostatectomy (RP) operation. The authors looked at a variety of markers of progression. Patients who consumed green tea (but not either black tea or water) had a significant decrease in the amount of nuclear factor-kappa B (NF-κB). NF-κB is a very important marker that is often associated with more aggressive cancers.

In fact, tea polyphenols (including EGCG) were detected in the prostate tissue of 32 of the 34 men who received green tea, but not in the two other groups. Evidence of a systemic antioxidant effect was observed only with green tea consumption. Also, only green tea led to a statistically significant decrease in serum prostate-specific antigen (PSA) levels.

The authors concluded, "Future longer-term studies are warranted to further examine the role of GT [green tea] for prostate cancer prevention and treatment, and possibly for other prostate conditions such as prostatitis."

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In September 2015, this conclusion was seconded by a well known urologist at New York University's Langone Medical Center, Samir S. Taneja, MD. Writing in the *Journal of Urology* (official journal of the American Urological Association), Taneja said: "The authors of this [UCLA] study provide a well executed trial with defined, measurable end points. While the study does not tell us if green tea will prevent prostate cancer or slow its growth, it offers insight into potential mechanisms and validates a biological effect of the agents, such that future clinical trials of efficacy appear warranted."

Such a trial will probably be less significant if the green tea in question is given solely as a brewed drink than in the form proposed by the Morrés, namely as Capsol-T. The reason for this has to do with the presence of ENOX2 at the surface of most cancer cells (including prostate cancer cells) and the ability of various substances, including green tea catechins, to inhibit in turn the functions of ENOX2.

It is important to note that Capsol-T must be taken according to a rigorous schedule. Dr. Morré told me:

> A major factor in the effectiveness of Capsol-T is the necessity to take the product every four hours even during the night. The effect of Capsol-T on ENOX2 is one of reversible inhibition. ... The effect of both green tea and Capsol-T is transient and goes away in a matter of a few hours. If cancer cells can be prevented from growing for more than three of four days they are likely to undergo programmed cell death. However, if the Capsol-T or green tea levels are intermittent, the cancer cells will resume growth when the levels reach a low blood level and the clock starts over again and will never be killed and through a "survival of the fittest" selection process may even become resistant. This is why, to be effective, Capsol-T must be taken every 4 hours, even during the night. (Personal communication, September 21, 2015)

For a better understanding, interested readers can and should read the Morrés' articles (e.g., Hanau 2014) and especially their groundbreaking book, *ECTO-NOX Proteins: Growth, Cancer, and Aging* (2013).

Conducting trials on Capsol-T with its mixed catechins, instead of just brewed green tea or concentrated EGCG, will probably yield better results, whereas trials that utilize green tea, without the adjunctive addition of mild red pepper, and without an understanding of what this combination has to do, might very well come up with equivocal results.

Graviola and Pawpaw: Promising ... but Dangerous?

One surprising finding in the Morrés' book is that a class of compounds known as acetogenins are also ENOX2-inhibitors. (ENOX2 is a growth-promoting protein found on the surface of almost all cancer cells.) Acetogenins, in turn, are ingredients or byproducts of a plant family known scientifically as Annonaceae. These are mostly tropical plants found in the rainforests of South America and Southeast Asia. The best-known of these is graviola, also known as soursop. There are over 130 of these acetogenin compounds (Mangal 2015). Scientists consider Annonaceae to be "chemically one of the least investigated family" of plants (ibid.). But they deserve greater attention and are now being investigated as possible anticancer agents.

Graviola (*Annona muricata*) is a well-known folk remedy for cancer, with a devoted following in some countries. It is used as a pesticide, antimalarial, antiparasitic, and antimicrobial and now as an anticancer agent. But these compounds also have some general cytotoxicity, which is related to their ability to interfere with the energy use by cells. This is what may make this herb toxic to normal cells under some conditions and has brought it to the attention of various writers, not all of whom are sympathetic to its use.

As the Morrés state in their book, "A more selective activity is necessary to explain the ability of certain acetogenins to kill cancer cells under conditions where normal cells are unharmed." This is where ENOX2 comes in. Twenty years ago, James Morré and his Purdue colleague, Jerry L. McLaughlin, PhD, carried out an experiment with one particular acetogenin, bullatacin. This is a fatty acid compound found in some Annonaceae fruit. They showed that bullatacin almost completely inhibited ENOX2 activity in HeLa cancer cells. Scientists in Atlanta, Georgia, recently showed that whole-plant extracts of graviola leaf are indeed toxic to cancer cells. However, they caution that this extract, "despite its superior in vitro and in vivo efficacy, resulted in death of the mice due to toxicity."

This raises the question of whether graviola is too toxic to use and, if it is used, how great is the risk to cancer patients? A particular concern is the presence of a neurotoxin, annonacin, in the leaves.

Alexander Schauss, PhD, a well-respected scholar in the field of natural products, has spoken out forcefully against the general use of graviola in food supplements. He says that there is an association between graviola consumption and "atypical" Parkinson's disease. He did research on this topic a dozen years ago in Guam, where the consumption of graviola is common. A 2006 report from Guadeloupe similarly made a connection between graviola and Parkinsonism. It stated that Parkinsonism on this Caribbean island was "associated with the consumption of plants of the Annonaceae family, especially Annona muricata... suggesting a possible toxic etiology. ... Consumption of Annonaceae may contribute to the pathogenesis of atypical parkinsonism in Guadeloupe" (Lannuzel 2006). These are chilling words.

For that reason, I would say that cancer patients should stay away from graviola, until further research shows that it is both effective at inhibiting ENOX2 in humans and that there is a safe level of consumption that will not cause or contribute to Parkinson's disease.

Pawpaw Tree

Another question is whether a related North American plant, pawpaw (*Asimina triloba*) might be a safe substitute for graviola. Otherwise known as the "Indiana banana," this tree produces a tropical-tasting fruit, even in the Eastern parts of the US. (I recently obtained one from a tree growing on a local university campus; chilled, it was surprisingly delicious.) The topic of pawpaw and cancer deserves an article of its own. But the aforementioned Dr. Jerry McLaughlin has written that pawpaw contains "promising new antitumor ... agents that are found only in the plant family Annonaceae" (Alali 1999). So there is promise in pawpaw.

References

Alali FQ, Liu XX, McLaughlin JL. Annonaceous acetogenins: recent progress. *J Nat Prod.* 1999;62(3):504–540. doi:10.1021/np980406d.

Hanau C, Morré DJ, Morré DM. Cancer prevention trial of a synergistic mixture of green tea concentrate plus Capsicum (CAPSOL-T) in a random population of subjects ages 40–84. Clin Proteomics. 2014;11(1):2. doi:10.1186/1559-0275-11-2.

War on Cancer

Henning SM, Wang P, Said JW, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. *Prostate.* 2015;75(5):550–559. doi:10.1002/pros.22943.

Lannuzel A, Höglinger GU, Champy P, Michel PP, Hirsch EC, Ruberg M. Is atypical parkinsonism in the Caribbean caused by the consumption of Annonacae? *J Neural Transm Suppl.* 2006;(70):153–157.

Mangal M, Khan MI, Agarwal SM. Acetogenins as potential anticancer agents. *Anticancer Agents Med Chem.* June 2015.

Morré DJ, Morré D. *ECTO-NOX Proteins: Growth, Cancer, and Aging.* New York: Springer; 2013. List price $267 but available from the Harvey H. and Donna M. Morré Foundation for Cancer Research, 1112 Cherry Lane, West Lafayette, IN 47906, by enclosing a check for a donation of $100 made out to the foundation and also by providing a mailing address.

Taneja SS. Re: Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. *J Urol.* 2015;194(3):704–705. doi:10.1016/j.juro.2015.06.050.

Watson E. Toxicology expert raises alarm over potential neurotoxins in graviola/soursop [online article]. Nutra ingredients-usa.com. May 10, 2012. http://www.nutraingredients-usa.com/Suppliers2/Toxicology-expert-raises-alarm-over-potential-neurotoxins-in-graviola-soursop.

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Calendar

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APRIL 15-17: SW COLLEGE OF NATUROPATHIC MEDICINE presents REGENERATIVE INJECTION THERAPY WORKSHOPS (Module 3): Lumbosacral Region & Pelvis in Tempe, Arizona. CONTACT: www.scnm.edu/RIT-WORKSHOPS

MAY 12-14: THE INSTITUTE FOR FUNCTIONAL MEDICINE'S 2016 ANNUAL INTERNATIONAL CONFERENCE - Creating Balance *Between* Motion and Rest in San Diego, California. CONTACT: www.functionalmedicine.org/AIC

MAY 17-20: INTERNATIONAL CONGRESS FOR INTEGRATIVE MEDICINE & HEALTH - Bridging Research, Clinical Care, Education, and Policy in Las Vegas, Nevada. With IHPC, ACCAHC, AIHM and ISCMR. CONTACT: www.icimh.org/

MAY 20-22: 2016 TRADITIONAL ROOTS HERBAL CONFERENCE in Portland, Oregon. CONTACT: traditionalroots.org/2016-traditional-roots-conference/

MAY 23-24: 18th INTERNATIONAL CONFERENCE ON COMPLEMENTARY, ALTERNATIVE, INTEGRATIVE MEDICINE & HEALTH in London, United Kingdom. CONTACT: waset.org/conference/2016/05/london/ICCAIMH/

JUNE 16-18: SOPMED (Society of Oxidative & Photonic Medicine) CONFERENCE in Salt Lake City, Utah. Oxidative, light, and energy medicine. Limited to 300 participants. CONTACT: 517-242-5813; info@sopmed.org;; www.sopmed.org

JULY 1-3: 3rd INTERNATIONAL CONGRESS ON NATUROPATHIC MEDICINE in Barcelona, Spain. CONTACT: icnmnaturopathy.eu

JULY 15-17: HORMONE ADVANCED PRACTICE MODULE – RE-ESTABLISHING HORMONAL BALANCE in National Harbor, Maryland (DC) CONTACT: www.functionalmedicine.org/Hormone

JULY 15-17: ENERGY REGULATION ADVANCED PRACTICE MODULE – Illuminating the Energy Spectrum in National Harbor, Maryland (DC) CONTACT: www.functionalmedicine.org/Energy

JULY 27-30: AMERICAN ASSOCIATION OF NATUROPATHIC PHYSICIANS' ANNUAL CONFERENCE & EXPOSITION in Salt Lake City, Utah. CONTACT: www.naturopathic.org/aanp2016.

AUGUST 10-13: 25th ANNUAL IAACN SCIENTIFIC SYMPOSIUM – Renovation of the Structural Integrity of the Human Body Through Biomolecular Interventions Beyond the Collagen Connections in Jacksonville, Florida. CONTACT: www.iaacn.org/symposium/

SEPTEMBER 19-23: APPLYING FUNCTIONAL MEDICINE IN CLINICAL PRACTICE – 5 day foundational course in Baltimore, Maryland. CONTACT: www.functionalmedicine.org/AFMCP

OCTOBER 6-9: AMERICAN ACADEMY OF ENIVIRONMENTAL MEDICINE ANNUAL MEETING – The Role of Mitochondria in Health & Disease in San Diego, California. CONTACT: AAEM, 316-684-5500; www.aaemconference.com

OCTOBER 22-23: 10th AUSTRALIAN HOMEOPATHIC MEDICINE CONFERENCE in Brisbane, Australia. CONTACT: www.homeopathyconference.com

OCTOBER 26-30: 10th ANNUAL MICROCURRENT CASE CONFERENCE in St. Pete Beach, Florida. CONTACT: microcurrent.info.

OCTOBER 28-30: DETOX ADVANCED PRACTICE MODULE – Biotransformation and Toxicity in Chicago, Illinois. Live Streaming Available. CONTACT: www.functionalmedicine.org/Detox

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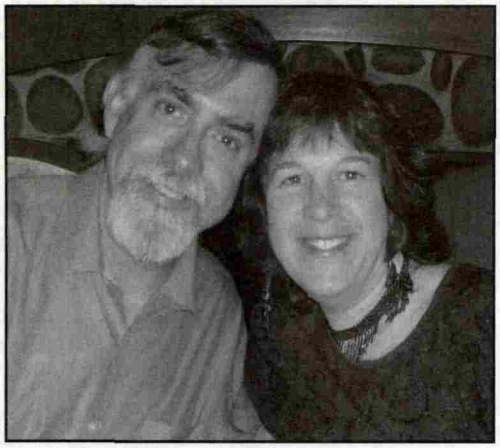

Healing with Homeopathy

by Judyth Reichenberg-Ullman, ND, DHANP, LCSW, and Robert Ullman, ND

www.healthyhomeopathy.com

Homeopathy for Children in Sweden: Celebrating 100 Years in a Surprisingly Restrictive Climate

The Promise of Homeopathic Treatment for Children with Neuropsychiatric Problems in Sweden

Yael Judisman, a mover and shaker among the Stockholm homeopaths, had a vision, and we fortunately became part of it. Yael, a Swedish homeopath married to an Israeli photographer and director of an innovative nonprofit foundation in Tel Aviv, doesn't just dream about change. She makes it happen! Our initial Skype conversation with Yael, after we accepted her gracious invitation to present at the conference on the Homeopathic Treatment of Children with Neuropsychiatric Disorders, was astonishing and disturbing. Despite Sweden's progressiveness and open-minded attitudes in so many areas of society, this is not the case with homeopathy. In fact, it is illegal to use homeopathic medicine with children under the age of 8 years, the homeopathic nosodes (including *Tuberculinum* and *Carcinosin*) are not allowed, and it is not legal for pregnant women to consult an alternative medical practitioner. This restrictive atmosphere comes, apparently, from an outdated scope of practice and the government's belief that small children and their pregnant moms should be *protected* from possibly harmful therapies. This, to our way of thinking, is ironic and misguided, since homeopathy is especially safe and effective in pregnancy and with young children.

To celebrate the 100th anniversary of the Swedish Association for Scientific Homeopathy, Yael invited some of the world's leading homeopaths in the field of treating children with behavioral, learning, and developmental problems and chose what she considered to be the finest conference venue in Sweden, Saltsjöbaden (an elegant, pristine saltwater bathing retreat about 40 minutes outside Stockholm). Her goal was to set the stage to change this outdated attitude and legislation. If anyone can accomplish that, from what we have observed, it is Yael!

Iceland: A Land of Active Volcanoes, Home-Grown Bananas, and Elves

We took advantage of our Swedish invitation to stop in Iceland for five days – a fascinating, underpopulated, geothermal, volcanic paradise which, over the past few years, has exploded in tourism. Travelers like ourselves, fascinated with the idea of exploring the land of the Vikings, find Reykjavík a convenient stopover between Europe and the US. We felt right at home with the volcanic landscape (like our homes in the Pacific Northwest and Southern Chile) and were very impressed by what this remarkably creative and self-reliant population of about 330,000 has been able to accomplish. The volcanoes, waterfalls, glaciers, thermal baths, and nearly untouched terrain are idyllic. This country is known for producing a remarkable number of innovative thinkers, considering its small population. Perhaps the scant daylight in the winter months contributes to this.

Recent accomplishments include growing Icelandic bananas in geothermal-powered greenhouses, and drawing 1,400,000 tourists to their pristine paradise during the past year. Their goal is to produce 100% of their own produce within three more years. Seeing what the Icelanders have been able to pull off, including digging themselves out of massive amounts of volcanic ash following their unexpected eruptions, we wouldn't put anything past them! Yet this is a country that kicked out its banks and bankers at the time of the economic meltdown (beginning in 2008); one with no army; one prison with only 180 beds (half of them generally occupied by foreigners); where folks may leave for other (usually Scandinavian) countries but inevitably return; where the unemployment is under 3%; where health care and education are free; and where 50% of the population is said to still believe in elves.

Sweden: Sophisticated, Robust, Socially Liberal

Our three unplanned days in Stockholm prior to the conference were filled with fascinating, multiethnic experiences and much time spent in museums and eating great, healthful food. We found ourselves captivated, and deeply moved, at the Nobel Museum by the diversity, dedication, and inventiveness of the laureates and returned a second day to be present for the announcement of the winner of the Literature Prize, Svetlana Alexievich of Belarus. The film interviews with many of the laureates were remarkable in their diversity and their brilliance. Our hope and dream is

that someday homeopathic medicine will be duly recognized and honored for its genius – perhaps the individual(s) who finally elucidate its method of action. Impressive in a different way was a small museum dedicated to the oppression of the Roma ("Gypsy") people, historically and, unfortunately, even today in Sweden. A lively and often misunderstood, diverse group of people with deeply ingrained traditions, they have long mesmerized us with their story, energy, and music. We were aware that they originated in Rajasthan (northern India); that they dispersed to Macedonia, Romania, Spain, and elsewhere; and that they had been decimated (500,000 to 1 million murdered) in the Holocaust. One of the Roma who has dedicated his life to the struggle for their equality was in fact at the museum offering a workshop to a group of Swedish students. Apparently field trips to museums and other public sites of interest are a large part of their education.

The Swedes were tall, blonde, muscular, and robust, much like the Icelanders.

The Conference: Unity and Diversity in Homeopathy

Our homeopathic experience began with a simple yet elegant home-cooked Mexican vegetarian meal at the home of Yael and Igal. The ice was quickly broken as we mixed comfortably with our Swedish, German, Dutch, British, Irish, Indian, and French counterparts and their partners, who hailed from as far as South Africa. Homeopathy was our common language, along with our shared awe at the sheer, pristine beauty of the conference site, which provided magical morning mist, clear blue skies, serene forest, and remarkable mirror images reflected in the still saltwater.

Bob led off with two long-term cases of children on the autism spectrum. His goal was to show that common homeopathic remedies could be used effectively to produce profound results in this population. He intentionally chose two children who began treatment prior to age 8, in order to bring home the safety and efficacy of starting early (especially since this is not allowed in Sweden). Although many of the homeopathic medicines that we use are not in fact legal in Sweden, he chose to avoid those in his presentation. Alexander Tournier, a British/French physicist who is establishing a laboratory for homeopathic research at the University of Heidelberg, provided a survey of contemporary homeopathic research. He is deeply convinced that it will be possible in the near future to finally demonstrate, from a research perspective, exactly how homeopathy works. We sincerely hope that he is right, since such scientific corroboration is long overdue and could potentially make significant inroads into the recognition and respect of homeopathy worldwide. (For further information, visit the website of the Homeopathic Research Institute, or HRI.) Joseph Schmidt, a German historian, provided a theoretic and historical overview of the medicine.

Hilery Dorrian, from the UK, focused on the gut–brain connection in autistic children and provided an overview of the bowel nosodes, a relatively little-known group of 12 homeopathic medicines introduced originally by Edward Bach of Bach Flower Remedy fame. She explained how these remedies can be used effectively in some cases along with the constitutional prescription. Philippa Filbert, also from the UK, provided an overview of previous research models, particularly concerning children with ADHD (including the 2005 study designed by Jennifer Jacobs, MD, in which the two of us were the prescribers), but also a successful Indian study of autistic children.

The second day of the conference began with a wonderful video presentation by Dinesh Chauhan from Mumbai, a longtime student, and later colleague, of our mentor, Dr. Rajan Sankaran. Dinesh has developed a brilliant method of drawing out children, including those who are nonverbal, through drawings, sounds, and patterns, to find the best remedy for them. His two cases, one of a child with asthma needing *Ambra grisea* (whale) and the second an ADHD case needing Python, were quite remarkable. Dinesh provided great insight into how to enter the world of the child and to find the corresponding *simillimum* (best homeopathic medicine) to help him or her. Jurgen Weiland of Germany presented two beautiful cases of young children with behavioral problems who responded beautifully to *Teucrium*, from the mint family, and *Mygale* (pink tarantula spider). Bert Brueker, a Dutch homeopath practicing in Sweden, provided an introduction to the CEASE method taught to him by Tinus Smits, a deceased Dutch homeopath whom we invited to present at our International Foundation for Homeopathy Case Conference around 1994. He developed a rather novel approach in treating children on the autism spectrum, which included "homeopathic detoxification" as well as isopathic preparations in ascending potencies of substances, such as pharmaceuticals, which may have contributed to the decline in the children's development. Finally, Judyth presented two fascinating long-term cases of children with violent behavior who needed homeopathic animal remedies, one *Lac leoninum* (lion's milk) and the other Peregrine Falcon. Both cases illustrated the significant role for substances from the animal kingdom in treating violent, aggressive children and hopefully argued for expanding the homeopathic pharmacopeia in Sweden to include these medicines. Judyth referred to the recent extensive and compelling Huffington Post exposé of Risperdal by Alex Brill, which is all the more reason to use a natural, do-no-harm approach such as homeopathy with sensitive, vulnerable, and sometimes damaged children.

A Meeting of Minds

Hopefully the goodwill, inspiration, and diversity of expertise of this international group of homeopaths can contribute not only to an ongoing sharing and meeting of the minds, but also to expanding the scope of practice of homeopathy in Sweden in some tangible way. At this time in history, perhaps more than any time previously, with the ever-growing rise in Big Pharma in the treatment of children with behavioral, developmental, and learning problems, we believe that gentle, safe, effective homeopathic approach is more needed than ever.

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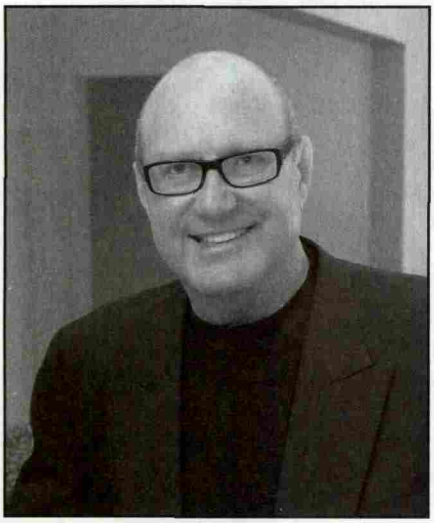


Monthly Miracles

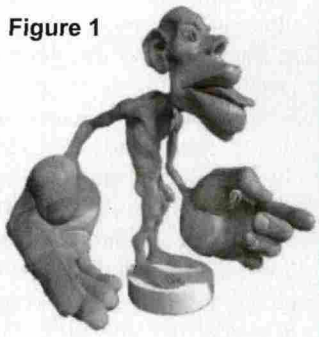
by Michael Gerber, MD, HMD
contact@gerbermedical.com

Homunculi: Low-Tech Biofeedback in Clinical Practice

Homunculus, Webster's definition: a little human being, dwarf, pigmy. A model of a human being used for demonstrating anatomy.

Although homunculus has many definitions, many of us remember the neuroanatomical chart showing the representation of cerebral cortical nerve distribution to motor and sensory nerves in the body (Figure 1). The eyes, lips, tongue, hands, and fingers have much more representation than arms and legs. The body repeats these relationships in many locations, according to many ancient and modern medical disciplines. These body maps can be seen in the eyes, ears, face, tongue, teeth, hands, feet, pulses, and probably others.

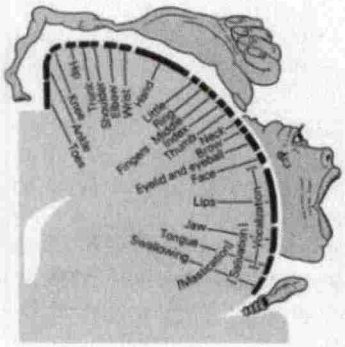
Figure 1



Let me say as a bit of a disclaimer that we use every modern laboratory evaluation for blood urine, saliva, and hair. We check EAV, viruses, bacteria, parasites, vitamins, minerals, neurotransmitters, genetic markers, heavy metals, allergy, mold, EEG, radiology, specialist referrals, and all the usual allopathic parameters when indicated. However, when we're faced with acutely and chronically ill patients, every bit of information about their physical and personality nature helps us dramatically.

Pulse

My patients frequently tell me that they have never been touched by a doctor before except perhaps via taking a blood pressure or stethoscope evaluation of heart or lungs. Taking the pulse puts the physician in touch with the immediate energetic situation of the patient and is a powerful homunculus. I have been taking Chinese pulses for 40 years, learning from Drs. Ping, Pang, and Kong in Marin County, California, in 1975. I also learned more Chinese medicine from the UCLA Medical Acupuncture Training Program in 1997 from Joseph Helms, MD. The Chinese pulses have been examined for 2000 years, and the Chinese learned from the Indian Ayurvedic physicians who have practiced pulse diagnosis for the last 10,000 years. In Chinese medicine there are 27 pulse types at the wrist (Figure 2).



Pulse Simplified

First, locate the radial pulse. Place the middle finger over the scaphoid bone which is the main, large bone above the wrist and then feel the radial ligament next to it and place the middle finger in the trough between them with the index finger and the ring finger in a straight line on each side up and down the wrist. You should get a pulse. If you can't feel a pulse, the patient is usually very hypometabolic and deficient in thyroid and adrenal energy, and complains of fatigue, anxiety, confusion, and insomnia. Something is sitting on the metabolism and ATP production. Conversely, when the pulse feels very powerful and strong, check for high blood pressure, or it may indicate that the patient is in very good physical shape. A fast, thin pulse may come with anxiety or coffee. Ask the patient, "Do you feel anxious?" If yes, apply progesterone cream to the forearms and watch symptoms melt away in 3 to 5 minutes.

The kidney/adrenal pulse is the third pulse above the left wrist. You should be able to compress it down to the bone and still get a pulse. If not, in my experience, it is a weakness of the adrenal. The third pulse above the right wrist, superficially, should bring the finger up off the skin; this is the Triple Warmer, which many acupuncturists relate to the thyroid. If it is not palpable, try thyroid supplementation until a pulse is felt. The pulse rate should usually not exceed 80.

Of course, it is easy to feel the irregularly irregular pulse of atrial fibrillation and missing beats of heart block, tachycardia, bradycardia, and PVCs by pulse without needing EKG. One can get an immediate sense of the energy of patients by taking their pulse. It leads the physician to ask relevant question regarding their health. Perhaps, above all, it establishes an energy relationship between doctor and patient. You get an immediate understanding of the person whom you are sitting with. Pulse dynamics are influenced by many factors and, of course, these recommendations are a superficial look at a very sophisticated study. Feel the pulse, touch the patient.

Office Dynamics

We have evolved a template of practical interaction with the patient which involves a scribe/assistant who records my recommendations and sits behind me in the examination room. He uses computer macros and informative handouts to explain nutrients, homeopathic remedies, and procedures, which are printed out and explained for the patient at the end of the office visit. As he records the suggestions on the computer for the patient, they are also simultaneously sent to the nursing department for lab draws, IVs, IMs, neural therapy set-ups, and other procedures. The checkout department at the same time receives the computer notes and assembles the day's

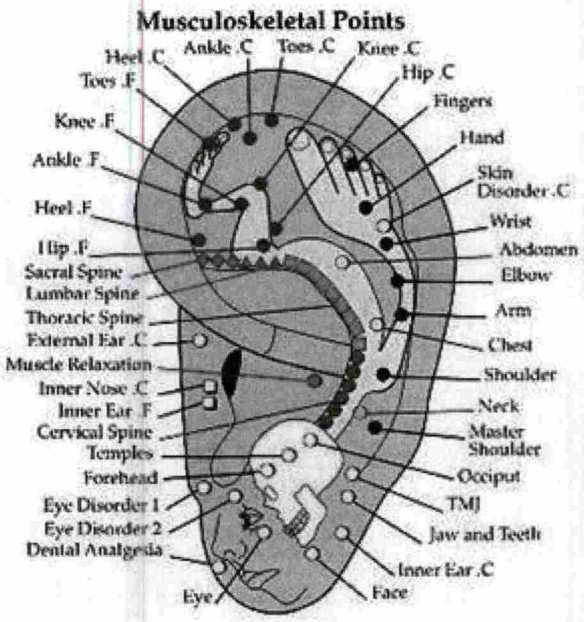


Figure 2

recommendations for homeopathic, nutrient, hormonal supplementation, and procedures with a reinforcing explanation. This approach has been successful for us in introducing a multivariate program for the patient. ◆

New Clinical Research: Nutritional Supplement Increases Red Blood Cell Glutathione Levels*

New research shows that the nutritional supplement Tri-Fortify Orange (Researched Nutritionals, Los Olivos, California) increased red blood cell glutathione levels by 27% in 2 weeks.

The study, conducted at the Penn State College of Medicine, also demonstrated that the liposomal glutathione increased natural killer cell toxicity by 152% and reduced oxidative stress by 9%.

This random human study is the first to clinically show that liposomal glutathione increases red blood cell glutathione levels and improves natural killer cell function and oxidative stress markers in healthy patients. Patients' glutathione levels are under constant attack by: environmental pollution/toxins; heavy metals; poor diet; oxidative stress; medications; stress; and age.

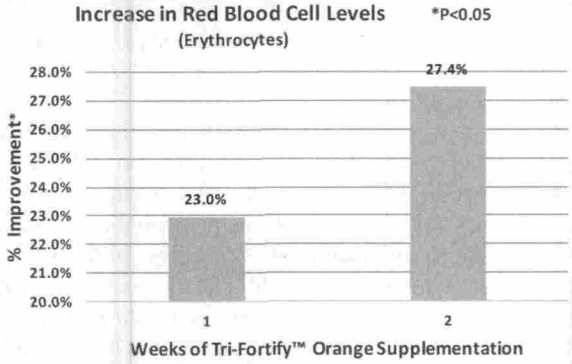
Chronic Disease Sufferers & Glutathione Deficiency

The onslaught of glutathione-depleting challenges is exacerbated among many chronic disease patients. One-third of chronic disease sufferers are missing the genes to create and manage glutathione levels.[1]

N-Acetyl Cysteine (NAC) to Increase Glutathione: Not Helpful for Most Patients

Even though NAC is the body's limiting factor to producing glutathione, this holds true *only* for individuals with insufficient sulfur amino acid intake.*

- 99% of Americans consume greater than the RDA*
- 50% consume more than twice the RDA*



For most Americans (and other nationalities with similar dietary habits), NAC is not helpful in raising red blood cell glutathione levels.[2]

To view liposomal glutathione clinical research highlights, please visit this link: https://www.dropbox.com/s/62kosjr5d0lsrfo/Liposomal%20Glutathione%20Clinical%20Research%20Highlights2.pdf?dl=0.

To view the Tri-Fortify Orange product sheet, please visit this link:. https://www.dropbox.com/s/9h2km3tzdcdncur/tri-fortify-orange.pdf?dl=0.

Notes

1. Mark Hyman, MD.
2. Jones DP. The health dividend of glutathione. *Nat Med J.* February 2011;3(2).

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease. ◆

Environmental Medicine Update

by Marianne Marchese, ND
www.drmarchese.com

Heavy Metal Testing Controversies: The Post-Provocative Urine Test

Introduction

Heavy metals such as mercury, lead, arsenic, and cadmium are pervasive in the environment. Some people are exposed to high doses in various occupations, but most are exposed to low doses through food intake, air, and water pollution. Low dose exposure to metals is linked to numerous health conditions. In order to determine if a person's health problem is due to metal exposure, a thorough environmental history is performed along with laboratory testing for the presence of metals in the body. Blood and urine tests are most commonly used, including the controversial post-provocative urine metal test. This column will explore the various methods of heavy metal testing to assess the presence of metal in the body.

Provocative Urine Testing

In the past few years, several organizations have come out strongly against the use of provocative urine heavy metal testing. The American College of Medical Toxicology (ACMT), an association of physicians with recognized expertise in the diagnosis, management, and prevention of human poisoning and other adverse health effects due to medications, occupational, and environmental toxins and biological agents, and the American Academy of Clinical Toxicology (AACT), a multidisciplinary organization uniting scientists and clinicians in the advancement of research, education, prevention, and treatment of diseases caused by chemicals, drugs, and toxins, are two organizations in particular.

Both have publically stated: "Metals are ubiquitous in the environment and all individuals are exposed to and store some quantity of metals in the body. These do not necessarily result in illness. Scientific studies demonstrate that administration of a chelating agent leads to increased excretion of various metals into the urine, even in healthy individuals without metal-related disease. These 'provoked' or 'challenge' tests of urine are not reliable means to diagnose metal poisoning and have been associated with harm."[1]

These are not the only organizations publically against the use of provoked urine metal testing. State and federal government agencies also oppose its use to diagnose metal toxicity. On August 26, 2015, the State of Minnesota Department of Health published information for health-care providers on heavy metal testing and chelation. It states: "The results of provoked urine studies have no role in determining the body's burden of toxic metals, nor the need for chelation therapy."[2] The source of information cited used to make this determination is an article published October 2013 in the *Journal of Metal Toxicology*, the official print journal of the American College of Medical Toxicology (ACMT).[3]

One of the main criticisms of the provoked urine metal test is that there are no standardized reference ranges. It is true that the reference ranges provided by a commonly used lab offering the provoked urine metal test are the same reference ranges found on the unprovoked urine test. In fact, if one reads the reports carefully, it states this on both the unprovoked and provoked test results. All labs offering the provoked urine test use unprovoked reference ranges. So, if there are no set reference ranges for a provoked urine metal test, how does the doctor determine that the level excreted in the urine on a provoked test is elevated? If there are no reference ranges, at what amount is the patient deemed toxic on a provoked test?

Another criticism of provoked urine metal testing is that there is no standardized method of administration. A provoked urine metal test is performed by administering a chelating agent to a person prior to urine collection. There are various chelating agents used for testing and various lengths of time for which the urine is collected. Different doctors use different chelating agents for testing, including dimercaptosuccinic acid (DMSA), dimercaptopropanesulfonate (DMPS), and ethylenediaminetetraacetic (EDTA). These chelators are given by varying routes of administration. Some are given orally, rectally, and intravenously. This varying nature of performing a provocative urine metal test makes it nonstandardized and difficult for a lab to develop provoked reference ranges.

One method commonly used to determine if elevated levels on a provoked urine metal test are significant is to compare the provoked urine test to an unprovoked test

obtained from the same person on the same day. This can be useful if the doctor understands the different effects that each chelating agent has on the body and the different means by which metals are metabolized and eliminated from the body. An ideal chelator has greater affinity for the metal to be bound, low toxicity, water solubility, and rapid elimination from the body. When a chelator forms a complex with a heavy metal, the chemical affinity of the chelator for the metal should be higher than the affinity of the metal for molecules in the body. Heavy metals have different chemical affinities. As a chelator binds metals with the highest affinity, there is an increase in excretion of metals with lesser affinity. Basically, each chelator pulls metals out in a different order.[4] This concept is key in determining if a provoked metal test truly resulted in an increase excretion of metals compared with the patients' unprovoked test. The doctor must chose the correct chelating agent to be administered based on the patient's history of exposure to metals.[4] A 2010 article published in the *International Journal of Environmental Research and Public Health*, "Chelation in Metal Intoxication," provides a great overview of which chelating agents are able to bind metals and form complex structures to be removed from the body.[5]

Does the Post-Provocative Urine Test Have Diagnostic Value?

The state of Minnesota says: "The results of provoked urine studies have no role in determining the body's burden of toxic metals, nor the need for chelation therapy."[2] Many doctors utilize the provocative urine metal test to determine a patient's body burden of metals or long-term past exposure to metals. There are limited data to establish a link between prior metal exposure and provocative test levels.[6] A 2001 study published in *Environmental Health Perspectives* assessed diagnostic chelation challenge with dimercaptosuccinic acid (DMSA) as a measure of mercury body burden among mercury-exposed workers. It concluded that DMSA chelation challenge is not useful as a biomarker of past mercury exposure.[7] This study was done with a population with known mercury exposure. In the studies done utilizing provoked urine testing, reviews show that almost everyone has a rise in urinary metals after a dose of a chelator regardless of exposure history, symptoms, or disease conditions.[8–11]

Diagnosing heavy metal toxicity in a patient typically means that an elevated level found in the body is linked to symptoms and disease. Treatment for these individuals would then involve removing the metal from the body; this is known as chelation therapy. Studies demonstrating a link between metals and disease are mostly done utilizing blood and unprovoked urine tests. In the book *8 Weeks to Women's Wellness,* heavy metals are linked to breast cancer, endometriosis, uterine fibroids, heart disease, infertility, osteoporosis, PCOS, and thyroid disease.[12] All links were made through blood and unprovoked urine tests. Critics of provocative urine metal testing state that there is no research to support its use as an accurate or reliable means of identifying patients who would benefit from chelation therapy.[6]

A study published in 2007 looked at the urine provoked metal test in children with autism compared with controls.[13] The aim of the study was to assess if children with autism are at increased risk of an excess chelatable body burden of heavy metals. Seventeen children with autism and 5 typically developing children were enrolled in a pilot study to test for body burden of arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg) after administration of oral DMSA. Evaluation included a questionnaire regarding potential exposure to heavy metals and diet restrictions. It included a baseline 24-hour urine collection and a DMSA-provoked urine collection. Unprovoked reference ranges were used in the interpretation of all collections including the provoked test. Fifteen autistic children and 4 typically developing children completed the study. Three out of 15 autistic subjects excreted one metal in greater quantity during the provoked excretion than baseline. Two of these were very close to the limit of detection using the unprovoked reference ranges. In the third case, the provoked excretion of mercury was between the upper limit of normal and lower limit of the potentially toxic reference range, again using unprovoked reference ranges. Fish was removed from this child's diet for greater than 1 month and the provoked excretion test repeated. The repeat excretion of mercury was within the normal range. The study concluded that the proportion of autistic participants whose DMSA provoked excretion results demonstrate an excess chelatable body burden of As, Cd, Pb, or Hg was zero. The confidence interval for this proportion is 0% to 22%.The purpose of this study was to assess the presence of metals in patients with autism using a provoked urine and not to evaluate the effects of chelation therapy in terms of improvement of symptoms of autism.

Other Methods to Test for Heavy Metals

Blood and unprovoked urine are the most commonly used methods of testing for heavy metal exposure. Neither of these tests is 100% accurate in detecting low-dose exposure to metals. Many times, this is due in part to the fact that a thorough exposure history was not performed first in order to determine the metal to which the patient was most likely exposed. This is an important part of the assessment process, so the correct method of testing is chosen based on where that metal will most likely be detected, blood or urine. For example, blood lead level (BLL) testing is the most useful screening and diagnostic test for recent or ongoing lead exposure. Lead has a relatively short half-life in the blood; most gets stored in the bone. Bone lead levels are best to assess past exposures.[14] Urine is not the best method to detect lead in the body.[15] If an unprovoked urine test is what's ordered, it may not detect the true level of lead present. The same can be said for various forms of mercury. It is critical to first determine what form of mercury, based on exposure history, that one thinks the person is exposed to before choosing the method of testing. Elevated

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mercury in the blood usually indicates exposure to organic mercury (such as from eating fish containing methylmercury) or recent exposure to a high level of elemental mercury vapor (such as from dental amalgams).[16,17] Urine is not the best method to assess mercury exposure from fish intake or recent exposure from dental amalgams. However, unprovoked urine is beneficial for nonrecent exposure from amalgams. Mercury vapor first enters the bloodstream and is then cleared through the kidney.[16,17] Again, it is important for the practitioner to understand the forms of metal and method of metabolism and excretion in order to choose the best test.

The reference ranges provided by most labs offering blood and unprovoked urine tests often do not detect low levels of metals – levels that are in fact linked to disease. The ranges are set too high and vary from lab to lab. Some labs report levels in terms of grams per creatinine and others in liters per 24-hour urine. Take arsenic, for example. A 24-hour urine adjusted for per gram creatinine is the best method for testing arsenic, but labs report results using different calculations. Physicians ordering these tests need to be aware of this fact to interpret the results properly. Mayo Clinic states that the reference range for a 24-hour urine is 0 to 35 ug/L and <50 mcg/g creatinine. The Agency for Toxic Substances and Disease Registry (ATSDR) states that urine levels should be <100 ug/L. LabCorp has different reference ranges for different forms of arsenic: total arsenic 0–50 μg/24 hours and inorganic arsenic <20 μg/L. Quest diagnostic's range is ≤ 80 ug/L. Last checked, Genova Diagnostics urine arsenic normal range was <50 and Doctor's Data <80.

Reference Ranges

The Centers for Disease Control and Prevention has established reference ranges for heavy metals based on the National Health and Nutrition and Examination Survey (NHANES), which looked at human exposure to environmental chemicals. The NHANES Fourth Report, which was published in 2009 and looked at 212 chemicals in the blood and urine of over 2500 persons in the US, states that 0 to 46 ug/L of arsenic in a 24-hour urine sample for someone between ages 20 and 50 who smokes is normal, and 0 to 55 ug/L for nonsmokers aged 20 through 50 is normal. NHANES reports the ranges in percentiles, stating that greater than 95th on its ranges is a concern. However, if looking at what level in the body puts the patient at risk for disease, anything over 80th is a concern. For example, arsenic is linked to DMII is with levels over the 80th percentile on the NHANES Fourth Report updates.[18] The Environmental Medicine column in the *Townsend Letter* reviewed the updates to the NHANES Fourth Report in the January 2015 issue. This report provides the most useful reference ranges for hundreds of chemicals detected in the blood and urine.

Summary

People are exposed to low doses of heavy metals daily. These metals can have adverse health effects, which is why a thorough workup is vital to linking exposure to a person's symptom or disease. The most commonly utilized methods of testing for the presence of metals in the body are blood and unprovoked urine. However, most labs reference ranges are set too high to make the link between metals in the body and disease. The CDC's NHANES *Fourth Report on Human Exposure to Environmental Chemicals* provides a guide on how to interpret blood and unprovoked urine tests no matter which lab is utilized. The provoked urine metal test is controversial due to the fact there are no provoked urine reference ranges or standardized means of administering the test. Many medical professional organizations, state health departments, and government agencies advise against the use of provoked urine metal testing to diagnose metal toxicity. Physicians trying to assess if metals in the body are related to a patient's health concerns should be well trained in the pharmacology and toxicology of metals, the most common source of exposure of each form of metal, and best method of detection for that form. This will help the practitioner decide on the best method of testing for heavy metals.

Notes

1. ACMT and AACT. Five things physicians should question [online article]. Choosing Wisely. http://www.choosingwisely.org/societies/american-college-of-medical-toxicology-and-the-american-academy-of-clinical-toxicology. Accessed September 25, 2015.
2. Heavy metal detection and the concept of chelation [online article]. Minnesota Department of Health. http://www.health.state.mn.us/divs/eh/hazardous/topics/chelatedoctor.pdf. Accessed September 25, 2015.
3. Ruha AM. Recommendations for the provoked challenge urine testing. *J Metal Toxicology*. 2013;9:318–325.
4. Marchese M. Provocative heavy metal testing; which chelator is best? *Townsend Lett*. 2011 Jan;89–91.
5. Flora SJS, Pachauri V. Chelation in metal intoxication. *Int J Environ Res Public Health*. 2010 Jul;7(7):2745–2788. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2922724.
6. American college of metal toxicology position statement on post-chelator challenge urinary metal testing. *J Med Toxicology*. 2010;6:74–75
7. Frumkin H et al. Diagnostic chelation challenge with DMSA: a biomarker of long-term mercury exposure? *Environ Health Perspect*. 2001 Feb;109(2):167–71.
8. Kales SN, Goldman RH. Mercury exposure: Current concepts, controversies, and a clinic's experience. *J. Occup Environ Med*. 2002;44:143–154.
9. Molin M, Schütz A, Skerfving S, Sällsten, G. Mobilized mercury in subjects with varying exposure to elemental mercury vapour. *Int Arch Occup Environ Health*. 1991;63:187–192.
10. Sällsten G, Barregård L, Schütz A. Clearance half life of mercury in urine after the cessation of long term occupational exposure: Influence of a chelating agent (DMPS) on excretion of mercury in urine. *Occup Environ Med*. 1994;51:337–342.
11. Frumkin H. Manning CC, Williams PL, et al. Diagnostic chelation challenge with DMSA: A biomarker of long-term mercury exposure? *Environ Health Perspect*. 2001;109:167–171
12. Marchese M. *8 Weeks to Women's Wellness*. 1st ed. Petaluma, CA: Smart Publications; 2011.
13. Soden SE et al. 24-hour provoked urine excretion test for heavy metals in children with autism and typically developing controls, a pilot study. *Clin Toxicol (Phila)*. 2007;45(5):476–481.
14. Lead toxicity: what tests can assist with diagnosis of lead toxicity? [online course]. Agency for Toxic Substances and Disease Registry. August 2010. http://www.atsdr.cdc.gov/csem/csem.asp?csem=7&po=12. Accessed October 9, 2015.
15. Sommar JN et al. Investigation of lead concentrations in whole blood, plasma and urine as biomarkers for biological monitoring of lead exposure. *J Expo Sci Environ Epidemiol*. 2014;24:51–57.
16. Understanding mercury exposure levels [Web page]. New York State Department of Health. 2008. https://www.health.ny.gov/environmental/chemicals/hsees/mercury/mercury_exposure_levels.htm. Accessed October 9, 2015.
17. Risher JF. Elemental mercury and inorganic mercury compounds: human health aspects [online report]. World Health Organization. 2003. http://www.inchem.org/documents/cicads/cicads/cicad50.htm. Accessed October 9, 2015.
18. Navas-Acien A et al. Arsenic exposure and prevalence of type 2 diabetes: updated findings from the National Health Nutrition and Examination Survey, *2003–2006 Epidemiology*. 2009;20(6):816.

Dr. Marchese is the author of *8 Weeks to Women's Wellness*. She received her doctorate in naturopathic medicine from the National College of Naturopathic Medicine in 2002. Dr. Marchese maintains a private practice in Phoenix, Arizona, and teaches gynecology and environmental medicine at Southwest College of Naturopathic Medicine. She was named in *Phoenix Magazine*'s Top Doctor Issue as one of the top naturopathic physicians in Phoenix. Dr. Marchese lectures on topics related to women's health and environmental medicine throughout the US and Canada. www.drmarchese.com.

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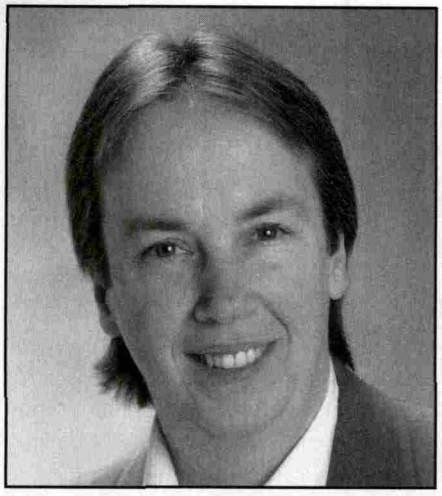

Women's Health Update

by Tori Hudson, ND and
womanstime@aol.com

Screening Mammogram Turmoil Continues

At the end of October 2015, the American Cancer Society (ACS) parted ways with the American College of Obstetricians and Gynecologists (ACOG), the American College of Radiologists (ACR), and the Susan Komen Foundation, in its screening mammogram guidelines for average-risk women. Until then, the ACS and the other three organizations recommended screening mammograms in average-risk women yearly, starting at age 40 and ending approximately in the mid-70s, although this is based on individual health and ability to withstand treatment regimens. This is what I have called "camp 1," and it has been the dominant school of thought in the screening mammogram guidelines (and controversies).

And as of this writing, the ACS rocked the delicate world of screening mammogram guidelines again and has come out with an update of its breast cancer screening guidelines based on an updated analysis of the literature. These recommendations are for women at average risk of breast cancer: women without a personal history of breast cancer, women without a suspected or confirmed genetic mutation known to increase the risk of breast cancer (e.g., BRCA), women who have no personal history of radiotherapy to the chest at a young age.

New ACS Recommendations are[1]:

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years.
   a. Women aged 45–54 should be screened annually.
   b. Women aged 55 years and older should transition to screening every 2 years or have the opportunity to screen annually (based on their decision between them and their health-care provider).
   c. Women should have the opportunity to begin annual screening between ages 40 and 44 (based on a decision between them and their health-care provider).
2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer.
3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age.

While departing from ACOG, ACR, and Komen Foundation, what the ACS did not do is agree with the US Preventive Services Task Force (USPSTF) guidelines, which were updated in 2009. The USPSTF was in a different camp than the others.

The key 2009 USPSTF recommendations are as follows:

- No universal screening mammography for women ages 40–49 and urging an individualized, informed decision making process based on specific benefits and harms
- Biennial screening mammography for women ages 50–69
- Screening extended to women between 70 and 74
- Insufficient evidence to assess the benefits and harms of screening mammography in women 75 and older
- Insufficient evidence to assess the benefits and risks of clinical breast exams in women aged 40 years and older who undergo mammography, digital mammography, and MRI versus film mammography
- Teaching self-examination is harmful and not recommended
- 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 key ACOG, ACR, and Komen Foundation guidelines for screening mammography in average-risk women are as follows:

- Screening mammograms starting at age 40 and annually thereafter
- Clinical breast exams yearly for ages 40 and older
- Clinical breast exams every 1–3 years for women 20–39 years of age

As of this column, the Susan Komen Foundation ushered a response with the primary assertion being that screening should be based on individual risk and is ➤

a decision for women and their health-care providers. One of their concerns (and others) is that if screening recommendations from some organizations are less than yearly, then insurance companies will not pay for yearly screening mammograms in those who want it or in those whose health-care provider has recommended it. It goes on to say that the screening should be based on individual risk for breast cancer and that the screening should be covered based on when the individual and her health-care provider decide is appropriate. The Komen Foundation acknowledges that screening guidelines differ among these different advisory groups as far as initial start dates and interval timing, but that they all agree that mammography is the best available tool for detecting breast cancer.

There are several key points that are not being addressed by any of the organizations. First, it would serve our overall goals much better if we moved toward determining individual screening based on a woman's risk with more determinants of that risk. Another concern is the discounting of clinical breast exams (and actually no recommendations about self-breast exam from ACS). To specifically not do a clinical breast exam at an annual exam seems downright wrong. And for a woman to cease knowing her own body and its changes is counterproductive as well in my view. While I understand that there are statistics and tedious analyses of the literature that go into these recommendations, knowing less and less about our patients, deliberately avoiding opportunities for simple exams, and telling women not to pay attention to their breasts seems counter to "doing no harm." Another key point is that all these recommendations are based on screening studies and mortality rates from data that are about 40 years old. Everyone is crunching old numbers. What would be far preferred is that we have updated research that reflects the modern numbers related to breast cancer diagnosis, treatment, and morbidity and mortality. And lastly, none of these screening guidelines make recommendations based on potential harms of exposing women's breasts to ionizing radiation (yes, granted, low dose; but now with 3-D mammograms, we have again increased the exposure) for 35 years.

What do I tell my patients – an update:

Camp 1 is the dominant school of thought followed by organizations including ACOG, ACR, and Komen Foundation. They all recommend 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 now the position of the ACS. It recommends that screening

for average-risk women should start at age 45 and continue annually until age 54, and then biannually from age 55 and continue as long as their overall health is good and they have a life expectancy of 10 years or longer.

Camp 3 is held by the USPSTF, which is quite a bit different with screening mammography. This recommendation is not to start mammography screening in low-risk women until age 50, and then to do it every other year.

Camp 4 is a model common in many European countries: screening mammography every 3 years, some starting at age 40 and others at 50. There is no evidence that countries using this model have any higher rates of breast cancer mortality than countries that employ more frequent screening.

Camp 5: No screening at all in average-risk women, based on calculations from one of the leading US researchers on analyzing screening mammography data. His conclusions are that it would be necessary to screen 2500 women every year for 10 years to avoid 1 death from breast cancer.[2] This camp is currently the position of the Swedish government.[3]

I also point out a few caveats to my patients. The first is that the data do not explain whether avoiding screening mammograms (and their potential for earlier detection and thus early treatment) will result in exposing a woman to more aggressive breast cancer treatments, and the ensuing impact on quality of life and adverse effects of those treatments, if she were diagnosed with a breast cancer after detecting a lump. The second is that breast cancer diagnosed in younger women, aged 40 to 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. Another way that I present this conversation is putting it in terms of goals. The goal of screening mammography is to detect a breast cancer before it can be felt. The subsequent mantra is that early detection means early treatment and thus results in fewer women dying as a result of breast cancer. The problem with screening mammography, after crunching all the numbers, is that early detection and early treatment are saving hardly any women's lives. In addition, all this screening has resulted in many more call-back mammograms and biopsies that yield no cancer, which has altered the landscape of benefit of screening mammography vs. harm of screening mammography. These factors are the drive for more individualized screening and individualized recommendations. Let's hope that we get there soon.

With the current disagreements among the different advisory groups on timing and interval of screening mammography, and the current lack of clarity as to who might really benefit from early detection and early treatment, too many women will remain confused and insecure about what they should do. After sharing all the above information about the five camps and the caveats, I believe that my patients are reasonably well informed and can make their own decisions, with my support.

Notes

1. Deffinger K, Fontham E, Etzioni R, et al. Breast cancer screening for women at average risk. 2015 Guideline Update from the American Cancer Society. *JAMA*. 2015;314(15):1599–1614.
2. Bleyer A, Welch G. Effect of three decades of screening mammography on breast-cancer incidence. *N Eng J Med*. 2012;267(21):1998–2005.
3. Tabár L et al. Swedish Two-County Trial: Impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology*. 2011 Sep; 260:658.

Dr. Tori Hudson graduated from the National College of Naturopathic Medicine (NCNM) in 1984 and has served the college in many capacities over the last 28 years. She is currently a clinical professor at NCNM and Bastyr University; has been in practice for over 30 years; and is the medical director of the clinic A Woman's Time in Portland, Oregon, and director of research and development for Vitanica, a supplement company for women. She is also a nationally recognized author, speaker, educator, researcher, and clinician.

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➤ *continued from page 96*

these metabolites, researchers found that among 5 healthy volunteers, 3-epi-25(OH)D accounted for up to 16.7% of the total 25(OH)D, and 7alpha C4 accounted for up to 38.7% of the total 25(OH)D that would have been reported by a standard laboratory method. In that study, the sum of 3-epi-25(OH)D and 7alpha C4 accounted for up to 55.3% of total 25(OH)D.[1] Thus, in some individuals, more than half of what is normally reported as 25(OH)D is actually other molecules. In a larger study (n = 1148) conducted in Thailand, 3-epi-25(OH)D was detected in all serum samples, in concentrations ranging from 1.8% to 24.8% of total 25(OH)D.[2] In another study, individuals with inflammatory diseases (i.e., rheumatoid arthritis and type 1 diabetes) had particularly high concentrations of 3-epi-25(OH)D, accounting for a mean of about 35% and 55%, respectively, of the total amount of 25(OH)D that would have been reported by a commercial laboratory.[3]

No one knows whether 3-epi-25(OH)D functions as a vitamin D agonist, antagonist, or modulator, or even if it is biologically active. 25(OH)D testing has now evolved from not knowing what the numbers mean to not even knowing what we are measuring: all the more reason not to recommend routine use of this test.

Alan R. Gaby, MD

Notes

1. Shah I et al. Misleading measures in vitamin D analysis: a novel LC-MS/MS assay to account for epimers and isobars. *Nutr J*. 2011;10:46.
2. Chailurkit L et al. Serum C3 epimer of 25-hydroxyvitamin D and its determinants in adults: a national health examination survey in Thais. *Osteoporos Int*. 2015;26:2339–2344.
3. Shah I et al. Exploring the role of vitamin D in type 1 diabetes, rheumatoid arthritis, and Alzheimer disease: new insights from accurate analysis of 10 forms. *J Clin Endocrinol Metab*. 2014;99:808–816.

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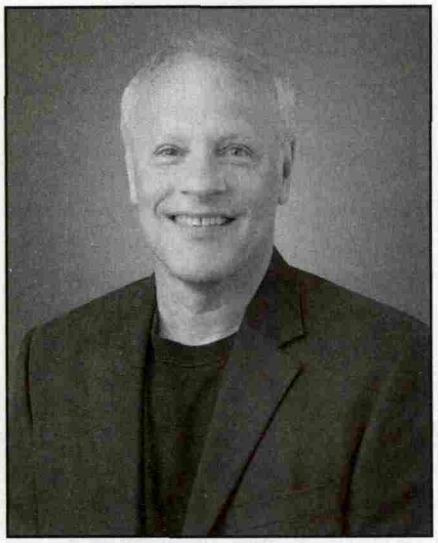

Testing 25-Hydroxyvitamin D Levels: It's Not What It Seems

Many practitioners recommend routine laboratory testing for serum 25-hydroxyvitamin D (25[OH]D) levels, and supplementing with vitamin D in dosages sufficient to achieve a target 25(OH)D concentration. The basis of this recommendation is that patients are frequently found by such testing to be deficient, and observational studies have shown that higher serum 25(OH)D levels are associated with better health outcomes. During the past several years, I have been arguing in the *Townsend Letter* and elsewhere that the serum concentration of 25(OH)D is not a reliable indicator of vitamin D status, and that basing vitamin D dosage recommendations on 25(OH)D levels has not been demonstrated to be either safe or effective. The arguments that I have made previously are summarized in the next paragraph, and the new evidence that raises even more doubt about the reliability of 25(OH)D testing is discussed in the subsequent paragraph.

There is reason to believe that many patients with low 25(OH)D levels are not really deficient in vitamin D. In recent years, laboratories changed the reference range for 25(OH)D, such that many more patients than before are now being classified as deficient. As I have argued previously, a case can be made that this change in the reference range is not supported by the evidence. Furthermore, 25(OH)D is only one of more than 50 circulating vitamin D metabolites that have been identified. Vitamin D status may be a function of complex interactions between many different vitamin D metabolites. Different people may have different serum 25(OH)D "set points" for adequate or "optimal" vitamin D status. In addition, the proportion of circulating 25(OH)D that is biologically active varies, depending on the concentration of vitamin D-binding protein, which can differ from one person to another. Moreover, 25(OH)D levels decline in response to inflammation; in patients with chronic inflammatory conditions, 25(OH)D levels might not reflect true vitamin D status. The observed association between higher 25(OH)D levels and better health outcomes might simply indicate that people without chronic inflammation are healthier than people with chronic inflammation. The question of whether it is appropriate to use high doses of vitamin D in order to achieve a purported optimal 25(OH)D level can only be answered by randomized controlled trials. The trials conducted to date contradict the findings from observational studies; they show that moderate vitamin D doses (such as 800–1200 IU per day) are at least as effective as, and possibly more effective than, large doses (such as 6500–13,000 IU per day). Because of these considerations, and because long-term use of large doses of vitamin D may increase the risk of kidney stones and atherosclerosis, I do not generally recommend 25(OH)D testing. If vitamin D supplementation appears to be clinically indicated, I advise most adult patients empirically to take 800 to 1200 IU per day, while reserving laboratory testing for selected situations (such as malabsorption syndromes or malnutrition).

Recent research has raised even more doubts about the reliability of the 25(OH)D test, finding that the methods used by commercial laboratories to measure 25(OH)D are highly inaccurate. These methods are unable to distinguish 25(OH)D from 25(OH)D epimers and isobars. An epimer is one of a pair of stereoisomers that differ only in the configuration around one asymmetric carbon atom. 3-Epi-25(OH)D is an epimer of 25(OH)D that is found naturally in serum; it accounts for varying percentages of total measured 25(OH)D in different people. An isobar is a compound that has the same molecular weight as another molecule. The main isobar that can interfere with the measurement of 25(OH)D is 7alpha-hydroxy-4-cholestene-3-one (7alpha C4), which is an endogenous bile acid precursor. Using a newly developed assay that can distinguish between

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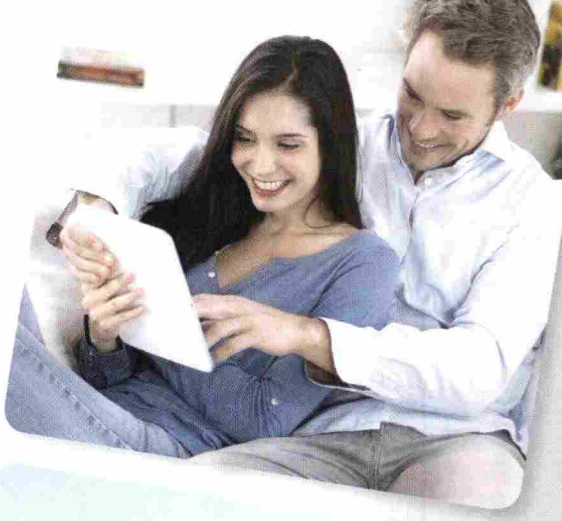

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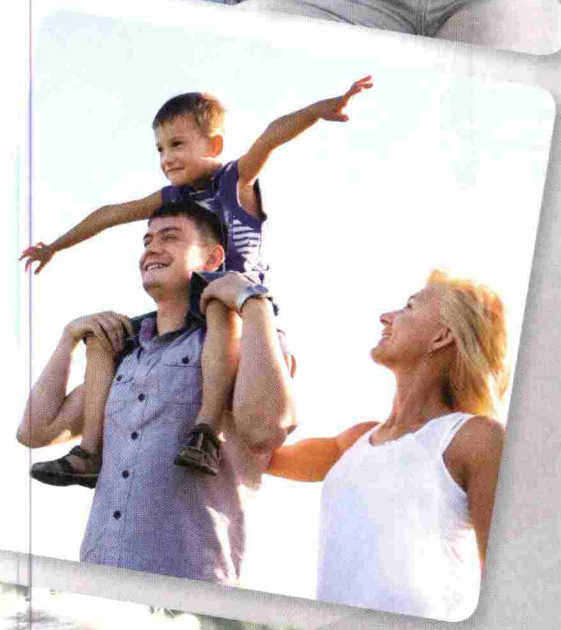

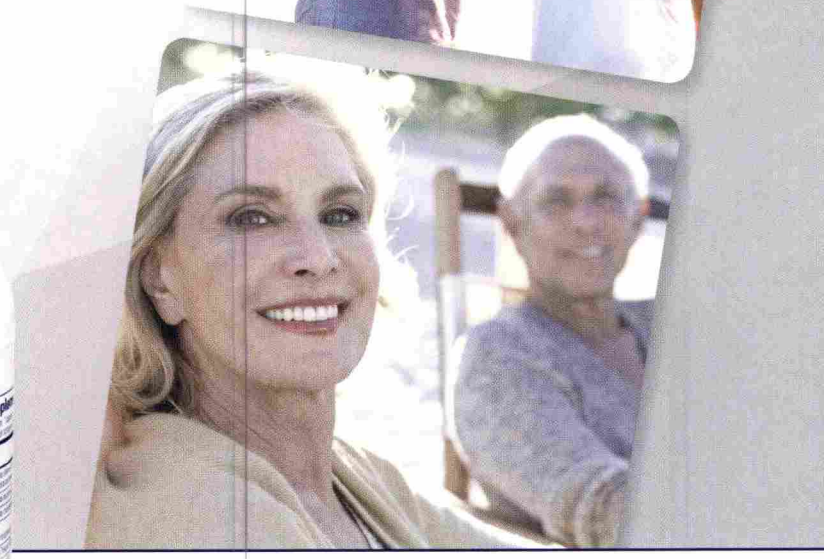

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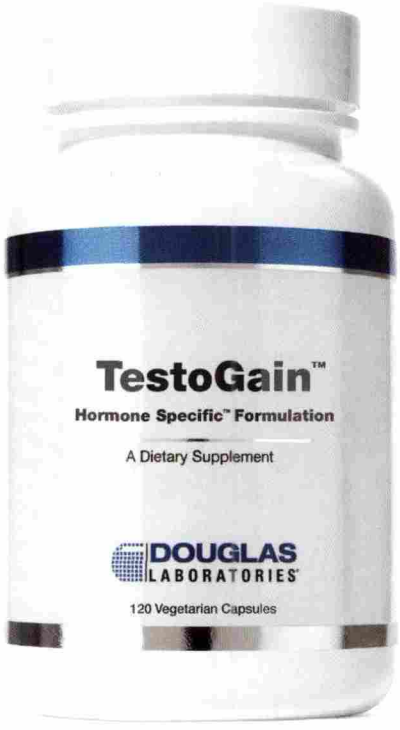

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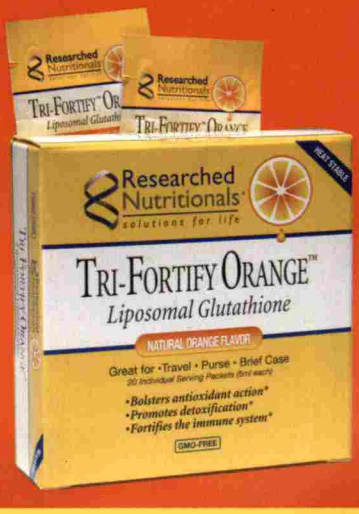

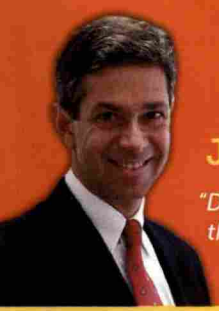

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