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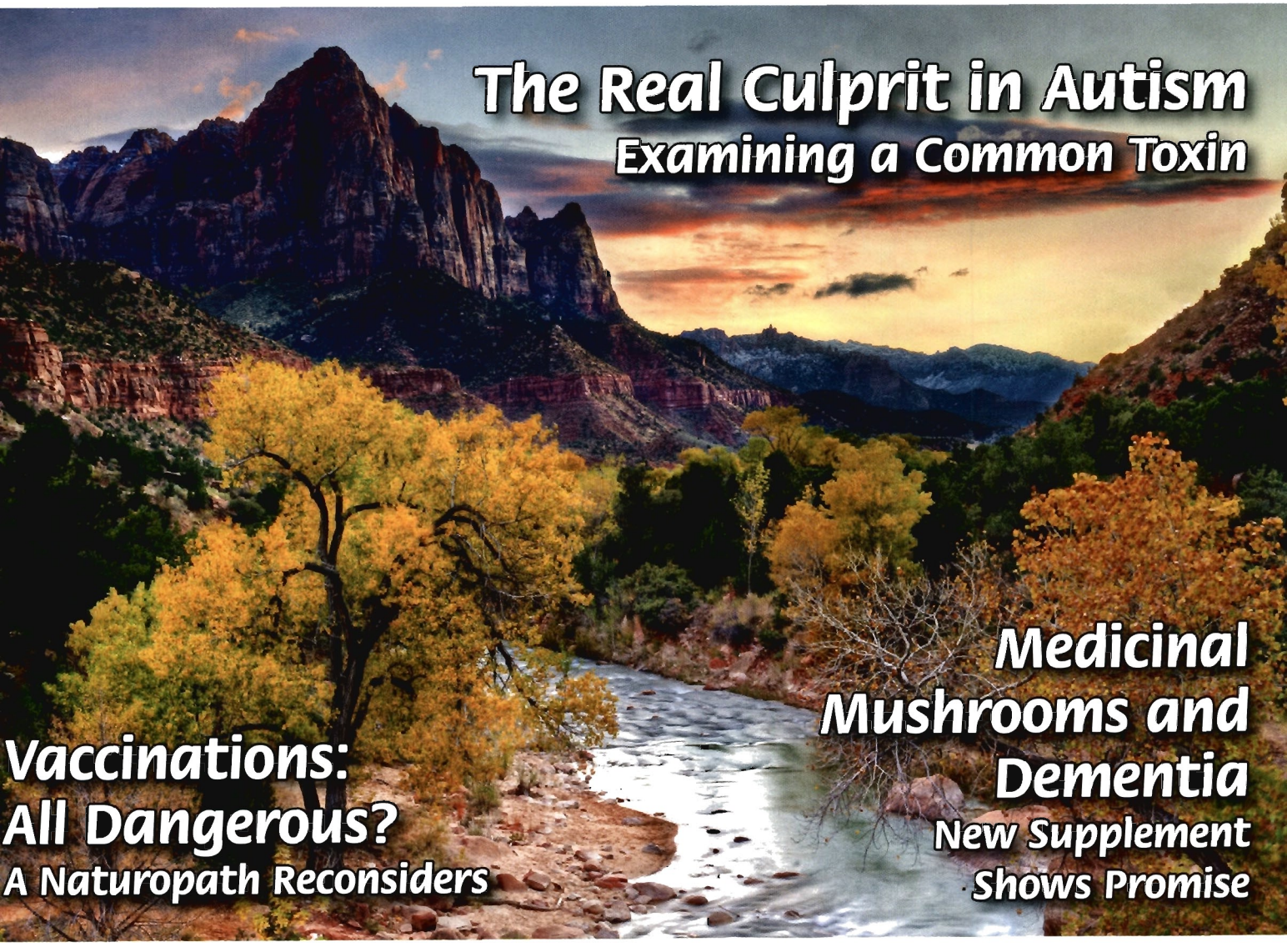

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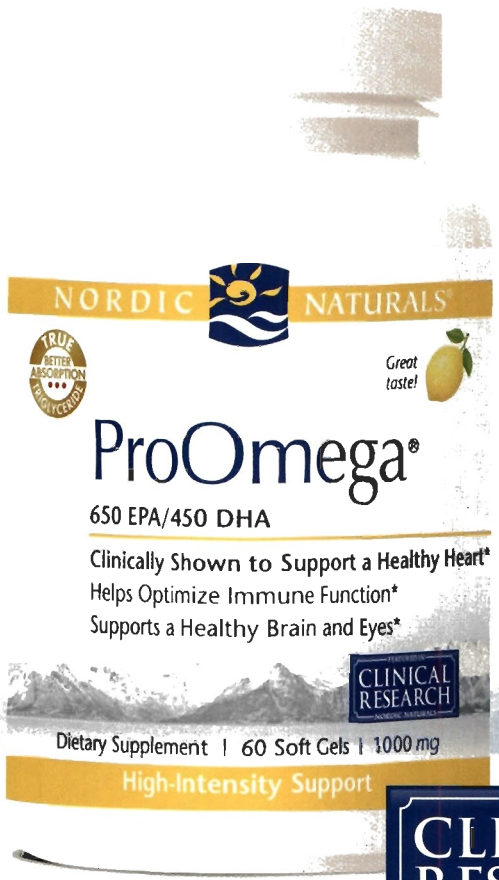

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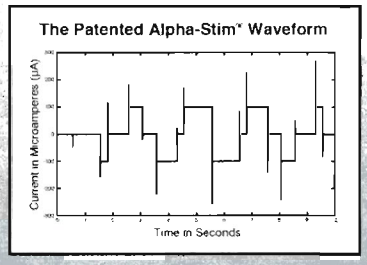

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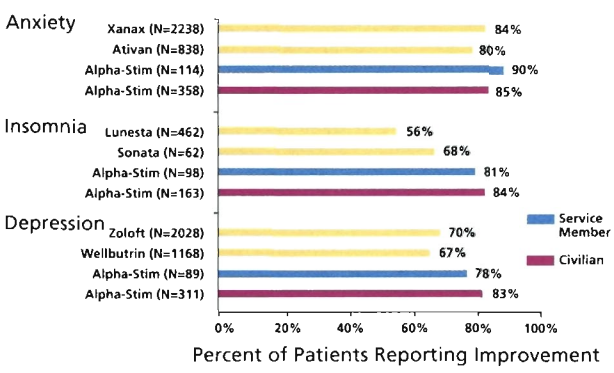

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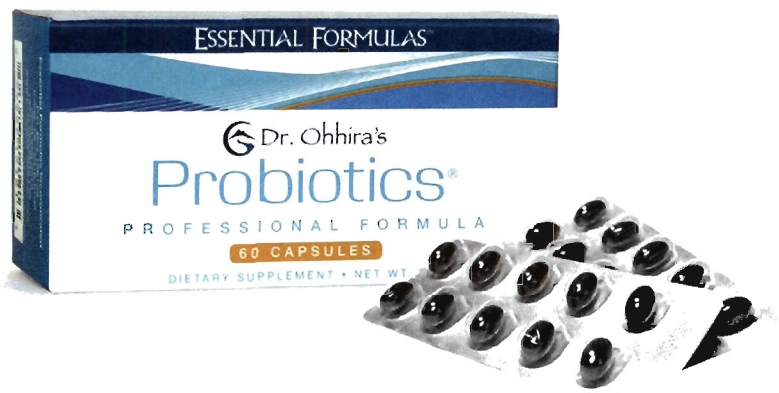

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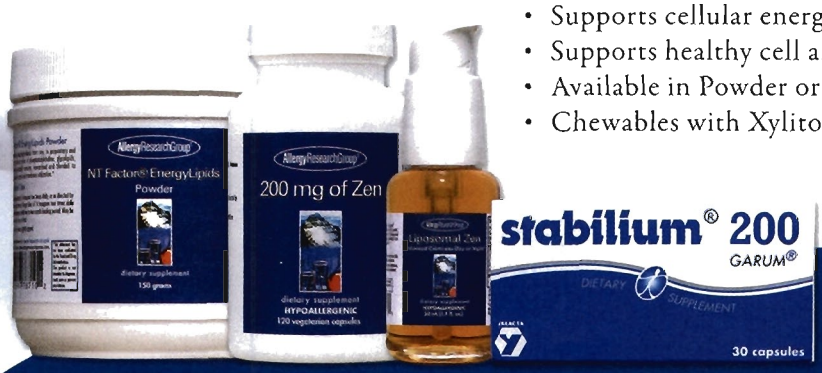

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From the Publisher

Postcard from Israel

At the beginning of the school year, children are often asked to write a report about their summer vacation – so I thought I would share mine. Deborah and I travelled to Israel in June to visit my aunt Lucy, who has lived in Tel Aviv since 1950. Most tourists see Israel only through the eyes of history, religion, and archaeology. Tel Aviv is the perfect spot to relax, walk on the beach, enjoy the café, and have a drink at a nightspot. Lucy loves to share stories of her life and bring us together with her friends. We enjoyed a sultry evening eating in the nearby old city of Jaffa with her friend Perry, who is a cancer surgeon. It was one of those perfect summer evenings that everyone cherishes – the right food and drink, the right company, the right setting by the beach at the port. We spent several days indulging in the mineral waters of the Dead Sea – I remind myself of those days whenever I soak in a bath of Epsom salts and hydrogen peroxide. Our experience in Israel was relaxing and restorative.

How different an experience we had of Israel and Gaza after returning to the US in July – of rockets and

continued on page 8 ➤

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Letter from the Publisher

➤ **continued from page 6**

bombs' destroying buildings and people being maimed and killed. Picasso's painting of Guernica comes to mind. The world clamors for a cease-fire while two opposing peoples are unable to come to terms and continue to inflict death and pain and suffering. It was and is situation with few answers, and Lucy and Perry concede that Israel will always fight aggressively whenever its security is threatened. They see little hope for a future peaceful existence. Of course, revolutionaries are fighting in ever-increasing numbers, not just against Israel but also against government and public safety throughout the Middle East, and in Africa, Europe, and Asia. Is there any answer except to fight back against fanaticism?

Aunt Lucy and Perry sharing dinner with Deborah and myself in Jaffa.

Deborah and I found so much to enjoy relaxing at the Dead Sea and in Tel Aviv. We need to savor those moments, knowing that violence and tragedy lurk around every corner.

Ebola: Newest Immigrant to US

Among the many milestones for 2014 has been the first-time arrival to the US on August 1 of Ebola, carried within a sick individual. In fact this date also marks the first human transportation of Ebola to both North and South America and to any place outside of Africa. Two American medical workers who were aiding medical personnel in Liberia fighting the infection contracted Ebola. The CDC directed that the sickened individuals be airlifted to the special quarantine unit at Emory University Hospital in Atlanta, Georgia. Ebola is transmitted through contact with virus-containing secretions. Hospital workers are directed to wear hazmat quarantine suits and are scrupulous about avoiding contact. Nevertheless, no method is foolproof, and it will be a wonder if no Emory Hospital health worker contracts the infection. The contagion period lasts at least 3 weeks, and one can only imagine the gut-wrenching tension that "civilian" US medical workers assigned to treat this patient will experience.

At this time, the "treatment" consists of basic measures such as administering fluids and palliative drugs until the patient either survives the infection or dies. The current

continued on page 15 ➤

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Photo: The Watchman as the Virgin River crosses below it in Zion National Park.

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Letter from the Publisher

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death rate is 60%. It is unclear if surviving patients will become carriers who may pass the infection to coworkers, family members, and friends. The World Health Organization and the CDC are now initiating a major increase in funding and sending more medical professionals to West Africa to contain the infection – a process that is now thought to likely last for 6 months.

In the interim, it would behoove health authorities to consider alternative medical therapies to help in containing Ebola. The top consideration would be the administration of intravenous vitamin C. Despite the fact that medicine has ignored the use of vitamin C for decades, it has been reported in many journals since the 1950s to palliate, control, or eradicate viral infections. Considering the danger posed by Ebola, it would be reasonable to use other medical alternatives such as ozone, colloidal silver, colostrum, prebiotics, probiotics, proteolytic enzymes, vitamin D, vitamin A, and minerals, including magnesium and zinc. As the situation is rapidly worsening and threatening to become an uncontrollable epidemic, it would be reasonable to mandate intravenous vitamin C for all infected individuals as well as health workers treating these patients. Such a mandate would be unprecedented, but urgency calls for unprecedented interventions.

The FDA Threat to Compounding Pharmacies Continues

In case you thought that compounding pharmacies have been out of the limelight, think again. In July a botched and prolonged execution in Arizona of an individual convicted of murder brought execution by lethal injection back onto the pages of the newspaper. Drug-induced execution has been carried out swiftly in the past – the prisoner dies within minutes, with no evidence of agony or discomfort. In the Arizona execution, the individual experienced shortness of breath repeatedly over a few hours. The problem is that the drugs used to kill the individual, pentobarbital and midazolam, are no longer formulated and manufactured by a drug company. Instead, a compounding pharmacy now prepares these injections. Drug companies have abandoned manufacturing drugs for lethal injection, wary of the political fallout and declining income. Still it is unsettling that the pharmaceutical company's cocktail of pentobarbital and midazolam worked effectively, while the compounded pharmacy's formulation did not. Why would

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Letter from the Publisher

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that be? Were the doses of the drugs too low? Were the drugs supplied to the compounding pharmacy improperly manufactured or adulterated? Did the compounding pharmacy fail to compound the drugs properly? These questions unfortunately come at a time when compounding pharmacies face severe scrutiny by the FDA.

It is not difficult to understand what the FDA intends to do about compounding pharmacies and prescriptions. In July the FDA confirmed that it intends to pursue tighter regulatory control over pharmacies and restrict what may or may not be compounded. However, the changes in regulations are still being designed and reviewed. In this issue of the *Townsend Letter,* the McGuff Compounding Pharmacy updates us on the proposed FDA regulations. There will be two compounding entities in the future: the compounding pharmacy and the outsourcing manufacturer. The compounding pharmacy will compound prescriptions, including injectable medicines for individual patients. The outsourcing facility will manufacture drugs, including injections that will be available for prescription. However, the outsourcing company will be limited to a restricted list of drugs that are not being manufactured by drug companies as approved by the FDA. Compounding pharmacies will be permitted to compound drugs and injections for individual patients only; theoretically there will be no general "office use" of prescription compounded drugs and injectables. In addition, there will be a list that the FDA is compiling of nonpermitted drugs that pharmacies may *not* use to compound. In the event that a drug is listed as forbidden to be compounded, it will be effectively banned from use. The FDA is deciding what compounds and drugs will be placed on the "forbidden" list.

It is difficult to know what options there may be if the prescribing physician needs a banned drug. Injectable vitamins and minerals are broadly available as unregulated oral supplements. However, oral chelation drugs are generally less effective than intravenous drugs. Consider if there were a ban of disodium EDTA and calcium EDTA. Chelation treatment would be effectively stopped. What if DMPS and DMSA were prohibited? Mercury chelation would be unavailable. Suppose intravenous ascorbic acid and sodium ascorbate were not permitted. "Myers cocktails" and vitamin C infusions would be eliminated. A ban of compounded glutathione would be a great treatment loss. There are many other vitamin, mineral, amino acid, herbal, and other products that could be banned, obstructing patient care. The FDA threatens to eliminate all drugs and compounds that it considers ineffective; only those agents having a USP Monograph will be safeguarded.

It is important for practitioners to discuss the FDA regulatory process with colleagues to consider political, legislative, and legal options. The Alliance for Natural Health (ANH-USA) is involved in battling the FDA over this compounding pharmacy regulation. Please join with the ANH-USA to protect access to compounded medications.

Timing of Vaccinations

Our daughter, Affinity, and son-in-law, Jeff were wed two years ago. At a pre-wedding dinner, we enjoyed conversing with our guests Michael Gerber, MD, and his wife, Inge. Michael and I have been friends for many years, sharing mutual interests in chelation and alternative medicine. At medical meetings, Michael delights in getting colleagues together to share new treatments and case histories. Michael enjoyed discussing holistic and homeopathic therapies with guests at the dinner. The conversation took an awkward turn when he told some of Affinity and Jeff's friends who were with babe in arms that they should not vaccinate their children, or at least delay doing so. The young parents are not involved in CAM and had been routinely vaccinating their babies – so they were unhappy with Gerber's advice. While there is a strong antivaccination sentiment among natural–medicine oriented physicians, there may be some sound medical theory in sequencing the administration of vaccines in a particular way.

In this issue of the *Townsend Letter,* Jacob Schor, ND, FABNO, examines the unexpected improvement in life expectancy derived from vaccinations but only when certain vaccines are administered in a timely fashion. Schor reports about the "nonspecific" effects of vaccinations that reduce the risk of unrelated infections. Several studies have demonstrated remarkably beneficial nonspecific effects from the measles vaccine that would not be expected simply from preventing measles. Similar unexpected improvement in preventing illness has been seen with the BCG vaccine for TB and the currently disused vaccinia vaccine for smallpox. What Schor discusses that is particularly remarkable is that when the measles vaccine is administered immediately after the final DPT vaccine, there is a remarkable improvement in infant mortality. For reasons that are not clear, the DPT vaccine in females but not males poses negative risk effects. Administering the measles or the BCG vaccine after the DPT vaccine mitigates those negative effects.

Additionally there is growing evidence that vaccines improve the immune system's ability to fight cancer. Schor reports the reduction in the incidence of melanoma in patients who have been vaccinated for BCG. BCG is not a common vaccine in the US, but should it be considered in fair-skinned individuals who are at high risk for melanoma? Although alternative practitioners have advised patients to avoid receiving vaccinations, there may be a need to rethink this issue.

Jonathan Collin, MD

A Legend in His Time: Abram Ber, MD(H)

July 14, 1940 – June 23, 2014

by Victoria Bowmann, PhD

Legend has it that in every generation there are perhaps 20 individuals who reside on earth with a greater vision: to bring healing on all levels to the earth and its people. Those who personally knew Abram Ber would consider him to be one representative of this legend.

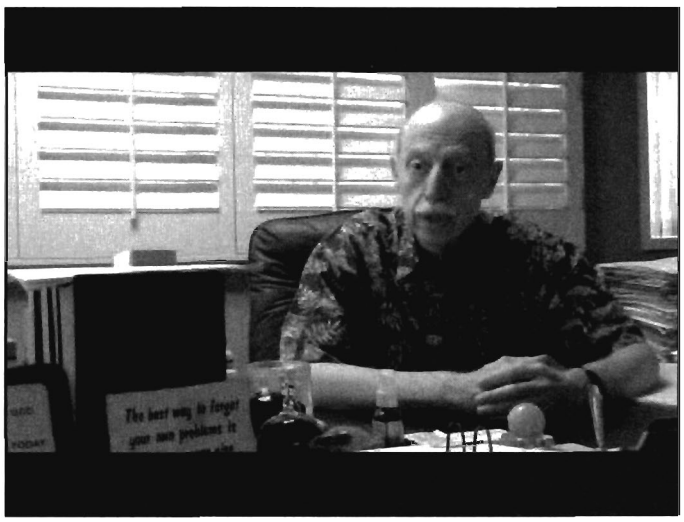
His life began on July 14, 1940, in Bacau, Romania. He was the only child of David and Freda Ber, as the war prevented them from having more children. After the death of his parents, a family friend told him of how they survived the Holocaust: a Romanian soldier took pity on his pregnant mother and removed them from a line of Jews who were about to be deported to the Romanian concentration camp Transnistria. Hershel, his grandfather, perished in that camp.

When Abe was 7, his family left Romania for Milan, Italy, and lived there for five years, while he attended the Hebrew day school Alessandro da Fano. In 1951, the family left Europe aboard the USS General Steward and landed in Halifax, Nova Scotia. They settled in Montreal, Canada, and lived there for 26 years. Abe was now fluent in Romanian, Yiddish, Italian, English, and French.

He attended McGill University, where he obtained his bachelor of science degree and then earned his medical degree in 1966. Abe completed a year of internal medicine at the Jewish General Hospital in Montreal. He was trained in anesthesiology and worked for a few years in anesthesiology at the Royal Victoria Hospital as well as the Queen Elizabeth Hospital. He became board certified in anesthesiology.

In 1974 Dr. Ber left the practice of anesthesiology to take over a recently deceased physician's general practice. He became interested in holistic medicine the following year after a patient gave him a book on vitamin E. In December 1977, he moved his family to Phoenix, Arizona, to join the A.R.E. Clinic. In 1978 he opened his own practice and became a leader in the holistic medical movement.

With the efforts of other holistic physicians and a grassroots movement of many patients, by 1982 the Homeopathic Medical Board was established and Abram became the first medical doctor to be licensed by the board. (His license number was 001.) He served as a member of the board in many capacities as well as being instrumental in establishing the Homeopathic Association, now known as the Arizona Homeopathic and Integrative Medical Association.



Dr. Ber lived a holistic lifestyle and was an example to many. His thirst for knowledge had him studying holistic medical journals and seminars to stay up on the latest strategies and protocols. Helping and healing were always foremost in his thoughts and actions. For those who shared patients with Abe, we would lovingly joke that his specialty was now spontaneous remissions and miracle cures.

His son, Eli, a naturopathic physician, predeceased him. Eli suffered with Crohn's disease for 25 years, and his final suffering and struggle with cancer left Dr. Ber heartbroken.

Abram Ber leaves behind his beloved wife, Beth, as well as his son Hershel and grandchildren from both sons. He maintained a warm and caring relationship with his first wife, Moselle.

Dr. Ber was profoundly affected by the Holocaust, whose impact permeated his very core. However, this immense sorrow moved him to help others. His charitable contributions were worldwide. He identified with Albert Einstein's saying, "Only a life lived for others is a life worthwhile."

On the wall in his office was a star registry, with a star named after him. So when you gaze into the clear night sky, know that Abe is twinkling down upon you. I would like to imagine if he could say some parting words, they might be, "May you shine in the darkest places where it is impossible to love. May you excel above your expectations. May you live your life to the fullest."

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Vitamins, Minerals Reduce AIDS Mortality Ignoring Supplements Means Unnecessary Deaths

commentary by Andrew W. Saul

Twenty-seven years ago, I worked with a client (woman, late 20s) who was HIV positive. She was a heavy drinker and drug user and smoker, and had a terrible diet and a series of bad personal relationships. Her health was deteriorating. Desperate, she decreased her drug and alcohol use. She still smoked, ate a poor diet, and was under great stress. She took multivitamin/multimineral supplements irregularly. But she took a lot of vitamin C very regularly, for over two decades. Twenty-six years later, doctors cannot detect HIV in her system. They now say that she never had it. She did. She probably still does. But they cannot find it. She has no symptoms. Robert Cathcart, MD, in California treated AIDS patients with up to 200,000 milligrams of vitamin C a day. He found that, with very large intakes of vitamin C, even advanced AIDS patients lived significantly longer and had far fewer symptoms.[1] Dr. Cathcart published in 1984, some 30 years ago. This clinical finding is very important. So important that it is hard to believe that the entire Wikipedia entry for Dr. Cathcart was deleted. His work was arbitrarily judged "too unsubstantial to provide notability."[2] Perhaps even Wikipedia might find it difficult to ignore this research: A 1993 study at Johns Hopkins demonstrated that larger-than-RDA multivitamin supplements slow AIDS, and even help halt it. The 7-year-long study of 281 HIV-positive men showed that those taking vitamins had only about half as many new AIDS outbreaks as those not taking supplements.[3] In 2004, a Harvard study by Fawzi et al. found that vitamins cut AIDS deaths by 27% and slow the progression to AIDS by 50%. The study authors said, "Multivitamins also resulted in significantly higher CD4+ and CD8+ cell counts and significantly lower viral loads. ... Multivitamin supplements delay the progression of HIV disease."[4] Here you have something truly interesting: In 1984, 1993, and 2004, studies showed that HIV patients taking vitamins are 50% less likely to develop full-blown AIDS, and that vitamin-taking AIDS patients live considerably longer, with far fewer symptoms. Have you heard anything about this on TV, or in a newspaper or magazine? Or a college course? Or from your health-care provider? And now a new study in the *Journal of the American Medical Association* confirms it yet again. In HIV-infected adults, "supplementation with a single supplement containing multivitamins and selenium was safe and significantly reduced the risk of immune decline and morbidity."[5] Yes, that was with a single multivitamin supplement with added selenium. Harold D. Foster, PhD, advocated the use of selenium and amino acids, plus antioxidants, for HIV/AIDS a decade ago.[6–8] But the new *JAMA* study does not appear to mention his work at all. Yet the public has been told, for months and years and decades, that it does not need multivitamins or other dietary supplements, supplements do no good, supplements are harmful, and supplements even increase death rates. In short, the public has been lied to. For decades. How many lives have been lost that could have been saved?

Andrew W. Saul is author or coauthor of 12 books, including 4 with Dr. Abram Hoffer. He is a member of the board of the Japanese College of Intravenous Therapy and has been inducted into the Orthomolecular Medicine Hall of Fame.

To Learn More

A good introductory article by Dr. Foster: http://www.doctoryourself.com/news/v4n12.html.

Interviews with him: http://www.doctoryourself.com/fosterinterview.html.

Dr. Foster's book: *What Really Causes AIDS*. Trafford; 2006. Download for a donation at http://www.hdfoster.com/publications.

Brighthope I, Fitzgerald P. *The AIDS Fighters*. (Out of print but available on the used-book market. Note the date of publication.) Keats Pub; 1988. ISBN-10: 087983482X and ISBN-13: 978-0879834821.

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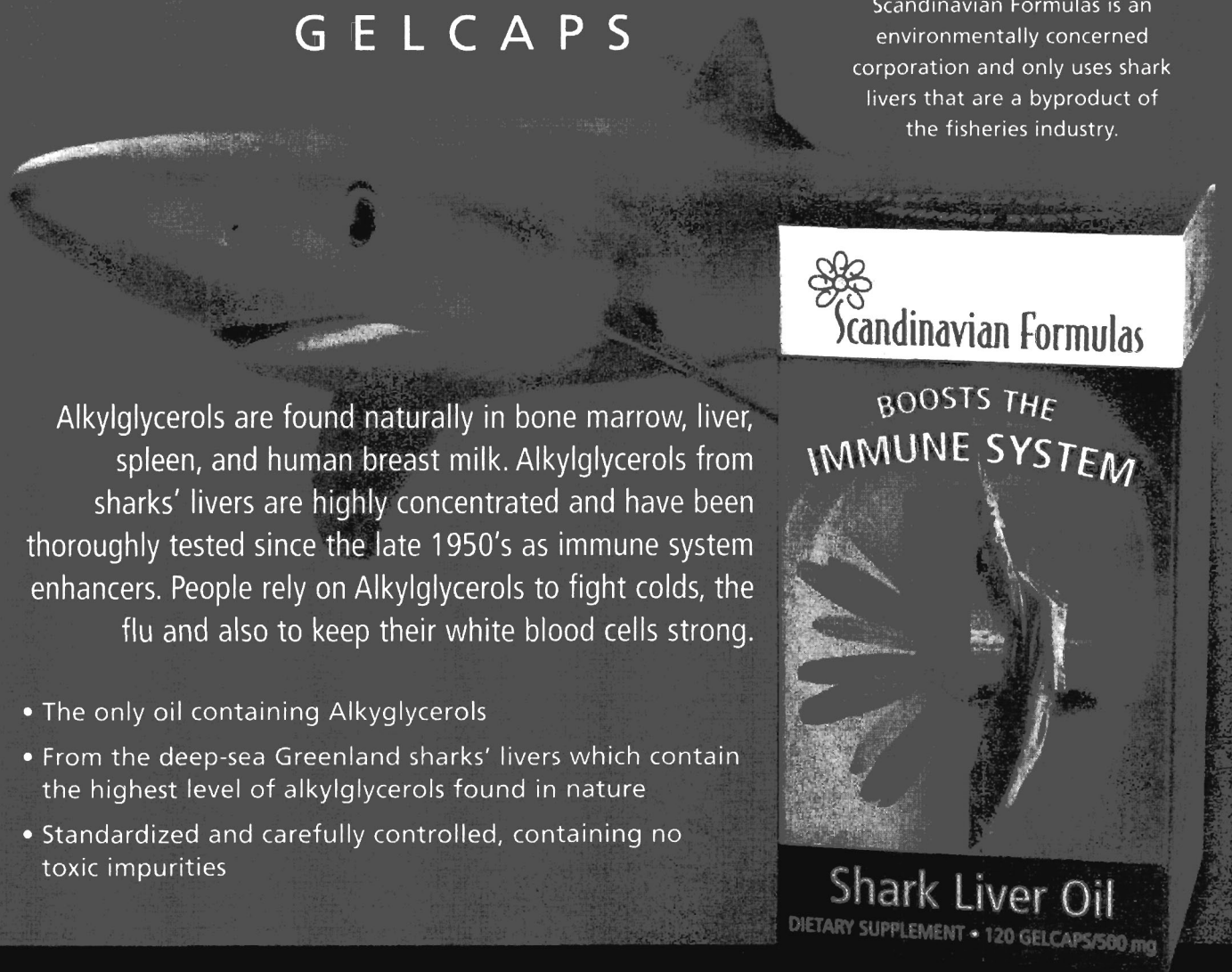

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Problems Found with the Quality and Labeling of Some 'Muscle Enhancement' Supplements

Athletes often turn to supplements such as creatine and branched-chain amino acids (BCAAs) to enhance muscle strength and recovery. These supplements may also benefit people with muscular diseases and those recovering from knee surgery. However, tests by ConsumerLab.com show quality problems with 36% of supplements recently selected for review.[1] Three creatine supplements were found to contain unacceptable levels of creatine breakdown compounds, and two of these products provided only tiny amounts of creatine. In addition, the BCAA "blends" in some products were found to consist mainly of compounds other than BCAAs, with only 5% to 10% of listed amounts being BCAAs.

"It can be very difficult for people to know what they are getting from muscle enhancement supplements," said Tod Cooperman, MD, ConsumerLab.com's president. "It is important to read labels carefully and be skeptical of contents unless verified by a third party," he added.

In addition to a range in quality, the price of products varied widely. The lowest cost to get the equivalent of 5 grams of high-quality creatine monohydrate from a supplement was 9 cents, and for 5 grams of BCAAs it was 31 cents, while the cost was well over $1 to get these same ingredients from some other products.

The new "Product Review of Muscle Enhancement Supplements" includes findings for 11 supplements selected by ConsumerLab.com and eight supplements that passed ConsumerLab.com's voluntary Quality Certification Program.[2] Two products similar to one that passed testing are also identified. Products covered in the report are Betancourt Nutrition Chewies, BIORhythm AfterGlow, Body Fortress Super Advanced Creatine, BodyTech 100% Pure Creatine Monohydrate, Dymatized Nutrition BCAA Complex 5050, EAS Phos HP, Life Extension Branched Chain Amino Acids, MET-Rx BCAA 2200, MRM BCAA+G, Muscle Marketing USA ATP Creatine Serum, Muscle Marketing USA Endurus Runners Serum, MusclePharm Creatine, Myology BCAA 2200, ON Micronized Creatine Powder, Precision Engineered BCAA 2200, Six Star Pro Nutrition Creatine X3, Solgar BCAA Plus, Ultimate Nutrition 100% Crystalline BCCA, Vitacost ARO Black Series Amino Plus, Vitacost Creatine, and VPX Creatine Plasma.

The report also provides information about the uses, dosage, and potential side effects of creatine and BCAAs and explains differences among forms of these ingredients, such as creatine monohydrate, creatine AKG, dicreatine malate, and KreAlkalyn.

Since 1999, ConsumerLab.com has been a leading provider of consumer information and independent evaluations of products that affect health and nutrition. Membership to ConsumerLab.com is available online, providing immediate access to reviews of more than 1000 products from over 400 brands. The company is privately held and based in Westchester, New York. It has no ownership from, or interest in, companies that manufacture, distribute, or sell consumer products.

Notes

1. Product review: muscle enhancers (creatine and branched-chain amino acids) [Web page]. Consumerlab.com. https://www.consumerlab.com/reviews/review_creatine_BCAAs/creatine.
2. About ConsumerLab.com: Quality Certification Program [Web page]. ConsumerLab.com. https://www.consumerlab.com/aboutcl.asp#certification.

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Best of Naturopathic Medicine 2015

The *Townsend Letter* is pleased to announce our seventh Best of Naturopathic Medicine competition. Naturopathic students, faculty, researchers, and practitioners are invited to submit research papers, reviews, and articles. Selected papers will be published in our February/March 2015 issue. The author of the winning paper will be awarded $850. Runner-up papers will be published and authors will receive an honorarium.

Papers submitted should be 1500 to 3500 words and referenced. Author guidelines are available at the *Townsend Letter* website: www.townsendletter.com. Papers should be submitted digitally, preferably as a Microsoft Word document. Papers authored by multiple writers are acceptable; the lead author should be an ND graduate or candidate of an accredited four-year naturopathic school. Papers submitted for the competition may not be submitted to other publications or have previously been published. All entries must be submitted by October 31, 2014.

Send papers to editorial@townsendletter.com. The subject line should read: "Paper for Best of Naturopathic Medicine 2015."

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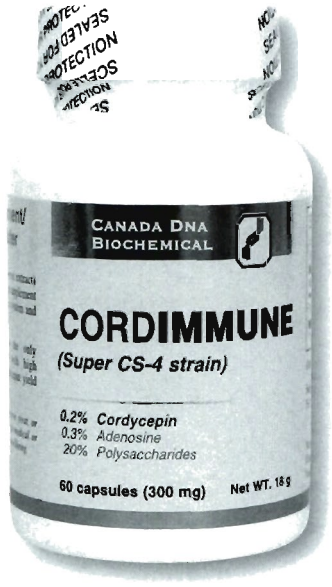

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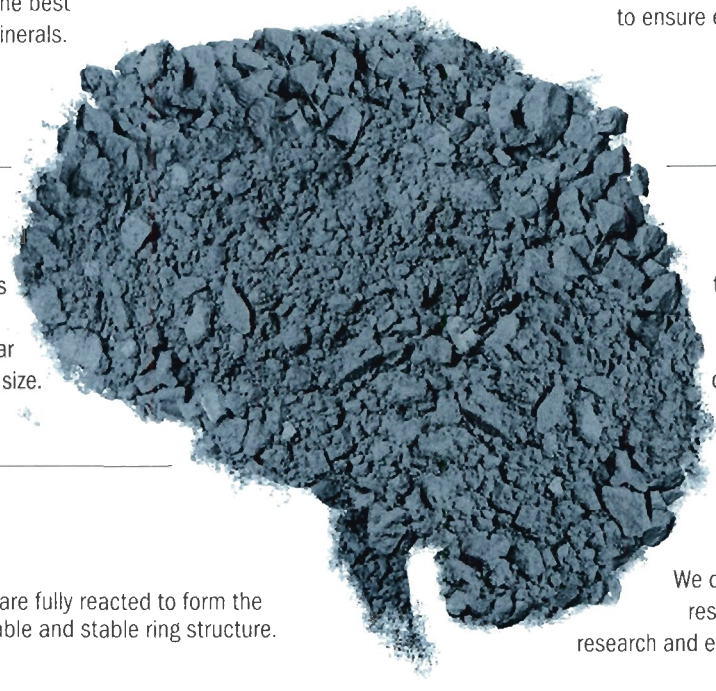

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Pathways to Healing

by Elaine Zablocki

Naturopathic Doctors Win Support in the States

In April, Maryland Governor Martin O'Malley signed a bill authorizing Maryland NDs to be licensed to practice naturopathic medicine. Passage of the bill, which received strong bipartisan support, represented years of coordinated efforts by naturopathic doctors in the state.

That's only one part of the story. In recent years there's been significant progress in quite a few states. Puerto Rico attained licensure in 2004, California and Kansas in 2003, Washington, DC, in 2005, Minnesota in 2008, North Dakota in 2011, and Colorado in 2013. Connecticut passed a law modernizing the scope of practice in 2014.

"The fact that so many states have become licensed in past decade, and especially in the last couple of years, means that their success is an inspiration to NDs elsewhere," says Mike Jawer, director of government and public affairs at the American Association of Naturopathic Physicians (AANP). "Our members all across the country are looking enthusiastically at what these colleagues have been able to do and saying, why not us? When there is a critical mass of practitioners in a given state, and folks decide they're willing to make the investment of time and money and energy to become licensed, they go for it."

Licensure requires a considerable commitment. It took Maryland four years for NDs to become licensed. "In Colorado, they were biting at that apple for over 20 years," Jawer says. "Colorado is one of the states where there are many traditional naturopaths, who were concerned that they might be put out of business. However, that's not the intent of these licensure efforts."

Currently there are 4500 licensed naturopathic physicians in the US. They have each graduated from an accredited four-year residential naturopathic medical school and passed an extensive postdoctoral board examination (the Naturopathic Physicians Licensing Examination) to receive a license.

Traditional naturopaths rely on varied forms of training, perhaps through online courses or community schools. In states that do not have licensure for NDs, anyone who wishes can use the name *naturopath* or *naturopathic physician*, or put ND after his/her name, because there is no regulation. "One significant reason to pursue licensure is that the public needs to understand the difference," says Jawer. "In a state that has licensure, when someone goes to a naturopathic physician who has ND after their name, it means this person has graduated from a recognized school with a rigorous training program."

At present, six additional states are working toward ND licensure. "There is a significant ongoing effort now in Massachusetts," Jawer says. "In Pennsylvania, the bill passed their House earlier this year and it's now being considered in the Senate."

Maryland NDs Achieve Licensure

The first step in passing legislation is to identify supporters in the state legislature. "We were not even sure if we were going to introduce the bill, but at a fund-raiser

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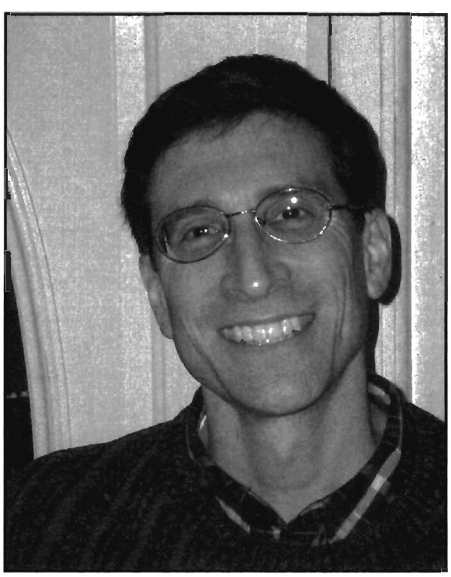

Mike Jawer

Emily Telfair, ND

➤

just before the legislative session we had an opportunity to meet a key legislator," said Emily Telfair, ND, president of the Maryland Naturopathic Doctors Association (MDDA). "He said, 'Just go ahead and introduce the bill and I'll make sure it gets a fair hearing.' It was an informal conversation that basically put the ball in motion."

MNDA started out with sample legislation from the AANP, and the next step was to find sponsors in the legislature. "On my first day in Annapolis I arranged meetings with my state senator and state delegates just to introduce myself," Telfair recalls. "I really struck gold when I walked into my state senator's office, because it turned out she was very supportive of natural medicine, and she is extremely well respected in the legislature."

Another crucial aspect of the process was support from naturopaths in the state.

Last year Telfair was part of a team of six who were involved throughout the process. Someone from the ND community was present at the legislature every day throughout its 90-day session: "By working together as a team, we were able to use each other's abilities for making a PowerPoint presentation or meeting with a legislator. We dressed the part, we were professional, and we made important relationships with legislators on a human level."

MNDA held many meetings and conversations with legislators and organizations, and assembled extensive materials to educate legislators and other providers about the profession. After opposing licensure for four years, the medical society representing Maryland physicians dropped its opposition, largely because of a growing number of MDs who strongly supported the bill. (The educational materials are now available on the AANP website as model resources for NDs in other states.)

The association also mobilized a significant grassroots effort, with patients writing individual letters about their healing stories. These letters were compiled and presented as part of MDNA testimony. When the bill came up for a vote in the General Assembly, practitioners encouraged patients to contact their legislators.

A turning point in the licensure effort came when Maryland's health secretary, Joshua Sharfstein, MD, and leaders from the General Assembly visited the Casey Health Institute in Gaithersburg. It is one of the very few integrative patient-centered medical homes. "The staff includes medical doctors, nurse practitioners, and a naturopathic doctor," Telfair says. "They hired her even though it was before licensure, because they saw the future that was coming and wanted to be right there to meet it. When we brought legislators to this facility, they met with medical doctors who had experience working with a naturopath. They were very impressed by the patient-centered, integrative approaches being used there to treat patients."

Telfair is available to consult with other NDs who are involved in similar efforts in their own states. "You know, when I was working on this, every time I reached out to someone, medical doctors or naturopaths in other states, they contacted me right away," she says. "What a gift that was! So many people have blazed a trail before me. Now, if I get to get to blaze a trail that will help someone else and their future students, that's what this whole process has been about."

Resources

American Association of Naturopathic Physicians
Mike Jawer, director of government and public affairs
http://www.naturopathic.org
For information on state licensure campaigns, including model legislation and educational materials: http://www.naturopathic.org/advocacy

Maryland Naturopathic Doctors Association
Emily Telfair, ND, president
http://www.marylandnd.org
dremilytelfair@gmail.com
For more information about the Maryland licensure law for NDs: http://www.marylandnd.org/licensure-faq

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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Naturopathic Licensure

Currently, 17 states, the District of Columbia, and two US territories have licensing or regulation laws for naturopathic doctors. They are:

- Alaska
- Arizona
- California
- Colorado
- Connecticut
- District of Columbia
- Hawaii
- Kansas
- Maine
- Maryland
- Minnesota
- Montana
- New Hampshire
- North Dakota
- Oregon
- Utah
- Vermont
- Washington
- US Territories: Puerto Rico and Virgin Islands

Source: American Association of Naturopathic Physicians

Shorts

briefed by Jule Klotter
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Antipsychotic Drug Paradigm Shift?

The effectiveness of long-term antipsychotic drug treatment for people with schizophrenia and other psychotic disorders has been challenged by a 2013 Dutch study led by Lex Wunderink, MD, PhD. The study assessed symptomatic and functional remission of patients 5 years after they had taken part in a 2-year study. In the original study, 128 patients receiving antipsychotic treatment for first-episode psychosis were randomly assigned to continue maintenance drug therapy or to taper down and eventually discontinue treatment after 6 months of symptom remission. As in other short-term studies (2 years or less), this trial showed that patients receiving dose reduction/discontinuation (DR) treatment had a significantly higher relapse rate than those on maintenance therapy (MT).

Five years after the trial's end, Wunderink and colleagues managed to contact 103 (80.5%) of the original participants for follow-up assessment. Most were still on drug therapy. However, 34 patients – 22 (42.3%) in the DR group and 12 (23.5%) in the MT group – had received no antipsychotic medication or very low doses for 2 years before assessment. Although relapse rates were significantly higher in the DR group in the first few years after first-episode psychosis, the researchers found that the two groups were about the same by the third year as symptoms declined in the DR group and increased in the MT group. "Maybe the MT strategy postpones the relapses compared with the DR strategy but does not prevent them," the authors say.

Although symptomatic remission was about the same in the two groups at follow-up, more patients in the dose reduction group had attained functional remission (24 of 52; 46.2%) compared with the maintenance group (10 of 51; 19.6%). The researchers define functional remission as "proper social functioning in the main domains of everyday life," including self-care, work/school, and relationships with others. Also, more than twice as many patients in the DR group had recovered, showing both symptomatic and functional remission for at least 6 months: 21 of 52 (40.4%) in DR vs. 9 of 51 (17.6%) in MT. "To our knowledge, this is the first study showing long-term gains of an early-course DR strategy in patients with remitted [first-episode psychosis]," say the authors. "Additional studies are necessary before these results are incorporated into general practice."

Thomas Insel, director of the National Institute of Mental Health, discussed the Wunderink study in his August 28, 2013, blog post. Insel comments on the value of antipsychotics for reducing symptoms but says that symptom reduction "is rarely sufficient for a return to normal functioning." He agrees that long-term maintenance treatment is not the best course for many patients.

Long-term antipsychotic treatment in not the only standard being questioned at NIMH. On April 29, 2013, Insel announced that NIMH is moving away from symptom-based diagnosis and DSM categories. Instead, the agency is researching "genetics, imaging, cognitive science, and other levels of information to lay the foundation for a new classification system."

Insel T. Director's blog: antipsychotics: taking the long view [blog post]. August 28, 2013. www.nimh.nih.gov/about/director/2013/antipsychotics-taking-the-long-view.shtml. Accessed July 19, 2014.

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The Autistic Brain

"Research and therapy have traditionally focused on understanding and compensating for cognitive problems in people with autism. ... But this emphasis on what's wrong with the autistic brain has obscured a recognition of something just as important: what's *right* with it," say Temple Grandin and Richard Panek (*Time*, October 7, 2013). Unlike the neurotypical brain, the autistic brain homes in on details, on individual components. It also excels at associative thinking and seeing similarities between diverse items and situations. This combination of associative thinking and attention to detail can produce creative breakthroughs: "'sudden, unexpected recognition of concepts or facts in a new relation not previously seen.'"

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Many people with autism are very intelligent, according to research led by Michelle Dawson at the University of Montreal. When given intelligence tests based on verbal and social skills, one-third of the autistic children were deemed "low-functioning." When given Raven's Progressive Matrices, a nonverbal test that measures fluid intelligence and analytical reasoning, their scores were significantly higher. Seven of the 38 children scored 90 percentile points or higher, and only 5% measured as low functioning. In contrast, neurotypical children performed about the same on both types of tests.

Dr. Laurent Mottron, who coauthored the study, has several people with autism on his research team. In his commentary "The Power of Autism," he says that their intelligence and attention to detail make them solid researchers. While the autistic brain is not geared for public relations and social interaction, it does have qualities useful in other fields – if those qualities receive the nurturing and support needed to blossom.

Mottron and Grandin both fault current education techniques that focus solely on suppressing autistic behavior and forcing neurotypical development. Grandin says, "... the focus on deficits is so intense and so automatic that people lose sight of the strengths." Granted, the strengths may sometimes be difficult to identify. "Some people's difficulties are simply too severe for them to ever have the same opportunities I have," says Grandin. "But for so many people on the spectrum, identifying their strengths can change their lives. Instead of only accommodating their deficits, they can cultivate their dreams."

Sixteen-year-old Jacob Barnett is a stunning example of what happens when a child's strengths and interests receive attention. A previously affectionate child, Jacob was diagnosed with autism at age 2 after he withdrew into silence. He stopped interacting with others. He became obsessed with patterns of light and dark. Experts offered little hope that he would perform basic functions. They told his mother that he would never read. His mother, Kristine Barnett, pulled him out of special education classes. Instead, she looked for ways to share his fascinations in order to connect with him. She took him to an open field at night to watch stars and to a local planetarium. Gradually, he began to reconnect and interact with her. Her program of "muchness" unlocked Jacob's isolation, and his interest in math and astronomy grew into genius. He attended math and science classes at Indiana University-Purdue University Indianapolis while still in elementary school. At 15, he joined other young physicists at Perimeter Institute for Theoretical Physics in Waterloo, Ontario, Canada. Kristine used the same technique of encouraging a child's passion – "spark" – with her other two sons and with neurotypical children who attended her day-care program. Kristine Barnett's memoir, *The Spark: A Mother's Story of Nurturing Genius,* is one of the most inspiring and valuable books that I've ever read about children.

Despite his genius, Jacob is still autistic. He feels most comfortable in small spaces. Buzzing lights disturb him. Tying shoelaces is challenging. "'He overcomes it every day,'" his mother told *USA Today*. "'There are things he knows about himself that he regulates every day.'" Jacob says autism is "part of who I am but it is not all of me. I am a physicist." Grandin says the same: "Autism is part of who I am, but I won't allow it to define me." They are far more than the deficits attached to the label "autism."

Dawson M, Soulières I, Gernsbacher MA, Mottron L. The level & nature of autistic intelligence. *Psychol Sci.* 2007;18(8):657–662. Available at www.traininautism.com/Mottron/2007%20Dawson%20psychological%20science.pdf. Accessed July 23, 2014.

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Weddle E. Boy genius' celebrity grows with new book, movie deal. *USA Today.* April 8, 2013. Available at http://www.usatoday.com/story/news/nation/2013/04/08/indiana-boy-genius-book/2064921. Accessed June 23, 2014.

Wells P. Jacob Barnett, boy genius. *Maclean's.* September 1, 2013. Available at http://www.macleans.ca/news/canada/jacob-barnett-boy-genius. Accessed June 26, 2014.

ADHD, Cell Phone Use, and Lead Levels

Yoon-Hwan Byun and colleagues looked at the relationship between cell phone use, blood lead levels, and ADHD symptoms in 2422 elementary school children as part of the longitudinal Korean Children's Health and Environmental Research (CHEER) study. Electromagnetic fields from cell phones have been linked to hyperactivity in children and to hyperactivity and cognitive impairment in rodents. Lead, a known neurotoxin, contributes to inattention and reduce cognitive function. The researchers relied on a questionnaire completed by parents/guardians to estimate children's cell phone exposure, use, and ownership. (The authors note that a validation study, comparing questionnaire response to telecommunications records, would have made the study stronger.) The questionnaire also asked about demographic information and ADHD risk factors. Blood lead concentrations were measured at baseline and two years later.

The researchers found a significant association between cell phone use (voice), high blood lead concentrations levels (≥ 2.35 μg/dl), and ADHD symptoms. In contrast, voice cell phone use did not increase ADHD symptoms in children with blood lead concentrations below 2.35 μg/dl. Neither text messaging, cell phone ownership, nor age of ownership increased ADHD in either the high or low lead group. "The finding that voice call mobile phone use was associated with ADHD symptoms supports the hypothesis that RF exposure to children's heads from mobile phone use increases their vulnerability to lead exposure and ADHD ..." say the authors.

Although text messaging was not linked to ADHD, the researchers found that playing games or using the Internet on a mobile phone "was associated with ADHD symptoms in a dose-response manner regardless of blood lead level and was statistically significant in children with a low blood lead level." (A low blood lead concentration does not mean that lead body burden is low. The body stores

lead in tissue, particularly bone.) Instead of viewing game playing and Internet use as a cause of ADHD, the authors suggest that "such behavior might be as a consequence of ADHD, i.e., reverse causality. ..." As with text messaging, playing games on a cell phone does not directly expose a child's brain to radiofrequency EMF energy.

Interestingly, ADHD symptom prevalence after 2 years decreased by 2.0% in the group as a whole. Symptoms decreased the most in children who quit using cell phones for voice call (−7.1%) and game playing (−7.5%). The authors state clearly that this study does not prove that radiofrequency exposure from cell phones causes ADHD; they did not look at when ADHD symptoms first arose. It does suggest, however, that restricting phone cell use can reduce ADHD symptom prevalence.

Byun Y-H, Ha M, Kwon H-J , et al. Mobile phone use, blood lead levels, and attention deficit hyperactivity symptoms in children: a longitudinal study. *PLOS ONE*. March 2013:8(3);e59742–e59742. Available at http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0059742. Accessed June 23, 2014.

ADHD Symptoms and Nature

Spending time in natural settings reduces ADHD symptoms (e.g., hyperactivity, poor concentration) and improves resilience and the ability to cope with stressful situations, according to multiple studies. A 2014 observational study, conducted by Louise Chawla and colleagues, found that interaction with nature was restorative for students of all ages, producing feelings of calm, reducing stress, and improving their ability to concentrate in class. The study took place at six different settings in Maryland and Colorado.

Early elementary students (aged 6–10) with dyslexia and other learning problems preferred to spend their recess time in a wooded area on their private school's property instead of playing on the playground. Children reported that the woods gave them a place to relax and freedom to be themselves without worrying about trying to meet expectations. Public school students in grades 4 through 6 who had access to an outdoor classroom with trees and a pond, meadow, and butterfly garden also reported feelings of peace and calm that contrasted with stresses inside the building. "Inside the building, students often engaged in arguments and rude, aggressive exchanges; but during more than 700 h of observations in the habitat, not a single incidence of such behavior was seen," say the authors.

High school students taking part in gardening programs also reported feeling peaceful, relaxed, and even meditative during and after gardening. The students attributed their calm to "being outdoors in fresh air in nature; feeling connecting to a natural living system; caring for living things successfully; and having time for quiet self-reflection." The restorative effect of gardening gave them a break from school-related anxieties. Fifty of 51 students reported increased ability to focus and work more effectively in the classroom after gardening. This study's findings, say the authors, are "consistent with evidence that access to nature around the home and neighborhood decreases children's symptoms of ADHD and rates of depression and facilitates coping with stress."

Nature has so many qualities that can evoke feelings of calm: fresh air, sunshine, smells from flowers and earth, bird songs, and energy from Earth's surface. Perhaps, its greatest gift is the sense of connection, of belonging. Sophie Sliepen, PhD, a Dutch education consultant who helps schools set up outdoor classrooms, told *Ode* magazine, "'There is a continual unspoken rejection and attraction between people. ... Our assessments of one another are never neutral, which creates a constant vigilance and restlessness. But a tree doesn't care about appearances. Nature is authentic and never underhanded.'"

Chawla L, Keena K, Pevec I, Stanley E. Green schoolyards as havens from stress and resources for resilience in childhood and adolescence. *Health & Place*. 2014:28:1–13. Available at http://jemicyschool.org/assets/documents/random/schoolyard-haven.pdf. Accessed June 23, 2014.

Maas J. Take a hike! *Ode*. September 2011; 22–25.

Probiotics and Emotions

Probiotics lessen brain reactivity and regulate emotional behavior, according to recent studies. Rodent studies indicate that some probiotic strains can reduce anxiety, pain sensitivity, and stress response. Probiotics may do the same in humans, according to a 2013 study led by Kirsten Tillisch. The researchers randomly assigned healthy women into 3 groups. Twelve ate a fermented milk product (about 125 g/ 4.38 oz twice a day) containing *Bifidobacterium animalis* subsp *Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus,* and *Lactococcus lactis* subsp *Lactis* for 4 weeks. Eleven, acting as a control, consumed a nonfermented milk product. The third group (n = 13) received no intervention.

Researchers assessed resting-state and evoked brain responses at baseline and at study's end using functional magnetic resonance imaging. The researchers used a ➤

standardized emotional faces attention task that provokes a response in areas linked to preparation for anticipated threat. After 4 weeks of treatment, the probiotic group showed less reactivity in brain regions that control central processing of emotion and sensation than the other groups. Also, resting-state midbrain activity decreased in the probiotic group: "This suggests a shift away from an arousal-based resting-state network and toward a regulatory network."

A 2011 mouse study, led by Javier A. Bravo, indicates that the vagus nerve may be one means by which gut microbes affect the brain. The researchers found that "chronic treatment with *L. rhamnosus* ... reduced stress-induced corticosterone and anxiety- and depression-related behavior" in normal mice but not in mice whose vagus nerve was cut below the diaphragm.

These studies suggest that some probiotic strains and the molecules that they produce can regulate a person's response to stress and anxiety. Might this be the beginning of a new treatment for stress-related disorders?

Bravo JA, Forsythe P, Chew MV, et al. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *PNAS*. September 20, 2011;108(38):16050–16055. Available at www.pnas.org/content/108/38/16050.full.pdf+html. Accessed June 23, 2014.

Tillisch K, Labus J, Kilpatrick L, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*. 2013:144:1394–1401. Available at www.ncbi.nlm.nih.gov/pmc/articles/PMC3839572. Accessed July 24, 2014.

Vitamin E and Alzheimer's Disease

"Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)," a 2014 randomized trial, found that a synthetic form of vitamin E (DL-alpha-tocopheryl acetate) slowed functional decline in people with mild to moderate Alzheimer's disease (AD), who were also taking an acetyl-cholinesterase inhibitor. The double-blind study, led by Maurice W. Dysken, evaluated effectiveness and safety of alpha-tocopherol, memantine (Namenda), and a combination of the two. In earlier studies, alpha-tocopherol slowed clinical progression in people with moderately severe AD. Memantine, a NMDA antagonist, is also effective in treating moderately severe AD. However, it has shown little effect on people with moderate or mild AD.

For this trial, researchers recruited 613 patients with mild to moderate AD from 14 Veterans Affairs medical centers. They randomly assigned participants into four treatment groups: 2000 IU/d of alpha-tocopherol (n = 152), 20 mg/d of memantine (n = 155), the combination (n = 154), or a placebo (n = 152). Researchers used the Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory every 6 months for 4 years to assess patients' functional ability to perform daily activities and self-care, including bathing and dressing themselves.

Alpha-tocopherol alone was more effective than memantine or the combination treatment in slowing functional decline. Functional decline in the alpha-tocopherol group, as evidenced by ADCS-ADL scores, was delayed by 10.6 months in the first year, 8.7 months in the second, 9.3 months in the third, and 1.8 months in the fourth year. Compared with placebo, alpha-tocopherol reduced the annual rate of functional decline by 19% over the 4 years. Because alpha-tocopherol helped patients retain daily function for more months, the burden on their caregivers did not increase as quickly, reducing the need for nursing home care. Caregiving time, a secondary outcome of the trial, increased least in the alpha-tocopherol group. "Because vitamin E is inexpensive, it is likely these benefits are cost-effective as alpha tocopherol improves functional outcomes and decreases caregiver burden," say the authors.

In addition to function, the researchers considered vitamin E safety. Unlike authors of the 2005 meta-analysis that indicated that doses ≥400 IU/d increased all-cause mortality risk, these researchers found no evidence that alpha-tocopherol increases mortality in this population: "The annual mortality rate was 7.3% in the alpha tocopherol group vs. 9.4% for the placebo group. The observed hazard rate for mortality was reduced by 13% (95% CI, -33% to 13%) in the alpha tocopherol group compared with the placebo group. ..."

Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA Cooperative Randomized trial. *JAMA*. 2014;311(1):33–44. Available at https://hsl.lib.umn.edu/sites/default/files/EEW%2014%20Clinical%20Trial%20Example%20Article.pdf. Accessed July 30, 2014.

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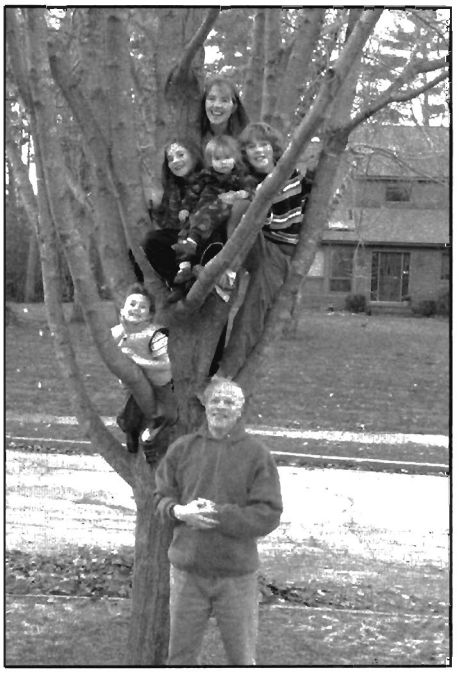

Literature Review & Commentary

by Alan R. Gaby, MD
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B Vitamins Prevent Brain Atrophy

In a previous randomized controlled study of elderly subjects with mild cognitive impairment, daily supplementation with B vitamins (0.8 mg of folic acid, 20 mg of vitamin B6, and 0.5 mg of vitamin B12) slowed shrinkage of brain volume over a period of 2 years, and there was an interaction between the effect of treatment and baseline homocysteine levels (*PLoS One*. 2010;5[9]:e12244). In follow-up research, the authors of the previous study demonstrated that B-vitamin treatment reduced, by as much as 7-fold, cerebral atrophy in the gray matter regions that are specifically vulnerable to the Alzheimer's disease process, including the medial temporal lobe. In the placebo group, higher homocysteine levels at baseline were associated with faster gray matter atrophy, but this effect was largely prevented by B-vitamin supplementation. The beneficial effect of B vitamins was confined to participants with high homocysteine levels (> 11 μmol/L).

Comment: Homocysteine is a toxic compound formed during the metabolism of the amino acid methionine. In observational studies, elevated homocysteine levels have been associated with an increased risk of age-related cognitive decline, atherosclerosis, stroke, thromboembolism, miscarriage, and osteoporosis. Supplementation with folic acid, vitamin B6, and vitamin B12 can lower plasma homocysteine levels by promoting homocysteine degradation or by enhancing its conversion back to methionine. Clinical trials have shown that reducing homocysteine levels with B-vitamin supplements can decrease the incidence of stroke, although the evidence regarding the prevention of other types of cardiovascular disease is conflicting. Most, but not all, clinical trials published to date suggest that supplementation of elderly people with B vitamins can slow the rate of age-related cognitive decline. The present study suggests that B vitamins might also help prevent Alzheimer's disease. There is circumstantial evidence that supplementing with magnesium can increase both the safety and efficacy of B-vitamin therapy.

Douaud G et al. Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci*. 2013;110:9523–9528.

Fish Oil for Age-Related Memory Loss

Thirty-six elderly individuals (mean age, 65 years) of low socioeconomic status and with mild cognitive impairment were randomly assigned to receive, in double-blind fashion, 3 g per day of fish oil (providing daily 450 mg of eicosapentaenoic acid [EPA] and 1290 mg of docosahexaenoic acid [DHA]) or placebo (corn oil) for 12 months. Compared with placebo, significant improvements were seen in the fish oil group on tests of short-term and working memory ($p < 0.0001$), immediate verbal memory ($p < 0.05$), and delayed recall capability ($p < 0.05$). Fish oil was well tolerated.

Comment: DHA is known to play a key role in the development of the fetal and infant brain, but there is only a small amount of research on the effect of this compound on age-related cognitive decline. The fish oil used in the present study contained 43% DHA, whereas most fish oil products on the market contain approximately 12% DHA. It is not known whether the beneficial effect of fish oil observed in this study was due to entirely or primarily to DHA. If it was, then one would have to take about 10 g per day of a typical fish oil product to achieve the results reported in this study. DHA from algal sources

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is also commercially available. In previous research, supplementation with algal DHA at a dose of 900 mg per day improved learning and memory function in adults with age-related cognitive decline. However, algal DHA at a dose of 2 g per day did not slow disease progression in patients with mild to moderate Alzheimer's disease.

Lee LK et al. Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial. *Psychopharmacology*. 2013;225:605–612.

Vitamin E Slows Decline in Alzheimer's Patients

Six hundred-thirteen patients from Veterans Affairs medical centers with mild to moderate Alzheimer's disease were randomly assigned to receive, in double-blind fashion, 2000 IU per day of vitamin E (alpha-tocopherol), 20 mg per day of memantine (an acetylcholinesterase inhibitor), both treatments, or placebo. During a mean follow-up period of 2.27 years, the mean Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory score declined by 3.15 units less in the vitamin E group than in the placebo group ($p = 0.03$). This effect translates to a delay in clinical progression of 19% per year compared with placebo, or a delay of approximately 6.2 months over the follow-up period. In the memantine group, the scores declined nonsignificantly less than in the placebo group ($p = 0.4$).

Comment: There is evidence that oxidative stress contributes to the pathogenesis of Alzheimer's disease. Antioxidants such as vitamin E might therefore be protective. In a previous study, 2000 IU per day of alpha-tocopherol slowed disease progression in patients with moderately severe Alzheimer's disease. The results of the present study demonstrate that alpha-tocopherol is also beneficial for patients with mild-to-moderate disease.

Supplementation with high doses of alpha-tocopherol can deplete gamma-tocopherol. Since alpha- and gamma-tocopherol may each independently protect against Alzheimer's disease (as suggested by observational data), mixed tocopherols (which contain both alpha- and gamma-tocopherol) may be more effective than alpha-tocopherol by itself for preventing and treating Alzheimer's disease. Additional research is needed to confirm that possibility and to determine whether vitamin E in doses less than 2000 IU per day is beneficial.

Dysken MW et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. *JAMA*. 2014;311:33–44.

Vitamin-and-Mineral Supplement for Adult ADHD

Eight adults (mean age, 35 years) with attention-deficit/hyperactivity disorder were randomly assigned to receive, in double-blind fashion, a high-potency vitamin-and-mineral preparation (EMPowerplus) or placebo for 8 weeks. The dosage was increased progressively over a 1-week period to 5 capsules 3 times per day. The proportion of patients who showed at least a 30% improvement on at least 1 subscale of the Conners Adult ADHD Rating Scale (64.3% vs. 36.8%; $p < 0.02$), and the proportion of patients who were much or very much improved on the Clinical Global Impression Improvement Scale (47.6% vs. 21.1%; $p < 0.02$) was significantly higher in the active-treatment group than in the placebo group. Adverse events did not differ between groups.

Comment: EMPowerplus is a proprietary micronutrient product based on the Hardy-Stephan micronutrient regimen, originally used by farmers to decrease aggressive behavior in pigs. It contains vitamins, minerals, several amino acids and herbs, and other natural substances. In previous research, this product has been used successfully to treat bipolar disorder. The results of the present study indicate that it is also an effective treatment for adult ADHD.

Rucklidge JJ et al. Vitamin-mineral treatment of attention-deficit hyperactivity disorder in adults: double-blind randomised placebo-controlled trial. *Br J Psychiatry*. 2014;204:306–315.

Creatine Increases Efficacy of Antidepressant Medication

Fifty-two women (mean age, 47 years) with major depressive disorder were treated with escitalopram (a selective serotonin-reuptake inhibitor) and were randomly assigned to receive, in double-blind fashion, 5 g per day of creatine or placebo for 8 weeks. The percentage improvement of the mean score on the Hamilton Depression Rating Scale (HAM-D) relative to baseline was significantly greater in the creatine group than in the placebo group after 2 weeks (44.9% vs. 24.1%; $p < 0.001$), 4 weeks (64.6% vs. 42.8%; $p < 0.001$), and 8 weeks (79.7% vs. 62.5%; $p < 0.001$). The frequency of adverse events was lower in the creatine group than in the placebo group.

Comment: Individuals with major depressive disorder appear to have abnormal brain bioenergetics. Oral administration of creatine has been shown to increase the cerebral reservoir of phosphocreatine, which can be used to produce adenosine triphosphate and potentially ameliorate the abnormal brain bioenergetics seen in depression. Creatine supplementation was beneficial in a rodent model of depression in females, but not in males. The results of the present study suggest that creatine is also beneficial as adjunctive treatment of depression in middle-aged women.

Lyoo IK et al. A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. *Am J Psychiatry*. 2012;169:937–945.

Vitamin C Increases Efficacy of Antidepressant Medication

Twenty-four children (mean age, 10 years) with major depressive disorder were treated with 10 to 20 mg per day of fluoxetine (depending on their age) and were randomly assigned to receive, in double-blind fashion, 500 mg of vitamin C twice a day or placebo for 6 months. Both groups demonstrated significant improvement in depression. The improvement was significantly greater in the vitamin C

group than in the placebo group according to the Children's Depression Rating Scale ($p < 0.0001$) and the Children's Depression Inventory ($p < 0.0001$), but not according to the Clinical Global Impression ($p = 0.9$). At 6 months, the mean score on the Children's Depression Rating Scale was 48% lower (better), and on the Children's Depression Inventory was 42% lower, in the vitamin C group than in the placebo group.

Comment: Vitamin C plays a role in the synthesis of serotonin and norepinephrine, and may also function as a mild monoamine oxidase inhibitor. Each of these actions might be expected to have a positive effect depression. The results of the present study suggest that vitamin C supplementation, when used as an adjunct to a selective serotonin-reuptake inhibitor, is beneficial for children with major depressive disorder. Depression is one of the manifestations of vitamin C deficiency, and vitamin C may have worked in part by compensating for suboptimal dietary vitamin C intake. It is also possible that vitamin C exerted a pharmacologic effect.

Amr M et al. Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *Nutr J.* 2013;12:31.

Xylitol Chewing Gum Prevents Dental Caries

Two hundred four children (aged 7–9 years) with a high caries risk (2–3 dental caries and a high salivary concentration of *Streptococcus mutans*) were randomly assigned to chew nonsucrose gum that did or did not (control) contain 36.6% xylitol. The gums were chewed for 5 minutes, 5 times per day, after main meals and snacks, for 6 months (total xylitol dose, 11.6 g/day). One hundred fifty-seven children who completed the trial were examined 2 years after the end of the trial for the development of carious lesions in the permanent first molars. At the end of the treatment period, xylitol significantly decreased salivary concentration of *S. mutans*. During the follow-up period, the proportion of first molars that developed new carious lesions was significantly lower in the xylitol group than in the control group (0.6% vs. 3.6%).

Comment: Xylitol is a sugar alcohol that promotes the growth of a strain of *S. mutans* that may be less cariogenic than other strains, because it adheres less well to tooth surfaces and produces less acid. The results of the present study confirm previous research demonstrating that regular use of xylitol chewing gum reduces the incidence of dental caries. Moreover, the beneficial effect of xylitol appears to persist long after the treatment is discontinued. Xylitol is more effective if started at least 1 year before permanent teeth erupt than if started later.

Campus G et al. Six months of high-dose xylitol in high-risk caries subjects - a 2-year randomised, clinical trial. *Clin Oral Investig.* 2013;17:785–791.

Gaby's Literature Review

Over-the-Counter 'Thyroid Support' Supplements Contain Thyroid Hormone

Ten supplements available at retail stores or via the Internet that were marketed for "thyroid support" were analyzed. Nine of the 10 supplements had detectable amounts of triiodothyronine (1.3 to 25.4 mcg per tablet), and 5 of 10 contained thyroxine (5.8 to 22.9 mcg per tablet). Taken at the recommended dose, 5 supplements provided more than 10 mcg per day of triiodothyronine and 4 provided thyroxine in amounts ranging from 8.6 to 91.6 mcg per day.

Comment: Thyroid hormones, when taken inappropriately or in excessive amounts, can cause adverse effects including osteoporosis, atrial fibrillation, angina, and even myocardial infarction. That is why thyroid hormones are supposed to be available by prescription only. Although the amounts of thyroid hormones in these over-the-counter products are relatively small, they are enough to cause adverse effects in susceptible individuals, such as the elderly, people with adrenal insufficiency, and people taking prescription thyroid hormone products.

Open-minded physicians are aware that many patients have clinical hypothyroidism and respond to treatment with thyroid hormone, even though their laboratory tests for thyroid function are normal. Undoubtedly, many people with undiagnosed "sublaboratory" hypothyroidism experience symptomatic improvement from over-the-counter thyroid products. However, these people would be better served by having a practitioner who can recognize subtle hypothyroidism, and switch them to a more standardized prescription product.

Practitioners interested in the evaluation and management of "sublaboratory" hypothyroidism are referred to my earlier writings, cited below.

Gaby AR. "Sub-laboratory" hypothyroidism and the empirical use of Armour thyroid. *Altern Med Rev.* 2004;9:157–179.

———. Hypothyroidism. Chapter 8 in: *Nutritional Medicine*. Concord, NH; 2011. www.doctorgaby.com.

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Drug Quality and Security Act: How It's Changing the Practice of Pharmacy and Medicine

by Ronald M. McGuff

Physicians, pharmacists, patients, state regulators, and many others are unsure how the federal Drug Quality and Security Act (DQSA) will change the practice of pharmacy and medicine. We are a compounding pharmacy, and we receive numerous questions about DQSA from our physicians and patients.

The purpose for this article is to provide a more open setting to share what we believe are practical answers to the questions that our physicians have asked about this new regulatory era.

We are not attorneys, but we have studied this topic as a compounding pharmacy and as a FDA-approved manufacturer with a separate regulatory affairs department. With all of this, we can only render our opinion of what the federal DQSA means.

Our attempt to inform you will conform to the aspirations of one of our favorite quotable persons – Albert Einstein: "Make everything as simple as possible, but not simpler."

Our attempt here, therefore, is to reveal only the parts of the law that are relevant to answer the questions posed. In our attempt for simplicity, we purposely do not include parts of the law that do not directly relate to the questions being asked.

Several sections of the DQSA relate to compounding, but two have great importance: 503A and 503B.

So What Does 503A Do?

503A permits a pharmacy to compound drugs if the pharmacy follows certain statutory requirements.[1]

The most important requirement that affects physicians, pharmacies, and patients is found in the very first paragraph of 503A: "Sections 351(a)(2)(B), 352(f)(1) and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient ..."[2]

This means that a pharmacy is exempt from compliance to a number of Federal Food, Drug and Cosmetic Act (FFDCA) requirements such as Current Good Manufacturing Practices (cGMP), adequate directions for use, and new drug applications if (and only if) " ... the drug product is compounded for an identified individual patient and the practitioner adds this statement on the prescription 'a compounded product is necessary for the identified patient.'"[3–5]

It is important to remember that if a pharmacy operates outside the 503A requirements, not only will it will be required to comply with all of the requirements of the FFDCA noted above, but it also may be subject to the possible issuance of an FDA Warning Letter stating that the drug products compounded at that facility are adulterated and/or "new drugs" or may be subject to enforcement actions such as an injunction or product seizure. This is something that could cause a ruinous outcome for the pharmacy and distressing impact for its physician and patient customers.

503A also designates other requirements of pharmacy and FDA.

Bulk drug substances used by pharmacy must:

- meet standards of an applicable United States Pharmacopoeia (USP) or
- National Formulary (NF) monograph or
- be a component of an approved drug or
- appear on a list developed by the Secretary (FDA approved list)

Ingredients used in compounding (other than bulk drug substances) must:

- meet standards of an applicable USP/ NF monograph, if one exists
- be on a FDA list of bulk drug substances not included in the USP/NF monographs

There are two FDA "do not compound" lists that restrict compounding pharmacies from compounding certain identified drug products:

- The FDA must create a list that identifies drug products that are deemed unsafe or not effective;
- The FDA must create a list of drug products that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of the drug product.

Prohibition on compounding essential copies of commercial drugs:

- A pharmacy may not compound drug products that are essentially copies of a commercially available drug product.

Memorandum of Understanding (MOU):

- limits interstate *distribution* of compounded drugs to 5% of a pharmacy's total prescription orders dispensed or distributed.

What Does Drug Quality and Security Act, Section 503B Outsourcing Facilities, Mean to Me?

This section of the law creates a new entity known as an "Outsourcing Facility" that can produce drug products. The first paragraph of section 503B states: "(a) In General – Sections 502(f)(1), 505, and 582 shall not apply to a drug compounded by or under the direct supervision of a licensed pharmacist in a facility that elects to register as an Outsourcing Facility if each of the following conditions is met. ... "[6]

The term *Outsourcing Facility* means a facility at one geographic location or address that:

- is engaged in the compounding of sterile drugs;
- has elected to register as an Outsourcing Facility; and
- "An Outsourcing Facility may or may not obtain prescriptions for identified individual patients."[7]

Outsourcing Facilities may provide drug products by dispensing (via receipt of a prescription) or distribution (other than by prescription). Customers may be physicians, clinics, hospitals, and so on, but the drug products cannot be resold, which means that the Outsourcing Facility will not be able to sell drug products to wholesalers.

An Outsourcing Facility is not required to be a licensed pharmacy; a 503B entity only requires supervision of a licensed pharmacist.

An Outsourcing Facility may not compound a drug substance unless:

- the bulk drug substance appears on a list established by the FDA identifying bulk drug substances for which there is a clinical need. (Note: at the time of this writing the definition of clinical need has not yet been codified or defined.);
- "the drug compounded from such bulk drug substance appears on the FDA (commercial) drug shortage list ... at the time of compounding, distribution or dispensing."[8]

This is very important to understand. Until FDA creates a list of approved bulk drug substances for which it has declared that there is a clinical need, Outsourcing Facilities may only compound drug products that appear on the FDA's commercial drug shortage list.

Outsourcing Facilities are further restricted to the same FDA lists that limit 503A pharmacies, such as:

- drugs withdrawn or removed because unsafe or not effective
- drugs presenting demonstrable difficulties for compounding

When Did DQSA Go into Effect?

The DQSA was signed by President Barack Obama on November 27, 2013.

Office Use for Compounded Drugs: Is It Gone Forever?

Maybe not ... but for now, it's gone.

"Office use" is the practice of a physician's ordering compounded drugs to be distributed to the physician's office in order for the physician to dispense the drug to a patient. Prior to the enforcement of 503A, each state determined if "office use" was appropriate. Currently, if a pharmacy compounds as a 503A pharmacy, it must do so based on the receipt of a valid prescription.[9] In general, current state laws require drugs ordered by prescription to be *dispensed* to the individual patient by a pharmacist.

Yet, there is still confusion surrounding the application of the Section 503A MOU with regard to allowance for "office use" *distribution* of drug products. Some may argue that the MOU allows 5% of the valid prescriptions *dispensed* and *distributed* to be *distributed* interstate. Clearly federal law indicates a pharmacy may *distribute* 5% of drug products to "office use" states. But we have to remember that federal 503A requires a valid prescription in order for a pharmacy to compound drugs and generally, by state law, a prescription received by a pharmacist must be dispensed to the patient. Here, federal intent is negated by current state law.

However, if the pharmacy is registered as a 503B Outsourcing Facility, it could theoretically deliver compounded drugs for office use because a prescription is not required under federal law. However, because Outsourcing Facilities are currently limited to producing commercial drugs on the FDA's commercial drug shortage list, they are of little help to physicians who need compounded drugs for their patients.

To add further uncertainty, we do not know how the FDA will apply "clinical need," a requirement for a drug to be included on the approved bulk drug substance list.

So, for now, "office use" is gone unless you are working with a 503B registered Outsourcing Facility that meets cGMP requirements and the drug that you need is on the FDA commercial drug shortage list, and you are licensed in a state that recognizes Outsourcing Facilities and a state that allows for "office use." Congress is already concerned that the FDA is not following congressional intent, especially regarding the office use issue.[10,11]

Please remember, commercially available drugs that are approved by the FDA and are manufactured continue to be available from a drug wholesaler and may be ordered for office use in those states that allow for office use.

503a Requires a Compounding Pharmacy to Receive a Valid Prescription. What Is a Valid Prescription?

The federal definition of a valid prescription is only found under controlled substance regulations: "A prescription is an order for medication which is dispensed to or for an ultimate user. ... To be valid, a prescription for a controlled substance must be issued for a legitimate medical purpose by a registered practitioner acting in the usual course of sound professional practice."[12] ➤

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Please be aware that the authors of 503A intentionally use the words "valid prescription order." We believe that the authors' intent is to make sure that prescriptions do not become pseudoprescriptions for office use.

The authors added teeth to the DQSA to assure that physicians write "valid" prescriptions for an individual patient and prohibit a prescriber from writing a false prescription.

Be aware! DQSA (federal law) now contains potential penalties for any prescriber that issues an intentionally false prescription.

> SEC. 103. PENALTIES.
> (a) PROHIBITED Acts. – Section 301 (21 U.S.C. 331) is amended by adding at the end the following: ...(2) With respect to a drug to be compounded pursuant to section 503A or 503B, the intentional falsification of a prescription, as applicable.[13]

There is a difference between a physician's communicating information that meets the valid prescription requirements and prescription information needed by a pharmacist to dispense a prescription under state law.

Generally, based on state law, the pharmacist must have all of the following elements in order to dispense a prescription:

- Date of prescription issue
- Practitioner's name, address, and license number
- Patient's name and address
- Date of birth
- Patient gender
- Allergies
- Current and relevant prior medications (e.g., prescription medications, OTCs, and herbal medications)
- Drug name
- Drug strength
- Dosage form
- Quantity prescribed
- Directions for use (Including route of administration if patient self-administers)
- Number of refills (if any) authorized
- The statement "This compounded product is necessary for the identified patient."

A pharmacist is required to have all of the prescription elements to dispense the prescription. Prescription elements not provided by the physician must be obtained from the patient or by contacting the physician, producing additional work which may possibly delay shipment of the prescription.

May I Write a Prescription for a Compounded Drug to Deliver to My Office vs. My Patient?

This depends on the state in which you are located. Some states allow a pharmacist to deliver a prescription to a physician's office and some do not. For the correct answer, you will need to call your state board of pharmacy.

I Typically Use One Vial of Medication in the Office for Multiple Patients. How Do I Write a Valid Prescription for This?

In general, state law requires the dispensing or administration of the prescribed compounded drug product to the patient identified on the prescription. The practice of sharing "office use" compounded drug products on multiple patients is no longer legal. For example, if a 10 mL vial of compounded drug is received on a prescription and only ½ of the contents is dispensed/administered to the patient over the course of treatment, the remaining contents must be discarded and may not be used for any other patient.

Please remember, commercially available drugs (those approved by the FDA) are available from drug wholesalers and may be ordered for office use in those states that allow for office use.

Can I Still Use a Multidose Vial for Multiple Patients?

No. A multidose vial may be administered only to the patient identified in the valid prescription.

How Does This Affect My Practice and Patients Economically?

There is no other way to say it but that the effect of 503A will increase the cost to you and your patients unless you have been writing prescriptions all along. The additional time required of the physician and staff to manage compounded drug prescriptions and compounded drug products within the office will increase. Additionally, it takes longer and costs more for the compounding pharmacy to process multiple patient prescriptions instead of one "office use" order.

Will I Be Able to Continue to Get All My Compounded Drugs?

Most, but not all. A pharmacy operating under 503A may compound bulk drug substances that:

- meet standards of an applicable USP or NF monograph or
- be a component of an approved drug or
- appear on a list developed by the secretary (FDA)

Many compounded drug products fall within the first three categories. What will appear on the secretary's (FDA) approved list is unknown at this time.

What's This About an Approved List of Pharmacies?

It is commonly misunderstood that because a pharmacy has voluntarily registered with the FDA as a 503B facility, it means that its facility or the drug products produced at the facility have been compounded in compliance with cGMP or have been inspected by the FDA. The FDA intends to inspect 503B Outsourcing Facilities utilizing a risk-based policy. A registered facility that has been inspected may have received a 483 inspection report identifying areas on noncompliance and may have received a Warning Letter. You may follow the current status of Outsourcing Facilities on the FDA's Outsourcing Facility website.[14]

Why Can't I Order My Compounded Drugs from an Outsourcing Facility Today?

Currently, an Outsourcing Facility may only produce commercial (FDA-approved) drugs that appear on the FDA's drug shortage list. Many of these drugs are of limited interest to physicians who normally prescribe individualized compounded drugs for their patients.

How Will the FDA-Approved Bulk Drug Substance List Affect My Practice?

When the FDA does publish the approved bulk drug substance list, the public will understand the intent of the FDA. If the 503A and 503B "approved" list includes most of the compounded drug products (2400 drug products have been submitted by International Academy of Compounding Pharmacists) submitted to Docket FDA-2013N-1524 for review, many of the compounded products that you currently prescribe will likely become available.[15,16]

How Will the FDA 'Do Not Compound' Lists Affect My Practice?

503A compounding pharmacy and 503B Outsourcing Facilities performance is also restricted by the FDA "do not compound" lists such as:

- drugs withdrawn or removed because unsafe or not effective
- drugs presenting demonstrable difficulties for compounding

On July 1, 2014, the FDA made 25 additions and 1 modification to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.[17] A list of compounded drugs presenting demonstrable difficulties for compounding pharmacy has not yet been created by the FDA.

With All the FDA Warning Letters to Compounding Pharmacies, Which Pharmacy Can I Trust?

Most 503A compounding pharmacies are not inspected by the FDA.

The best compounding pharmacies seek out independent third-party inspections and certification to demonstrate that the pharmacy is in conformance to state, national, and international law and regulatory requirements. This is expensive and time consuming for the pharmacy but yields dividends to physicians and patients, as they can rely on the due diligence of independent inspections and certifications. Independent third-party accreditation and certification authorities are:

- Pharmacy Compounding Accreditation Board (PCAB)[18]
- National Association of Boards of Pharmacy, Verified Pharmacy Program (VPP)[19]
- International Standards Organization, ISO9001, 2008[20]

Why Do I Have to Write a Prescription for Compounded Drugs but Not for Commercial Drugs?

We believe that regulatory thinking behind the prescription requirement is to restrict order volume by creating a complex order processing structure to eliminate the "mass ordering" business model used by the New England Compounding Center. However, we believe that there are other methodologies available to identify and evaluate mass ordering that are less expensive and less invasive. ➤

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What is it about a prescription that protects a patient to a greater degree than an office use order? The answer may be, not much, and therefore calls into question the continued insistence for a prescription requirement. The FDA indicates that off-label use of commercial drugs is appropriate under the following conditions:

> Good medical practice and the best interests of the patient require that physicians use legally available [NDA and ANDA approved commercial] drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling [i.e. known as Off-Label prescribing and use], they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.[21]

Generally, compounded drugs are not FDA approved. The FDA does not verify the safety or effectiveness of compounded drugs, nor does it verify the safety or effectiveness of commercial drugs used for off-label indications.[22] Further, compounded drugs are made from active pharmaceutical ingredients and ingredients found in commercially available drugs and/or USP monographs that reduce patient risk. This increases the similarity of approved drugs used for off-label indications and compounded drugs.

If a physician fulfills the responsibility to be well informed about the drug product, to base the drug products use on firm scientific rationale and on sound medical evidence, why should the two drug products, one commercial and one compounded, differ in the method used to order and deliver the product?

Moving Forward ... and What You Can Do.

Unintended consequences; unknown FDA intent; conflict between federal and state law: all combine to create an unstable business/healthcare environment with unnecessary added costs and time wasted by stakeholders.

Unfortunately, our federal lawmakers chose to revive 1997 expertise to meet 2014 needs. 503A has proved to be flawed and is not appropriate for today's health-care environment. 503A smothers the physician's ability to administer the most effective drugs to his or her patient. Reviving 503A has done little to address the root cause of sterility and quality control failures raised by the New England Compounding Center meningitis outbreak of 2012.

An area that may limit the number of compounded drugs available to physicians is the possibility for the FDA to limit bulk drug substances on the "approved list." An important method to increase the number of compounded drugs available to physicians is to increase the number of USP monographs.

The US Pharmacopeial Convention (USP) is a scientific nonprofit organization that sets standards for the identity, strength, quality, and purity of medicines distributed and consumed worldwide.[23] The USP also has monographs that apply to compounding, including compounded preparation monographs that include directions for compounding the preparation, its packaging and storage requirements, and beyond-use dates.[24]

Simply stated, the more monographs the USP produces, the more compounded drug products will be available. The USP is independent of the FDA, and pharmacists may compound drugs using bulk drug substances that have an appropriate USP monograph. Physicians, patients, pharmacists, and other stakeholders are valued partners to the USP and have previously collaborated to create public standards such as USP monographs.[25]

As physicians, pharmacists, and patients, we have a vested interest in the USP's ability to update and develop compounding and other monographs because those monographs are a vital part of our ability to access quality medications. The USP needs us, and by helping the USP we help ourselves. Information, expertise, and insights that you already have can support these efforts:

- Share your lists of the most frequently dispensed compounded preparations and the formulas for the USP to jumpstart the processes of developing new monographs (go to http://www.usp.org/usp-nf/development-process/submit-new-monographs).
- Donate your time and expertise as a volunteer on one of the USP's expert committees or panels to lend your knowledge and experience to the process of updating and developing new monographs (see https://callforcandidates.usp.org).
- Find out about USP's development activities and philanthropic opportunities by e-mailing development@usp.org.

Also, join Alliance for Natural Health (ANH-USA), a grassroots consumer advocacy organization. ANH-USA carefully tracks proposed legislation and regulations, then informs physicians and consumers and offers a means to take action.[26]

Make your federal legislators aware of your thoughts about DQSA and how it affects your business, your patients, and health care. Suggest changes such as allowing for office use orders. They do listen. To find your representative, go to http://www.contactingthecongress.org.

Ronald M. McGuff is the owner of McGuff Company Inc., a national and international medical products wholesale company. "McGuff" consists of four companies: McGuff Compounding Pharmacy Services Inc. (sterile and nonsterile compounded drugs); McGuff Pharmaceuticals Inc., a FDA-registered drug manufacturer (aseptically filled drugs); McGuff Medical Canada Inc. (Canada drug distribution); and McGuff Company Inc. (wholesale medical products). As president and CEO, Mr. McGuff chairs the management team that crafts policy and determines company resources and direction for all major programs. Mr. McGuff is a member of the International Society of Pharmaceutical Engineers and of Orange County Regulatory Affairs Discussion Group, and associate clinical professor, Clinical Pharmacy Department, University of California, San Francisco, School of Pharmacy. He has been an invited lecturer to speak on such topics as "IV Solutions and Additives Utilized in Therapeutic Solutions," "Therapeutic IV Solutions," and "Safe and Effective Administration of Chelating Agents," and is a consultant for Guidepoint Global. Mr. McGuff has been actively supporting complementary and alternative medicine (CAM) physicians for over 35 years and continues to support clinical trials that may lead to new treatment options for CAM physicians.

We are all on this adventure together, whether you are a physician, pharmacist, patient, or entrepreneur. We all want to build value and contribute to better health care. Our best chance to create a sustainable, value-added, physician, pharmacist, patient compounding solution is to take action and press for appropriate change.

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The Nonscience Witch Hunt Against Hormone Replacement Therapies for Deficiency Syndromes Must End

An A4M Position Paper on Physician-Prescribed HRT

Introduction

> Unless we put medical freedom into the Constitution, the time will come when medicine will organize into an undercover dictatorship to restrict the art of healing to one class of Men and deny equal privileges to others; the Constitution of the Republic should make a Special privilege for medical freedoms as well as religious freedom.
>
> Benjamin Rush (1745–1813), physician, writer, educator, humanitarian, and Founding Father of the US

Since the inception of the anti-aging medical movement in 1991, various establishment parties have ruthlessly leveraged their positions of power in academic, political, and regulatory arenas for the purpose of attempting to limit the use of hormone replacement therapies (HRT) in adults with documented clinical deficiencies. For over 15 years, a prolonged and calculated campaign of deceit, fraud, and suppression has threatened physician licensures and liberties to treat and prescribe life-improving therapies, leading potentially to the direct compromise of patients' health and longevity. Dozens of physicians have been sanctioned and punished with loss of license and academic standing. This pernicious abuse of position and power is particularly prevalent with regard to recent challenges made against human growth hormone (HGH), testosterone (TRT), and DHEA replacement therapies that are trumpeted by the mainstream media. Biased reporters frequently – and inappropriately – demonize legitimate physicians and clinical compounding pharmacies that are reluctantly positioned on the frontline of a decades-old agenda to limit freedom of choice and information, and the physicians' most essential responsibility to select the best course of therapy and medication for their patients.

This conflict is being played out of late in the arena of anti-aging medicine, a clinical specialty that has flourished in its 22

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year long history, garnering the support of more than 100,000 physicians and scientists worldwide who practice or research life-enhancing, life-extending interventions today. Prof. Dr. Imre Zs.-Nagy, of the University of Debrecen Medical and Health Science Center (Hungary), and founder of the Archives of Gerontology and Geriatrics (published by Elsevier), observes: "In my role as a basic and clinical scientist, I have had an opportunity to witness more than four decades of advances and declines in the arena of preventive medical care ... there has been little else as dramatic, important, beneficial, and significant as the anti-aging medical movement."[1]

Continual vigilance is necessary to countermand those whose financial and professional successes depend on repeated, calculated attempts to discredit the science and substance of anti-aging medicine.

Remarks Tanjung Subrata, MD, of Udayana University School of Medicine (Indonesia):

> Anyone who does not believe in evil is not paying attention to the recent affairs of the past twenty years. We are living in a time of unprecedented tribulation and changes at-large – and in health care, in particular. All that is necessary for evil to prevail is for men of good will to do nothing. In this modern age of zero tolerance for alternatives to establishment medicine, and the willingness of our governmental officials to resort to police state tactics to suppress innovative schools of thought, progress in medicine halts and dies.[2]

A4M Position

The American Academy of Anti-Aging Medicine (A4M), its numerous worldwide affiliated scientific and medical societies, and befriended organizations support the judicious application of modern and advanced medical technologies to address the changes in chemical, hormonal, physical, and nutritional needs that occur with aging. Such repletion includes the restoration of hormones to an optimal physiological state when deficiency is determined by objective assessment.

Hormone replacement therapy (HRT) is an essential and extensively documented protocol for clinical intervention in the disorders of aging. HRT maintains an unblemished safety and efficacy profile that has been documented by 20 years of clinical application. Yet, a perfect storm of misguided media, combined with biased parties whose livelihoods hinge on disparaging the anti-aging medical movement, has grossly compromised access to HRT, placing the lives of hundreds of thousands of patients worldwide in potential jeopardy.

Experienced anti-aging physicians have been prescribing HRT for more than 20 years. PubMed contains more than 20,000 peer-reviewed studies of HRT, of which a preponderance document the life-enhancing and/or life extending benefits of HRT in aging adults. See Appendix A "Literature Review," which presents a selection of such studies that represent the objective evidence that supports the A4M position.

The Anti-Aging Medical Movement

The goal of anti-aging medicine is not to merely prolong the total years of an individual's life, but to ensure that those years are enjoyed in a productive and vital fashion. As established in 1991 by the physicians of the American Academy of Anti-Aging Medicine (A4M), the field of anti-aging medicine developed as a direct extension to the science of elite sports medicine of the 1980s. Just as sports medicine aims to keep the athlete's body functioning at its optimum level, anti-aging medicine seeks to keep the human physiology performing at its peak. In other words, the similar principle, of extending and maximizing the healthy human lifespan, is at the core of both anti-aging medicine and sports medicine.

The Official Definition of *Anti-Aging Medicine*

The clinical specialty of anti-aging medicine thus is defined as follows:

> Anti-aging medicine is a clinical specialty is founded on the application of advanced scientific and medical technologies for the early detection, prevention, treatment, and reversal of age-related dysfunction, disorders, and diseases. It is a health-care model promoting innovative science and research to prolong the healthy lifespan in humans. As such, anti-aging medicine is based on principles of sound and responsible medical care that are consistent with those applied in other preventive health specialties. The phrase "anti-aging," as such, relates to the application of advanced biomedical technologies focused on the early detection, prevention, and treatment of aging- related disease.

Anti-aging medicine utilizes diagnostic protocols that are supported by scientific evidence to arrive at an objective assessment upon which effective treatment is assigned. Physicians who dispense anti-aging medical care are concerned with the restoration of optimal functioning of the human body's systems, organs, tissues, and cells. Attempting to rebrand what they cannot deny, those in positions of power in academic, political, and regulatory arenas are inventing new catchphrases including *longevity medicine*, *successful aging*, *healthy aging*, and the like, in an effort to dilute and absorb the A4M's original definition of anti-aging medicine. To implement this campaign, we suspect that these individuals have pejoratively solicited major media outlets to denigrate the A4M, its officers, and its members.

Anti-aging medicine is, in essence, a euphemism for early detection and advanced preventative medicine. It is a health-care model that emphasizes personalized, patient-focused, high-quality metabolic-specific medical care.

Critics with A Dark Agenda (Political Elites)

Scientifically based and well documented in leading medical journals, anti-aging medicine is among the fastest-growing medical specialties throughout the world. As an innovative model for advanced preventive health care that cannot be denied, anti-aging medicine has been disparaged by individuals with their own political and financial agendas in attempts to restore monopolistic control over the field of aging intervention. Critics of the science of anti-aging medicine most commonly hail from academia: as such, these naysayers many times have little or no medical training in aging intervention and may be nonclinicians.

Perhaps the most inconceivable reality is that at the very highest levels of academia, government, and science, truth and

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objective scientific method are not at all sacred to the political elites. We in clinical medicine via our training, discipline, and conditioning naively believe and act in the public interest, for the good of our patients' health, and by professional standards of medical ethics. The (elite) medical establishment operates contrary to this position, reports investigative reporter Tim Bolen (www.bolenreport.com), who for 30 years has amassed data and evidence exposing a calculated effort to deride innovative medical therapeutics. Bolen observes:

> Without a doubt, a stealthy control group – a cabal, if you will, in status-quo medicine exists. Approved by Big Pharma, parts of academia, and segments of the government, this group exerts its control in many different ways. I have uncovered information showing anonymous, and not-so-anonymous, funding of groups, loosely describing themselves as "Quackbusters or Skeptics" whose only purpose is to attack cutting-edge health care offerings. Those groups, in turn, train, and fund sub-groups. Data suggests that the "Quackbusters or Skeptics" donated over $1 Million US to Wikipedia to purchase control over pages with medical content. More, the Skeptic training camps teach their recruits how to operate together to control that same Wikipedia and Search Engines. Further, these covert groups drive media on issues particularly pertaining to alternative health care, in an effort to limit coverage of innovative discoveries and to vilify therapies that are not part of AMA/FDA/Big Pharma establishment medicine health care.
>
> There are TWO main "skeptic" organizations – the James Randi Educational Foundation (JREF) and the Center For Inquiry (CFI). Both are well funded from secret sources.
>
> JREF reported, in 2010, a total income of $999,971.00 and a Total Asset claim of $1,736,101.
>
> The Center For Inquiry, Inc (CFI), based in Amherst, New York shows on their Form 990 that they took in $5,242,304 in Total 2009 Income, and they had, that year, Total Assets of $3,017,144. Their Schedule B ANONYMOUS contributions totaled $2,318,652.
>
> More, CFI claimed that they received, in 2009, in addition to their anonymous contributions, a so-called "Management Fee Income" of $2,458,156. What do you suppose they managed? And who paid them to manage it? Maybe they manage Wikipedia health care articles? How about Search Engine Optimization (SEO) bringing skeptic, including Stephen Barrett's (Quackwatch), articles to the first page of Google?
>
> Much more – This cabal minimizes and delays innovative medical advancements by lodging anonymous complaints to state licensing boards against cutting-edge practitioners. Their insidious campaign also controls grant monies and research funding, somewhat silencing the voices of innovative medicine in favor of mainstream views. By leveraging control of the media in direct jeopardy of journalistic integrity, this control group seeks to suppress all in medicine that is not fully controlled by the establishment. To permit this level of manipulation and disinformation is wrong and ethically corrupt. The fate of a valuable avenue of medical innovation for the public interest – anti-aging medicine – stands at-risk.[3]

A *JAMA* commentary purported to address the legality of human growth hormone (HGH, GH) treatment by physicians for growth–hormone deficient (GHD) patients.[4] It is the view of A4M that the commentary contained a number of incorrect, misplaced references and studies, and multiple basic scientific errors, in an apparent attempt to damage the anti-aging medical profession and the physicians practicing solid, evidence-based medical health care focused on improving and maintaining patients' quality of life. It is A4M's further opinion that the authors selected self-serving studies, in which they failed to qualify the conclusions in an effort to bolster what A4M believes is a disinformation campaign. It is A4M's opinion, for example, that they incorrectly intermingled Internet sales of homeopathic pseudo-"GH" sprays, amino acids, and sports nutritional over-the-counter products in order to inflate their incorrect claims suggesting an illegal diversion of HGH by physicians and pharmacies, implying a black market in FDA-approved prescription injectable HGH for hormone replacement treatments by anti-aging physicians where none exists.

Misrepresentation in Competitive Sports

As an unfortunate consequence of media confusion and outright deception aiming to deliberately misrepresent anti-aging medical care, the reality of the clinical practice of hormone replacement therapy has become muddled. A recent *Sports Illustrated* article states: "In the sports world, the term 'anti-aging' has often come to signify therapy that uses hormones – usually testosterone and HGH – and ... DHEA."[5] This erroneous definition grossly misrepresents the legal and ethical physiological use of hormones and supplements as being synonymous with the inappropriate use of hormones for sports enhancement. The A4M is squarely opposed to this myopic interpretation of "anti-aging" and urges reference to the official definition of anti-aging medicine as presented above.

Any use of performance-enhancing drugs or hormones banned from professional sports constitutes inappropriate misuse. It is a violation of the A4M Physician Member Code of Ethics to prescribe for the explicit purposes of performance enhancement. The A4M does not endorse or condone the use of any illicit substances for sports cheating. However, the A4M does support the continued availability of such substances to adult patients with objectively assessed hormone deficiencies. Such judicious use of HRT does not equate to a banned drug issue.

A4M's physician cofounders Robert Goldman, MD, PhD, DO, FAASP, chairman, and Ronald Klatz, MD, DO, president, are coauthors of *Death In the Locker Room* (1984), a first-ever exposé of the illicit use of anabolic steroids in sports, and *Grow Young with HGH* (1997), a best-selling book that explores the clinical benefits of judicious and appropriate HGH therapy in deficient adults. *Death in the Locker Room* is widely regarded as the seminal text on the dangers of anabolic and performance-enhancing substances in sports. It was the first book to alert the public and the medical community to

such issues, and it subsequently led directly to much of the drug testing, control, and educational programs now in place across a number of professional sports and on the global level.

Statute 21 USC § 333(e), a provision of the Food, Drug, and Cosmetic Act (FDCA), states, in pertinent part, that "whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by [FDA] and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison."[6] We need to take a critical look at the historical context and legislative intent of a law before we interpret it. The law did not originally address HGH. The 1988 law was written and passed regarding anabolic steroids. The legislative history of the statute shows an intent to focus on steroid trafficking to athletes, particularly adolescent athletes, amid increasing reports of amateur and professional sports doping and concerns about the 1988 Summer Olympics (at which, ironically, Canadian sprinter Ben Johnson's positive steroid result ignited a global firestorm).

Goldman served as special adviser and lecturer to the US Drug Enforcement Agency (DEA) Demand Reduction Education Programs nationally, as well as to the US Olympic Committee, spearheading the design of drug policy and testing procedures. In his activities with the DEA, Goldman was directly involved in an advisory capacity with the process that led to the creation of the Anabolic Steroid Control Act of 1990. "The Anabolic Steroid Control Act was never intended to restrict practicing physicians involved in the clinical treatment of hormone deficiency syndromes," comments Goldman, who explains: "Rather, this law was specifically directed to prevent the trafficking of anabolic steroids to athletes."[7]

The Anabolic Steroid Control Act of 1990 lifted steroids out of the FDCA and into the Controlled Substances Act. Congress was presented with the option of making HGH into a controlled substance, too. However, following expert medical testimony that HGH lacks the adverse psychological and physical effects of steroids, Congress chose not to take such a drastic approach to HGH.[8,9] Instead, Congress took the lesser approach of inserting HGH, to replace steroids, in the FDCA law that was written to stop trafficking to cheating athletes. In fact, HGH was inserted as an afterthought, with no penalties mentioned, as editorial comment; there was no intention to criminalize its judicious use in the clinical setting by trained physicians. The focus of lawmakers and Congress has always been to address nonmedical use; that is, improper use by competitive elite athletes, sports enthusiasts, and teenagers. It is A4M's view that the *JAMA* commentary fails to understand or appreciate such legislative history and legislative purpose.[4] A4M is advised that one of the authors of the *JAMA* commentary stated to United Press International (UPI) in reference to the statute, "They basically put in language that made it crystal clear that it is illegal to use growth hormone as an anti-aging intervention."[10] This is a very odd and, A4M believes, an incorrect statement, considering the fact that when the law was written, there were no anti-aging doctors or profession in existence. In fact, the anti-aging medical profession did not even exist until five years after the 1988 statute was enacted. The concept of HGH as an anti-aging drug did not exist until the problem of Rudman's study.[12]

The Anabolic Steroid Control Act never intended to infringe upon physician freedoms to prescribe hormone therapy when clinically appropriate. It was specifically intended to prevent steroid trafficking in professional sports. Whereas education should have been a primary goal in implementing the Anabolic Steroid Control Act, instead an enforcement environment that granted limitless power unto itself was created. A multimillion dollar industry of drug testing was born and subsequently flourishes.

Disinformation Campaign

History is replete with examples of medical pioneers whose innovations and foresight were trivialized, ignored, challenged, or violently opposed by the establishment, only to ultimately become accepted by society at large. Leopold Auenbrugger was ridiculed for percussing and auscultating his patients' chests; Ignaz Semmelweiss's recommendation for doctors to wash their hands before each patient landed him in a mental asylum; and more recently, cardiologists denied Nathan Pritikin's program for dietary modification to modulate cardiovascular risk until after his death. Given time and objective, undeniable evidence, scientific truths are ultimately borne out. In the words of Augenbrugger, "It has always been the fate of those who have illustrated the arts and sciences

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by their discoveries to be beset by envy, malice, hatred, destruction, and calumny."

Misguided Attacks on HRT

Statute 21 USC Section 333(e), a provision of the Food, Drug, and Cosmetic Act (FDCA), supports the use of hormone replacement in mature, clinically GH-deficient adults as both treatment of a disease and a medically authorized use granted by the FDA.[6] Any implication that the statute was intended to target medical hormone replacement by ethical doctors in the new and emerging field of anti-aging medicine is therefore incorrect and misleading.

To obfuscate the truth, critics of the anti-aging medical science offer deliberately misleading claims concerning HRT with the specific and ultimate goal to severely restrict the use of hormone therapy. Most notably, the *JAMA* commentary purported to address the legality of HGH treatment by physicians for GHD patients.[4] The commentary, however, was flawed by a number of incorrect, misplaced references and studies, and multiple basic scientific errors.

In the May–June 2009 issue of the prestigious *Archives of Gerontology and Geriatrics*, an international journal integrating experimental, clinical, and social studies on aging published by Elsevier, founder and editor-in-chief Zs.-Nagy expresses his opinions on the use of the HGH as an anti-aging medical intervention.[1] Zs.-Nagy's editorial points out the main clinical results of HGH replacement therapy (hGHRT) in light of the "membrane hypothesis of aging" (MHA), which he submits as offering a solid basis for the interpretation of the observed beneficial effects of HGH. Zs.-Nagy's profile of the sharp and protracted conflict of views between the gerontological establishment and the A4M exposes a "disregard by certain individuals bearing some of the most prestigious affiliations in the gerontological establishment, for truth, academic integrity, and scientific professionalism." Zs.-Nagy says: "[T]he gerontological elite has ... sought to obfuscate the facts of the anti-aging medical movement. I submit that the reason for this is nothing less than an abject fear by the gerontological elite to avert their loss of control, power, prestige, and position in the multi-billion dollar industry of gerontological medicine."

Elite athlete and professional sports/medical writer Monica Mollica observes: "For reasons that are not readily apparent, there appears to be a conservative political movement that opposes the use of testosterone in older men. ... The political climate is working against testosterone replacement therapy in older men despite overwhelming scientific data supporting this appropriate pursuit as a strategy to prolong healthy longevity."[11]

HGH

On July 5, 1990, Daniel Rudman, MD, a pioneer researcher in the use of HGH, and his colleagues at the Medical College of Wisconsin made medical history with an article in the *New England Journal of Medicine*.[12] It detailed the first clinical trial of elderly men on HGH therapy, which compared the effects of 6 months of HGH injections on 12 men, aged 61 to 81 years, with an age-matched control group. The result made headlines all over the world. Those taking the hormone injections gained an average of 8.8% in lean body mass and lost 14% fat, without diets or exercise. Their skin became thicker and firmer and the lumbar bones of the spine increased. In other words, HGH had virtually turned their flabby, frail, bodies into those of their sleeker, stronger, younger selves. In language rarely used in conservative medical journals, the researchers wrote: "The effects of 6 months of HGH on lean body mass and adipose-tissue mass were equivalent in magnitude to the changes incurred during 10 to 20 years of aging."

HGH is one of the most studied compounds in medicine, with almost 100,000 journal references currently in PubMed. The majority of these data demonstrate the positive benefits of HGH therapy in multiyear studies, well beyond the typical 6- to 12-month study protocols.[13,14]

Growth hormone replacement therapy has been shown to improve muscle strength and mobility, cognitive function, cardiovascular disease, osteoporosis, immune function, body composition, obesity, sarcopenia, fibromyalgia, Crohn's disease, other illnesses, and quality-of-life issues.[15–21]

Low GH is associated with decreased longevity in humans, with more than 20 years decreased lifespan with low GH.[22,23] Older men with higher IGF-1 do not show the same decrease in lean body mass and increase in fat mass. "GH determines life's potential."[24]

Childhood or adult GH deficiency is associated with 2 to 3 times increase in mortality.[25]

Low GH and its downstream hormone IGF-1 are associated with poor health and quality of life outcomes.[22] The June 2012 issue of the *Journals of Gerontology: Series A* published a series of articles documenting the clinical benefits of insulin-like growth factor (IGF-1).[26] Of note, Higashi et al. provide "a comprehensive update on IGF-1's ability to modulate vascular oxidative stress and to limit atherogenesis and the vascular complications of aging."[27] Further, Ungvari et al. cite the "cardiovascular protective effects of [IGF-1]" to "[provide] a landscape of molecular mechanisms involved in cardiovascular alterations in patients and animal models with ... adult-onset IGF-1 deficiency," submitting: "Microvascular protection conferred by endocrine and paracrine IGF-1 signaling" suggest "its implications for the pathophysiology of cardiac failure and vascular cognitive impairment, and the role of impaired cellular stress resistance in cardiovascular aging."[28]

The "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines" reports that treating GH deficiency in patients with chronic heart failure beneficially affects the primary endpoint of peak oxygen consumption, which showed "remarkable" increases of 7.1 ml/kg/m in GH-treated patients, as compared with a decrease of 1.8 ml/kg/m among control subjects.[29] In that left ejection fraction rose by 10% in the GH-treated patients (declined 2% in controls), with a greater effect on left ventricular and systolic volume index of – 22 ml/m2 (as compared with increase of 8 ml/m2 in controls), the American College of Cardiology Foundation/American Heart Association Task Force writes: "The improvements ... are consolidated

predictors of survival." Notably, there were no major adverse events among the GH-treated patients.

As stated by Savine: "If mean IGF-1 of 300 is mean normal for 20–30 year olds, almost all men and women over the age of 40 have an IGF-1 deficit."[30] Most patients beyond age 60 have total 24 hour HGH secretion rates indistinguishable from those of hypopituitary patients with organic pituitary gland lesions.[30] Therefore the A4M submits that the empirical data suggest that when treating adult GHD (AGHD), physicians are treating a documented deficiency disease and not performing off-label treatment as the *JAMA* commentary authors suggest. In fact, HGH deficiency is associated with significantly decreased longevity in human siblings.[4] Longevity and healthy aging are directly related to GH/IGF-1 levels.[31] As Savine points out, "Life without GH is poor in quantity and quality."[30]

When AGHD is treated with GH, there are usually increases in GH, IGF-1 and IGF binding protein 3 (IGFBP-3), which all have a role in clinical results. Although IGF-1 is pro-mitotic and taken out of context could promote cancer, IGFBP-3 is anticancer.[32] The mechanism is explained by stimulation of anticancer gene p53. Teenagers with the highest GH and IGF-1 have low rates of cancer. When treating with GH, a balance is produced between IGF-1 and IGFBP-3.[33] A central question in GHRT is, does GHRT increase the risk of cancer? Multiple studies and reviews have concluded that there is no increase in cancer risk compared with the general population. Jenkins review is aptly titled "Does Growth Hormone Cause Cancer?" and provides the conclusion:

> Extensive studies of the outcome of GH replacement in childhood cancer survivors show no evidence of an excess of de novo cancers, and more recent surveillance of children and adults treated with GH has revealed no increase in observed cancer risk.[34]

Moltich's review has similar conclusions:

> Although there has been some concern about an increased risk of cancer, reviews of existing, well-maintained databases of treated patients have shown this theoretical risk to be nonexistent.[35]

With regard for the potential for an increased cancer risk with HGH treatment, peer-reviewed literature suggests the opposite. HGH treatment may upregulate binding proteins of IGF, specifically IGF-6; this has been noted in studies to prevent many types of cancer, such as prostate, ovarian, brain and endometrial.[36–40,42] It is also well documented that cancer-survivor children who received HGH did not exhibit any increased cancer risks. In fact, there are no peer-reviewed long-term clinical studies that document human cancer risks from HGH administration.[38–40] To the contrary, cancer mortality and recurrence has been found to be reduced, or survival time increased in cancer patients on HGH. Patients deficient in HGH are reported to have a 400% increase in cancer mortality and a 200% increase of cancer incidence.[41,42] Noted was also a reduction by 50% of cancer risk to patients with long-term HGH replacement (60 months).[21] Additionally, the Growth Hormone Research Society has stated, "Current labeling for GH states that active malignancy is a contraindication. ... There are no data to support this labeling. Current knowledge does not warrant additional warning about cancer risk."[43] However, caution should always be exercised in patients with a history of cancer, and HGH therapy is not for every patient.

Ruiz-Torres et al. completed a study that compared aging parameters of young (up to 39 years) and old (over 70 years) individuals having similar IGF-1 blood levels.[24] In follow-up, the researchers studied the decline in IGF-1 levels, comparing its behavior in the first half with that in the second half of adult life. The investigators concluded: "GH secretion in adulthood plays a determinant role not only for some regressive manifestations, but also for life potential."

Media reports about the federal law concerning HGH have created unnecessary confusion, and some reports have confused nonmedical over-the-counter homeopathic sprays and nutritional products with pharmaceutical-grade, FDA-approved injection medications for AGHD patients. It is A4M's opinion that such misleading journalism incorrectly equates sports and homeopathic nutritional supplements sold through websites with pharmaceutical-grade injectable HGH prescribed for patients with diagnosed AGHD. Such poor presentations of the science and commentary, in A4M's view, have erroneously suggested that the replacement of HGH in aging adults is illegal and has led to sensationalized headlines. Patients are not given HGH for a diagnosis or treatment of "anti-aging," but for on-label use for AGHD syndrome, a diagnosed disease. It should be noted that, before initiating ➤

HGH supplementation, anti-aging physicians first encourage the increase of growth hormone by increasing exercise, enhancing sleep cycles, balancing other hormone deficiencies, and decreasing sugar intake, as evaluated by Gardner et al.[44]

In a landmark court case, James Forsythe, MD, HMD, won a clear and unanimous victory that reaffirmed the right of a physician to prescribe HGH to adults with deficiency conditions, including aging and arthritis.[45] Forsythe comments: "It is a perversion of the law for state licensing boards to mistreat and harass physicians for this legal, just, and appropriate use of this lifesaving medication – human growth hormone."[46]

DHEA

Dehydroepiandrosterone (DHEA) is the most abundant steroid in the human body and is involved in the manufacture of testosterone, estrogen, progesterone, and corticosterone.

There is evidence to suggest that DHEA may stimulate human growth hormone (HGH). Morales et al. published results of a double blind, placebo-controlled, crossover study involving 71 women and 13 men, aged 40 to 70 years.[47] Subjects took 50 mg of DHEA for three months, followed by a placebo for three months. While subjects were receiving DHEA, their levels of DHEA and DHEA-S rose to that of young adults within 2 weeks of DHEA replacement and were sustained throughout the 3 months of the study. Furthermore 84% of women and 67% of men reported an improved sense of both physical and psychological well-being, including improved sleep quality, increased energy levels, improved ability to handle stress, and increased sense of relaxation. Five of the volunteers also noted improvement in chronic joint pain and mobility. The researchers also found that DHEA caused a significant rise in IGF-1 levels, although it did not affect the 24-hour measurement of HGH levels. They speculate that restoring the levels of DHEA may stimulate the liver to produce more IGF-1 or generate more HGH receptors. In other words, we may find that the anti-aging benefits attributed to DHEA may actually be due to the stimulation of the HGH-IGF-1 system.

When DHEA levels are in an optimal range, there can be less risk of developing atherosclerosis.[22] Rabijewski found that DHEA could lower insulin levels and decrease the risk for developing type 2 diabetes.[48] DHEA also decreases the risk of cancer because it enhances the immune system response. DHEA is also thought to be neuroprotective.

Professor Etienne-Emile Baulieu, world-known researcher and endocrinologist at INSERM in Paris, former president of the French Academy of Sciences, honorary member of College of France, known for his work on contraception and on steroid hormones, was the first to synthesize DHEA in the 1960s. Baulieu conducted numerous conclusive researches on the efficiency and benefits of DHEA. His findings underline the systematic positive results of administrating DHEA in his experimental and clinical studies, especially in men. His findings demonstrate that 50 mg of DHEA in 280 participants during a year significantly improved their bone mass, skin thickness, and pigmentation, as well as the libido in both men and women; general physical and mental well-being were improved too.[49,50] In an interview for a study on anti-aging medicine, Baulieu declares: "One of the most important effects of DHEA has not yet received enough attention: it acts on the receptors of neurotransmitters. There is very encouraging research on the well being and improvement of memory in old age."[51]

Testosterone

Testosterone is the main hormone produced in the testicles and secreted by the testes. Testosterone deficiency has pleiotropic deleterious effects. There is increased cardiovascular system dysfunction, which can lead to the increased incidence of acute myocardial infarctions and strokes. Citing separately published data finding that "serum testosterone levels were proved to be an independent negative predictor for developing arterial stiffness, assessed from the peak systolic and end diastolic diameters of the common carotid artery and simultaneous brachial artery blood pressure," Kelly and Jones submit: "Testosterone has demonstrated anti-inflammatory effects clinically and [testosterone replacement therapy] can improve atherosclerosis assessed non-invasively in hypogonadal men and in animal studies."[62]

Testosterone optimization is anti-inflammatory.[22] Testosterone prevents cytokine production and initiates the acute phase response, which elevates C-reactive protein, serum amyloid A, and fibrinogen. Testosterone also prevents the formation of the adhesion molecules vascular cell adhesive molecule (VCAM) and intercellular adhesive molecule (CD 54/ICAM), which are necessary components of the process of atherosclerosis. Thus, testosterone replacement is a very powerful anti-inflammatory treatment that can help to prevent atherosclerosis. Testosterone has also been shown to be of benefit in the treatment of chronic heart failure. Pugh et al. found that testosterone increases cardiac output, decreases left ventricular load, and has no adverse cardiovascular effects.[53] Malkin et al. show that testosterone replacement moderates inflammatory cytokines and improves heart failure outcomes.[54] Turhan et al. found that men with low free testosterone levels have greater than 3 times the risk for the development of coronary artery disease.[55]

There is a common misconception that testosterone has adverse cardiovascular effects.[22] However, the opposite has been shown with current research. The lower the free testosterone level, the more likely that coronary artery disease will be present. Testosterone replacement therapy (TRT) improves ST depression and dilates coronary arteries. TRT also may improve lipids, and low testosterone is associated with dyslipidemia. English et al. found that low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. Rosano et al. found that "Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease."[56] The same researchers also concluded that intracoronary testosterone has direct dilating effects on the coronary arteries. Finally, Hak et al. found that low levels of endogenous androgens increase the risk of atherosclerosis in elderly men.[57]

Testosterone can be a very powerful tool for the control of insulin resistance.[22] Replacement doses decrease insulin resistance. Low levels of testosterone play a role in the development of type 2 diabetes. Low testosterone is associated with metabolic syndrome, hypertension, type II diabetes, fibromyalgia, and coronary artery disease. Boyanov et al. studied the effect of testosterone supplementation in men with type 2 diabetes, visceral obesity, and partial androgen deficiency.[58] Subjects received testosterone undecanoate, and the results reflect that supplementary testosterone reduced hemoglobin A1C levels by 17.3%, led to a decrease in visceral obesity, and improved symptoms of androgen deficiency, including erectile dysfunction. Observing, "There is strong evidence that a low testosterone level and clinical hypogonadism have a high prevalence n men with metabolic syndrome and/or type 2 diabetes," Muraleedharan and Jones conclude: "Testosterone deficiency is a risk factor in itself for the subsequent development of the metabolic syndrome and type 2 diabetes."[59]

Testosterone is the major predictor of skeletal mass, and it is synergistic with growth hormone (GH) and insulin-like growth factor-1 (IGF-1).[22] Bhasin et al. show that testosterone can improve strength even without exercise, but there is a marked improvement if testosterone is taken in combination with exercise.[60] Declining testosterone levels are associated with accelerated osteoporosis, decreased muscle mass, and anemia; that is, frailty.

Numerous studies have documented testosterone's positive effects on body composition. Mudali and Dobs write: "Studies in hypogonadal men have shown that testosterone replacement is effective in increasing muscle mass and strength and decreasing fat mass. ... Current evidence suggests that testosterone replacement may be effective in reversing age-dependent body composition changes and associated morbidity."[61] LeBlanc et al. analyzed data collected on 1183 men, ages 65 years and older, following the subjects for 4.5 years.[62] Body composition was measured using dual energy X-ray absorptiometry (DEXA) scans, and physical performance was measured through a series of exercises that assessed grip strength, lower extremity power, walking speed, and ability to rise from a chair without the use of arms. Results showed that higher levels of testosterone were associated with reduced loss of lean muscle mass in older men, especially in those who were losing weight. In these men, higher testosterone levels were also associated with less loss of lower body strength. The study authors concluded: "Higher endogenous testosterone is associated with reduced loss of lean mass and lower extremity function in older men losing weight. Endogenous testosterone may contribute to healthy aging." Kovacheva et al. report that testosterone supplementation reverses sarcopenia in aging via regulation of myostatin and "multiple signal transduction pathways in sarcopenia," concluding; 'Testosterone reverses sarcopenia through stimulation of cellular metabolism and survival pathway together with inhibition of death pathway."[63]

Testosterone levels correlate with cognitive function, and TRT can improve cognitive function.[22] Moffat et al. found that serum free testosterone concentration can be used to predict memory performance and cognitive status in elderly men.[64] Gouras et al. showed that testosterone replacement therapy prevents the production of amyloid-beta precursor protein in men, which suggests that testosterone replacement may play a role in the prevention of Alzheimer's disease.[65] A pilot study by Tan on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease revealed that mental status of those given testosterone replacement therapy improved over one year, whereas the mental status declined in those given a placebo.[66] Janowsky et al. found that increasing testosterone to 150% of baseline levels in older men resulted in a significant enhancement of spatial cognition.[67] A review of testosterone and cognition in elderly men by Holland et al. concluded: "Results from cell culture and animal studies provide convincing evidence that testosterone could have protective effects on brain function. Testosterone levels are lower in Alzheimer's disease cases compared to controls, and some studies have suggested that low free testosterone (FT) may precede Alzheimer's disease onset. ... Positive associations have been found between testosterone levels and global cognition, memory, executive functions, and spatial performance in observational studies."[68]

Studies have shown that men who have their testosterone levels restored with TRT are less likely to suffer from depression, less moody, and more sociable and have more energy. O'Connor et al. investigated the effects of TRT on self- and partner-reported aggression and mood.[69] Eight hypogonadal men received 200 mg intramuscular testosterone biweekly for 8 weeks. Results showed that TRT led to significant reductions in negative mood, tension, anger, and fatigue. Aydogan et al. assessed the relationship with testosterone levels and psychological symptoms in young male patients with congenital hypogonadotropic hypogonadism (CHH).[70] 39 young male patients with CHH and 40 age-matched healthy males were enrolled in the study. Results showed that hypogonadal participants had more severe symptoms of sexual dysfunction, anxiety, and depression and worse quality of life. However, 6 months of TRT led to improvements in anxiety and depression scores and the life qualities of participants. TRT also improves sexual function. Khera et al. investigated if 12 months of treatment with a testosterone gel improved sexual function in hypogonadal men, as measured by the Brief Male Sexual Function Inventory (BMSFI).[71] Results showed that the mean total BMSFI score significantly increased from baseline at 12 months (27.4 ± 10.3 to 33.8 ± 9.8, $p < 0.001$) and at each visit in all domains (sex drive/libido, erectile function, ejaculatory function, level of bother). Regression analysis indicated that increased total BMSFI score was significantly associated with increased total testosterone levels at 6 months. The authors concluded: "In hypogonadal patients, 12-month administration of topical testosterone gel resulted in increased total testosterone and free testosterone levels and significantly improved sexual function."

A Cochrane systematic study reviewed the benefits of testosterone for peri- and postmenopausal women. The authors concluded, "There is evidence that adding testosterone to hormone therapy has a beneficial effect on sexual function in postmenopausal women. There was a reduction in HDL cholesterol associated with the addition of testosterone to the

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hormone therapy regimens. Due to lack of targeted research, it is difficult to estimate the effect of testosterone on sexual function in association with any individual hormone treatment regimen."[72]

Rhoden et al. point out that benign prostatic hyperplasia (BPH) symptoms are not exacerbated with testosterone supplementation.[22,73] Cooper et al. studied the effect of exogenous testosterone on prostate volume, serum, and semen prostate specific antigen (PSA) levels in healthy young men.[74] Participants were given testosterone intramuscularly at doses of 100, 250, or 500 mg a week. Serum testosterone increased, and there was no change in prostate volume or serum and semen PSA. Morales and Prehn both concluded that there is no evidence to suggest that exogenous androgens promote the development of prostate cancer.[75,76] Morley states, "There is no clinical evidence that the risk of either prostate cancer or BPH increases with testosterone replacement therapy."[77] A collaborative analysis published in the *Journal of the National Cancer Institute* in 2008 found that there was no association between the risk of prostate cancer and any hormone measured, including testosterone, DHT, and estradiol. Gould et al.'s review of 15 studies of testosterone replacement, up to 15 years in duration, showed no increase of prostate cancer risk.[78] Agarwal and Sarosdy found that testosterone treatment studies of patients with prostate cancer after radical prostatectomy and brachytherapy have shown no recurrences or significant increases of PSA.[79,80] Morgantaler's study reported dramatic evidence on the safety profile of TRT: 13 testosterone-deficient men with biopsy-proven prostate cancer were treated with TRT.[81] After 2.5 years, repeat biopsies were done and no cancer was found in 54%; there was also no local progression or metastasis found.

Attacks on Compounding Pharmacies

Compounding has been a foundational aspect of the practice of pharmacy. While today the majority of prescription medication is mass produced by pharmaceutical companies, many patients require custom-made preparations that are prescribed by their physician and compounded by a trained pharmacist.

Compounding pharmacies are strictly regulated by the respective state boards of pharmacy. Presently, US Senate Bill S.959 would transfer control of compounding pharmacies to the FDA. This legislation would give sole authority of the FDA to determine what medications could be used in the practice of compounding. Knowing its long-time antipathy to bioidentical hormones, you can rest assured that the FDA would inevitably ban compounded bioidentical hormones. This has been its plan since the late 1980s. A series of federal court cases has prevented this. Despite this pending legislation, courts have repeatedly upheld pharmacists' rights to compound, even with repeated attempts by the FDA to challenge the activity. In May 2006, a US District court judge ruled that the compounding of ingredients to create a customized medication in accordance with a valid prescription does not create a new drug subject to the FDA's approval process (see *Medical Center Pharmacy et al. v. Gonzales et al.*). Additionally, the US Supreme Court has held as unconstitutional the FDA's repeated attempts to regulate pharmacist compounding.

Attacks on Credentialed Physicians

The American Board of Anti-Aging & Regenerative Medicine (ABAARM) issues board certification to individuals with MD (doctor of medicine), DO (doctor of osteopathic medicine), DPM (doctor of podiatric medicine), and MBBS (bachelor of medicine/bachelor of science) degrees; the American Board of Anti-Aging Health Practitioners (ABAAHP) issues diplomate certification to doctors of chiropractic (DC), doctors of dentistry (DDS), naturopathic doctors (ND), registered pharmacists (RPh), scientists (PhD and similar), registered nurses, nurse practitioners, and physician assistants, and licensed acupuncturists (LAc).

Through ABAARM and ABAAHP, the A4M is one of approximately 270 specialist medical societies and medical boards, only 24 of which in total have been approved by the American Board of Medical Specialties (ABMS). A self-appointed organization, ABMS most recently approved a medical specialty – nuclear medicine – in 1985, 28 years ago as of this writing. In a field of over 270 specialist medical societies, ABMS approval is an arduous, time-intensive, and resource-depleting process. The A4M is one of nearly 250 societies that have yet to receive ABMS approval. Statements that anti-aging medicine is not yet an ABMS-recognized medical specialty mischaracterize the reality of gaining such approval and to infer – improperly – a lack of credibility on the part of A4M.

Currently, A4M's educational programming awards category 1 AMA/Physician's Recognition Award (PRA) physician credits, the highest level available for physicians and surgeons. The content of A4M's academic congresses are closely monitored and supervised by AMA-approved CME accreditation bodies. A4M's educational programming has consistently received the highest ratings and excellent reviews for the quality of medical educational content by peer-reviewed organizations. A4M's educational programming has received recognition and support of national governments and universities worldwide.

Hormone Replacement Therapy

History

Hormone replacement therapies with controlled substances such as testosterone and growth hormone have been used since many years. The first treatment of testosterone deficiency in adult men started around 1940; and, since then, for more than 40 years growth hormone has been administered to treat short-stature children; since 1985, with the safer, uncontaminated recombinant growth hormone, a product of biotechnology. In the latter 1980s, the first clinical trial of adults with GHD were published, and since the beginning of the 1990s, growth hormone treatment of adult patients started in private medical practice.

The concept of interventional endocrinology acknowledges the fact that not everyone experiences symptoms of deficiency – relative or absolute – at the same levels. Therefore, taking a comprehensive medical history and physical can act to substantiate the application of replacement/supplementation

protocols, in accordance with accepted standards of care. Clear documentation in this regard helps support the physician's approach in treating the patient.

Safety and Efficacy

To date, no adverse effects of hormone replacement therapies administered to adults with diagnosed deficiency(ies) have been reported to the FDA's Adverse Event Reporting System (FAERS), the national database providing postmarketing safety surveillance for drug and therapeutic biologic products. Likewise, as of this writing, the US CDC's Medication Safety Program contains no reports of adverse effects relating to HRT.

HGH therapy has been in use for over 40 years in adults and children, with one of the best safety records in modern pharmacy and whose dose in adults is typically only 1/5 to 1/7 of the pediatric dose and under the strict supervision of an endocrinologist or anti-aging specialist.[82] As of this writing, the US National Library of Medicine's PubMed database lists over 100,000 peer-reviewed citations on HGH therapy; not a single death or permanent life-threatening morbidity has been reported on its use in otherwise healthy AGHD patients.

The side effects of GH replacement therapy, if any, are usually minor and are reversible by decreasing the dose or in a few cases discontinuing the treatment. Significant side effects are rarely seen in clinical practice. Also, when the same total dose is divided daily over a week-long period (instead of administering 3 days a week), side effects are diminished or absent. If side effects do occur, it has been clinically demonstrated that they disappear with cessation of treatment.

The Clinical Anti-Aging Setting

Most traditional endocrinologists have had no intense training in treatment of testosterone and growth hormone deficiencies. They generally have excellent training in the treatment of diabetes, but lack of interest and expertise in how to treat testosterone and AGHD and some other hormone deficiencies that may accelerate aging.

Because of this lack of knowledge, many of them have rejected these treatments and confused them with the improper use at excessive doses by sports athletes searching to improve their performance. The A4M, its numerous worldwide affiliated scientific and medical societies, and befriended organizations do not approve the improper use of these substance in sports but do point to the right of all patients suffering from one of these deficiencies to get relief from their complaints by the adequate hormone treatment.

Critics of the anti-aging medical science do acknowledge that HGH prescribing is perfectly legal in connection with (1) "treatment of a disease" or (2) an "other recognized medical condition" that has been authorized by FDA. At no time has Congress evinced any intent to restrict ethical physicians from prescribing HGH to mature or elderly adults for medical reasons within their sound judgment. Nothing in the statute dictates to physicians how to diagnose the indications for diseases which may be treated by HGH. Any inference that the statute was intended to prohibit physicians from prescribing HGH for hormone replacement purposes in GH-deficient adults is, in A4M's view, misplaced.

The therapeutic value of HGH was validated by a study conducted in Stockholm, Sweden.[83] Data concerning visits to the doctor, number of days in hospital, and amount of sick leave were obtained from patients included in KIMS (Pharmacia International Metabolic Database), a large pharmacoepidemiological survey of hypopituitary adults with GHD, for 6 months before GH treatment and for 6 to 12 months after the start of treatment. Assistance required with normal daily activities was recorded at baseline and after 12 months of GH therapy. Quality of life (QoL; assessed using a disease-specific questionnaire, QoL-Assessment of GHD in Adults) and satisfaction with physical activity during leisure time were also assessed. For the total group ($n = 304$), visits to the doctor, number of days in hospital, and amount of sick leave decreased significantly ($p < 0.05$) after 12 months of GH therapy. Patients also needed less assistance with daily activities, although this was significant ($p < 0.01$) only for the men. QoL improved after 12 months of GH treatment ($p < 0.001$), and both the amount of physical activity and the patients' satisfaction with their level of physical activity improved after 12 months ($p < 0.001$). In conclusion, GH replacement therapy, in previously untreated adults with GHD, produces significant decreases in the use of health-care resources, which are correlated with improvements in QoL.

Concluding Remarks

Repeatedly since the genesis of the anti-aging medical movement in 1991, the media have sought to demonize the use of hormone replacement therapies in healthy but deficient adults. Relying on partisan – and often misinformed – critics, the media fuel and encourage hysteria among the public, which thereby results in a climate of misguided federal and state actions that seek to restrict these safe, proven, life-enhancing therapies.

Attempts to criminalize the practice of medicine wherein variations to state–board favored traditional care threaten the continued advancement of innovative medicine. In these situations, there are no injured patients and no victims, yet criminal proceedings are waged against progressive health professionals. State officials abuse their authority in recasting minor administrative issues criminal acts; this is unjust and may be considered as criminal abuse of their publicly elected positions. Sensationalization by media confuses the public, with false allegations suggesting that HRT in clinically documented cases of adult deficiency syndromes equates to the abuse of performance-enhancing anabolic steroids.

The American Academy of Anti-Aging Medicine (A4M) is resolute in defending the rights of patients working in conjunction with their physicians in choosing any and all justifiable therapies, drugs, and interventions that can be shown to improve either the quality or duration of the human lifespan or the form and function of the individual's physiology in order to achieve greater vitality and health at every age. It is in fact the physician's duty to advocate for the patient's right to obtain the full lawful measure of scientific medical therapeutics necessary for optimum health and personal freedom of choice in health care.

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A4M Position Paper

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The observation by George Orwell (1903–1950), in the prognostic classic novel *1984*, that "War is peace. Freedom is slavery. Ignorance is strength" predicts that in a world where lies are supported by the establishment, to stand firm for truth is a dangerous and revolutionary action. Physicians of conscience and good will must unite to take back the future – or all freedoms, including freedom of choice in health care, will be lost forever.

Appendix A: Literature Review

This section presents a selection of published peer-reviewed studies that document the life-enhancing and/or life-extending benefits of HRT in aging adults. For further references, see the A4M's White Paper "Guidance for Physicians on Hormone Replacement Therapy"; May 2007; available at http://www.worldhealth.net/white-papers-official-statements.

HGH

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Endorsing Organizations

American Academy of Anti-Aging Medicine (A4M)
Academy of Anti-Aging Medicine – China
Asia-Oceania Federation of Anti-Aging Medicine (AOFAAM)
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European Society of Anti-Aging Medicine (ESAAM)
German Society of Anti-Aging Medicine (GSAAM)
German Society of Hemotoxicology
Hellenic Academy of Antiaging Medicine
Indonesian Society of Anti-Aging Medicine
International Academy of Anti-Aging Medicine
Japan Anti-Aging Medical Spa Association (JAMSA)
Japanese Society of Clinical Anti-Aging Medicine (JSCAM)
Korea Anti-Aging Academy of Medicine (KA3M)
LatinoAmerican Federation of Anti-aging Societies
Romanian Association of Anti Aging Medicine
Sociedad de Medicine Antievejenimiento y Longevidad de Gran Canaria
Society for Anti-Aging & Aesthetic Medicine Malaysia (SAAAMM)
South African Academy of Anti-Aging & Aesthetic Medicine (SA5M)
Spanish Society of Anti-Aging
Thai Academy of Anti-Aging Medicine
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World Anti-Aging Academy of Medicine (WAAAM)

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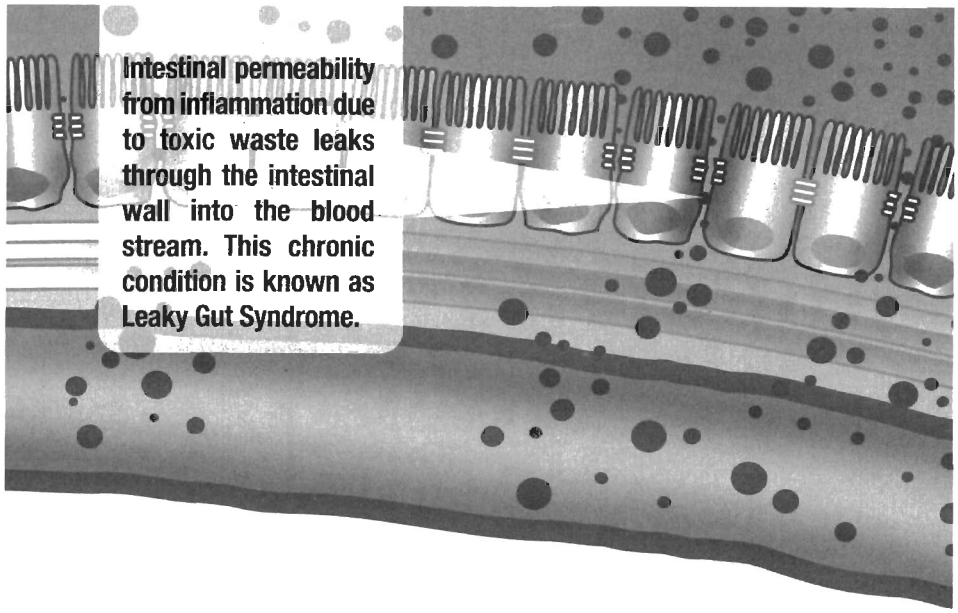

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The Current Understanding of the Pathogenesis of Rosacea: Research Review

by Debbie Whittington, ND

Despite its being one of the most common skin disorders affecting more than 16 million Americans, the pathogenesis of rosacea remains uncertain and controversial.[1] Although the symptom triggers are well recognized, the underlying causes of rosacea have not yet been completely identified. Most agree that the pathophysiology involves a complex interaction of different factors, which lead to a chronic inflammatory and vascular response.

Transient or persistent central facial erythema, telangiectasia, and associated papules and pustules most often characterize rosacea. Rosacea signs and symptoms may be exacerbated by a number of environmental and lifestyle factors that differ from one individual to another. Common triggers include alcohol, spicy or hot foods, foods high in histamines (red wine, aged cheeses, yogurt, beer, cured pork products such as bacon, etc.), stress, caffeine, chronic sun exposure, cold weather, and overly dry climates.

Although epidemiological studies indicate a genetic link, a rosacea gene has not been detected.[2] Other causes or correlative factors that have been associated with rosacea are the dysregulation of the cutaneous innate immunity, overgrowth of the *Demodex folliculorum* mite in the skin, small intestinal bacterial overgrowth (SIBO), *Helicobacter pylori infection*, and increased vitamin D3 signaling.[3–11]

Innate Immune System Anomalies: Antimicrobial Peptides Indicated in Rosacea Inflammation

Exciting new research indicates that rosacea may be caused by an overactive or excessive inflammatory immune response.[3,4,12] Our skin is the first barrier against the outside environment. The skin is equipped with various innate mechanisms against invading microbial pathogens. Antimicrobial peptides (AMPs) play a key role in cutaneous innate immunity and help protect against microbial infections. Cathelicidins were among the first AMPs identified in human skin. Cathelicidins have antimicrobial activity that kills pathogens directly; as well, they initiate a powerful response to infection resulting in cytokine release, inflammation, and a cellular response.[4] Research has shown that rosacea sufferers have an abnormally high level of cathelicidin peptides in their facial skin and that the proteolytically processed forms of cathelicidin peptides found in rosacea are different from those present in normal individuals.[13,14] These "rosacea" forms of cathelicidin peptides promote increased inflammation, whereas the types most commonly found on normal skin function mostly as antibiotics and have little inflammatory activity.[14] One of the most common forms of cathelicidin found in rosacea is LL-37. In healthy skin, cathelicidin expression is barely detected in keratinocytes. During infection or injury, cathelicidin production is found in much higher amounts. When cathelicidin LL-37 is upregulated it causes inflammation, erythema, and telangiectasia.[3,10]

Once the mechanisms of cathelicidin gene regulation and peptide processing become more evident, treatment strategies will be clearer to mediate the effects of cathelicidin and decrease the symptoms of rosacea.

Demodex Folliculinum Mite: Skin Microbe Inducing Rosacea Symptoms

Rosacea can be treated with a variety of antibiotics, both oral and topical, such as tetracycline or metronidazole. Current research confirms that in many cases of rosacea, particularly those that have a papulopustular subtype, there can be an overgrowth of a normal skin mite and bacteria that it harbors.[5,16–19]

The *Demodex folliculinum* mite can be a normal skin microbe found in hair follicles and sebaceous glands. It is commonly found on facial skin including forehead, cheeks, chin, and nasolabial folds.[19] This parasite can create inflammation, directly and indirectly, which is seen in the papules and pustules as well as granulomas in rosacea-affected skin.[17] Studies have shown that the density of *Demodex* mites in the skin of rosacea patients is higher than in nonrosacea patients, which suggests a role for these mites in the initiation of rosacea symptoms.

Additionally, a variety of microbiota in *Demodex* mites, such as the bacterium *Bacillus oleronius*, have been isolated in rosacea-affected skin.[18] *B. oleronius* is known to be sensitive to the antibiotics used to treat rosacea.[16] It appears that not only can overgrowth of *D. folliculinum* play a role in pathogenesis of rosacea but also there could be an additional bacterial component.[5]

Small Intestinal Bacterial Overgrowth: Correlation of SIBO and Rosacea

SIBO is a condition wherein there is an overgrowth of bacteria in the small intestine. The bacterial overgrowth can be composed of both native and nonnative bacteria causing excessive

fermentation, inflammation, or malabsorption in the small intestine.[20] The prevalence of SIBO in rosacea patient populations has been found to be anywhere from 46% to 66%.[6,7] A recent double-blind, controlled study showed that after SIBO eradication with antibiotic treatment, 71% of patients (28/32) had complete clearance of rosacea. Patients treated with placebo had no change in rosacea symptoms or had symptoms worsen. Once the placebo patients were treated with antibiotic therapy, 75% of patients had resolution of rosacea symptoms.[6]

The current data demonstrate that rosacea patients often have a significantly higher SIBO prevalence than non-rosacea patients Furthermore, in a majority of patients, treatment and eradication of SIBO significantly reduced all rosacea symptoms.

Helicobacter Pylori: Gastric Bacterial Infection Triggers Rosacea Symptoms

Helicobacter pylori infection as a causative factor in rosacea has long been controversial. Recent studies have provided more evidence that *H. pylori* is associated with rosacea and could certainly be an important factor in the development of rosacea symptoms.[8,9]

H. pylori is a bacterium that survives in the stomach or duodenum. It is highly adapted to survive the gastric environment where it lives. It disrupts the mucosal layer underlying the gastroduodenal tissue, making this underlying tissue more susceptible to acidic damage. The innate immune response to *H. pylori* also causes an inflammatory reaction, which causes further tissue injury.[8,9]

In a recent study, 65% of patients with rosacea were found to have a positive *H. pylori* serology and, once treated, rosacea symptoms significantly improved. It is important to point out that not all patients had actual *H. pylori* or gastric symptoms.[9] However, it has not been determined if patients without gastric symptoms have an increased prevalence of *H. pylori* infection.[8]

Vitamin D3

As discussed earlier, abnormal cathelicidin peptide processing and function has been linked to the increased inflammation and angiogenesis in rosacea. Until recently it has been unknown what underlying mechanisms were responsible for cathelicidin regulation. It appears that the vitamin D3 pathway is a major regulator of cathelicidin expression.[4] This could explain why rosacea occurs mainly in the face and is aggravated by ultraviolet (UV) light/sun exposure. It is well known that UV light triggers the activation of vitamin D3. In turn, vitamin D3 synthesis induces cathelicidin peptide expression in the skin, particularly in the keratinocytes.[3,10,15]

A deeper understanding of the molecular mechanisms is needed in order for therapies to be initiated. However, therapeutic interventions could involve targeting the vitamin D3 pathway, thereby decreasing the cathelicidin overexpression and inhibiting the skin aggravating cathelicidin fragments.[15]

Conclusion

It is clear that the development of rosacea is multifactorial and complex. Fortunately, ever-expanding data show that the symptoms of rosacea can be managed most effectively if we can treat multiple issues and triggers at one time.

Avoiding known triggers is key to the management of rosacea symptoms. Many clinics test for SIBO and *H. Pylori* routinely in rosacea-affected patients. Additionally, D. folliculinum overgrowth is tested for and treated with topical and/or oral antibiotics and anti-inflammatory medications.

Managing symptoms and giving patients both physical and aesthetic symptom relief is very important. However, continuing the research on the innate immune system and its function in the development of rosacea is imperative in developing possible treatments of the underlying cause of the disease.

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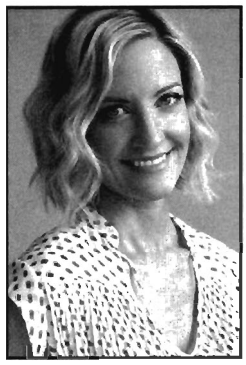
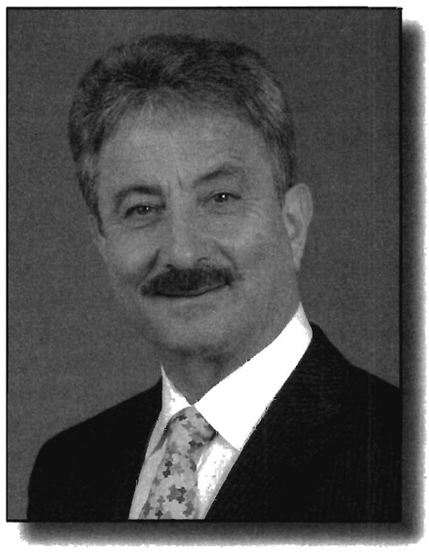


Blood-Brain Barrier Damage and Neuroautoimmunity

Aristo Vojdani, PhD, MSc



The human brain contains more than ten billion capillaries, which translates to one vessel for each neuron. These capillaries form a circulatory network with over 400 miles (644 km) of blood vessels that nourish the brain, transporting as much as 20% of cardiac output. The entire length of this network is protected from toxins by the blood-brain barrier (BBB), a complex structure lining the capillaries throughout the brain.

When the BBB is damaged, circulating antibodies that cross-react with neurological tissues can infiltrate the brain and nervous system, with the potential destruction of neurologic tissues. The cycle of neuroautoimmunity begins with a breach of the gut and/or blood-brain barriers. BBB permeability and the effects of "leaky brain" contribute to many devastating neurological and autoimmune conditions, including traumatic brain injury (TBI).

New breakthroughs in laboratory testing make it possible to identify BBB permeability in trauma ranging from suspected concussions to TBI. The testing is also relevant to neurological disorders as advanced as Alzheimer's dementia and as subtle as chronic headaches or memory loss. Testing for key antibodies makes it possible to diagnose many of these conditions at a preclinical stage, before frank symptoms of injury or disease are present. Increased permeability can manifest as CNS symptoms of neurotoxicity, autoimmunity, or even cancer.

Indications

Breaching or damage to this vast network is an underappreciated factor in a wide range of neurologic and autoimmune conditions, including:

- ADD, ADHD, autism spectrum disorder, developmental disorders
- Autoimmune conditions – celiac disease, type 1 diabetes, Hashimoto's encephalitis, lupus with CNS involvement, rheumatoid arthritis, and sarcoidosis, as well as neuroimmune conditions such as CFS and FMS
- Concussions and traumatic brain injury
- Mental illness – obsessive-compulsive disorder, schizophrenia, and others
- Neurodegenerative disorders and diseases of aging – AIDS dementia, ALS, Alzheimer's disease, epilepsy, multiple sclerosis, Parkinson's disease, peripheral neuropathy, senile dementia, stroke
- Neurologic symptomology – cognitive impairment or decline, memory problems, chronic headaches, sleep disturbances, fatigue, dizziness, tremors, poor coordination, anxiety, depression

Barrier Dysfunction and Disease

Composed of highly specialized brain and endothelial cells, the BBB is fully differentiated to the neurovascular system, and present in all brain regions, except in those regulating the autonomic nervous system and the endocrine glands. Capillaries permit diffusion of blood-borne molecules, screening out molecules larger than 400 Daltons (Da), approximately the size of blood glucose. Larger molecules such as proteins, which can occur in the range of 50,000 to 100,000 Da, are denied access to the nervous system when the BBB is intact. Specific carriers, or transporters, in apical and basolateral membranes, control the influx of small polar solutes needed by the brain (nutrients such as glucose and amino acids) and the efflux of many waste products. Transporters also exclude many potentially

toxic compounds, such as xenobiotics, food antigens, and peptides present in the circulation.

Absence of Immune Tolerance

Innumerable endothelial tight junctions in the BBB function to prevent the passage of large soluble molecules into the CNS. Consequently, the barrier also prevents developing B-cells from contact with brain antigens. During immune maturation, B cells are not exposed to the variety of unique brain antigens expressed on neurons, oligodendrocytes, microglia, and astrocytes. The immune system apparently has no innate mechanisms for establishing tolerance to brain antigens or for preventing the production of antibodies against them. When exposure to an environmental trigger occurs that opens the BBB, the immune system, by producing antibodies against the CNS, attacks the CNS tissues.

Numerous exposures can trigger BBB permeability:

- Inflammatory responses associated with chronic or acute traumatic brain injury and concussions
- Environmental exposures – viral (CMV, Guillain-Barre, hepatitis B, herpes 6); bacterial (streptococcus, *Chlamydia pneumoniae*); molds and mycotoxins; EMF from power lines, computers, cell-phones, microwaves; and radiation
- Inhalation or touch contact – chemicals including formaldehyde, insecticides, pesticides; solvents such as benzene; heavy cigarette smoke.
- Intestinal permeability and exposures via the gut – dysbiosis, endotoxins from bacterial overgrowth; PCBs and other toxins ingested in food or water
- Other internal exposures and dysfunction – toxic metals such aluminum and heavy metals such as mercury; certain medications; silicone implants; shock, stress, and inflammation; hypertension; ischemia

Breaches of the BBB can result in the damaging effects of TH 1 and TH 17 lymphocytes, as well as antibodies that can target and damage neurons and tissues such as myelin basic protein. Autoantibodies can become pathogenic on penetration into the CNS through either BBBD (blood-brain barrier dysfunction) or extravasation into cerebrospinal fluid from the sub-arachnoid space.

Testing for Barrier Dysfunction

Advanced antibody testing now allows accurate evaluation of BBB competence. Patients with neuroautoimmunity frequently have high levels of antibodies against various components of the nervous system, particularly antibodies to S100-B and to occludin and zonulin.

BBB protein antibodies. The blood-brain barrier includes endothelial cells, tight junctions, the capillary basement membrane (BM), pericytes (PCs), and astrocyte end-feet that tightly ensheath the vessel walls. Astrocytes located beneath the endothelial cells prevent the entry of unwanted molecules and produce a protein identified as BBB protein, which is now used in laboratory testing as a marker to identify the presence of neuroautoimmune reactivity. Elevated antibody titers for BBB protein and other brain proteins have been described in Alzheimer's disease and epilepsy. In senile dementia, the presence of BBB protein antibodies is one of the early markers of cognitive decline. (Specific testing for BBB protein antibody is provided in Cyrex Laboratories' Array 20.)

Occludin and zonulin antibodies. Paracellular space between the endothelial cells of the BBB is protected by an extensive network of tight junctions, consisting of transmembrane proteins that include occludin, claudin, and junction adhesion molecule (JAM), as well as cytoplasmic proteins, specifically zonulin-1 (ZO1), zonulin-2 (ZO2), and zonulin-3 (ZO3). Many patients with autoimmune disorders produce antibodies against their own occludin and zonulin, which serve as useful laboratory markers in diagnostic testing. (This evaluation is provided in Cyrex Array 2.)

Lipophilic toxins. Tight junctions between the cells of the BBB endothelium form a physical barrier, significantly reducing passive diffusion through the paracellular pathway, and forcing any molecular traffic to occur mainly across the endothelial transcellular pathway. However, gases such as oxygen and carbon dioxide can easily diffuse across the barrier via the lipid membranes. This provides a security breach through which toxic lipophilic chemicals including petroleum-based products and other fat-soluble chemicals can cross the BBB, invading the CNS. (Antibodies targeting lipophilic toxins are among the 12 substances evaluated in Cyrex Array 11.)

A growing body of research has implicated the effects of BBB dysregulation in acceleration of chronic neurodegenerative disorders, including:

- Faulty BBB clearance of potential brain toxins in Alzheimer's and Parkinson's disease
- Inefficient clearance of excitotoxins across the BBB after an ischemic insult or TBI
- Increased transport of leukocytes across the activated BBB in AIDS dementia, Alzheimer's disease, multiple sclerosis, and during neuroinflammatory CNS responses
- BBB breakdown in Alzheimer's disease, amyotrophic lateral sclerosis, epilepsy, and multiple sclerosis.

The mechanisms by which toxic chemicals disrupt the endothelial tight junctions are shown in Figure 1 (p. 60), through processes that result in damage to astrocytes, microglia activation, the production of autoreactive antibodies, free radical generation, and immunoexcitotoxicity. ➤

Blood-Brain Barrier

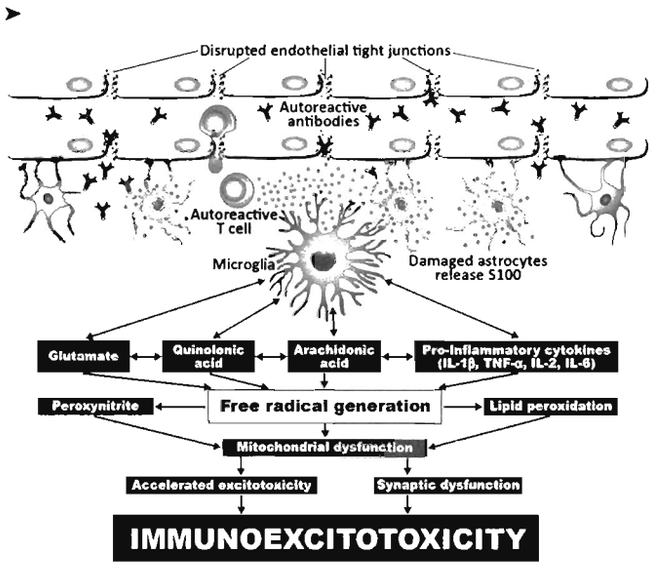


Figure 1. Proposed mechanism for excitotoxicity from leaky BBB. Environmental triggers, brain inflammation, and disruption of the BBB leads to the release of free radicals and immunoinflammatory factors, causing acute microglia activation, which contributes to immunoexcitotoxicity.

Secondary Disorders

Chronic inflammation and deterioration. Chronic inflammation in the brain can be caused by environmental triggers such as infection or toxic chemicals that activate neurons, astrocytes, and microglia to produce cytokines. As is shown in Figure 1, environmental triggers and inflammation in the brain cause brain cells to produce TNFα, IL-1b,and IL-6, which contribute significantly to neuronal cell destruction and neuroautoimmunity.

Cancer. Polychlorinated biphenyls (PCBs) are a prime example of a toxin that can disrupt blood-brain barrier integrity and promote brain metastasis formation. When these exposures occur, the chemical opens the barrier, damaging the astrocytes, which then can no longer protect the barrier. The same process can occur with infections such as *Borrelia burgdorferi*, cytomegalovirus, Epstein-Barr virus, herpes type 6, and other environmental triggers which directly or indirectly damage the barriers, resulting in neuroautoimmunity and even cancer.

Specific Exposures

Traumatic brain injury (TBI). Injuries such as those occurring in accidents, military combat, or in many sports can lead to repeated disruption of the blood-brain barrier. It is estimated that in the United States alone, 4 million people experience sports and recreation-related concussions annually. In football, for example, approximately 40% of players experience concussions. The repeated head trauma and TBI associated with contact sports such as boxing, basketball, and soccer have also been shown to induce BBB permeability, followed by antibody production against BBB proteins through a number of processes:

- Autoantibodies targeting the BBB – indication of pathological alteration of the protective brain barrier.
- Neurotransmitter dysregulation – manifest in both pre- and post-synaptic dysregulation of neurotransmitters.
- Excitotoxicity – this pathology involves free radical formation, brain swelling, and the entry of locally produced molecules such as cytokines and chemokines, disrupting metabolism and contributing to neuroinflammation and oxidative stress.

These processes have been confirmed in clinical research such as a study of 57 football players, medically evaluated before and after games, measuring the level of S100-B proteins. Serum S100-B was detected in players who experienced the greatest number of sub-concussive hits. Since this is a large protein molecule (21 kDa), even trace amounts handled by cells involved in the immune system resulted in antibodies against S100-B. The presence of this protein in a blood sample means that the BBB has been breached or damaged, and antibodies produced against S100-B have invaded the CNS.

The high degree of sensitivity of this testing was confirmed in a French study involving 2,000 patients with minor head injuries, comparing CT scans with plasma S100-B levels. TBIs were identified by antibody testing with 99% sensitivity and 20% specificity, confirmed by CT scan with the conclusion that S100-B testing is a highly promising screening tool.

Environmental Exposures

Inhaled exposures. Particulate matter due to environmental pollution can also cause breaching of the BBB and lead to the induction of neuroimmune disorders. Traces of toxic chemicals such as benzene and formaldehyde and heavy metals such as mercury proliferate in air, water, and soil. Particulates of these toxins can enter the human body through the lungs or digestive tract, activating lung and intestinal tissue enzymes and triggering inflammation. In the lungs, tight junctions normally seal the gap between epithelial cells of the airway preventing entry of antigens, microbial toxins, and particulate matter. The breakdown of tight junction protein complexes in the lungs (as well as the tight junctions in the gastrointestinal and BBB barriers) contributes to the entry of antigens, xenobiotics, and chemicals into the circulation, resulting in inflammatory responses followed by the formation of autoantibodies that readily cross the compromised BBB.

These autoantibodies can attack key nervous system components such as GAD-65, transglutaminase-6, and cerebellar tissue, potentially leading to neuroinflammatory

and neurodegenerative disorders. Thus, detecting significant elevations in IgA, IgG, and IgM antibodies against barrier-forming proteins is key to understand the environmental pollutant mechanistic pathways affecting epithelial and endothelial barriers. The mechanisms by which environmental pollutants can affect the barriers and lead to neuroautoimmunity are shown in Figure 2.

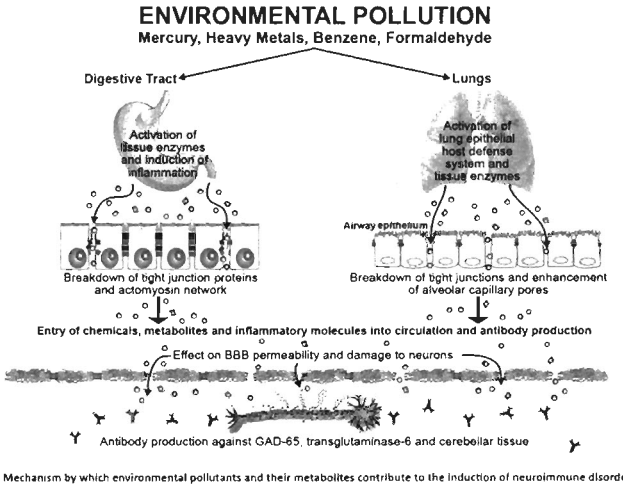


Figure 2. Proposed mechanism for the effect of environmental pollutants on the BBB, leading to neuroautoimmunity. Environmental pollutants enter the system either through inhalation or consumption, activating enzymes and inducing inflammation. This opens the tight junctions, allowing pollutant molecules to enter the circulation, causing autoantibody production. Autoantibodies attack neuronal cells of the CNS, leading to demyelination and neuroautoimmunity.

Chemical toxins. Simply measuring chemicals in urine or blood is not enough to indicate exposure. In 80% of patients, these chemicals are successfully excreted, but in an estimated 20% of patients, chemicals form a complex with human tissue and remain in the body, possibly for life. When these chemicals bind to human tissue (for example as deposits in fat cells), they induce antibody production against both the toxins and human tissue.

Whenever autoimmunity is present, it is vital to ask why the immune system is producing antibodies against the patient's own tissue. The answer is usually because toxins or antigens of an infectious agent from the environment are binding to the patient's tissues, causing antibody production.

Research was conducted measuring antibodies in blood samples from 400 so-called healthy subjects (200 males and 200 females of different ethnicities with a median age of 36.2 years). Researchers found that 25% of participants were producing antibodies against various chemicals, indicating chronic exposure to chemical haptens. The formation of chemical-protein adducts could be one of the mechanisms by which environmental chemicals induce autoimmune reactivity.[1]

Exposure to molds and mycotoxins or infection. A significant number of patients experience symptoms in response to molds and/or mycotoxin exposure. Various other types of infectious agents can also have these effects, including Lyme disease. Autopsy research has reported that brain tissue of Lyme patients evidenced plaque and tangles typically characteristic of patients with Alzheimer's disease.

Viral hitchhiking. The BBB works efficiently to prevent brain infections. However, viruses can penetrate the barrier by attaching onto circulating cells of the immune system. Systemic LPS (lipopolysaccharides) enhance both immune cell and free virus transport across the intact BBB. *In vivo* and *in vitro* studies, for example, have found that free HIV-1 can be taken up by brain endothelial cells and cross the BBB. LPS act at the luminal surface of the brain microvascular endothelial cell monolayer, which induces abluminal secretion of cytokines and other factors that subsequently act on pericytes. The pericytes then secrete substances that enhance viral transcytosis across the BBB.

Electromagnetic fields. Effects of cell phone radiation on the BBB were initially identified 20 years ago. In an animal study evaluating radio frequency radiation, Adlkofer found albumin leakage in 32% of the 184 animals evaluated. Human clinical trials have shown that exposure to radio frequency radiation results in the leakage of albumin from the brain and is also associated with symptoms of memory loss and forgetfulness. Radio frequency energy is transmitted by cell phones, tablets, and laptop computers through blue tooth and other wi-fi connections.

Table 1.
Cross Reactivity Between Environmental Triggers and Neurological Tissues

Environmental Triggers	Neurological Tissues Impacted
Camplobactor jejuni, streptococcal proteins; gliadin, lipopolysaccharides	Asialoganglioside
Chlamydia pneumonia, herpes 6, streptococcal protein; gliadin	Myelin basic protein
Streptococcal protein	Tubulin
Gliadin	Synapsin
Milk butyrophilin	Myelin oligodendrocyte glycoprotein
Gliadin, milk butyrophilin	Cerebellar

Intestinal Permeability

Leaky gut. The elegant barrier of epithelial tight junctions in the gut provides four or five different layers of protection that are not easily breached. However, environmental ➤

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exposures of sufficient magnitude can trigger a cascade of events that open the tight junctions. When that occurs, undigested molecules, lipopolysaccharides (LPS), and other bacterial toxins enter the submucosa through the circulation.

The gut-brain connection has been well studied in the existing literature. Gut epithelium resembles the BBB in many respects, with perhaps 75% similarity in structural composition. Due to antigen similarity between tissue proteins in gut endothelium and in BBB proteins, "leaky gut" can result in "leaky brain." If the gut barrier is not repaired, those molecules now open the BBB, resulting in inflammation and autoimmunity in the nervous system.

Dysbiosis. Dysfunctional flora or overgrowth is a well-recognized trigger of leaky gut. Certain dietary components such as gluten, dairy, and other antigens can also open the BBB, resulting in antibody production against nervous system antigens and brain receptor cells. Due to the similarity between gluten and casein (both a-casein and b-casein), and synuclein and oligodendrocytes in the brain, resulting antibodies can attack nervous system antigens, resulting in neuroautoimmunity.

Food antigens. LPS is not the only molecule that has been shown to transport viruses across the BBB. In an animal study, wheat germ agglutinin (WGA), a lectin protein from wheat, was injected into subjects. WGA was found to bind to sialic acid and N-acetylglucosamine, inducing vesicle-mediated internalization of WGA by brain endothelial cells, a process called adsorptive endocytosis. Lectin-induced vesicles provide a mechanism by which enveloped viruses can be internalized by cells. These study results strongly suggest that glycoprotein gp120 or gp120/gp41 induces adsorptive endocytosis and the uptake of HIV-1 by brain endothelial cells. This action explains how free, blood-borne viruses can infect the CNS while the BBB remains intact.

Environmental factors, if they are powerful enough, can initiate the cascade of events that directly or indirectly opens the tight junctions. If we do not repair the gut barrier, those molecules can open the blood-brain barrier, triggering adverse effects that include inflammation, oxidative stress, neurotoxicity, autoimmunity, degenerative disease, or cancer.

Advanced Antibody Testing: Array 20

This array is relevant to the assessment, diagnosis, and management of disease risk, progression, and progress in healing for patients with suspected trauma, TBI, and neurodegenerative and autoimmune disorders.

Evaluating preclinical symptomology. The test has efficacy in the assessment of preclinical conditions to evaluate potential breaching of the blood-brain barrier due to trauma, environmental triggers, or dementia with useful findings even in the absence of a clearly defined diagnosis.

Assessment of minor injuries. This lab work is useful for patients who play contact sports and/or have experienced trauma to determine whether a concussion or TBI has occurred. The test is cost-effective, so it can be used in situations involving minor injury such as high school athletics, for example, when an MRI would seem excessive and could be prohibitively expensive.

Rehabilitation. Array 20 can also be used to monitor injuries, indicating when it will be safe to return to normal activities. One of the major concerns after a first injury is the prevention of recurrent injuries before the brain is completely healed. Repetitive brain injury that occurs before complete healing and repair of the neuroinflammatory response can accelerate and exacerbate chronic activation of the microglia, with serious consequences.

Management of complex neurological disease. Antibody testing provides a noninvasive tool for assessing the effectiveness of interventions for neurodegenerative disorders such as Alzheimer's disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), epilepsy, multiple sclerosis, Parkinson's disease, stroke, and vascular dementia.

CLINICAL THOUGHT PROCESS

When the patient presents with a complex chronic condition, which of these tests do we perform, in what order, and why?

Are the barriers intact (leaky gut, leaky brain)?
Array 20 – Blood brain barrier – evaluation for the presence of BBB protein antibodies, indicating a breach of the BBB

Array 2 – Leaky gut and brain barrier – antibodies directed against occludin, zonulin, lipopolysaccharides, or endotoxins.

Are there environmental triggers?
Array 3 – Dietary components – gluten, dairy
Array 4 – Cross-reactive foods
Array 11 – Body burden of toxic chemicals – simultaneous detection of antibodies against 12 different major chemicals including aflatoxins, formaldehyde, isocyanate, heavy metals such as mercury, parabens, bisphenol A, and tissue antigens.

Which issues are being targeted?
Array 5 for multiple autoimmunity – antibodies against 24 different tissue-specific antigens including 5 neuron-specific antigens. This one test can be used to assess more than 50 different autoimmune reactivities.

Clinical Strategies

Antibody testing is an evaluation with high clinical utility. Identifying reactivity to foods or environmental exposures provides clear-cut action steps the patient can take to reduce immune activation. If the trigger is a food or a chemical, eliminate it – remove it from the environment of the patient. Once the exposure is reduced, typically patients experience major improvement in two to six months. If, for example, testing shows elevated lipopolysaccharides in the gut indicating leaky gut, then repairing the gut can also help to repair the brain barrier. Supplements that can be recommended include probiotics, curcumin, resveratrol, glutamine, n-acetyl-cysteine, vitamin A, vitamin D, omega 3, or omega 6 essential fatty acids. These are all nutrients that can help to repair the barriers. This evaluation also serves to motivate patients, since it provides the logic for specific interventions with scientific evidence to back up recommendations.

Rationale for Testing

The need for effective neurological evaluation today has never been greater, considering the millions of people who experience traumatic brain injury in any given year, including soldiers, accident and trauma victims, and athletes. Additionally, millions of individuals across the age spectrum suffer from cognitive disorders, ranging from children with ADD, ADHD, ASD, developmental disorders, or epilepsy to seniors with ALS, autoimmune conditions, MS, Parkinson's, stroke, or various forms of dementia. The prevailing method of choice for detecting intracranial injury in patients with even minor injury is computed tomography (CT) scan or MRI (magnetic resonance imaging). Although the CT scan has high sensitivity in detecting intracranial injury, it is expensive, exposes patients to high doses of radiation, and identifies clinically relevant lesions in less than 10% of cases. In addition, neither MRI nor CT scan can detect autoimmune reactivities.

Antibody testing is an evaluation technique that has demonstrated 99% sensitivity in the clinical setting. This is a viable adjunct or alternative to imaging for the full range of neuroautoimmune disorders, including traumatic brain injury, progressive dementia, neurodegenerative disease, and autoimmunity.

Aristo Vojdani PhD, MSc

Aristo Vojdani is presently a professor of neuroimmunology at the Carrick Institute for Graduate Studies and past associate professor at the UCLA School of Medicine and Science. He obtained his MSc and PhD in the field of microbiology and clinical immunology with postdoctoral studies in tumor immunology at UCLA. His ongoing research, spanning a 45-year career, focuses on the role of environmental factors in complex diseases. Dr. Vojdani's research on predictive antibodies has resulted in the development of numerous antibody arrays for the detection of autoimmune disorders. He is the CEO and technical director of Immunosciences Lab in Los Angeles and chief scientific advisor for Cyrex Labs in Phoenix. Owner of 15 US patents for laboratory assessments, Dr. Vojdani has published more than 140 scientific articles and sits on the editorial boards of six scientific journals. He is recipient of the Herbert J. Rinkel Award (2006) from the American Academy of Environmental Medicine, the Linus Pauling Award (2009) from the American College for Advancement in Medicine, and the Carrick Research Institute's Lifetime Achievement Award (2012).

Resources

Cyrex™ Labs is an advanced clinical laboratory focusing on mucosal, cellular, and humoral immunology. Cyrex specializes in antibody arrays for the early detection and monitoring of complex conditions such as thyroid disorders, as well as gluten reactivity and other food-associated autoimmunities, and related neurodysregulation. Cyrex's scientific advisory board, comprised of experts from a variety of medical and research disciplines, brings together the latest findings from medical research and the assessment needs of today's healthcare professionals for the development of innovative arrays. For additional information, see www.CyrexLabs.com.

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NEW JOURNAL: *Brain and Gut*

Mary Ann Liebert, Inc., publisher, announces the launch of a new peer-reviewed journal, ***Brain and Gut,*** launching summer 2014. David Perlmutter, MD, a board-certified neurologist, will serve as Editor-in-Chief. Aristo Vojdani, PhD, Director of Immunosciences Lab, Inc., Los Angeles, California, and Gerard E. Mullin, MD, Associate Professor of Medicine, Johns Hopkins University School of Medicine, will both serve as Editors. The journal will publish leading-edge research with a whole ➤

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systems approach to digestive disorders, cognitive issues, mood disorders, autoimmune conditions, diabetes, and cancer, encompassing the intersection of neurology, gastroenterology, and immunology.

EDITORIAL

This article is drawn from the writing of Aristo Vojdani, PhD, and also includes interview content. The editor, Nancy Faass, MSW, MPH, provides support for authors in the development of articles, books, manuals, white papers, and writing for the Web via her company, HealthWritersGroup.com

Our thanks to Jerry Stine, NC, for technical support on this article; see www.Lifespan-Institute.com.

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The Brain Gain: Improving Brain Health

by Danielle Citrolo, PharmD

Diseases affecting the brain are an area of ever-increasing prevalence and concern in the health of our nation. According to the Alzheimer's Association, Alzheimer's disease – a progressive, degenerative disorder that attacks the nerve cells of the brain – currently affects more than 5 million people in the US. The drastic increase in recent Alzheimer's diagnoses has even led Congress to unanimously pass a national plan, known as the National Alzheimer's Project Act, that will aggressively address the issue with increased funding for scientific research, similar to previous work done for the AIDS crisis and cancer.

Still, despite ample awareness of brain health issues, the brain itself remains one of the biggest mysteries of human anatomy due to its unparalleled complexity. Yet, with today's highly sophisticated technology, doctors and scientists are learning new ways to tap into the brain's full potential and improve brain function. These brain specialists study the connections within the various parts of the brain to discover ways to help our memory and attention as we age and develop disease.

Science has taught us that the brain powers 100 billion neurons, which constantly fire messages (like tiny electrical charges) across trillions of microscopic gaps between the brain's cells. As with all functions in the human body, the brain draws on energy housed within the mitochondria within each and every cell of the human body. So, what additional steps can be taken to improve the brain's mitochondrial function and potentially combat cognitive decline?

First, an active lifestyle and healthful eating habits provide a great foundation. Steven Pratt, MD, author of *Superfoods Rx: Fourteen Foods Proven to Change Your Life,* suggests foods such as blueberries and broccoli as options to help protect the brain against oxidative stress. Other foods, such as fish, eggs, milk, and algae-derived supplements, contain omega-3 essential fatty acids that are imperative for brain function. Finally, nuts and seeds provide a good source of vitamin E, of which adequate levels are linked to less cognitive decline.

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Studying Citicoline Supplementation

In healthy adult women:

The Brain Institute conducted a study focused on the administration of citicoline oral supplements to healthy adult women. The randomized, double-blind, placebo-controlled clinical trial involved 60 healthy adult women – ages 40 to 60 – who were administered a daily oral dose of 250 mg citicoline or 500 mg citicoline over a 28-day period. The results concluded that participants who were given either dose of citicoline produced better results in a cognitive inhibition test; and findings suggest that supplementation with citicoline positively affects cognitive scores, attention, and performance after only a 28-day timeframe.

In the aging population:

In another placebo-controlled study, a group of elderly subjects who exhibited memory deficits (not including dementia) were observed after oral administration of 1000 mg and 500 mg of citicoline. After a 4-week administration period, the results indicated that citicoline, compared with a placebo, improved memory in free recall tasks and resulted in significant improvement in word recall. The study suggests that citicoline improved memory deficits in these elderly subjects.

In healthy adolescent males:

Recently, a study conducted by the Brain Institute found that oral supplementation with citicoline enhanced motor skills and attention in healthy adolescents. The double-blind, placebo-controlled 28-day trial took place with 75 adolescent males who received oral supplementation of 250 mg or 500 mg of citicoline daily. The research indicates that individuals who were administered citicoline – regardless of dosage – showed multiple improved cognitive domains, measures of attention, and motor speed. The study was groundbreaking not only in its results, but for its rarely tested young, healthy population.

Improving Brain Health

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Second, according to the Mayo Clinic, social activity can help fight cognitive decline and depression, and in turn boost brain health. There have also been reports that mentally stimulating games, such as crossword and Sudoku puzzles, can help keep the brain sharp.

Finally, nutrients or a well-researched dietary supplement, such as citicoline, can also contribute to better brain function when ingested in the body. Citicoline is referred to by the scientific community as a "brain nutrient" because of its ability to support healthy mitochondrial activity required for sustained mental effort. While the brain produces its own levels of citicoline naturally to protect its cell membranes' integrity and help ward off disease, numerous studies show that oral supplementation may be beneficial when natural citicoline levels are insufficient due to stress, illness, or possibly aging. Several clinical studies also suggest that citicoline supplementation can work to increase brain energy and function, including supporting memory and concentration in study participants (see sidebar, p. 67). Remarkably, consumer awareness of citicoline remains very low, despite the positive research results and potential impact on preservation of brain health.

As hard-working researchers continue to investigate ways to boost the efficiency of the brain, ward off deterioration, and enhance the longevity of overall brain health, it's important to keep all options open. While there is likely no single solution, what scientists and nutritionists have discovered and will continue to discover is important to take into consideration. As the market for brain health grows, consumers, marketers, and regulators will continue to seek out efficacious ingredients backed by science and free of safety concerns.

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Stress, Pain and Addiction Affect the HPA, HPG, and HPT Axis: Part 1

by Dalal Akoury, MD

With the fast-moving life of today, one tends to find oneself always trying to cope with constant stressors. The fast evolution and constant change that characterizes this era of rapid technology has altered the fabric of our society. Everything and everyone has evolved abruptly, especially over the past 10 years or so. This hasty shift in technology, work conditions, family makeup, and expectations can easily create very steep imbalances, predisposing individuals to fall into what we call stress. Stress may be triggered by the slightest event, including family, friends, and peer pressure. Our society is inflamed; hence stress and pain are becoming fuel for the addiction epidemics.

The debilitating stress effects of pain have also significantly contributed to an indoctrinatory overprescription pattern of painkillers. In particular, opioid prescription and abuse have increased in the last decades. Prescription of opioids for management of noncancer chronic pain is increasing over the years, providing the main source of opioid access. The long-term effects of opioids use on the metabolism, particularly the endocrine system, is one of the prime foci of recent research studies. Opioids act on the hypothalamic-pituitary-adrenal (HPA) axis; increased levels of prolactin and GH; and decreased oxytocin, testosterone, LH, and estradiol in humans. However, the effects of opioids on arginine vasopressin and ACTH are conflicting.

Stress, Reward System, and Dopaminergic Pathway

Stress can be defined as any stimulus that alters physiological and psychological homeostasis or equilibrium. The nature and effects of stress may vary that stimulate or suppress several molecular and/or cellular signalling molecules. The stress response generally varies from one person to another due to distinctive coping styles.[1,2] Acute and chronic stress may lead to physiological and psychological disorders, including predisposition to addiction.[3]

Humans respond to stress via the HPA axis, activation of corticotrophin-releasing factor outside the hypothalamus and activation of sympathetic nervous system via adrenaline or noradrenaline.[4–6]

Alcohol and stress can induce the hypothalamus to release corticotrophin-releasing hormone (CRH) that facilitates release of β-endorphin. CRH is then transported to the anterior pituitary gland that synthesizes proopiomelanocortin (POMC), a key factor for stress hormones including ACTH and beta-lipotropin. ACTH is a potent stimulator of cortisol release. Other stress inducers, including noradrenaline, serotonin, and GABA, regulate CRH release. Similar pathophysiological

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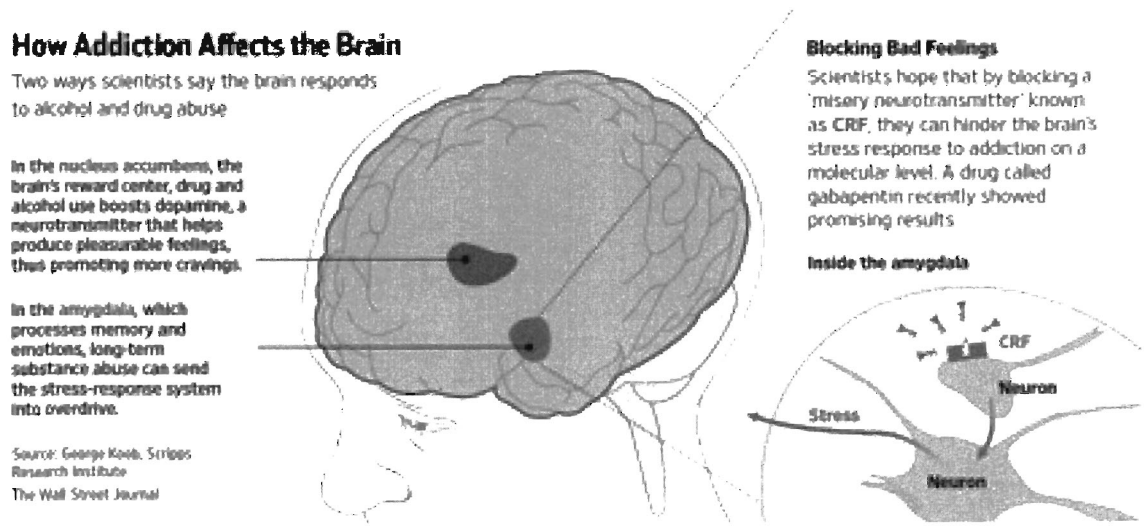


changes are observed in addicted individuals.[7–10] In stress conditions, sympathetic nerves contribute to adrenaline and noradrenaline release from the adrenal gland and cause stress.[11,12]

Increased CRF production outside the hypothalamus stimulates the mesocorticolimbic dopaminergic system, which is dopamine dependent. This system includes nucleus accumbens, amygdala, hippocampus, and ventral tegmental area (VTA). In addictive individuals, the brain's reward pathway is primarily mediated by the mesocorticolimbic dopamine system. Apart from addiction, the limbic system and hypothalamus are involved in the stress response and stimulation of CRF activity.[13–15]

Dopamine Levels in Acute Stress and Chronic Stress

Preclinical and human clinical studies have demonstrated the influence of stress on dopamine synthesis or mesocorticolimbic dopaminergic activity. Radiological studies have demonstrated that amphetamine, alcohol, and other addictive drugs have triggered dopamine release.[16–18] The pathophysiological relationship between stress hormones, drug addiction, and mesocorticolimbic dopamine activity is well documented.

Pruessner and colleagues have confirmed that stress during early stages of life could promote dopamine release in the ventral striatum that causes psychosocial stress and addiction.[19] The study results were confirmed by Oswald et al., suggesting the links between stress-associated cortisol release, dopamine levels, and amphetamine.[20] Psychological studies have confirmed that cortisol is a key contributor for dopamine release in stressed individuals.[21] However, the levels of cortisol and dopamine vary in acute and chronic stress conditions.

In adrenalectomized experimental animals, the body's stress response via the HPA axis contributes to glucocorticoids and dopamine suppression in the nucleus accumbens.[22,23] When the adrenal glucocorticoids were replaced with corticosterone injections, normal dopamine levels were restored. These studies have suggested the role of adrenals on dopamine release; acute stress could moderately affect the adrenals, and contributes to moderate dopamine increase. However, in chronic stress, it could be vice versa.

In acute stress, the expression and activity of dopamine is comparatively less than in chronically stressed individuals. The negative effects in the former are generally reversible and moderate. However, in chronically stressed individuals, the altered dopamine levels lead to hormonal, psychological, and behavioral dysregulation that increases the predisposition to addiction.

Dopamine Receptor Levels in Acute and Chronic Stress

The effects of dopamine on stress conditions depend on the expression of dopaminergic receptors. Humans exhibit genetic variability in the expression of dopaminergic receptors such as D2 and/or D3 receptors, dopamine turnover in response to stress-related stimuli.

Experimental studies have suggested that the effects of acute or chronic stress on the mesolimbic system and behavioral patterns are influenced by epigenetic patterns. Acute stressors induce 3,4-dihydroxy phenylacetic accumulation in the brain with significant reduction in dopamine levels.[24]

In experimental animals, repeated or prolonged stress could lead to hyposensitivity of D2 presynaptic receptors. Continuous exposure to restraint stress leads to decrease in D2 receptor density with normal levels of D1 receptor density in the nucleus accumbens. The direct relationship between the dopamine receptors and stress conditions is also confirmed by electric foot-shock tests. In experimental animals, activation of D1 and D2 receptors are vital for attenuation of fear, motor suppression, and so on.

Prenatal stress could alter the response to stress and expression of dopamine agonist/antagonist receptors. In prenatal stressed experimental animals, a significant increase in D2 receptor binding in the nucleus accumbens was observed. Significant decreases in D3 receptor binding in the core nucleus accumbens and shell were also observed.[25] In some individuals, chronic stress could decrease the density of D2 receptors but not the affinity.

Dopamine Uptake in Acute and Chronic Stress

Several research studies have suggested that removal of dopamine in chronic stressed animals is an adaptive mechanism of mesoprefrontal cortex. Increased D1 receptor stimulation during stress allows the posterior cortical and subcortical structures to regulate behaviors. Stress could alter the mesoprefrontal dopamine fibers and affect biochemical responsiveness of the dopamine subcortical innervations.

In experimental animals, repeated stress reduced basal locomotor activity and utilization of dopamine in the brain. The effects could be reversed by acute administration of D1 or D2 receptor antagonists.

In prolonged, mild stress conditions, dopamine uptake levels are affected, leading to altered behaviors.[26–28]

Moderate uptake of dopamine is important for normal behaviors, and excessive dopamine activity or impaired uptake leads to altered spatial working memory functions. This condition is common in acutely and chronically stressed individuals. However, the uptake of dopamine differs in both stress conditions.

Dopamine Metabolism in Acute and Chronic Stress

Repeated or prolonged stress has negligible effects on dopamine and serotonin metabolism. This may be due to adaptive mechanisms of the higher centers via the stress response mechanisms. However, acute stress conditions could decrease the hypothalamic epinephrine levels and return to normal within few hours.

Dopamine metabolism is affected due to hypothalamic adrenaline concentration and turnover in response to acute and chronic stress. Impaired adrenaline and noradrenalin turnover affects dopamine metabolism and causes behavioral changes, including predisposition to addiction.[29,30]

As with stressed individuals, decreased dopaminergic functions are reported in cocaine addicts. This could be due to reduced D2 receptor availability or expression, or impaired dopamine metabolism in cingulate gyri, frontal lobes, and orbitofrontal cortex.

Dopamine dysmetabolism could lead to loss of control with compulsive reinforcement that predispose to addictive behaviors.[31]

Dopamine Factors and Predisposition to Addiction

Significant neurobiological links between stress, dopamine factors, reward pathways, and risk of addiction are well documented. The reinforcing properties of habit-causing drugs are associated with the activation of the mesolimbic dopaminergic pathways such as prefrontal cortex, ventral striatum and ventral tegmental area.[32,33] Apart from stress mechanisms, the dopamine pathway is also associated with reward processing, adaptation, and learning.[34]

The role of dopamine factors in drug reward mechanisms is reported in opioid and alcohol abusers. This is due to activation of mesolimbic dopamine systems with drug cravings and euphoria.[35–38]

Experimental animal studies have suggested that stress exposure with increased glucocorticoid release could increase dopamine release in the nucleus accumbens.[39] Suppression of glucocorticoids could reduce extracellular levels of dopamine in resting and during response to stress and addictive substances.[40]

Chronic elevation of glucocorticoids inhibits dopamine synthesis and turnover in the nucleus accumbens. This mechanism suggests that alterations in the HPA and glucocorticoid levels could affect dopamine transmission. Drug abuse, stress, and increased levels of CRF and/or glucocorticoids could increase glutamic acid activity in the ventral tegmental area. This leads to enhanced activity of dopaminergic neuron.[41]

Human brain imaging studies have further shown that stress-induced cortisol elevation is associated with dopamine accumulation in the ventral striatum. Some evidence also reveals that amphetamine-induced increases in cortisol are associated with both dopamine binding in the ventral striatum and ratings of amphetamine-induced euphoria.[42]

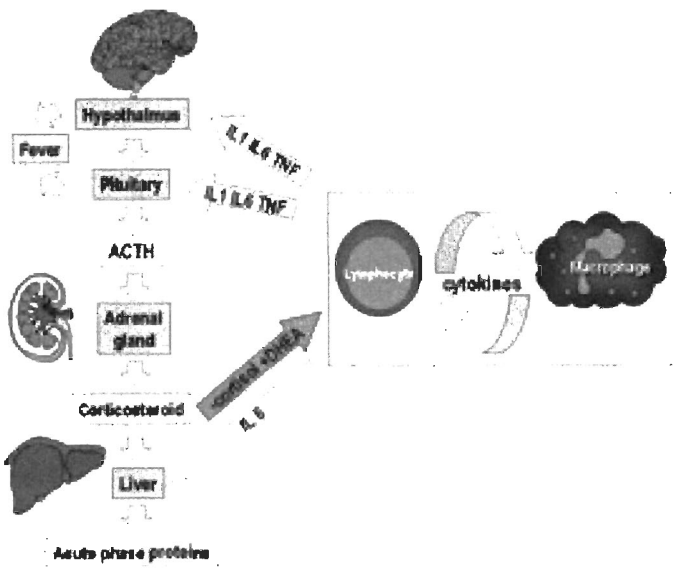
Drug abuse and stress activate the mesolimbic pathways, which results in synaptic adaptations in the ventral tegmental area of dopamine neurons with adaptive morphological changes in the medial prefrontal cortex areas.[43] The ventral striatum is a main regulator of behavioral response, stress, and mesolimbic dopamine pathways.[44] Mesolimbic dopamine pathways are linked with rewarding, stress adaptation and goal-directed behaviours. These pathways are also important for emotion control, stress processing, decision making and impulse control. Altered status leads to impaired stress processing, impulse control, and predisposition to addiction.[45]

Opioid abuse can impair secretion of pituitary hormones and cause hypogonadism and menstrual disorders.[46] The negative interaction between addiction and the hypothalamic-pituitary-gonadal (HPG) axis is well studied.

Effects of Addiction of Endocrine Pathology

Effects on HPA, Pituitary, and Sex Hormones

It is documented that prolonged elevation of glucocorticoid level is associated with persistent, chronic pain or stress disorders. Furthermore, in certain individuals, the administration of opioids for pain leads to negative effects on the HPA axis. Moreover, chronic opioid use and or abuse leads to decreased glucocorticoid response to acute activation of the hypothalamus-pituitary-adrenal axis, leading to adrenal insufficiency. It is worth noting that opioids exert direct stimulatory effects on adrenal glucocorticoid secretion via μ- and κ-receptors.[47,48]



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The influential role of opioids on the hypothalamic-pituitary-gonadal HPG axis was studied extensively. A dose-dependent response was observed between morphine and LH release in experimental animals.[49,50]

Opioids can effectively inhibit hypothalamic GnRH secretion and suppress LH levels in humans.[51] Chronic morphine abuse is related to inhibition of GnRH secretion in humans.[52] Li and Pelletier reported that morphine can reduce the biosynthesis of GnRH by downregulation of GnRH mRNA levels.[53] Opioids can regulate biosynthesis of gonadal sex steroidal hormones, the end products of the HPA axis via the feedback inhibition process. In experimental castrated-animal studies, estradiol- or testosterone-induced LH decrease was reversed by naloxone administration.[54]

Chronic morphine abuse has no direct effect on serum LH levels. However, it can increase the hypothalamus sensitivity to the testosterone-related negative feedback mechanism. In females, prolonged opioid abuse leads to estradiol–surge induced LH hypersecretion and increases estradiol-mediated negative feedback mechanisms. Thus, it is clear that morphine can amplify positive and negative feedback on gonadotropin release.[55,56]

Opioids, including exogenous and endogenous, can influence the increase and decrease of gonadal steroid hormones. Opioid peptides can cause decrease in LH pulse frequency.[57] In female experimental animals, central opioid neuron-mediated tonic inhibition of LH levels significantly affected the luteal phase. This leads to reduced LH surge and associated amenorrhea or oligomenorrhea.[58] Effects on opioids on the HPG axis can reduce the LH levels in humans.[59,60] The negative effects of opioids on the HPG axis depend on the circulatory levels of sex steroids during the menstrual cycle.[61] The adverse events of opioids on the HPG axis vary with age and increase during the pubertal stage.[62] During early and middle puberty, the negative feedback mechanism of estradiol on the HPG axis is independent of opioid receptor pathways.[63] In humans, chronic opioid administration leads to reduced LH levels; however, the serum FSH levels remain normal. Studies have confirmed that opioids can affect LH release only in the presence of sex steroids. This is due to negative feedback inhibition of hypothalamus GnRH secretion.[64] It is now clear that sex steroidal hormones are essential for modulation of opioid sensitivity in the HPG axis.

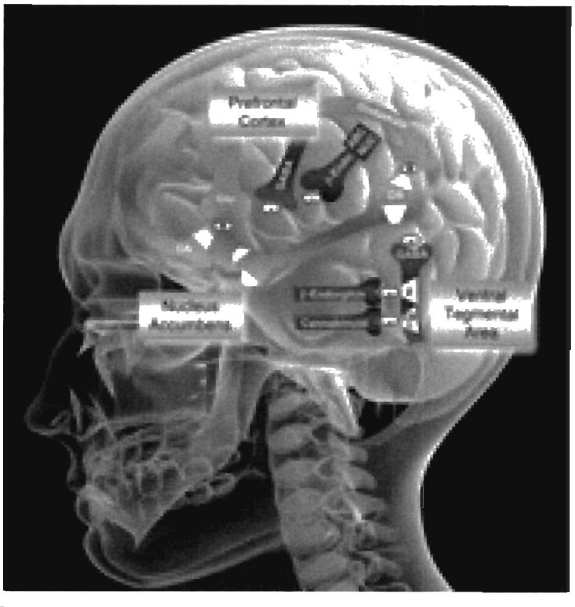
Effects of Opioids on Arginine-Vasopressin

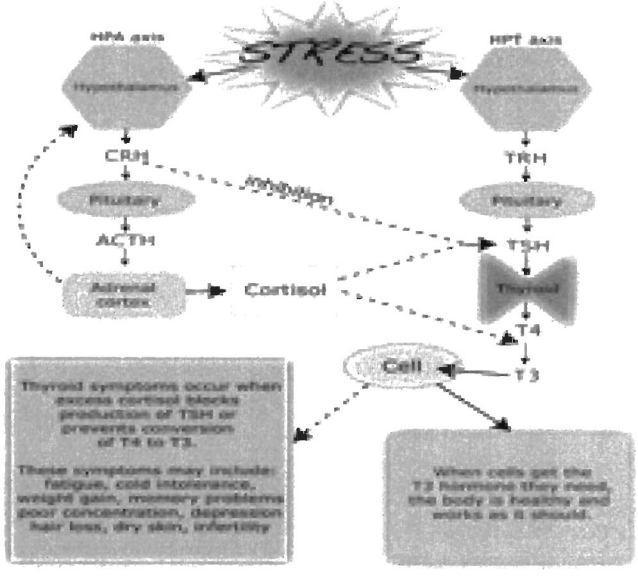
Effects of Narcotics on Oxytocin

Opioids selectively inhibit oxytocin secretion in humans. Prolonged morphine abuse could affect biosynthesis and release of oxytocin. Opioids suppress oxytocin regulation by directly acting at the pituitary and hypothalamic regions with key involvement of both κ- and μ-receptors.

Effects of Addictive Drugs on the Pathophysiology of Thyroid Hormones

In humans, administration of morphine could significantly increase the TSH levels among normal and hypothyroid individuals.[65] The TSH-stimulatory effects of morphine were confirmed by several other studies.[66] When compared with normal individuals and cigarette smokers, decreased levels of TSH were observed among opium users. The underlying pathophysiological mechanism could be stress conditions.[67]





Opioids stimulate TSH secretion in humans due to interaction with endogenous enkephalins. The hypothalamus is the key site for opioid action on the hypothalamus-pituitary-thyroid (HPT) axis. κ-receptors are the primary binding sites involved in the opioid action on TSH.

Roles of Addictive Substances on Sex Hormonal Disorders +

Administration of morphine reduces LH secretion as a result of decreased concentrations of sex steroidal hormones. Opioids significantly impair female menstrual cycle by suppression of progesterone, LH, estradiol and FSH levels.[68] Irregular menstrual cycle with amenorrhea is a prominent symptom of hypogonadism in women.

Opioids cause decreased synthesis of adrenal androgen production and androgen-dependent loss of libido. Controlled clinical trials have suggested that prolonged use of heroin could affect sexual desire and performance in men.

In heroin- and methadone-addicted men, decreased levels of testosterone were reported. About 89% of male hypogonadism is associated with oral opioid abuse. Oral opiates can significantly reduce FSH, LH, estradiol, and dihydrotestosterone among men.[69,70] With addition of hypogonadism and loss of libido, opiates can cause symptoms of depression.[71,72] Depression with sexual–dysfunction related stress is a key risk for addictive behaviors that can drive the individuals towards habit-forming drugs such alcohol, morphine, marijuana, and heroin.

This review article clearly indicates how complex is the stress, pain, addiction, and neuroendocrine interplay. Therefore a more comprehensive wholesome understanding of this stress, survival, and reward symphony is a must for us to effectively address and cure this disease of pain, stress, and addiction imbalance. I therefore propose an integrative addiction educational forum led by the experts in natural addiction therapy.

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Dalal Akoury, MD, is the founder of AWAREmed Health and Wellness Resource Center and the director of the Wellness U program. Dr. Akoury is board certified in anti-aging, functional, and regenerative medicine, as well as having accumulated more than 20 years of experience in emergency medicine and pediatrics, and a master's degree in public health. Dr. Akoury has also served fellowships in pediatric hematology/oncology and performed research in leukemia and the effects of smoking. This lifetime of experience, along with a unique sensitivity, genuine compassion, and driving passion to inspire health in everyone, has prepared "Dr. Dolly" to be in this place at this time. About developing her dream, AWAREmed and Wellness U, Dr. Akoury says, "My mission is to ignite the spark of health deep within everyone, and to allow this sparkle of wellness to shine through everyone's eyes, becoming one with the universe, and aligning body, mind, and spirit."

The Aging Brain

by Dan Moran

Introduction

By 2030, 72 million Americans, or 20% of the population will be over 65 years of age (from AgingStats.gov). Improvements in hygiene and health care have created the largest and healthiest aged population ever recorded. However, with age comes chronic illnesses and increasing risks of cognitive dysfunction and brain dementias such as Alzheimer's disease. In 2013, an estimated 5 million Americans aged 65 and older had Alzheimer's disease.[1] By 2050, this number may rise to 13.5 million (CDC Healthy Brain Initiative, 2013).[2] Approximately 10,000 persons reach age 65 every day in the US (www.pewresearch.org/daily-number/baby-boomers-retire). This is due to the Baby Boom generation, but the decline in birth rates assures that this change in demographics will continue long after this generation expires (ibid.). The aging population is an economic and general health concern; little has been done to educate the population on how to age successfully.

Aging has both physical and cognitive components. In terms of cognitive abilities, aging causes reaction times to slow down. From perception to conceptualization, and to decision-making and response, the processes involved in reaction time are reduced in aging. The level of complexity that requires a response adds to the reaction time. Cognition in normal aging might also be said to impinge on executive control. This concept includes the range of processes that involve planning, organizing, coordinating, implementing, and assessing many normal but non-routine activities of daily life. Older people may not show a drop in intelligence or in the ability to learn, but short-term memory is impaired and a different approach to problem-solving is used as the brain circuitry compensates for age-related changes at the cellular level. While the ability to learn is not damaged, the time needed to learn is extended in aged persons. Although attention skills are not affected in the aged, multitasking is reduced. Language skills work well, though processing time can be slower than in younger adults. Older people have conversational skills that are robust and are better than the conversation skills of younger adults.[3] However, loss in hearing and vision may be ascribed to cognitive deficits in persons misdiagnosed as cognitively impaired. While over 94% of seniors continue to live independently until their death, age-related changes in cognition are a reality that older people say they do not want.[4]

From birth to old age, the human brain undergoes extensive but subtle changes in shape, size, and neuronal wiring. Through young adulthood, the brain increases its connectivity. The maximum brain size is achieved around age 20 and shrinkage occurs at a rate of about 1 gram per year afterwards.[5] Throughout life, the brain's wiring will change as learning and memories continue to form. The branching and connectivity of the brain form memory, recall, and cognitive power. This is particularly true for regions dedicated to cognition including the hippocampus, frontal cortex, amygdala, and parietal lobes. A single neocortical neuron has 2500 connections at birth, but by age 2, it may have up to 15,000 synaptic connections.[5,6] The brain's 100 billion cells will make 150 trillion connections in a lifetime.

After age 20 or so, as the brain begins to shrink, the number of neuronal cells drops by 10% but the glial cells, which support the neurons, are fully formed in youth and do not drop significantly in old age. The neocortex shrinks an average of 10% by age 80.[5] However, the white matter accounts for 24% of this shrinkage, while the gray matter does not shrink or lose thickness much.[7] A nearly 50% loss in myelinated fibers occurs from age 20 to age 80.[7] This is the equivalent of a 180,000-kilometer highway system being cut in half (the US has around 80,000 km of highway). The ventricles of the middle brain enlarge in response to this loss of white matter. An average of 85,000 brain cells dies every day; this is 1 cell per second, or 31 million a year.[5] There is a reduction in dendritic spines and blood vasculature, and dead cells begin to accumulate, which indicates the processes of brain maintenance slowdown.[8] As the connections between neurons (the neuropil) are progressively lost in the aging brain, so are memory, sensory learning, and neuroplasticity.[9] Cells that do not die, eliminating their connectivity, undergo a reduction in the size and the stability of their connections, resulting in weaker synapses less capable of short-term plasticity.[10] This activity is fundamental to dynamic responses in cognition.

Aging is the greatest risk factor for neurodegenerative diseases of the brain. This is true for Alzheimer's

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disease, Parkinson's, ALS, and other dementias and disorders.[5] When age-related changes are compared with pathological brains such as those of Alzheimer's victims, the results are exponentially worse. Areas of the brain involved in learning and memory are not diminished, they are devastated. At death, the heart of memory, the hippocampus, is obliterated of cells. Strangely, the reported changes in the normal aging of individuals are confounded when measures of cognitive performance are used to test the elderly. The results show a continuum of values between demented and nondemented persons.[11] This is disconcerting, since no clear demarcation between diseased and normal-aged persons can be drawn, and it suggests that the future for many normal individuals is impairment, memory loss, and some degree of behavioral change as they age.[5]

Neurology 101

The brain contains several major cell types, the neuron that transmits electrical impulses and glial cells that support the health and function of neurons. Neurons can transmit electrical signals down the length of their axons by generating an action potential. Action potentials are generated by voltage-gated ion channels embedded in the plasma membrane. Innervation causes these channels to open, allowing sodium ions to pass to the inside of the cell. The cascade of the electrochemical signals runs down the length of the cell's axon, creating a traveling spike of electrical activity. As the sodium channels close, potassium channels open, allowing potassium ions to exit the cell, repolarizing the neuronal membrane. A slight hyperpolarization occurs due to the charge difference between potassium and sodium ions across the membrane. This afterhyperpolarization varies in duration for different signals due to the length of time for potassium channels to shut. The afterhyperpolarization forces the depolarization in one direction and plays a role in the response time of neurons to reach resting potential. When this signal reaches the synapse, the junction between two neurons, a second set of voltage-gated channels allow calcium into the axon terminals. Calcium ions (Ca2+s) activate the release of neurotransmitters across the gap. Receptors on the postsynaptic neuron located on the dendritic spine of the synapse bind the neurotransmitters, causing local depolarization of the membrane at these junctions. Sufficient depolarization of the postsynaptic membrane reaches a threshold at which a second action potential is induced and the impulse is successfully transmitted to the next neuron. In aging neurons, nerve cell excitability is altered in several ways that is reflected in changes in reaction time and hence cognition.

Brain Function at the Molecular Level

Aging is a multifactorial process of change, with the Ca2+ as a common denominator. In fact, aging is highly correlated to the ability of brain cells to regulate the Ca2+. Ca2+s are used to mediate the biology of muscle contraction, protein secretion, respiration of sugars, cell division, chemical transport, gene activity, memory consolidation, neuronal plasticity, and even thought through a network of intracellular messaging systems.[12] In neurons, proteins form the channels, pores, messenger signals, sensors, buffers, and pumps that manage the calcium concentration across internal and external membranes of the cell.

Three major regions of high calcium concentration exist with respect to the inside of the cell. These are the external membrane, the internal membrane (endoplasmic reticulum, or ER) and the mitochondria. Calcium concentrations are kept some 10,000 times higher outside the cell than inside the cell. Internal stores of calcium are sequestered to the ER (internal membranes) and the mitochondria. Channels, pumps, pores, and ion transporters control the entry and exit of calcium from across the cell membrane. Internal stores of calcium release the Ca2+ into the cytosol upon activation by signals received across the cell membrane. The Ca2+ activates Ca2+ release inside the cell through signal transduction mechanisms found at the cell membrane. The ER extends throughout the neuron as a complex system of endomembranes. Calcium activation of Ca2+ release from the ER initiates waves of internal ion release, creating an internal depolarization. The type of wave communicates the changes in synapse morphology and by this the nature of synaptic plasticity, short-term versus long-term memory formation.[13] Mitochondria most often act as emergency sinks for excess calcium, adding to the fine-tuning of calcium concentration in the cytosol of the cell.[14] The mitochondria hold the Ca2+ until safe concentrations of the ion are obtained by membrane pumps and transporters. Even the location of these cellular organelles is controlled by the neuron to optimize the local homeostasis of the Ca2+.[14,15]

A good example of calcium-activated release of ER stores of calcium is found in muscle cells. Innervation by the brain transmits electrical signals to the membrane of the muscle cell. This innervation of muscle cells causes a massive release of internal calcium from stores of the ER. The calcium is bound by the muscle protein troponin, which changes conformation to expose an ATPase domain on its protein partner the myosin chain. ATP then drives the contraction of these intertwined proteins, causing them to slide past one another, creating contraction. The burst of calcium release from the ER of muscle cells is buffered by the presence of calcium-binding proteins such as calbindin-D9k and parvalbumin. This allows contraction of the muscle cell while holding the overall calcium concentration at nontoxic concentrations until the

$Ca2+s$ are sequestered by the ER once again. This sequestering of calcium is done by energy-dependent ATP-driven pumps in preparing for the next contraction event. These pumps are abundant, comprising 80% of the membrane proteins of the muscle ER and occupying 30% of the membrane surface.[16]

Much has been gained in model species such as rodents, fruit flies, nematodes, and the microscopic rotifer, a multicellular animal with complete digestive, nervous, and sexual reproductive systems. Early studies on aging revealed that as animals age their intracellular calcium concentration rises above the basal concentration of younger cells. It was noted that as rotifers age, they stop sexual reproduction, locomotion slows down, and feeding and reaction times become sluggish until the animal dies in about 10 days.[17] The internal calcium concentration increased in rotifers as senescence set in. With the calcium–channel blocking drug nifedipine, age-related decline and a longer life span (15%) were demonstrated in the rotifer.[18,19] Rotifers grown in a low-calcium environment lived up to 50% longer than those grown in higher-calcium solutions.[20] Aging not only slowed but was reversed in these studies.

Calcium plays a multitude of roles in brain cell physiology, including such events as the generation of the action potential that innervates neurons, the calcium-induced release of neurotransmitters at the synaptic junction that transmits the electrical activity of one neuron to another, and the calcium activation of genetic events leading to the formation and the modification of synaptic junctions.[12] This latter event mediates neuronal plasticity, the dynamic formation or modification of neuronal wiring. In contrast to a former hypothesis that the brain was a static organ, neural plasticity is known to modify the fundamental architecture of the brain throughout life. It is now understood that memory formation is a product of neural plasticity and the brain's cellular connections are the foundation to creating hardwired networks for memory, learning, recall, and ultimately cognition. Cognition, of course, is defined as the existence of mental processing. This must include accessing a working memory, reasoning, comprehension, deliberation, communicating, and decision-making. Calcium is thus the mediator of our awareness and ultimately the toxin that disturbs and dims our consciousness as we age.

As we age, molecular changes in calcium regulation impinge on neuronal physiology. Changes in brain cell biology have ramifications for the health of the brain and may compromise cognitive function, reducing the quality of life and potentially staging older people for serious cognitive impairment or conditions such as Alzheimer's disease. Understanding the fundamentals of brain cell biology can help in designing research programs to aid in the prevention and treatment of age-related cognitive decline. A number of promising technologies and health initiatives are in place to support successful aging. In the next article, the details of molecular and cellular biology of aging brain cells will explain the basis for changes in cognition. Although aging is not yet defined as disease, there are known preventive measures to retaining brain health and hopeful strategies to support cognitive function in old age.

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Dr. Moran is the director of manufacturing science for Quincy Bioscience and has over 25 years of practical recombinant fermentation experience. He is responsible for the development of practical and efficient manufacturing techniques for apoaequorin and also for accomplishing scale-up capabilities to include continuous batch manufacturing. Dr. Moran holds a PhD in genetic engineering and a master's degree in microbiology from Ohio University.

FCT Documented Case of Curing Autism, Thanks to Cause-Based Approach to Chronic Diseases

by Savely Yurkovsky, MD

A while ago I received a rather typical e-mail inquiry concerning a disease, along with a list of related laboratory abnormalities.

It was a case of a 3-year-old boy with autism, ADHD, food and environmental allergies, picky eating, chronic cough, difficulty sleeping through the night, and poor energy level. As usual, lab findings looked impressive, and, based on these recommended treatments, seemed logical and necessary.

See the copy below.

> Dear Dr. Yurkovsky,
>
> My son was diagnosed with PDD and we went to a DAN (Yasko) doctor.
>
> Blood tests showed
>
> - gene mutation called compound heterozygous MTHFR and as a result inability to process group B vitamins (the results came just for B12).
> - casein intolerance
> - bacteria overgrowth (mycoplasma and Lyme),
> - Diphtheria virus positive
> - myelin antibodies positive
> - high level of copper and zinc.
>
> The following protocol was suggested:
> - MB12 shots, omega fish oil, probiotic, multivitamin. No cow's milk.
> - chelation
> - allergy tests (needles)
> - MRIs
> - Antibiotic treatment for Lyme and mycoplasma
>
> I would appreciate your reply.
> HB

My brief reply, in essence, was that these seemingly impressive lab reports were void of the single most important information in all chronic diseases that is their primary cause. Concretely, what might be the possible and exact causes of that gene mutation, what is causing intolerance to casein or other foods, why is he producing antibodies against his nervous system, why does he have mineral and metal imbalance, why is he susceptible to Lyme and mycoplasma infections?

Also, have these lab abnormalities necessarily caused his autism and other health problems, or are all of these just symptoms caused by deeper and primary sources of all of his medical problems? In light of these considerations, I advised the mother that the proposed treatment plan seemed to be directed more at symptoms than at their causes or the real disease. And, as a rule, such approaches rarely succeed.

I advised her that the best chance to attempt to establish primary causes of his illness was to give him a series of sessions with bioresonance testing wherein identified causes will be addressed through his strictly tailored Field Control Therapy (FCT) homeopathic treatment. The parents nevertheless decided to try some supplements, then classical and complex homeopathy, but without success. Following this, they brought the boy into office.

First Bioresonance Testing, Treatment, and Clinical Response

The boy's testing indicated the first layers of causes – metallic mercury likely inherited through mom's mercury fillings, even more neurotoxic – methyl mercury – petroleum pollutants, thanks to urban living, and a slew

of worms. All of these morbid agents had a multisystemic, or literally brain-to-toes, pathological effect on many of his organs, as per bioresonance testing. The testing also indicated television and computer rays imprinted in his brain. That is why besides the treatment, recommendations were also made to drastically reduce television and computer exposure and acquire an electromagnetic field (EMF) protective technology, Memon, to reduce overall electromagnetic stress in their residence and car used for his transportation. All of these EMF-related measures were necessary to reduce the direct destructive effects on the brain and immune and other systems, and to reduce blocking effects of EMFs on the body's attempts to release heavy and other toxic metals. Also, even bodily minerals such as calcium, magnesium, zinc, and trace elements such as selenium, molybdenum, manganese, all of which are necessary for the normal functioning of thousands of enzymes, hormones, neurotransmitters, and immune modulators, are metals too. Since all metals are electromagnetic conductors, our innate metals would react to EMFs by shifting their physiological or well-recognized by body chemistry natural energetic charges toward distorted and less recognized ones. This would potentially undermine numerous physiological functions of body chemistry and its related state of health.

Interestingly, following the testing, the mother stated that the boy's significant drop in speech coincided with hiring a new babysitter who liked watching television. The sitter also used an iPad and DVD player to keep the boy busy. As with most parents, the boy's parents did not see anything wrong with their child's being exposed to this virtual electrocution of his brain and body.

Response to the First Treatment and Recommended EMF Measures

Quoting the mother: "He is unbelievable. He correctly tells the book's story that was read to him and even composed a poem! The preschool teacher asked if we did something unusual. He is very interactive and sociable now. Much less irritable, stopped demanding and crying for TV and iPad. He was singing all week after the treatment. When he wakes up at night, he falls asleep on his own and does not insist on coming to our bed. Since we started using Memon in the car, he stopped stimming there."

Response to the Second Treatment and Subsequent Clinical Course

The second bioresonance testing and its corresponding homeopathic treatment correspondingly indicated and addressed the following health problems: presence of metallic mercury, worms, multiple environmental pollutants, toxic metals, and fluorescent light, with the boy's classroom likely being its primary source, in the brain. Abnormal energetic findings also included numerous impaired organs such as different zones of the brain, as well as immune, gastrointestinal, endocrine, and others.

As usual, only FCT homeopathic treatment was administered. The response was much progress in eye contact and speech, improvement in following requests and directions, energy normalizing throughout the day, and no further need for naps. The teacher in his new preschool was puzzled as to a disparity between the boy's mental health assessment from the previous preschool and the actual child.

His further clinical course with periodic testing/treatments has continued upward most of the time, in spite of encountering intermittent plateaus. The latter were due to an increase in television time, reinfection with worms due to hygiene problems or his food handlers' being infected themselves, and construction work in his old apartment building. The latter has coincided with bioresonance testing finding lead, asbestos, paint, and other noxious chemicals in his body. The corresponding homeopathic treatment was administered. Also, Lyme bacteria within the immune system and measles virus in

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the brain were detected through bioresonance testing and promptly cleared by homeopathic treatment.

In spite of a few and only minor health problems still remaining and being much reduced such as picky eating and tending to be distracted, his autism, ADHD, and other major health problems are things of the past. The boy can carry out calmly prolonged conversations and appropriately answer many questions. He is being evaluated now for entering a normal classroom setting in his preschool, with some individual help as necessary.

Conclusion

While the proverbial "Many roads lead to Rome" might be still true in geography, in medicine the surest and shortest way to get there remains one that effectively deals with real causes of diseases. The current epidemics of autism and ADHD, which grow by the day, are only a few most recent examples of this. While governments and benevolent foundations have been pouring hundreds of millions of dollars into autism research, not even a shred of real progress has been made. The returns on even trillions of dollars spent on research into other chronic diseases, over decades, remain just about as poor. All because no primary causes of these have been found. These still remain the best-kept secret of our cells' energy fields.

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The Statement of a Pediatric Neurologist/Developmental Specialist

Neurological Evaluation

What was immediately obvious was that he no longer fulfills criteria for a diagnosis of autism, as his eye contact and joint attention was quite appropriate. He certainly can interact appropriately when he chooses to do so.

D___ is an almost five year old young man with a past history of autism and learning difficulties. After reviewing all pertinent medical and education records, it is clear that D___ has made remarkable progress and no longer fulfills criteria for a diagnosis of autism. In addition, his academic and social skills have improved and he is doing quite well in an integrated preschool setting.

Savely Yurkovsky, MD, is a cardiologist and is board certified in internal medicine. He has evolved a novel bioenergetic medical system that integrates a great deal of pertinent knowledge from conventional and alternative medicine, as well as exact sciences and other pertinent disciplines. It is aimed at the pursuit of the exact causes of chronic diseases through the most capable modalities to diagnose and treat these causes. Such modalities, he has found, are represented only by bioresonance testing and a novel homeopathic approach, both of which are scientifically rooted in physics and are uniquely capable of interacting with the very core of our homeostasis – cellular and molecular energy fields. His first book, *Biological, Chemical, and Nuclear Warfare – Protecting Yourself and Your Loved Ones: The Power of Digital Medicine* (with over 400 scientific references) has been endorsed for scientific validity by two prominent physicists: MIT professor of physics George Edgin Pugh, PhD, and former Stanford University chairman of materials science Professor Emeritus William A. Tiller, PhD. It was also endorsed by Mehmet Oz, MD, from Columbia University Medical School.

In collaboration with the Department of Gastroenterology of Johns Hopkins University School of Medicine, Dr. Yurkovsky has contributed a chapter on homeopathy and bioresonance diagnosis to the textbook *Integrative Gastroenterology*, published by Oxford University Press in 2011. He also has authored numerous articles on different medical subjects, some of which have appeared in this periodical.

Dr. Yurkovsky presented his diagnostic-therapeutic bioenergetic medical system at the annual BTR (bioterrorism) conference in 2005: Unified Science & Technology for Reducing Biological Threats & Countering Terrorism, affiliated with the Department of Homeland Security and the US Army. He has founded a teaching organization, SYY Integrated Health Systems Ltd., that is dedicated to sharing his medical system under the concept of FCT (Field Control Therapy). Since 1999, it has been taught extensively in the US and Europe to medical doctors and alternative health-care professionals, with special emphasis on energy-based diagnostic and therapeutic methods aimed at identifying exact causes of chronic diseases, restoration of damaged internal organs, and overall homeostasis.

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Beneficial Neurological Effects of Amyloban 3399: A Product Made from Bioactive Extracts of Lion's Mane (Hericium Erinaceum)

by Sensuke Konno, PhD

Introduction

As we get older, we all become more vulnerable to various disorders/diseases commonly associated with the *aging process*. Particularly, memory loss and brain atrophy are believed to be hallmarks of *aging*. Dementia is a collectively term for progressive degenerative brain disorders that severely impair mental abilities to perform daily tasks.[1] The most common or primary form of dementia is infamously known as Alzheimer's disease (AD), representing 60% to 80% of cases.[2] AD is a neurodegenerative disorder characterized by progressive memory loss and impairment in cognitive functions (visual perception, speech, reasoning, attention, etc.). It is not only a personal burden but also a socioeconomic burden: the cost of care is actually equal to or greater than that of heart disease or cancer, with the recent estimates of $159 to $215 billion a year in the US.[3] Exact etiologies of dementia and AD are unknown, although several risk factors such as older age, genetics, family history, history of head trauma, hypertension, diabetes, and obesity have been postulated.[4] No effective medications or medical interventions have yet been available or established, although some of them could improve symptoms.

A variety of *mushroom extracts* are now available as nutritional supplements for a general health maintenance or medicinal purpose. Among them, in July 2008, Amyloban 3399 was launched as a dietary mushroom supplement that might support healthy brain function, protecting brain nerve cells and stimulating the synthesis of nerve growth factor (NGF). As Amyloban 3399 sounds promising and could be useful for the prevention/treatment of AD or other neurodegenerative diseases, the scientific and medical studies of this supplement are reviewed herein for its beneficial neurological effects.

Medicinal Properties of Lion's Mane (*Hericium Erinaceum*)

Amyloban 3399 is a product made of Amycenone from the fruit body of lion's mane (*Hericium erinaceum*), which is standardized to contain hericenones (0.5%) and amyloban (6%). Lion's mane (see Figure 1, p. 84) is an edible mushroom that has long been used in cooking and medicine in China and Japan for centuries. Amycenone has been patented in Japan (Patent 5208036), presumably having beneficial neurological effects and capable of activating brain function. Now, let's take a look at two components of Amycenone, *hericenones* and *amyloban*.

Hericenones, Extracts of Lion's Mane

In 1990, a Japanese group isolated two novel cytotoxic phenols known as hericenones (A and B) and a new fatty acid from the fruit body of lion's mane.[5] Three more hericenones (C, D, and E) were isolated in 1991, followed by isolation of three additional hericenones (F, G, and H) by 1993.[6,7] These hericenones have been found to exhibit important neurological activities, including the induced synthesis of nerve growth factor (NGF), the diminished cytotoxicity of β-amyloid peptide, and the protection of neuronal cell death (apoptosis) against oxidative or endoplasmic reticulum (ER) stress.[6–11] *This* was indeed the first time that hericenones (C–E followed by F–H) isolated from a natural source (lion's mane) demonstrated the activity to promote the synthesis of NGF. In fact, such activity was found to be nearly comparable to that of epinephrine, which can significantly activate NGF synthesis.[6] Now, what is a biological significance of NGF?

Nerve Growth Factor: NGF is one of the family of neurotrophic proteins (neurotrophins) known as neurotrophic factors (NTFs) and also the very first to be identified.[9] NGF in the brain is

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believed to play a key role in regulating neuronal cell death (apoptosis) during the proliferation process and helping recover damaged neurons. Hence NGF can exert neuroprotective actions against the degeneration of neurons from brain injury or aging, implying its potential for a treatment of neurodegenerative disorders such as AD. However, NGF is a protein that cannot pass through the blood–brain barrier (BBB) to where it would exhibit an effect.[9] Intranasal injections of NGF have not been successful, and intraventricular administration of NGF resulted in negative side effects.[9,12] The direct NGF delivery to the brain is risky and impracticable. Thus, a safer and practical approach for delivering NGF to the brain is required for a potential treatment of AD.

Induction of NGF Synthesis by Hericenones: Meanwhile, it is more practical if the synthesis of NGF could be somehow *induced* in the brain by certain compounds, instead of directly delivering NGF to the brain. As briefly mentioned above, hericenones (C–E) isolated from lion's mane were the first natural compounds capable of inducing NGF synthesis demonstrated in rodent astrocytes in vitro.[6] This was the significant finding, implying the newly synthesis of NGF by hericenones possibly against AD or dementia.

AD is the most common senile dementia due to the formation of senile plaques and neurofibrillary tangles. A major component of senile plaques is amyloid β peptide (Aβ, with 39–42 amino acids), which plays a central role in the pathogenesis of AD.[13] Although the underlying mechanism of Aβ-induced neurotoxicity has not been fully elucidated, it was found to be primarily mediated through ER and oxidative stress.[14,15] In particular, as ER stress is believed to represent a major Aβ-induced neuronal cell death, it is plausible that the inhibitory or suppressive compounds against such ER stress may prevent neuronal cell death (leading to AD). With this assumption, the effects of hericenones on Aβ-induced toxicity in mice has been examined.[16] Especially, Aβ (25–35) is the potent peptide forming senile plaques, which can impair the learning and memory function (cognitive dysfunction).[17] In an experiment, powdered lion's mane (containing hericenones) was given orally to mice to assess its effects on cognitive dysfunction induced by intracerebroventricular administration of Aβ (25–35). The results showed that hericenones (in lion's mane) had passed through the BBB, promoted NGF synthesis in the brain, and prevented cognitive dysfunction.[16] Therefore, hericenones, active components of lion's mane, could be useful in the prevention of Aβ-induced cognitive dysfunction.

Amyloban, Fat-Soluble Fraction of Lion's Mane

As mentioned earlier, Amycenone contains hericenones as well as a fat-soluble fraction of lion's mane known as *amyloban*. This amyloban is a nootropic product containing dilinoleoyl-phosphatidylethanolamine (DLPE) and hericenone derivatives and has been patented in Japan (Patent 3943399).[10,11]

DLPE (dilinoleoyl-phosphatidylethanol-amine): A phospholipid isolated from lion's mane was identified as DLPE, which demonstrated a crucial protective activity on cell death due to *ER stress* in the mouse neuroblastoma cell line (Neuro2a cells).[10] As mentioned above, ER stress would often induce neuronal cell death, triggering the onset of neurodegenerative diseases, including AD, Parkinson's, Huntington's, and prion diseases.[18] DLPE appears to be an interesting compound capable of suppressing ER stress, thereby presumably preventing the incidence of these devastating diseases.

Hericenone derivatives: Following the isolation of DLPE, three new compounds have also been isolated from lion's mane. Those are considered hericenone derivatives, 3-hydroxyhericenone F, hericenone I, and hericenone J.[11] The in vitro study using Neuro2a cells revealed that only 3-hydroxyhericenone F had the protective activity (like DLPE) against ER–stress induced cell death, but two other compounds had no effects.[11] Yet, it should be noted that these ineffective compounds could also have significant biological activities that have not been identified. Further studies are currently in progress.

In brief summary, as amyloban contains DLPE and hericenone derivatives as active ingredients, it may play a pivotal role in protecting neuronal cells particularly from ER–stress exerted assault, ultimately preventing the onset of neurodegenerative diseases (AD).

Animal Studies of Amyloban 3399 (Amycenone)

As mentioned earlier, *Amyloban 3399 (Amycenone)* is made up of hericenones and amyloban, whose biological and medicinal properties have been just described above. Accordingly, Amyloban 3399 appears to have beneficial neurological activities, which were indeed demonstrated by the in vivo study using rats.[9] An experimental rat model with AD was created by administration of Aβ, and those AD rats were treated with either Amycenone or donepezil (a common drug used for AD) for evaluating their "memory" with the Morris water maze test.[19] Such study showed that AD-induced rats treated with Amycenone or donepezil performed the test far better than untreated AD rats, and they also had nearly the same capacity for memory as control (normal) rats.[9] Thus, these results suggest that Amycenone is as effective as a common AD drug to help improve a cognitive function (in AD rats).

In addition, the amounts of NGF present in all rats' brains were evaluated as well. Rats treated with Amycenone or donepezil were found to have more NGF than normal rats.[9] These findings thus support the notion that Amycenone is capable of inducing NGF synthesis in vivo.

Although a number of in vitro and in vivo studies demonstrated the neurological effects of various bioactive extracts of lion's mane (including Amycenone), the same question is always raised in the end: how would Amyloban 3399 made from Amycenone actually work in clinical settings? Not many clinical studies/trials on Amyloban 3399 have yet been performed, but a limited number of currently available studies will be mentioned herein.

continued on page 84 ➤

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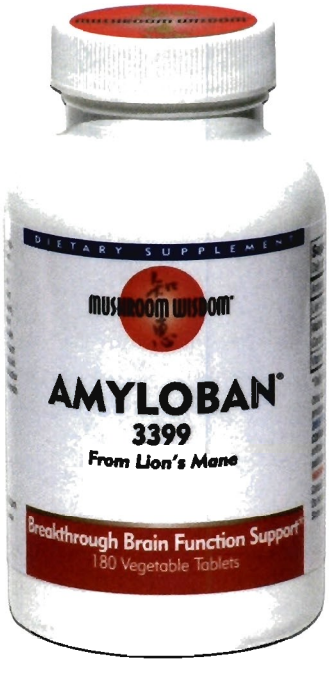

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Amyloban 3399

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Clinical Studies/Cases of Amyloban 3399

Antidementia

Prior to the introduction of Amyloban 3399 in 2008, a double-blind, placebo-controlled study on patients with mild cognitive impairment (due to dementia) was conducted with a tablet form containing 96% of dry powder of lion's mane.[20] Thirty elderly men and women (50–80 years old) were randomized into two groups (n = 15): the experimental group (treated with tablets) and the placebo group (no treatment). During a 16-week study period, the experimental group showed significantly increased scores of a cognitive function scale compared with the placebo group even at 8 weeks (12 and 16 weeks as well). However, at 4 weeks (no tablet intake) following the end of the 16-week trial, even the improved scores of the experimental group significantly decreased.[20] Thus, lion's mane does have the bioactivity to improve cognitive function in those patients; however, its continuous intake seems to be required for sustaining its efficacy.

Following this inspiring study, some clinical trials or individual case studies were conducted to address whether Amyloban 3399 could prevent a decline in cognitive function in dementia or would be possible to treat such dementia. In a relatively large-scale study, patients with the different stages of dementia (primarily the AD type) were placed on an Amyloban 3399 regimen.[9] Daily dosage of Amyloban 3399 varied with the conditions of individual patients. Within a year, an Amyloban 3399 regimen resulted in marked improvements of cognitive function in those with a year of onset of dementia or mild cognitive impairment. Even those with diminished cognitive functions resulting from taking a hypnotic, anxiolytic, or antidepressant showed apparent restoration of cognitive function. Hence, Amyloban 3399 can raise the level of consciousness in patients with dementia, perhaps reviving the normal brain actions/functions. It is encouraging that mild cognitive impairment (due to dementia) could be significantly prevented and improved with Amyloban 3399.

On the other hand, the cognition-enhancing activity of Amyloban 3399 on healthy subjects has also been assessed.[21] A 2-month clinical trial was conducted by measuring *memory improvement* and *mood* in 8 healthy participants (aged 52–78). Some participants felt "more upbeat and energetic" or "more focused, composed, and disciplined." Overall, Amyloban 3399 has improved memory, mood, and sense of well-being in all participants who were free of any medications.[21] In other words, Amyloban 3399 may help enhance cognition and alertness in normal people. Moreover, Amyloban 3399 was generally well tolerated with no adverse effects observed in any participants during a trial. Therefore, these findings suggest that Amyloban 3399 is safe to be taken regularly to possibly prevent or reduce the risk for developing dementia, including AD.

Improvements of Schizophrenia

Apart from the beneficial effects of Amyloban 3399 against neurodegenerative diseases, it has also been shown to have positive effects on other neurological or mental disorders/diseases.

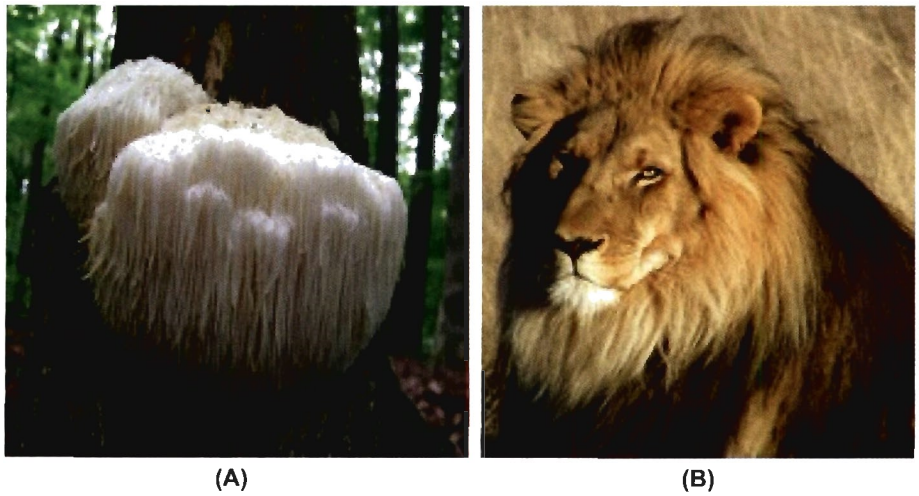
Schizophrenia is a mental disorder primarily characterized by cognitive dysfunction: those with impaired cognition cannot tell what is real from what is imagined and would have a poor social and occupational functioning.[22] In the study, 10 patients with schizophrenia were treated with Amyloban 3399 to assess possible improvements in cognitive symptoms.[23] Although all patients were refractory to current antipsychotic agents, they all showed the improved symptoms with Amyloban 3399, evidenced by the improved average scores of the positive and negative syndrome scale (PANSS). Thus, this study indicates that Amyloban 3399 could be beneficial for treating schizophrenic patients with cognitive impairments.

Hypersomnia and Sleep Apnea

Since Amyloban 3399 can increase alertness, its possible effect on people with hypersomnia was studied. Hypersomnia, or excessive sleep, could be attributed to a structural disorder of the brain; in fact, sleeping in the daytime is often seen in patients with dementia. In the study, Amyloban 3399 was found to raise the level of alertness, resulting in the increased hours in staying awake (or the decreased sleeping time).[9] Thus, Amyloban 3399 may simply help bring sleep times back to normal.

In addition, the effects of Amyloban 3399 were examined on sleep-related breathing disorders such as apnea, a condition in which breathing becomes very shallow or may even completely stop during sleep. Nine patients received Amyloban 3399 for 2 months and tested for sleep apnea-hypopnea and snoring. The study showed the gradual improvements in apnea-hypopnea index as well as snoring index in these patients.[9] Therefore, this finding suggests that Amyloban 3399 appears to improve sleep apnea and control snoring.

Figure 1: Lion's Mane (*Hericium Erinaceum*) (A) and Lion (B)



(A) (B)

Depression and Anxiety

Depression and anxiety could be considered mental illness because they can lead to emotional and physical problems. In one clinical case, an 86-year-old male patient with recurrent depressive disorder was placed on an Amyloban 3399 regimen. After 6 months, his mild cognitive impairment (due to depression) was significantly improved and his body weight was also restored.[24] Moreover, it is worthwhile mentioning another clinical study of 30 female patients with depression and/or anxiety, although it was conducted using the powdered lion's mane instead of Amyloban 3399.[25] Patients were randomized into an experimental group (treated with lion's mane) or placebo group (no treatment). After 4 weeks, all test scores indicated the *reduced* levels of depression and anxiety in the experimental group compared with the placebo group.[25] The same outcomes are yet anticipated with Amyloban 3399. Thus, these results imply that Amyloban 3399, a product of lion's mane, could be useful in people who suffer from depression and anxiety.

Conclusions

Amyloban 3399 is a natural, potent bioactive product made from Amycenone (a standardized lion's mane extract), consisting of hericenones (0.5%) and amyloban (6%). A sufficient number of studies indicate that Amyloban 3399 has beneficial effects on neurodegenerative diseases, capable of inducing NGF synthesis, diminishing Aβ neurotoxicity, and protecting neuronal cell death from oxidative or ER stress. Thus, Amyloban 3399 could be used for the prevention and/or treatment of neurodegenerative diseases/disorders (dementia and AD). In addition, it may also have the beneficial effects on neurological or mental disorders/disease such as schizophrenia, depression, anxiety, hypersomnia, sleep apnea and other unidentified entities.

Moreover, lion's mane, the original source of Amyloban 3399, appears to have other significant bioactivities, including antitumor, antiviral, antimicrobial, immune-enhancing, antioxidant, hemagglutinating, hypolipidemic, and hypoglycemic activities.[8,25] It is thus tempting to further explore other hidden potentials of Amyloban 3399 besides its neurological effects, and such studies are currently under way.

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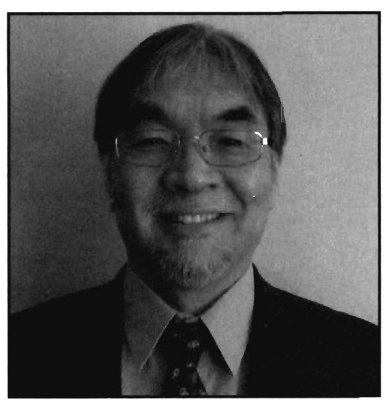
Dr. Konno received his Ph.D. in Biochemistry and Molecular Biology in 1991 and is currently serving as an Associate Professor and Director of Urology Research at the Department of Urology, New York Medical College (Valhalla, NY). His primary research focuses on establishing the more effective therapeutic modalities for three prevalent urological cancers such as prostate, bladder, and kidney cancers. Particularly, he has been exploring the alternative, *unconventional* modalities using natural agents/substances, such as bioactive extracts from mushroom, grape seed, watercress, broccoli etc. For potential adjuvant therapy, he has been also investigating combinations of these natural agents and chemotherapeutic drugs or interferons in order to improve the therapeutic efficacy. In addition, searching for possible prevention and/or treatment of kidney stone (nephrolithiasis) or renal ischemia/reperfusion injury, he has been working on certain antioxidants, which might exhibit the renoprotective effects against those renal disorders by diminishing oxidative stress. Because of his special interest in oxidative stress, recently he also started exploring possible beneficial effects of specific mushroom extracts with antioxidant activities on neurodegenerative diseases such as Alzheimer's disease. His work has been presented and well received at numerous domestic and international meetings/conferences and published in a number of the major journals. Moreover, Dr. Konno also serves as a peer-reviewer for several scientific/medical journals as well as a moderator at the meetings. He is a professional member of American Urological Association (AUA), American Association for Cancer Research (AACR), and American Association for the Advancement of Science (AAAS).



Autism, the Brain, and Mercury

by Rashid A. Buttar, DO

Ask virtually any medical doctor about autism spectrum disorder (ASD), and you will get the same story: it's a genetic condition for which nothing can be done.

I cringe when I think about how my own son's life would have been had I just accepted what the so-called experts told me when I was facing his issue of autism. And I can't imagine what life would be like for the hundreds of children with vaccine injuries whom we've treated and who have even nearly died from common medical "treatment," had God not blessed me with the faith, wisdom, and conviction that anyone and any condition can be healed as long as you're willing to take the road less traveled. The sad thing is that there are literally hundreds of thousands, if not millions, of people still out there who could regain their lives, if only they chose to take the path less traveled.

So What About You? What Brings You Here at This Point in Your Life?

I personally believe that it's no accident that you're reading this article right now! Chances are, you've found it because you're at a crossroads with your own health – perhaps even your life or that of your child. Maybe you've received a frightening diagnosis, or perhaps you just feel awful and don't know why. Or maybe it's a loved one who is facing these challenges.

I believe that we as a society have reached the point where our entire perspective on the subject of disease and healing needs to be questioned – the fact is, the current medical model is simply not working.

Scientists have discovered that people with autism have faulty wiring in the brain, leading to misfiring in communications between brain cells. In the brain, nerve cells transmit important messages that regulate body functions – everything from social behavior to movement. Imaging studies have revealed that autistic children have too many nerve fibers, but they're not working well enough to facilitate communication between the various parts of the brain.[1]

So, What Might Be the Cause of This Misfiring?

I believe the largest culprit to be mercury.

In a single doctor's visit, babies can get 60 times the Environmental Protection Agency's mercury limit from the "required" vaccines. For years, mercury in vaccines has been associated with autism, attention deficit/hyperactivity disorder, language and speech delays, and more.

Today children are being diagnosed with autism in unprecedented numbers. The reason is clear, and the ideology that caused this is mercury. Not only is the mother given all types of vaccines, but also the child gets vaccinations within one day of being born. Then those vacccinations are repeated again over the next 1 to 2 years. This causes a tremendous amount of exposure to mercury for the child. This level of mercury exposure is extremely neurotoxic. In fact, mercury is known to be the second most toxic metal known to humanity. The degeneration of the neurofibers caused by mercury essentially rips the neurons apart so that they can no longer function.

Whether mercury is inhaled, consumed in the diet, within the body in the form of dental amalgams, or enters the body through vaccination, it places a burden on the body. Mercury ions alter the cell membrane structure of developing neurons.[2]

To better understand mercury's effect on the brain, let's discuss the form of neurons in the brain and how mercury affects them.

Brain neurons have a central cell body and numerous neurite processes. At the end of each neurite is a growth cone where structural proteins are assembled to form the cell membrane. Two principle proteins involved in growth cone development are actin, which is responsible for the pulsating motion, and tubulin, a major structural component of the neurite membrane. Neural fibers protect the tubulin.

When mercury is introduced to the neurons even in small doses, within minutes the tubulin stops growing and starts to degenerate. Other

heavy metals such as aluminum, lead, cadmium, and manganese do *not* produce this effect. Mercury prevents tubulin ions from being able to bind together, which then causes the designation of the tubulin. This degeneration causes malfunction within the brain. By removing the mercury, the degeneration is then removed, which allows the body to heal.[3]

A report by Eli Lilly's Material Safety Data Sheet states: "Early signs of mercury poisoning in adults are nervous system effects, including narrowing of visual field and numbness in the extremities. Exposure to mercury in utero and in children can cause mild to severe mental retardation and mild to severe motor coordination impairment."[4]

Are you aware that the major veterinary association recognized that mercury in vaccines is harmful to our pets and removed the mercury from the vaccines, but the CDC still says that it is OK for our children? Did you also know that even though thimerosal is no longer on the label for vaccines, it is still in the vaccines from the manufacturing process?

If you look at it of autism over the past decade, the rate has exponentially increased. It can be traced goes back to mercury within the vaccinations received by the child and the mother. Dental amalgams and the diet of the mother are also factors, which also trace back to mercury. A child born today has a much higher level of mercury within the body than a child born 50 to 100 years ago. The last set of shots given to a child at around 12 to 18 months of life is often the "straw that broke the camel's back," so to speak, because itcauses the body to reach a tipping point and be overloaded with toxicity from the mercury. Some children will immediately have drastic reactions such as seizures or very high fever, while others may take longer for the reactions to be noticed. Within a week to several weeks, the parents may see the effects begin. The child may begin to lose ability to speak, experience personality changes, make uncontrollable motions, and so on.

We know that the data released by the CDC in 2003 showed that 1 out of 3 women of child-bearing age is mercury toxic. We also know that the American Academy of Pediatrics

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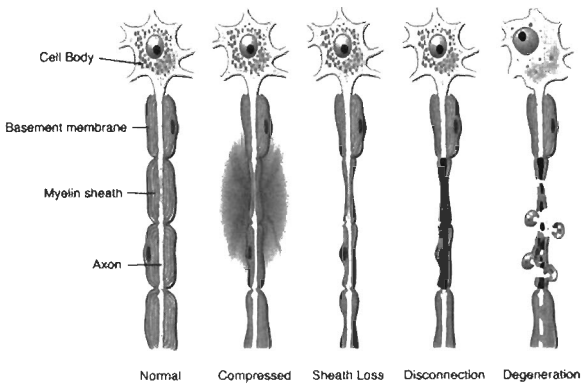
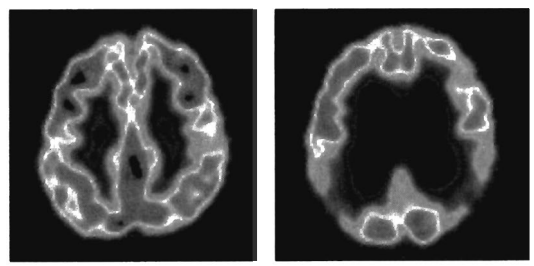
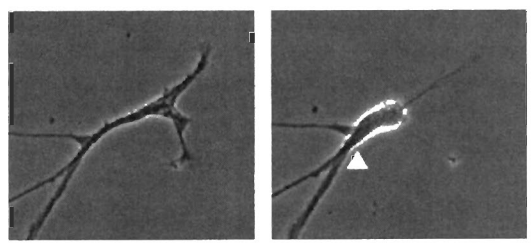
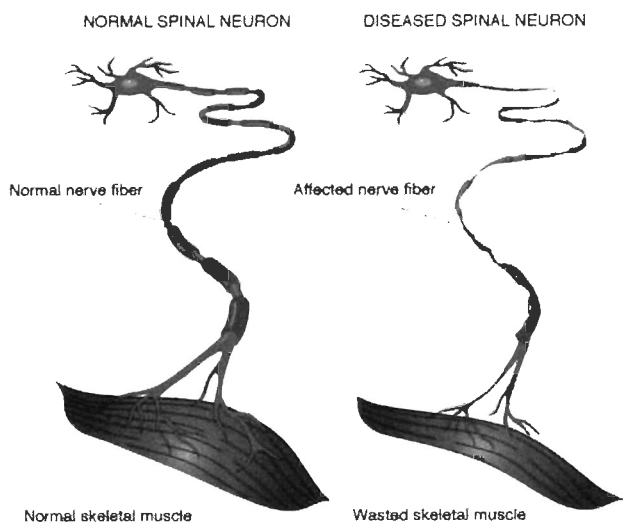


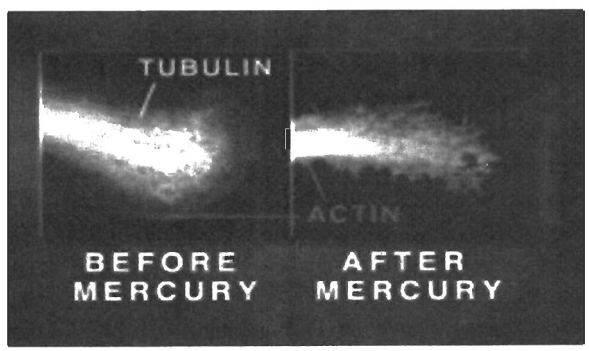


A SPECT scan of a normal brain (L) and an Alzheimer's brain (R)



A neuron before (L) and 30 minutes after (R) introduction of a dilute mercury solution





as well as Safe Mind released data that 1 out of 6 children in the US is born with some type of neurological impairment. It doesn't take a rocket scientist to realize that there is a coalition here.[5-7]

When we measure mercury in tests, we are not just measuring the amount of mercury in the body. There is no way to accurately do that unless multiple site biopsies are done, which is not conducive to life. The only method being used right now to determine mercury issues is by the amount of mercury being pulled out and shown on tests. In the autistic and Alzheimer's population, there is a phenomenon called *impaired detoxification pathway*. This means that these patients cannot excrete mercury, or other toxins for that matter. When we test them, their tests do not show mercury because the body is holding onto and not releasing the mercury.

Michael Godfrey found essentially what is going on here: there is a genetic predisposition (apoE), and there are many genetic predispositions that cause the body not to be able to excrete the toxins. The vast majority of people fall into this category, even in twins. The system cannot eliminate the toxicity to which it has been exposed. Until we persistently treat these patients to stimulate their detoxification pathways to start the process rolling, they will never show their true toxicity levels on testing. Most patients who can get rid of metals on their own will dump easily when they are tested because we are giving them a chelator/challenge treatment that actually helps them pull the metals out. Those who can't get the toxins out on their own need recurrent, continuous, and often aggressive therapy to start that pathway so that the body can start to detoxify the way that it was designed to do.[8]

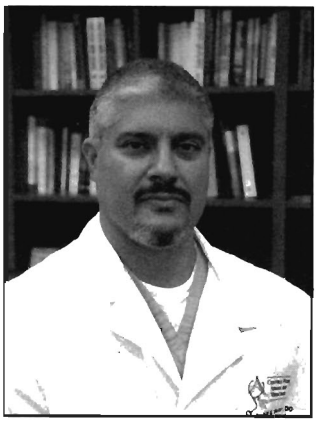
I often get asked about hair analysis. Hair analysis is not an accurate way of assessing metal toxicity. It is a good screening tool, but it also tends to have a very high false negative rate. That means that if the test shows positive for metals in hair, then you know for sure there is a metal toxicity. However, the test's not showing metal toxicity doesn't mean that metals are not present within the body. It only means that the test didn't show the metal levels because the body is not releasing the metals.

Holmes, Blacksil, and Haley showed in a study published in the *International Journal of Toxicology* that hair analysis done on children with autism compared with neurotypical children showed normal children to have a higher level of mercury than children with autism. The more severe the autism, the lower the mercury level. It was said that this study showed that mercury had nothing to do with autism because the children with autism showed lower or no mercury levels when tested. The problem with that conclusion is that children with autism can't get rid of the mercury. Those commenting on the study fail to understand that the mercury is still in the child's system and cannot be eliminated. Therefore, the mercury is not registering on the tests. The tests only show what is being eliminated, not what is being held onto by the body.[9]

In our practice, we see a significant relationship as to how fast a child is going to get better based on what the mercury level it test shows. If the baseline hair shows no or very little mercury, we know that it is going to take longer to get this child to heal because s/he is holding onto the toxicity, which means that the body will need to be challenged to release the toxins.

Is mercury the sole cause? No, it is not. Lead causes impaired brain development and function, and also interferes with the normal functioning of other body organs and systems. Aluminum induces neuroimmune disorders. A high copper to zinc ratio causes many health issues such as mental problems, diabetes, decreased digestive enzyme activity, food sensitivities and allergies, autoimmune diseases, IBS, and chronic candida. Other metals have potential neurological implications as well. However, nothing has been shown to cause the degradation of the neurofibers like mercury.

As we are treating the patient for mercury, we treat for all the other



Rashid A. Buttar, DO, FAAPM, FACAM, FAAIM, is a pioneer in advancing the science of medicine, providing the foundation of health through effective systemic detoxification, immune modulation and physiological optimization leading to sustainable health. He has been ranked among the top 50 US physicians from three separate sources and has achieved fellowship status in three different medical societies. He is an internationally acclaimed lecturer and best-selling author of *The 9 Steps to Keep the Doctor Away*, and has formulated numerous unique highly efficacious therapies. Dr. Buttar practices in Cornelius, NC, where he is the medical director of the Center for Advanced Medicine and Clinical Research, a clinic specializing in the treatment of cancer, heart disease, autism, and other chronic conditions in patients' refractory to conventional treatments with a special emphasis on the interrelationship between metal toxicity and insidious disease processes. To learn more about Dr. Buttar, visit www.MedicalRewind.com and www.DrButtar.com.

metals as well. For children with autism, we mainly use our proprietary transdermal versions of EDTA and DMPS, which remove not only the mercury but also other metals such as arsenic, plutonium, uranium, lead, and cadmium. As the metals are being removed, the essential minerals are also being removed, so it is extremely important to replace them.

It is also important to address food allergies and gut issues. Most children with autism have huge gut dysbiosis and gut vacillation issues, as well as poor digestion and absorption.

The bottom line is that you must *first* remove the metals (the fire burning the house down), then you can work on getting the metabolic pathways up and running. As long as the mercury is present in full force, you will never be able to do so.

Excerpts for this article were taken from the international best-selling book *The 9 Steps to Keep the Doctor Away*, by Rashid A. Buttar, DO, and lectures that Dr. Buttar has done throughout his career. Get your copy of the book at www.the9steps.com.

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Nonspecific Effects of Vaccination

by Jacob Schor, ND, FABNO

I want to write about some relatively recent research published about vaccines, as I think that it may change the way that we think about vaccinations. These studies may help define our concerns about vaccinations and also suggest ways to make better use of specific vaccines.

It is time to expand the definition of vaccines. The old definition suggests that they improve immunity only against a particular disease: "A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from a weakened or killed form of the microbe, its toxins or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and remember it so that the immune system can more readily recognize and destroy any of these organisms that it later encounters."[1]

A newer and more expansive definition is needed, as current evidence tells that us vaccines not only protect against the specific diseases that they are intended to but may also affect resistance to other infectious diseases. This is called their *nonspecific effect*, and these actions can be strongly beneficial or equally detrimental.

This is nothing new. Shortly after Edward Jenner introduced vaccinia treatments in 1796, the vaccine was reported to have other "... positive side-effects such as healing of chronic skin rashes, reduced susceptibility to various infectious diseases, e.g. measles, scarlet fever and whooping cough, and even [had] prophylactic use... against syphilis...".[2] In 1927, Carl Näslund, the physician in charge of introducing tuberculosis (Bacillus Calmette-Guérin [BCG]) vaccinations in northern Sweden, reported that vaccinated children had an almost three times better chance of reaching their first birthday than unvaccinated children.[3] Tuberculosis rarely affected this age group.

Modern research on nonspecific effects of vaccinations was triggered by a mistake.

In 1994, Peter Aaby reported the results of a randomized trial of a new measles vaccine in Senegal. The vaccine was given earlier than usual, at 4 to 5 months of age rather than 9 months. Vaccinated girls were twice as likely to die as those using the older vaccine.[4] Or at least, so it seemed at first.

Aaby works on vaccination programs sponsored by the World Health Organization (WHO) in areas with high rates of infectious disease such as Guinea-Bissau and Senegal. His 1994 report led to a systematic investigation of all vaccines. This examination revealed that measles, BCG, and vaccinia (smallpox) vaccines all seem to have nonspecific effects that are beneficial, reducing death rates from a wide range of infectious disease, while DPT can increase risk of females'' dying from infections other than the three diseases that it protects against.[5-8] It turns out that Aaby's 1994 data were misinterpreted. DTP vaccinations had been administered after the measles vaccine, canceling out the beneficial nonspecific effects that should have been seen.

Let us review the evidence one vaccine at a time.

Measles

A 2012 Africa study reported that measles vaccine cut by a third deaths from all other infections combined, mainly by protecting against pneumonia, sepsis, and diarrhea. In developing countries, measles-vaccinated children have lower mortality rates from all infectious diseases.[9,10] In 2005, Veirum reported that measles-vaccinated children had a 49% decreased risk of fatality from infectious disease. In pneumonia cases, there was a 72% decrease risk of dying in the vaccinated children.[11]

Measles vaccine appears to cancel out the negative impact of DPT. In a randomized trial conducted from 2003 to 2009 in Guinea-Bissau, an additional dose of measles vaccine was given at 4.5 months. The children had received three DPT shots prior to starting this study. Compared with children who received measles vaccine at 9 months of age, those who received the vaccine at 4.5 months and 9 months had a 30% decrease in all-cause mortality up to 3 years of age. Less than 5% of this reduction in mortality could be explained by measles prevention.[12]

Bacillus Calmette-Guérin (BCG)

BCG vaccine also has a beneficial nonspecific effect. In two studies on low birth-weight (LBW) neonates, early vaccinations cut infant mortality by nearly half, preventing death from other infectious diseases besides tuberculosis.[13]

The sequence in which vaccinations are received may make a difference. The nonspecific effect of the last vaccine received is the one that lingers. In 2012, Hirve reported that BCG given out of sequence, so that it is the last vaccination instead of DTP, was associated with lower mortality. Two-thirds of a group of 4138 children born between 1987 and 1989 in 45 adjacent villages in western India received their BCG and DTP vaccines out of sequence, receiving either both vaccinations at the same time or the BCG after the DTP. The mortality rate ratio for those children was 0.15 compared with those who had been vaccinated on schedule.[14]

An April 2013 paper reported BCG revaccination resulted in a stronger IFN-γ response in 345 infants in Guinea-Bissau. BCG also affected the pro-/anti-inflammatory balance, reducing TNF-α and increasing IL-10 responses to LPS, the effect being stronger in children who had already been vaccinated with DTP.[15]

A June 2013 published study reports that infant BCG vaccination resulted in more effective responses to subsequent vaccinations. The concentration of antibodies triggered by subsequent vaccines was higher in the BCG-immunized children (except for hepatitis B).[16] We might argue that BCG should be the first and last vaccine administered in vaccination programs. Of course such an argument would be moot, as BCG is rarely administered in the US.

One does have to contemplate whether the homeopathic preparations using these bacteria might have a similar effect.

Vaccinia (Smallpox)

This vaccine has already been phased out in much of the world, so the recent studies compare older vaccinated cohorts versus younger unvaccinated groups. In low-income countries, having a vaccinia scar is associated with a 40% reduction in overall mortality among adults. Having been vaccinated with smallpox is associated with a significantly reduced risk of malignant melanoma and infectious disease hospitalizations.

Risk of hospitalization in Danish adults decreased nearly 20% if vaccinated before 3.5 years. Risk increased the longer vaccination was delayed.[17] Vaccination with both BCG and smallpox vaccines was associated with a 36% reduction in melanoma risk.[18]

On the topic of melanoma, it should also be mentioned that the yellow fever vaccine is also associated with lower risk for melanoma; 10 years after receiving the vaccine, the odds ratio of getting melanoma for the vaccinated was 0.26 compared with the unvaccinated.[19]

Diphtheria, Tetanus, and Pertussis (DTP)

We have good reason to be concerned about DPT. While measles, BCG, and smallpox vaccines have beneficial nonspecific effects, DTP vaccine appears to have a negative effect, particularly in females. Girls have higher mortality than males who receive DTP. Negative effects are seen if DTP is the most recent vaccination. Giving BCG or measles vaccine after DTP appears to neutralize the negative effects of DTP. Thus vaccine sequence is important, and understanding this has helped unravel some of the confusing data published over the years.

Why?

One problem with this entire business of nonspecific vaccine effects is that it makes little sense. There has been no clear mechanism of action to explain what is seen and when observations counter current theory, the data become easy to ignore.

For example, a WHO-commissioned review concluded that the benefit of measles vaccine was simply because the vaccine decreased incidence of measles.[20] While 2 studies support this conclusion, 10 others reached the opposite conclusion.[21]

This concept may not be as implausible as it seems. For naturopathic physicians, it is easy to conceive that every exposure that an individual's immune system has to infections or vaccinations leaves an imprint that affects future responses of both the innate and adaptive responses to new pathogens. This concept is referred to as *heterologous immunity*, which explains that nonspecific effects may result from vaccines encoding antigens that cross-react with other pathogens. T-cell responses could be informed by prior infections with unrelated viruses.

Vaccination may leave the innate immune response in a heightened state of alertness. This may be an example of *trained innate immunity*, in which either a primary infection or vaccination confers protection against secondary infections. The increase in nonspecific resistance of the host to reinfection involves innate immune cells such as macrophages and natural killer (NK) cells and results in improved pathogen recognition and enhanced responses. It's been put forth that the molecular mechanisms which induce trained immunity involve epigenetic reprogramming.

Perhaps we should leave discussion of these mechanisms until such time when the debate among the scientists on the details has slowed.

A paradigm shift is taking place in understanding how vaccines act; the new view is that vaccines have nonspecific effects on health and survival greater than merely protecting against particular diseases.

There seems to be a trend that live vaccines such as BCG, measles, and vaccinia are associated with beneficial nonspecific effects that ➤

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reduce all-cause mortality. In contrast, the inactivated vaccines, DTP in particular, increase risk of other unrelated infections and more so in females.

This should give us cause for concern. If receiving a live vaccine afterwards offsets the negative impact of DTP, what happens if this rarely occurs? BCG, in particular, while once widely used in Europe, has never been routine in the US. Even in Europe, BCG is no longer mandatory. While we may talk about BCG's lowering infectious disease rates in undeveloped West African countries, we hardly ever use it in the US and so know little about how it affects our population.

Because Europe has stopped using BCG, might we expect an eventual spike in melanoma cases? Krone reported in 2003 and 2005 that the odds ratio of being diagnosed with melanoma dropped by more than half for people who had received BCG or vaccinia compared with those who had not received these vaccines.[22,23] If "vaccine deficiency" more than doubles risk of melanoma, we might want to reconsider some of our practices.

The WHO research reported benefit from the measles vaccine but does not tell us if the MMR combination will do the same. Current CDC guidelines suggest giving children their final DTP vaccination at about the same time or after their final MMR vaccination. Might it be wiser to finish with the MMR vaccine instead of DTP? Or should we bring back a measles-only vaccine? For patients who are unwell after DTP vaccination, perhaps a dose of measles or MMR would cancel out that suppression? Might even a dose of BCG vaccine help restore healthy immune function?

Given the significant effects that BCG, vaccinia, and yellow fever vaccine have on lowering risk of melanoma, should we encourage high-melanoma-risk patients to get vaccinated? What of patients with existing melanoma? Would these vaccines help them?

What about flu vaccine? At least one paper suggests that it has a nonbeneficial nonspecific effect. Cowling reported in June 2012 that children given flu vaccine were more than four times as likely to suffer from non-flu viral infections than children given placebo. [24] That's bad news.

Our esteemed colleague Thomas Kruzel, ND, has for many years vaccinated his cancer patients against typhus. Not that he's worried that they will catch typhus living in Phoenix, but he believes that the vaccines enhances a patient's ability to fight cancer. He administers an initial dose, followed by a second dose 90 days later, and then gives yearly boosters. Kruzel justifies his protocol on Denk and Karrer's 1970 report that tracked 5400 Austrians who suffered from typhus between 1945 and 1947. In 1967, 2800 were still alive. Mortality rate due to cancer was significantly lower than the predicted rates. The authors supposed "the possibility of an immuno-prophylaxis of carcinoma by unspecific stimulation of the defensive mechanism ... "[25] These patients had suffered from the disease; they were not vaccinated.

Vaccines have another advantage: they may stimulate broad immunity without triggering chronic disease the way that having the disease might.

While it is more natural to trigger these nonspecific immune reactions by exposure to actual diseases, these days, few infants will be exposed. Vaccines might be seen as substitute exposure. Actually getting the vaccines may be preferable to the disease. We should be relieved to miss out on such opportunities. Actually experiencing these diseases may have lasting unwanted consequences. Having tuberculosis, pertussis, or measles increases the risk of developing bronchial hyperresponsiveness, asthma, eczema, and other allergic diseases. The vaccines do not increase risk of these symptoms but actually lower risk.[26–28] A 2012 meta-analysis reported that having had tuberculosis was linked to greater risk of asthma and eczema, but past immunization with BCG did not raise risk.[29]

Our profession has a long history of being suspicious of vaccinations. No doubt this is due to our professional forebears' seeing adverse reactions, knowledge of which was passed to us through generations of practitioners. It may also be due to our habit of careful observation; our caution with DPT vaccine appears to be justified. Yet, we should not rush to judge all vaccines as dangerous. This new research certainly suggests that some vaccines have their uses.

This concept of heterologous immunity, the idea that one substance might train the immune system to fight a variety of different infectious agents, sounds congruent with our naturopathic worldview. Could this explain how the polysaccharides found in medicinal mushrooms and other botanical extracts act to enhance overall immunity? Could we use this concept to predict other useful interactions?

Jacob Schor, ND, FABNO, has practiced as a naturopathic physician in Denver, Colorado, with his wife, Rena Bloom, ND, since they graduated from National College of Naturopathic Medicine in 1991. He was humbled in 2008 when presented with the Vis Award by the American Association of Naturopathic Physicians (AANP). He has had the honor of serving the members of the Oncology Association of Naturopathic Physicians as a board member and currently as president. Dr. Schor began a term on the AANP's board of directors in January 2012. He is a frequent contributor to, and associate editor of, the *Natural Medicine Journal*.

Heresy it may be, but here is my new bottom line:

Exposure to various disease entities may be required for the human immune system to be activated. Vaccines may provide a safer substitute than exposure and actual infection with the disease. Using vaccines against diseases that no longer threaten may still have value for their nonspecific effect stimulating general immunity. Some vaccines have harmful nonspecific effects; we need to discriminate between them.

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Letter to the Editor

Anacardic Compounds to Cure and Prevent Tooth Infections

I suspect that anacardic acids would kill *Streptococcus* and *Staphylococcus* bacteria and other gram-positive infections such as anthrax. I have found that the anacardic acids in raw cashew nuts and maybe mangoes do an excellent job of curing an abscess from gram-positive bacteria, the most prevalent cause of tooth decay and tooth aches.[1]

I would urge you to explore making these medicines available in the pure form from pharmacies for a *Streptococcus* medicine or in toothpaste. This would have several advantages:

1. A variety of application methods would be possible: needles, brushes, swabs, sprays, and so on.
2. It would probably eliminate allergy.
3. It would probably be less expensive than cashews.
4. It would be easier to apply massively locally.
5. It would be easier to test against the pathogenic species involved.
6. It would be more emotionally acceptable to the medical profession who tend to prefer chemicals over anything as amateurish as natural products.
7. It would be easier to control amounts.
8. It would be easier to carry it on camping trips, etc.
9. It would probably have an infinite shelf life.

Anacardics would be much more effective in killing decay bacteria than fluoride and without the dangerous side effects.[2] This would be especially valuable since these medicines would probably prove to be valuable against other gram positive diseases such as acne, leprosy, *Streptococci, Staphylococcus aureus*, anthrax, *Listeria monocytogenes, Actinomyces naeslundii, Corynebacterium diphtheriae, Streptococcus agalactiae, Propionibacterium* spp., and maybe even tuberculosis as well.

Acute *Streptococcus pyogenes* infections may present as pharyngitis (strep throat), scarlet fever (rash), impetigo (infection of the superficial layers of the skin), or cellulitis (infection of the deep layers of the skin). Invasive, toxigenic infections can result in necrotizing fasciitis, myositis and streptococcal toxic shock syndrome. Patients may also develop immune-mediated poststreptococcal sequelae, such as acute rheumatic fever and acute glomerulonephritis, following acute infections caused by *Streptococcus pyogenes*. *Streptococcus pyogenes* produces a wide array of virulence factors and a very large number of diseases. Virulence factors of Group A streptococci include:

1. M protein, fibronectin-binding protein (Protein F) and lipoteichoic acid for adherence;
2. hyaluronic acid capsule as an immunological disguise and to inhibit phagocytosis; M-protein to inhibit phagocytosis
3. *invasins* such as streptokinase, streptodornase (DNase B), hyaluronidase, and streptolysins;
4. exotoxins, such as pyrogenic (erythrogenic) toxin, which causes the rash of scarlet fever and systemic toxic shock syndrome (See http://textbookofbacteriology.net/themicrobialworld/strep.html.)

Charles Weber

PS: Dr. Rastmanesh, a nutritionist from Iran, would like to secure a position in an English-speaking university because of religious or political problems. He has an impressive CV. If you know of an opening, I will send you his CV. It would be a travesty to leave that fine scientist in that criminal country after he got rid of rheumatoid arthritis for us.

Notes

1. You may see my article on this subject at http://charles_w.tripod.com/tooth.html. It is also discussed briefly in *Medical Hypotheses*. 2005;65:289–292. Wikipedia discusses anacardic acids at http://en.wikipedia.org/wiki/Anacardic_acid.
2. See http://charles_w.tripod.com/fluoride.html.

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Prescribing Calcium for Osteoporosis Might be Deadly

review by Owen R. Fonorow

Death By Calcium, by Thomas E. Levy, MD, JD
Medfox Publishing LLC; medfoxpub.com; 866-359-5589
© 2013; $29.95; softcover; 429 pp.

Every reader will learn something from Dr. Thomas Levy's comprehensive new book *Death by Calcium*. Levy's emphasis is obvious from the title, but *Death by Calcium* is more than a warning against taking supplemental calcium. The material represents a culmination of his years of research into vitamin C, infectious disease, and toxins. Levy's crusade for truth, his experience with the administration of vitamin C, and his innate ability to simplify and reduce complex problems led him down a path that resulted in his remarkable unified theory of disease. This elegant new theory is based on the presence of increased oxidative stress in the affected tissues and cells.

The wide-ranging information in *Death by Calcium* should be in medical textbooks. Levy has finally put into print his extensive suggested treatment protocols for cancer, heart disease, osteoporosis, and chronic degenerative diseases in general. Importantly, he has assembled a lengthy appendix titled "A Guide to the Optimal Administration of Vitamin C" that should answer the questions of most practitioners. This appendix is a comprehensive guide on the different forms and applications of vitamin C, including intravenous vitamin C, that does not exist elsewhere.

You may experience cognitive dissonance reading *Death by Calcium*. Rarely has the mineral calcium been mentioned in the same discussion as toxicity. It is interesting that calcium is the single nutrient that the government recommends in greater than gram amounts daily. However, as we have come to expect from his writings, Levy cites massive scientific evidence to support his case that ingestion of calcium is unwise and that higher tissue and blood levels are toxic. The surprising message, conveyed by the book's title, is clear: the more calcium there is in the blood and tissues, the greater the increase in mortality, even for osteoporosis patients. Levy writes that rarely, if ever, are calcium supplements justified, and he even warns against foods high in calcium, such as dairy. He offers protocols that are potentially more effective ways for dealing with chronic conditions, previously thought to be caused by calcium deficiency, such as osteoporosis.

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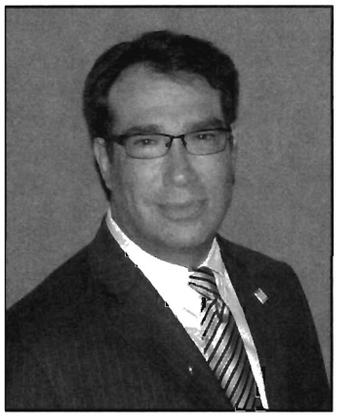

Anti-Aging Medicine

by Ronald Klatz, MD, DO, and
Robert Goldman, MD, PhD, DO, FAASP
www.worldhealth.net

An Anti-Aging Approach that Preserves Cognitive Skills as We Age

A study of video gamers suggests that age-related declines in cognitive motor skills may begin as early as age 24 years. Simon Fraser University (Canada) researchers conducted a social science investigation, involving the digital performance records of 3305 people, ages 16 to 44 years, who play the videogame StarCraft 2. These performance records, which can be readily replayed, constitute big data because they represent thousands of hours' worth of strategic real-time cognitive-based moves performed at varied skill levels. Using complex statistical modeling, the researchers ascertained how players responded to their opponents, as well as how long they took to react. Data analysis revealed that by over 24 years of age, one may have already reached his/her peak in terms of cognitive motor performance. Interestingly, the study authors comment, "Older players, though slower, seem to compensate by employing simpler strategies and using the game's interface more efficiently than younger players, enabling them to retain their skill, despite cognitive motor-speed loss."

In this column, we share recent scientific studies that suggest a role for a variety of nondrug strategies to protect cognitive skills as we age.

Thompson JJ, Blair MR, Henrey AJ. Over the hill at 24: persistent age-related cognitive-motor decline in reaction times in an ecologically valid video game task begins in early adulthood. *PLoS One*. 9 April 2014.

Speaking Two Languages Benefits the Aging Brain

Bilingualism has a positive effect on cognition later in life. Thomas Bak and colleagues from the University of Edinburgh (UK) analyzed data from the Lothian Birth Cohort 1936, comprising 835 native speakers of English who were born and living in the area of Edinburgh, Scotland. The participants were given an intelligence test in 1947 at age 11 years and retested in their early 70s, between 2008 and 2010. Two hundred and sixty-two participants reported to be able to communicate in at least one language other than English. Of those, 195 learned the second language before age 18, 65 thereafter. Findings indicate that those who spoke two or more languages had significantly better cognitive abilities compared with what would be expected from their baseline. The strongest effects were seen in general intelligence and reading. The effects were present in those who acquired their second language early as well as late. The study authors conclude: "Our results suggest a positive effect of bilingualism on later-life cognition, including in those who acquired their second language in adulthood."

Bak TH, Nissan JJ, Allerhand MM, Deary IJ. Does bilingualism influence cognitive aging? *Ann Neurol*. June 2, 2014.

Funny Moments Counter Memory Loss

Lee Berk and colleagues, from Loma Linda University (California, US), showed a 20-minute humorous video to a group of healthy seniors, as well as a group of seniors with diabetes. These groups were compared with a group of seniors who didn't see the video. The two groups that watched the funny video showed significant decreases in cortisol levels and greater improvements on memory tests, compared with the group that didn't see the video. The diabetes group showed the largest decrease in levels of cortisol – the stress hormone that can damage memory and learning as we age, while the healthy group had the greatest improvement on memory tests. The study authors propose that: "[humor and laughter] may be another non-pharmacological lifestyle intervention to provide health, wellness & adjunctive therapeutic benefits."

Berk L, Alphonso C, Thakker N, Nelson B. Humor similar to meditation enhances EEG power spectral density of gamma wave band activity (31-40Hz) and synchrony (684.5). *FASEB J*. April 2014;28:684.5.

Meditation Assists Memory

While there are a number of types of meditative techniques, all seek to reduce stress, improve concentration, promote self-awareness, and boost the process of thoughts and feelings. One type is concentrative meditation, where the meditating person focuses attention on his or her breathing or on specific thoughts and, in doing so, suppresses other thoughts. The other type may be called nondirective meditation, where the person who is meditating effortlessly focuses on his or her breathing or on a meditation sound, but beyond that the mind is allowed to wander as it pleases. Jian Xu and colleagues from the Norwegian University of Science and Technology (Norway) explored how the brain works during different kinds of meditation. Fourteen people who had extensive experience with the Norwegian technique Acem Meditation were tested in an MRI machine. In addition to simple resting, they undertook two different mental meditation activities, nondirective

meditation and a more concentrative meditation task. The researchers observed that nondirective meditation led to higher activity than during rest in the part of the brain dedicated to processing self-related thoughts and feelings. When test subjects performed concentrative meditation, the activity in this part of the brain was almost the same as when they were just resting. The study authors report: "Nondirective meditation, which permits mind wandering, involves more extensive activation of brain areas associated with episodic memories and emotional processing, than during concentrative practicing or regular rest."

Xu J, Vik A, Groote IR, et al. Nondirective meditation activates default mode network and areas associated with memory retrieval and emotional processing. *Front Hum Neurosci.* 2014 Feb 26;8:86.

Too Little – and Too Much – Sleep Ages the Brain

Elizabeth Devore and colleagues from Brigham and Women's Hospital (Massachusetts, US) evaluated associations of sleep duration at midlife and later life, and change in sleep duration over time, with memory in 15,263 participants of the Nurses' Health Study. Participants were female nurses, aged 70 or older, and free of stroke and depression at the initial cognitive assessment. The team found that women who slept 5 or fewer hours or 9 or more hours per day, either in midlife or later life, could have memory declines equivalent to nearly 2 additional years of age. Further, the researchers noted that women whose sleep duration changed by greater than 2 hours per day over time had worse memory than women with no change in sleep duration. The study authors submit: "Extreme sleep durations at midlife and later life and extreme changes in sleep duration over time appear to be associated with poor cognition in older women."

Devore EE, Grodstein F, Duffy JF, Stampfer MJ, Czeisler CA, Schernhammer ES. Sleep duration in midlife and later life in relation to cognition. *J Am Geriatr Soc.* 2014 May 1.

Move More to Maintain Memory

A study by Michigan State University researchers investigating young, healthy adults reveals that aerobic fitness affects long-term memory. Kimberly M. Fenn and colleagues tested 75 college students during a 2-day period and found that those who were less physically fit had a harder time retaining information. Reporting, "Findings revealed an association between aerobic fitness and memory function such that individuals with lower cardiorespiratory fitness exhibited poorer implicit memory performance and poorer long-term memory retention," the study authors submit: "These data indicate that cardiorespiratory fitness may be important for the optimal function of neural networks underlying these memory systems."

Pontifex MB, Parks AC, O'Neil PC, et al. Poorer aerobic fitness relates to reduced integrity of multiple memory systems. *Cogn Affect Behav Neurosci.* March 2014.

Anti-Aging Gene May Also Support Cognition

Indeed, cognition and anti-aging are closely intertwined, as scientists reveal that a hormone that helps us live longer could also confer cognitive effects. A variant of the gene KLOTHO is known for its anti-aging effects in people fortunate enough to carry one copy. Lennart Mucke and colleagues from the University of California/ San Francisco (UCSF; US) report that the KLOTHO variant may also lend beneficial cognitive effects by increasing overall levels of klotho in the bloodstream and brain. In a mouse model, the team observed that elevating klotho enhanced the formation and flexibility of neural connections, the cellular basis for learning and memory; and the effects were evident in mice young and old. Further, the team found that among three separate cohorts of people participating in aging studies (over 700 subjects totaled), their analysis showed that people with one of the life-extending variants of the KLOTHO gene scored better on cognitive tests. The effect didn't correlate with age in humans. In both mice and humans, klotho appears to work in a manner independent of aging and may increase cognitive reserve at different life stages. The researchers submit that in healthy, aging humans, the positive cognitive effects of carrying one copy of the KLOTHO variant may even exceed the harmful effect of carrying the notorious E4 variant of the APOE gene, which is thought to contribute to Alzheimer's disease.

Dubal DB, Yokoyama JS, Zhu L, et al. Life extension factor klotho enhances cognition. *Cell Rep.* 2014 May 22;7(4):1065–1076.

To stay updated on the latest breakthroughs in natural approaches to preserve your cognitive skills as you age, 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.

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Optimizing Metabolism

by Ingrid Kohlstadt MD, MPH
www.INGRIDients.com

A Field Guide for Brown-Bag Lunches

Introduction: It's Time for Some Brown-Bag Bragging

Change when possible, accept when necessary, and wisely distinguish between the two. Sometimes called the Serenity Prayer, this advice seems equally apt to the practice of nutritional medicine. The good news is that savvy practitioners who have wisely placed lunch in the "accept when necessary" category may now find that change is finally possible. This *Townsend Letter* column highlights practical resources for packing a healthful lunch.

Brown Paper Bag Rescues

"These aren't just for hyperventilating patients," I explain to colleagues as I pull a handful of brown paper bags out of the mountain survival kit. "Rebreathing can normalize blood chemistry in a mountain rescue scenario. Using these bags for refueling also saves lives."

My medical fieldwork has reinforced the importance of meticulous packing. Preparation was a watchword during my sojourn as an Antarctic station physician, humanitarian efforts in Sudan, and immunization efforts in the South America, where we traveled from village to village by canoe.

Everyday expeditions to school and to work benefit from smart packing, too. Unfortunately, many of us work in "accept when necessary" workplaces and attend "accept when necessary" schools. We really are going on an expedition. Without planning ahead for a healthful lunch, people find themselves in that uncomfortable dilemma: skip the meal or eat junk.

The medical effects of skipping lunch are significant. The most noticeable effects are difficulty in work performance, especially cognitive function. A drop in blood sugar relative to insulin is now considered the leading food (or lack of food) trigger for migraine headaches. The same physiologic effect sparks unrelenting food cravings leading to compulsive eating and resulting self-discouragement. Nor is eating junk worth the collateral damage.

Refueling Instructions PickNIC: A Rescue for Everyday Expeditions

Here's my field guide for the brown paper bag refueling rescue. It's called PickNIC 2014 and is freely accessible at http://www.ingridients.com/publications.

The e-book is free because of tremendous support for the project through our crowd-funding effort. Thank you to *Townsend Letter* for the shared vision. I'd be telling a lot of people "Thanks. I owe you lunch." So it's a good thing that we had lunch "in the bag."

PickNIC stands for Pick Nutritious Ingredients Cost-effectively. It's a list of 100 best-for-you brown-bag lunch ideas.

The 100 nutritious and cost-effective ingredients include something more – diversity. Lunch is an opportunity to be adventurous and take gastronomic expedition. In a celebration of multiculturalism, PickNIC gives every continent a bit of brown-bag bragging. Happy globetrotting!

Dollars and Sense

I am empathetic to the sometimes extra expense that healthful choices can incur, and that is why PickNIC has suggestions for low pricing and economic sense. That said, if you circulate PickNIC and receive some resistance about cost, you may want to probe for other reasons that people are resistant to change. Here are some recent examples.

- Packing a lunch is usually less expensive than buying one on the spot. It just takes more initiative.
- From my perspective as a mom, regional public schools have made tremendous strides in food service based

on federal mandates, while local well-heeled private schools have voiced their reticence and have chosen not to revamp lunch.

- An only-pizza meal remains the most common way to fulfill an advertisement for a free lunch lecture at a premier US school of public health and school of medicine. Were the school leadership to change the policy to be consistent with overwhelming health evidence, the favorable publicity (or avoidance of negative publicity) would be of greater value than the increased cost of the lunches.

John La Puma, MD: Get to the Real Reasons and Incentivize

If it's not time and cost, what creates barriers to change? The reasons are many, but it may be more effective to reframe the question. Whatever the reasons for resistance, what can encourage my patient to healthful lunch-time food selection here and now?

Friend and *New York Times* best-selling author Dr. John La Puma provides an outstanding answer in his recent book *Men Don't Diet, Men Refuel*. Aimed at incentivizing men in positive health behaviors, he promises and delivers a plan to shed fat, boost testosterone, and pump up strength and stamina. Here's an important take-away, recapped in my words: Want a six-pack? Pack lunch.

He preps readers towards a plan of action:

- Place lunch items in your [desk] drawers at work for a whole week, and replenish the next week.
- Bribe your spouse into packing lunch for you.
- What do you do when the boss wants to split a pizza? Say, "I'm going to try this carpaccio and get a bowl of minestrone soup, but the pizza looks good." Still stuck? Say that having food high in protein makes you a better employee: "I'm more productive and have a lot more energy." Smile when you see him or her yawning during your 2:00 meeting.

Jennifer Salos, MS, CNC: Send Your Patients 'Packing' Before They Come to See You

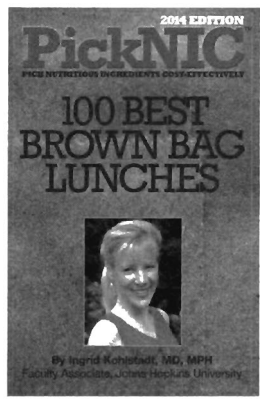
Practitioners may be appropriately concerned that talking with patients about their food selection may detract from equally important topics in a short clinic visit. My friend and colleague Jennifer Salos flips it around. She literally sends them packing before they come to see her. Instead of waiting until the clinic visit, her office staff provides nutrition-themed messaging as a form of office promotion, and uses healthful brown-bag stuffers as giveaways for those who take health actions before visits. More than selecting nutrition-aware patients, Jennifer is shaping them. Visit ChesapeakeHolistic.com for examples of the newsletter, which keeps her clinic at the forefront of her patients' "to do" list.

Conclusions

We'll be back packing in November 2014 for PickNIC 2015. Meanwhile, please send your favorite brown-bag stuffer suggestions. Because longevity is something that we can often influence through healthful choices, I conclude this column as it began, with a folk saying. "An [Irish] toast to your coffin: May it be made of 100-year old oak and let's plant the tree tomorrow."

For healthful lunches that are tasty, trendy and not too spendy, visit http://www.ingridients.com/publications.

If you are interested in participating in PickNIC 2015, you may wish to view the PickNIC 2014 crowd-funding campaign at http://www.fundable.com/picknic-by-ingrid-kohlstadt-md-mph.



Ingrid Kohlstadt, MD, MPH, FACPM, FACN
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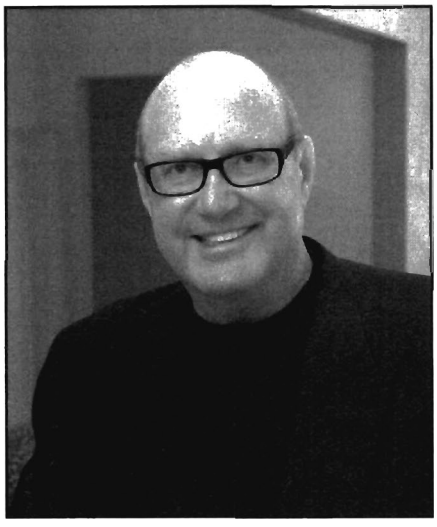
Editor, *Advancing Medicine with Food and Nutrients*
(CRC Press; 2013)



Monthly Miracles

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

Panic, Anxiety, Insomnia, and Progesterone Therapy

Rarely does a new treatment modality for sympathetic dominant behavior cause me to revamp my therapeutic approach has utilizing high-dose topical progesterone cream. I will recall some great case histories and give a brief review of progesterone and its metabolites on neurotransmitter functioning and behavior.

Progesterone, GABA, MAO, and COMT

Progesterone via one of its primary metabolites, allopregnanolone, upregulates GABA A receptors, as do benzodiazepines, barbiturates, and propofol (Diprivan).[1-3] Progesterone concentrations in the brain have been shown to 20 times higher than in blood.[4] Progesterone balances the excitatory effects of estrogen and is calming. GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that aids relaxation and sleep. Pregnanolone and allopregnanolone are synthesized de novo by astrocytes and oligodendrocytes, starting from cholesterol. Receptors for gonadal hormones have been identified in the amygdala, hippocampus, cortex, basal forebrain, cerebellum, locus coeruleus, midbrain raphe nuclei, glial cells, pituitary gland, hypothalamus, and central gray matter.[5-7]

MAO (monoamine oxidase) is upregulated by progesterone, thus reducing the levels of serotonin, norepinephrine, and dopamine. This induces calming by a second mechanism. While the relationship of progesterone to serotonin and dopamine is complex, acutely it induces calming by increasing the metabolism of norepinephrine.

COMT (catechol-O-methyl transferase) activity is enhanced by progesterone also increasing turnover of dopamine, epinephrine, norepinephrine, and serotonin. There are many other complex neurotransmitter responses to progesterone.[8,9]

40 Years of Prescribing Progesterone and Missing a Big Point

I, like many alternative, orthomolecular, integrative medical doctors, have been prescribing progesterone for women's ills: PMS, dysmenorrhea, fibrocystic breast disease, endometriosis, ovarian cysts, fibroid tumors of the uterus, mastalgia, infertility, miscarriage prevention, and osteoporosis/osteopenia for 40 years since 1975 when I first read the writings of Ray Peat, PhD, reviewing the work of Katrina Dalton, MD, who in 1950s England cured her cyclical migraine headaches with progesterone.

A patient alerted me to Dr. Michael Platt's book *The Miracle of Bio Identical Hormones*, and he graciously agreed to lecture for the Nevada Homeopathic and Integrative Medical Association annual seminar last fall, where he asserted that progesterone is not feminizing and should be given to men and children with anxiety, insomnia, and ADHD as well. Progesterone is an adrenal hormone that is high in the adrenal cortical hormone cascade. It falls in line after cholesterol converts to pregnenolone and then to progesterone, which is a precursor to cortisol, testosterone, aldosterone, and many other of the adrenal cortical hormones. Platt is releasing a new book titled *Adrenalin Dominance*, which reviews this trait and its treatment with progesterone.

'Doctor, I'm Coming Apart'

This information was all an academic experience for me until I started keeping high-dose progesterone, 50 or 60 mg per pump, at my desk side (OTC and usual dose progesterone is only 20 mg per pump), when I realized a startling discovery.

I had a string of panic and anxiety patients, five or six of them in the last 6 weeks sitting in my exam chair. "Dr. Gerber, Dr. Gerber, I'm having a panic attack; on a 0 to 10 scale I'm at a 12 and my heart is beating out of my chest. I need drugs right now take me to the emergency room!" I then squirted the progesterone on the inner wrists and forearms (50 to 100 mg) and instructed the patient to rub it in a circular motion together until it went into the skin.

Three minutes later I would ask the patient, "How do you feel now, Ms. Smith?" Shifting her gaze several times, she asked incredulously, "Could I be calm?" And, indeed she was calm. Her 12 on this anxiety scale had reduced to a 2 or 3. This was a better result than intravenous diazepam without the side effects or a long nutrient and amino acid

drip after 3 hours to accomplish the same effect, and it empowered the patient to do this at home as often as needed. Even a new patient, man, woman, or child, who is very anxious talking to a new doctor is immediately relaxed with a little progesterone.

Not all anxiety patients achieve the same results, yet I have found that at least 80% have a reduction in symptoms, and it usually ranges from significant to profound.

A Paradoxical Reaction

As is my practice, I always test everything with EAV or ART for an initial screening for appropriate resonance with the patient. Sometimes even though there is initial resonance, the patient's body rejects a particular remedy. One such episode happened when a patient, who had been addicted to lorazepam (Ativan) and who had initially tested well on progesterone, experienced a rebound of panic and crying. I asked if after the progesterone dose she felt as if she were having a withdrawal symptom from the Ativan, and she said it was identical. I believe that the progesterone was displacing the lorazepam from GABA receptor sites.

"I Can't Stop Crying"

A 54-year-old woman who had great results in our practice with asthma, fatigue, anger, insomnia, and weight gain presented with the problem of emotional lability and couldn't stop crying. She didn't have a particular reason to be crying currently, although she had been in an abusive marriage for 30 years. Emotional lability is frequently an adrenal cortex weakness symptom, and after a treatment with progesterone on the forearms, she said she was no longer teary after 3 to 5 minutes.

Insomnia and Progesterone

Oral progesterone has been used at doses of 100 to 200 mg before bed to aid sleep. However, it is also very useful to apply the cream not only before bed with a low-glycemic snack but also upon awakening in the night. It helps patients to go back to sleep after awakening in a few minutes. I always remind patients that if there are any stresses which affect the adrenal cortex, then it doesn't store blood sugar (glycogen) into the liver adequately and the body runs out of blood sugar in the night. When the blood sugar drops, the brain is alarmed and signals the adrenal gland to release adrenalin and cortisol into the bloodstream. These hormones mobilize fat from the fat stores and take it to the liver, where it is turned into blood sugar. The body doesn't die from want of blood sugar, but there is an adrenalin release. It is like trying to sleep on speed, awakening the individual whose mind then goes to the unresolved problems of the day and aggravates the stress response. Progesterone suppresses this adrenalin response and allows sleep to return more quickly.

There are more than 20 conditions that are benefited by supplementing progesterone for our patients. Overdose may cause fatigue and, rarely, depression. There are many reviews available online. However, immediate panic, anxiety, and insomnia relief with progesterone is very impressive and empowering.

Notes

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Calendar

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SEPTEMBER 26-28: INTERNATIONAL COLLEGE OF INTEGRATIVE MEDICINE CONFERENCE on PAIN in Dearborn Inn, Michigan. CONTACT: http://www.IntegrativeMedicineConference.com

SEPTEMBER 26-28: METAGENICS' 3rd ANNUAL LIFESTYLE MEDICINE SUMMIT – Transformational Patient Care: Powering the Paradigm Shift in Nashville, Tennessee. CONTACT: 800-692-9400 (US); 800-268-6200 (Canada); http://www.metagenics.com/2014summit

SEPTEMBER 27: THE NOBLE GASES IN HOMEOPATHY FOR STATES OF LIMBO, ISOLATION & OVERWHELM @ Bastyr University in Kenmore, Washington (near Seattle). 7 CEUs. CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

OCTOBER 1-5: 8th ANNUAL MICROCURRENT TRAINING AND CASE CONFERENCE in St. Pete Beach, Florida. CONTACT: 800-430-9328; http://www.microcurrentconference.org

OCTOBER 3-4: 2014 RIORDAN IVC AND CANCER SYMPOSIUM-Addressing the Metabolic Roots of Cancer in Wichita, Kansas. 16.5 CMEs. **OCTOBER 2:** Riordan IV protocol academy. CONTACT: 316-682-3100; http://www.ivcandcancer.org

OCTOBER 4: ORGANIC ACIDS TESTING: AN INVALUABLE TOOL FOR DISCOVERING THE UNDERLYING CAUSES OF CHRONIC ILLNESS WORKSHOP in Seattle, Washington. Also, **DECEMBER 6** in Houston, Texas and **FEBRUARY 21** in San Diego, California. Presented by The Great Plains Laboratory, Inc. CONTACT: http://www.GPL4U.com/workshops

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OCTOBER 17-18: A4M INTRAVENOUS NUTRIENT SYMPOSIUM in New Orleans, Louisiana. CONTACT: http://www.a4m.com/conference-schedule.html

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OCTOBER 23-26: INTEGRATIVE SOLUTIONS FOR 21st CENTURY MEDICINE in Albuquerque, New Mexico. Pre-conference workshops on electromagnetic hypersensitivity, mold, mycotoxins, and low-dose allergens. CONTACT: De Fox, 316-864-5500; defox@aaemonline.org; http://aaemconference.com

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NOVEMBER 6-9: 40th ANNUAL BIOFEEDBACK SOCIETY OF CALIFORNIA CONFERENCE in San Francisco, California. *TL* readers and 1st-time attenders get 50% registration discount by mentioning this ad. CONTACT: http://www.biofeedbackcalifornia.org

NOVEMBER 6-9: 17TH CLINICAL APPLICATIONS FOR AGE MANAGEMENT MEDICINE in Las Vegas, Nevada. CONTACT: conference@agemed.org; https://agemed.org/default.aspx

NOVEMBER 7-9: HOLISTIC COUNSELING: Discovering & Healing the Root Cause of Illness @ Bastyr Unversity in Kenmore, Washington (near Seattle). CONTACT: 425-602-3152; http://www.bastyr.edu/continuing-education

NOVEMBER 7-10: HEALTHY MEDICINE ACADEMY'S FOURTH ANNUAL INTEGRATIVE CANCER MEDICINE SYMPOSIUM in Phoenix, Arizona. Focus on clinical applications. Keynote Speaker: Keith Block, MD, the father of integrative oncology. 32.25 AMA; 36 ND CMEs; & more. CONTACT: 303-499-1223; http://www.healthymedicineacademy.com/; info@healthymedicineacademy.com.

NOVEMBER 7-10: ESSENTIALS OF CHINESE MEDICINE PEDIATRICS with Stephen Cowan, MD & Efrem Korngold, OMD in Miami, Florida. CONTACT: NSEV Healing & Acupuncture, 305-532-0777; http://www.nsevhealing.com/

NOVEMBER 8: A HOLISTIC APPROACH TO OVERCOMING THYROID DISORDERS with David Brownstein, MD in San Antonio, Texas. CONTACT: Biotics Research, 800-231-5777; http://www.bioticsresearch.com

NOVEMBER 8: NUTRITIONAL PERSPECTIVES ON NEUROLOGICAL DISORDERS with Court Vreeland, DC, DACNB, in Daytona Beach, Florida. CONTACT: Biotics Research, 800-231-5777; http://www.bioticsresearch.com

NOVEMBER 8-9: ARIZONA NATUROPATHIC MEDICAL ASSOCIATION FALL CONFERENCE in Scottsdale, Arizona. CONTACT: 480-921-3088; http://www.AzNMA.org

NOVEMBER 14: INTEGRATIVE THERAPIES FOR OPTIMIZING HEALTH IN CHILDREN @ University of Kansas Medical Center in Kansas City, Kansas. CME & CNE credits. CONTACT: 877-404-5823; http://kumcce.ku.edu/IntegrativePeds

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NOVEMBER 21-22: EXTRAORDINARY PRACTICE CONFERENCE with James Roach, MD in Midway, Kentucky. CONTACT: http://drroach.net

DECEMBER 10-13: AMERICAN ACADEMY OF ANTI-AGING MEDICINE ANNUAL WORLD CONGRESS, FELLOWSHIP MODULES & BOARD CERTIFICATION EXAMS in Las Vegas, Nevada. CONTACT: 888-997-0112; http://www.A4M.com

JANUARY 9-12, 2015: THE BENGSTON ENERGY HEALING METHOD® WORKSHOP with Dr. William Bengston in San Diego, CA. Contact: 312-786-1882, http://www.equilibrium-e3.com

MARCH 21: PATH FOUNDATION presents THE SECRET WEAPON & THE WAR ON DRUGS: BRAIN RESEARCH in New York City, New York. CONTACT: 646-367-7411; http://www.pathfoundationny.org

JUNE 5-7: HOMEOPATHY RESEARCH INSTITUTE 2015 CONFERENCE – Cutting Edge Research in Homeopathy in Rome, Italy. CONTACT: http://www.HRIRome2015.org

NOVEMBER 14-16: 12th INTERNATIONAL CONFERENCE OF THE SOCIETY FOR INTEGRATIVE ONCOLOGY in Boston, Massachusetts. CONTACT: http://www.integrativeonc.org/index.php/sio-international-conferences

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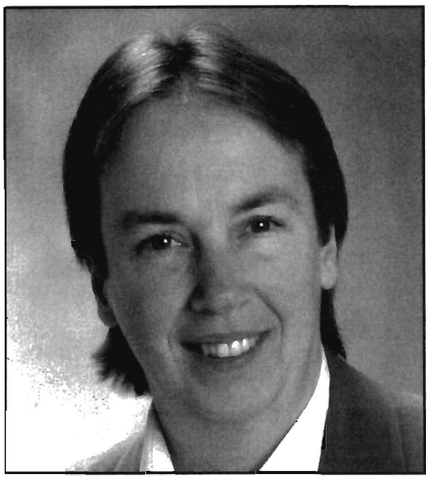

Women's Health Update

by Tori Hudson, ND
womanstime@aol.com

Single Safe Herbs and Challenging Issues: Anxiety and Acute Migraine

Oral Lavender Essential Oil in Generalized Anxiety Disorder

This randomized, double-blind, placebo-controlled trial investigated two doses of oral lavender essential oil in comparison with a selective serotonin reuptake inhibitor, paroxetine, in patients who have been diagnosed with generalized anxiety disorder (GAD). The primary outcome of this study was the effect of lavender essential oil in comparison with placebo, on GAD, as measured by the Hamilton Anxiety Rating Scale (HAM-A) total score. This instrument assesses 14 symptoms of anxiety through a scale ranging from 0 (absent) to 4 (severe). The secondary outcome was the effect of lavender essential oil compared with paroxetine on GAD.

A total of 616 patients were recruited and then 536 patients randomized to treatment. These were men and women, between ages 18 and 65 year old, from 57 general and psychiatric practices in Germany, who had a diagnosis of moderate to marked severity of GAD for an average of 2.5 years. Inclusion criteria were those individuals with a HAM-A score of ≥ 18, and with scores for anxious mood and tension symptoms of 2 or greater, in addition to a score of 21 or less for psychic anxiety. An additional anxiety scale was used as well, the Clinical Anxiety Scale (CAS), and the inclusion criteria were those with a score of 9 or greater. Individuals with any additional psychiatric illnesses were excluded. Psychiatric medications other than the paroxetine were not allowed during and for 30 days prior to entering the study. A total of 128 were in the 160 mg lavender group, 135 in the 80 mg/day group, 137 in the paroxetine group, and 136 in the placebo group.

Individuals were given a lavender essential oil made from the steam-distilled fresh flowering top of lavender standardized to contain approximately 70% of two constituents, linalool and linalyl acetate. The product was given as either a 80 or 160 mg dose and then 1 placebo or 2 placebo pills daily. The paroxetine was given in capsules of 20 mg. Treatment was given for 10 weeks, and measurements of safety and efficacy were done at 2, 4, 6, 8, and 10 weeks. During a week of "down-titration" following the study, patients on the paroxetine took the treatments every other day to account for any withdrawal problems caused by paroxetine. Patients in the lavender essential oil group took placebo.

After 4 weeks of the study and at other time points, the intake of 160 mg/day of lavender essential oil resulted in a significantly greater change in the HAM-A score compared with placebo ($p < 0.01$). After 6 weeks and beyond, those taking the 80 mg/day of lavender essential oil had a significantly greater change in the HAM-A scores compared with placebo ($p = 0.02$). At week 6, the HAM-A score in those taking paroxetine approached significance ($p = 0.06$) but then were not significantly better than placebo after that point.

Significantly more patients in the 160 mg/d lavender group showed an improvement in the HAM-A score of 50% or more compared with the placebo group (60.3% vs. 37.8%). This was also observed in the 80 mg/d group (51.9% vs. 37.8%). The HAM-A score was <10 in significantly more of those patients taking the lavender product compared with the placebo (46.3% vs. 29.6%). According to the clinical global impression (CGI), all three treatment groups (the 80 mg/day, 160 mg/day, and paroxetine) contained a greater percentage of patients who were "much/very much improved" or had a "moderate/marked" therapeutic effect as compared with the placebo group. The adverse events reported were 25% of those in the 160 mg/day lavender group, oddly higher in 34.8% of the 80 mg/day group, 40.9% in the paroxetine group, and 30.9% in the placebo group. These adverse events were reported as gastrointestinal disorders, infections, and nervous system problems.

Comment: Both doses of oral essential oil of lavender were effective in treating GAD and more effective than the conventional medicine, paroxetine. Adverse events in those taking lavender were similar in those taking

placebo and lower than those taking paroxetine. This is another welcomed positive study in using an oral lavender essential oil standardized to linalool and linalyl acetate in the treatment of GAD. Conventional medications, whether antidepressants, anxiolytics, or barbiturates, are fraught with side effects, which makes the lavender essential oil product that much more appealing.

Kasper S, Gastpar M, Müller WE, et al. Silexan is effective in generalized anxiety disorder – a randomized, double-blind comparison to placebo and paroxetine. *Int J Neuropsychopharmacol.* Epub January 23, 2014:1–11. doi:10.1017/S1461145714000017.

Chamomile and Generalized Anxiety Disorder

This randomized, double-blind, placebo-controlled trial was conducted in patients with mild to moderate generalized anxiety disorders (GAD) and compared *Matricaria recutita* (chamomile) extract with placebo.

Patients, all 18 years old or older, from a community health outpatient clinic were enrolled. All had a diagnosis of mild to moderate Axis I GAD and a minimum baseline total Hamilton Anxiety Rating (HAM-A) scale of 9 or more; those with comorbid minor depression were not excluded. Patients were excluded if depression was the primary disorder or if they had a current diagnosis of major depressive disorder, bipolar disorder, panic disorder, phobic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, substance-induced anxiety disorder, psychosis, dementia, or substance abuse or dependence within the preceding 3 months. Concurrent use of anxiolytics, antidepressants, mood stabilizers, sedatives, or other herbal/nutritional remedies was not permitted. A total of 57 were randomized to either chamomile extract (n = 28) or placebo (n = 29) for 8 weeks.

Patients were given either pharmaceutical-grade German chamomile extract standardized to 1.2% apigenin or 220 mg, or placebo. Patients were given 1 capsule daily for the first week and then increased to 2 capsules daily during the second week of treatment. At week 3, those patients with a 50% reduction or less in the total HAM-A score compared with baseline score were increased to 3 capsule daily during week 3 and then to 4 capsules daily during week 4. In those who continued to have a 50% reduction or less, they were increased to 5 capsules daily during weeks 5 through 8. Outcome measurements were done at baseline, and after weeks 2, 4, 6, and 8.

Sixty-one patients were originally enrolled, and 57 patients had a baseline visit and began treatment. Four were screen failures; 8 discontinued treatment before completing the trial.

There was a significantly greater reduction over time in the primary outcome with a mean total HAM-A score for chamomile versus placebo ($p = 0.047$). Although not statistically significant, there was a meaningful trend favorable to chamomile in the Beck Anxiety Inventory, the Psychological General Well Being index, and the Clinical Global Impression Severity rating.

Comment: Chamomile has a long, rich tradition of use for inducing relaxation and its calming effect. Its exact mechanism of action is not known, but some evidence suggests that one or more of its flavonoid constituents may have an anxiolytic effect by affecting noradrenalin, dopamine, serotonin transmission, and gamma-amino butyric acid. The apigenin constituent have been shown to bind to benzodiazepine receptors as well as reduce gamma-amino butyric acid activated activity. One might wonder if the results of this study would have been better if it had used larger doses of the chamomile extract than the maximum of 1100 mg/day. The study also did not have standard timing of the dosing, which may have altered the effectiveness. It is also possible that another species of chamomile would have produced different results. A study done on patients with just a mild to moderate disorder (rather than severe anxiety) and such a small sample size are limitations, but nonetheless the results were statistically significant and did include those with not only mild symptoms but moderate as well. The results of this study are worth exploring in terms of more clinical rigorous use and dosing of chamomile extracts for mild to moderate GAD.

Amsterdam J, Li Y, Soeller I, et al. A randomized, double-blind, placebo-controlled trial of oral Matricaria recutita (chamomile) extract therapy for generalized anxiety disorder. *J Clin Psychopharmacol.* 2009;29:378–382.

Ginger vs. Sumatriptan for Common Migraine

This double-blind, randomized, controlled clinical trial compared the efficacy of ginger with sumatriptan in the treatment of common acute migraine episodes. Assessments include the time of headache onset, severity, time interval from headache beginning to taking drug, and patient self-assessment of response for five consecutive migraine attacks.

Study subjects were 100 sufferers of common migraine headaches, from the Neurology Clinic of Zanjan Hospital in Iran. The average age of participants was 35.1 in the sumatriptan group and 33.9 in the ginger group. Women comprised 68% of the sumatriptan group vs. 74% of the ginger group. The average duration of a migraine diagnosis was similar in both groups at approximately 7 years. The average number of headache attacks in the sumatriptan groups were 5.8 and 4.9 in the ginger-treated group. Inclusion criteria for the study included a confirmed diagnosis of migraine without aura by a neurologist, age of 18 years and older, high school diploma or higher, and a frequency of 2 to 10 headaches/month.

Individuals were randomly given either 1 ginger capsule of 250 mg or 50 mg of sumatriptan upon onset of headache. Questionnaires were completed for each headache attack, recording time of headache onset; severity; timing of drug taking; and response self-assessments at 30, 60, 90, and 120 minutes and 24 hours. Any adverse effects were also recorded. The overall study duration was 1 month.

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Women's Health Update

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Both sumatriptan and ginger powder decreased the mean severity of common migraine attacks within 2 hours of use. No significant difference existed between the two treatments. Before taking the medication, 22% of the sumatriptan group and 20% of the ginger group had severe headaches. The mean headache severity at 2 hours after sumatriptan or ginger use demonstrated similar effectiveness for both groups. There was 4.7 unit reduction in the headache severity in the sumatriptan group and a 4.6 reduction in the ginger group. Favorable relief was achieved in 70% of the sumatriptan-treated headache individuals and 64% of the ginger-treated patients at 2 hours following intake. Both the sumatriptan and ginger significantly provided pain relief, and no significant differences were achieved.

There were more side effects from sumatriptan use, including dizziness, sedation, vertigo, and heartburn. The only clinical adverse effect of ginger was dyspepsia.

Comment: I am quite impressed that the current study reveals that both sumatriptan at 50 mg and ginger powder at 250 mg decreased the mean severity of a common migraine attack and within 2 hours of use. Pain relief and patient satisfaction did not show any significant difference, although side effects due to ginger were far less than those with sumatriptan. This is not the only study showing benefit for ginger and acute migraine pain. In a 2005 study, a ginger-feverfew extract alleviated migraine headache completely in 48% of individuals and partially in 34% within 2 hours of taking the ginger.[1] In a double-blind, placebo-controlled study, this same ginger-feverfew medication (Gelstat) resulted in a significantly higher pain-relief rate of 65% vs. 36% at 2 hours posttreatment. [2]

In my experience, the natural-medicine strategies for reducing the frequency and severity and duration of migraines are quite effective and include basic lifestyle and nutritional plans but, more significantly, involve a multifactorial approach using riboflavin, ginger, feverfew, 5-HTP, butterbur, magnesium, CoQ10, and sometimes cyclic estrogen patches in women with menstrual migraines. I have never felt very optimistic about acute intervention for acute pain relief with these supplements or others in reducing the severity of an acute migraine. There are anecdotal reports of oral ginger for acute migraine, 500 mg at onset and repeated every 4 hours, and an open-label study of ginger with feverfew for acute mild migraine headache pain. I am encouraged, though, by this study that use of ginger capsules for acute migraines may provide pain reduction with an overall 44% palliation in all headache attacks within 2 hours.

Maghbooli M, Golipour F, Esfandabadi A, Yousefi M. *Comparison between the efficacy of ginger and sumatriptan in the ablative treatment of the common migraine. Phytotherapy Res.* 2014;28:412–415.

Notes

1. Cady R, Schreiber C, Beach M, Hart C. Gelstat migraine for acute treatment of migraine when administered during the mild pain phase. *Med Sci Monit* 2005;11(9):165–169.
2. Aurora S, Vermaas A, Barrodale P. Gelstat is effective in relieving migraine pain in a double-blind, placebo-controlled study. American Headache Society 48th annual scientific meeting. June 22–25; Los Angeles, CA; 2006.

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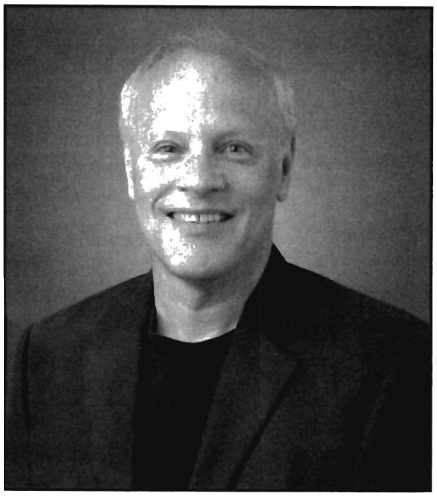

Chelation Therapy Gains More Credibility

In an editorial in the August 2013 issue of the *Townsend Letter*, I reviewed a study published in the *Journal of the American Medical Association* (*JAMA*) that examined the effect of treatment with ethylenediaminetetraacetic acid (EDTA), commonly known as chelation therapy, in patients with a history of myocardial infarction.[1] The study, known as the Trial to Assess Chelation Therapy (TACT), had a double-blind, placebo-controlled, 2 × 2 factorial design, in which patients received 40 intravenous infusions of EDTA, a daily high-potency 28-component multivitamin-multimineral formula, both treatments, or placebo. During a median follow-up period of 55 months, compared with placebo, chelation therapy resulted in a statistically significant 18% reduction in the composite end point of total mortality, recurrent myocardial infarction, stroke, coronary revascularization, or hospitalization for angina. An 18% reduction in cardiovascular disease-related events is a relatively modest benefit – less than that achieved with statin drugs and certain other medications commonly used for heart patients. However, most of the patients enrolled in the study were already receiving state-of-the art medical therapy for heart disease, including statins, aspirin, beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and platelet inhibitors. An 18% improvement above and beyond that achieved by state-of-the-art medical therapy is not clinically insignificant.

Since this research appeared in *JAMA*, two new reports have been published that provide additional data from the TACT. Three important points emerge from these new studies. First, daily use of a high-potency multivitamin-multimineral formula, a common recommendation among doctors who offer chelation therapy, may have value irrespective of the use of chelation therapy. This benefit appears to be most pronounced in patients who are not taking statin drugs. Second, the combination of chelation therapy and the high-potency micronutrient formula may be more effective than either of these treatments alone. Third, the beneficial effect of chelation plus micronutrients is particularly strong among patients with diabetes.

With regard to the first point, a study published in the *Annals of Internal Medicine* examined outcomes in the TACT according to whether patients were receiving the high-potency micronutrient formula.[2] Compared with patients in the placebo group, those receiving vitamins and minerals had an 11% reduction in the composite end point. While that reduction was not statistically significant ($p = 0.21$), it is consistent with the possibility of a modest benefit of micronutrient supplementation. When the analysis was restricted to the 27% of patients who were not taking statin drugs at baseline, vitamin and mineral supplementation significantly decreased the primary end point by 38%. In contrast, among patients taking statin drugs, micronutrient supplementation decreased the primary end point nonsignificantly by 3%. Thus, high-potency vitamins and minerals may have a pronounced beneficial effect in heart patients for whom statin drugs are not indicated or who cannot tolerate these drugs. Because findings from subgroup analyses tend to be less reliable than findings from primary analyses, additional research is needed to confirm these observations.

Regarding the second and third points, a study in the *American Heart Journal* examined the outcomes in each of the 4 subgroups of patients in the TACT.[3] The primary end point occurred in 31.9% of patients receiving chelation plus vitamins and minerals, 33.7% of patients receiving chelation alone, 36.6% of patients receiving vitamins and minerals alone, and 40.2% of patients receiving

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placebo. Compared with patients receiving placebo, those receiving chelation plus vitamins and minerals had a statistically significant 26% reduction in the primary end point ($p = 0.016$). When the analysis was restricted to the 37% of patients who had diabetes, compared with placebo, chelation plus vitamins and minerals decreased the primary end point by 51% ($p < 0.001$). These results are not only statistically significant, they are potentially of great clinical importance, with benefits equaling or surpassing those obtained with many conventional treatments for cardiovascular disease.

Because of certain weakness in the TACT, including a relatively high dropout rate, the results cannot be considered definitive. Nevertheless, they provide evidence of a beneficial effect of chelation therapy plus high-potency vitamins and minerals among certain subgroups of patients with cardiovascular disease. An editorial accompanying the *American Heart Journal* study noted the irony of the conventional medical community denigrating and dismissing the results of this scientific research.[4] For years, conventional medicine has claimed that "alternative medicine" is not evidence-based. But, now some conventional doctors have gone out of their way to criticize this study, apparently in part because it does not conform to their beliefs and biases regarding chelation therapy. One such criticism is that some of the investigators in the TACT have been disciplined by their state medical boards for providing ineffective treatments. That criticism rings hollow when one realizes that many of the disciplinary actions were for providing chelation therapy, which some state boards have proclaimed by fiat to be ineffective. The editorial concluded appropriately that the findings from the TACT should prompt new research to attempt to replicate the initial "provocative" results. Hopefully, such research will provide further insight regarding the efficacy of a treatment that has been used for so many years, and which remains so controversial.

Alan R. Gaby, MD

Notes

1. Lamas GA et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. *JAMA*. 2013;309:1241–1250.
2. Lamas GA et al. Oral high-dose multivitamins and minerals after myocardial infarction: a randomized trial. *Ann Intern Med*. 2013;159:797–804.
3. Lamas GA et al. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: the factorial group results of the Trial to Assess Chelation Therapy. *Am Heart J*. 2014;168:37–44.e5.
4. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: when evidence conflicts with beliefs. *Am Heart J*. 2014;168:4–5.

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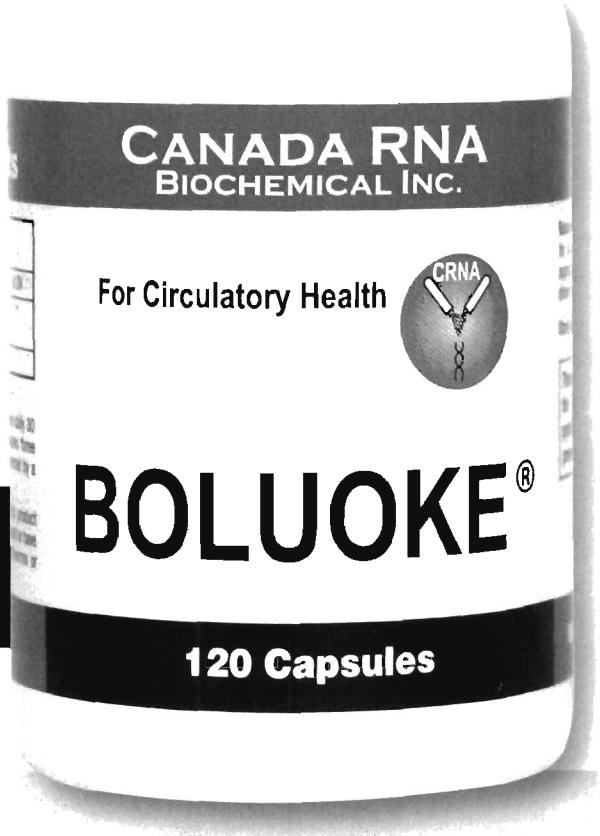

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