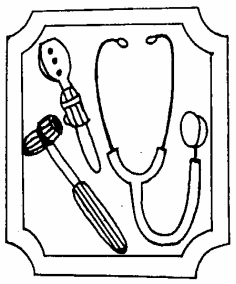

THE Original Internist

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CLINT PUBLICATIONS

VOL. 15, NO. 2 · ISSN 1529-4722 · JUNE 2008

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THE ORIGINAL INTERNIST

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The Original Internist is published quarterly. Publication months are March, June, September and December, barring any unusual or unforeseen circumstances.

News items and/or letters pertaining to natural health care are welcome. The editorial staff reserves the right to edit and/or reject all material received. Letters to the editor may be condensed in order to fit the allotted space. An address and telephone number where the author may be reached during normal business hours should also be included for verification purposes. Deadline for article submission is the 15th of the month preceding publication.

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CALENDAR OF EVENTS

June 7-8, 2008 *(Charlotte, NC)*
Lower Gastrointestinal Disease
Instructor: *Frank Strehl, DC DABCI*

June 21-22, 2008 *(Chicago, IL)*
Cardiovascular Disease: Prevention / Diagnosis / Management
Instructor: *Jack Kessinger, DC DABCI*

June 28-29, 2008 *(Dallas, TX)*
General Examination and Associated Pathology
Instructor: *Jack Kessinger, DC DABCI*

July 12-13, 2008 *(Charlotte, NC)*
Reports/Clinical Documentations/ Drug Reactions
Instructor: *Jack Kessinger, DC DABCI*

July 18-20, 2008 *(Cincinnati, OH)*
ANNUAL CDID SYMPOSIUM
Westin Hotel *....see page 103 for details*

July 26-27, 2008 *(Chicago, IL)*
Electrocardiography and Phonocardiography
Instructor: Jeremy Thornton, DC DABCI

July 26-27, 2008 *(Dallas, TX)*
Diseases and Exam of Pelvis and Associated Pathology
Instructor: *Frank Strehl, DC DABCI*

August 16-17, 2008 *(Chicago, IL)*
Chronic Degenerative Disease
Instructor: *Jack Kessinger, DC DABCI*

August 23-24, 2008 *(Dallas, TX)*
Multi-Channel Blood Chemistries, CBC, Thyroid Panel, TSH
Instructor: *Jack Kessinger, DC DABCI*

September 6-7, 2008 *(San Antonio, TX)*
CHIROPRACTIC FAMILY PRACTICE
Instructor: *Jack Kessinger, DC DABCI*

September 20-21, 2008 *(Chicago, IL)*
Pharmacognosy (Herbal therapy)
Instructor:*Daniel L. Richardson, MSc, DN, PhD*

September 27-28, 2008 *(Dallas, TX)*
Additional Blood Tests/Tumor Markers for Internal Disorder Pt.
Instructor: *Dustin Cheney, DC DABCI*

September 27-28, 2008 *(Portland, OR)*
CHIROPRACTIC FAMILY PRACTICE
Instructor: *Jack Kessinger, DC DABCI*

October 11-12, 2008 *(Los Angeles, CA)*
Introduction to Chiropractic Internal Disorders
Instructor: *Jack Kessinger, DC DABCI*

October 18-19, 2008 *(Chicago, IL)*
Pediatrics
Instructor: Delilah Anderson*, DC DABCI*

October 25-26, 2008 *(Dallas, TX)*
Blood Interpretation Workshop
Instructor: *Jack Kessinger, DC DABCI*

November 8-9, 2008 *(Los Angeles, CA)*
History Taking
Instructor: *Jack Kessinger, DC DABCI*

November 15-16, 2008 *(Chicago, IL)*
Spirometry and Pulmonary Disease
Instructor: *Jack Kessinger, DC DABCI*

November 22-23, 2008 *(Dallas, TX)*
Cardiovascular Disease: Prevention / Diagnosis / Management
Instructor: *Jack Kessinger, DC DABCI*

December 6-7, 2008 *(Topeka, KS)*
CHIROPRACTIC FAMILY PRACTICE
Instructor: *Jack Kessinger, DC DABCI*

December 13-14, 2008 *(Dallas, TX)*
Electrocardiography and Phonocardiography
Instructor: Jeremy Thornton*, DC DABCI*

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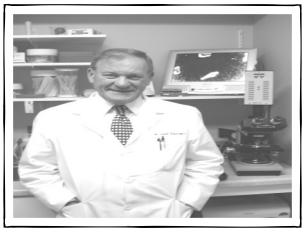
From the Editor's Desk



Dr. Jack Kessinger

by Jack Kessinger, DC, ND, DABCI
jack@drkessinger.com

ANTIAGING IS FASTEST GROWING AND MOST PROFITABLE MEDICAL SPECIALITY

Anti-aging medicine has become the fastest-growing and most profitable medical specialty. The anti-aging specialties are beginning to recognize, and adopt, the undeniable benefits of natural therapies. They are looking at delaying the aging process through detoxification, promoting a healthy lifestyle (avoiding tobacco smoke, minimal alcohol consumption, and regular exercise), diet, antioxidant and nutritional supplementation. The public awareness for all things natural continues to define the developing parade in this newest specialty in health care.

The demand for better health care is due to the fact that, overall, our current health care system is failing. The failure is evidenced by chronic conditions worsening as well as steadily growing numbers of disabled. Chronic degenerative conditions continue to consume 80% of health care dollars for conditions that are mostly preventable. Our senior citizens are faring no better.

The alternative therapies now promoted by the anti-aging medical specialties are the same healthy concepts the chiropractic and naturopathic professions have refined and practiced for well over 100 years. Our professions should aggressively gear up to provide the safer, and often more successful, health care many senior citizens are seeking.

According to the *U.S. Department of Commerce, Economics and Statistics, U.S. Census Bureau*, there are now over 35 million senior citizens, and that number is predicted to double between now and 2030. This group of senior citizens reportedly will be the longest-lived, the most educated, and have the most discretionary income of any age group.

As the average person approaches senior citizen status, health becomes a priority. The trend forecast in the *"New Millennium Chiropractor"* reported that beginning in the late 60's alternative medicine began to find its way into mainstream America. Baby boomers will be the largest segment to become senior citizens. Unlike their parents, and their parents' friends, they are the first generation to question the demagog like authority of "conventional medicine." They are looking, with open minds, at a variety of alternative health care therapies.

A significant percentage of baby boomers are deciding they do not want to live out their own last decades risking languishing as inmates in nursing homes. The youth conscious baby boom generation is becoming educated in doing what it will take to maintain and improve their health. They are willing to spend a lot of money for treatment and direction for maintaining optimum health, both of which fall into alternative providers style of practice. The continuing trend for all things natural presents both challenges and opportunities for the established alternative health care professional.

The first fundamental rule for caring for senior citizens is understanding that ***older people are sick because they are sick, not because they are old***. Health can only be attained by reducing known risk factors and supporting the overall health of the individuals through natural therapies. Traditional medicine continues to ignore this fact, increasing their prescription pads for medications rather than for essential nutritional support.

Due to the rapidly increasing neurodegenerative diseases, a study to determine the cause and effect was commissioned by Congress and reported to the "Office of Technology Assessment." The study focused on neurotoxic substances that affect our nervous system. They found the chemicals that adversely effect our nervous system are: (1). Industrial chemicals (2). Pesticides (3). Therapeutic drugs (4). Recreational drugs (5). Food and food additives and (6). Cosmetics. The U.S. Environmental Protection Agency reports over 105,000 chemicals are in their inventory of toxic chemicals. Many of these chemicals have proven to adversely affect the nervous system. Neurotoxic effects from chemicals can often go unrecognized for many years because symptoms are varied, ranging from impaired movement, anxiety, and confusion to memory loss and death. Neurotoxic chemicals are reported to constitute a major public health threat, but are largely ignored by traditional medicine.

Several news agencies, including Fox News and The New York Times, reported on March 10, 2008, that a vast array of pharmaceuticals — including antibiotics, anti-convulsants, mood stabilizers and sex hormones — have been found in the drinking water supplies of at least 41 million American municipalities.

A study by the U.S. Adminstration on Aging reports

(Continued on next page)

that *"Manutrition in the Elderly"* is a national crisis of epidemic proportions and is costing the nation billions of dollars needlessly. Malnutrition is directly linked to disability, dysfunction, and morbidity, as well as loss of quality of life and independent living. Older people should not have to wait until they are ill before risk factors of poor nutrition are addressed. Complex carbohydrates, cis fats, orthomolecular nutrition, and exercise are all well-documented to be essential for optimum health. However, while we are often told to consume fruits and vegetables, very little information is provided as to exactly why. Only, "they are good for you."

Poor nutritional status and malnutrition in the elderly population contribute to progressive decline in health. This fact is commonly ignored by biomedicine. A common assumption is that nutritional deficiencies are an inevitable consequence of aging and disease, and that intervention for these deficiencies is only minimally effective. Nutritional assessment and treatment should be a routine part of care for all elderly persons, whether in the outpatient setting, acute care hospital or long-term institutional care setting. Older citizens tend to eat less and unbalanced meals. In addition to the xenobiotic load, this is a major cause for possible vitamin depletion. Also, many medicines not only change the way nutrition is absorbed, but also decreases intestinal selective permeability, leading to the leaky gut syndrome.

It is reported that 90% of food now consumed in America is processed foods. Many can be identified as non-food items, such as soft drinks, white flour, refined sugars, etc. These add to the detoxification burden without any benefits, and should be replaced by a selection of natural foods.

The ability of antioxidant vitamins and other nutrients to inhibit free radical activity can help to prevent the major life-threatening diseases. There is solid evidence that supplemental antioxidant nutrients can help to prevent atherosclerosis, cancer, arthritis, and other aging related diseases.

Antioxidant micronutrients are particularly found in fruits and vegetables, and inadequate amounts are correlated with degenerative diseases. Aging and/or stress reduces levels of antioxidants and increases their need. In addition to limited information concerning fruits and vegetables commonly shared with patients, little is reported about the powerful antioxidants found in amino acids.

Alpha Lipoic Acid is well-documented to be a powerful antioxidant and a co-factor in vital energy-producing reactions in the body. It is a naturally occurring antioxidant, scavenges reactive oxygen species followed by an increase in apoptosis of human hepatoma cells. *The Journal of Endocrinology. 2008 May;197(2):287-96* reports Alpha Lipoic Acid is implicated in the beneficial effect of antioxidants in obesity-/dyslipidemia-induced insulin resistance in humans. Alpha Lipoic Acid has been shown to significantly reduce peripheral neuropathy in doses between 300 – 600 mg daily for three months. The *Physicians Desk Reference for Nutritional Supplements* reports that, in Germany, Alpha Lipoic Acid is approved as a drug for the treatment of polyneuropathies from diabetes, alcohol and liver disease. In addition to being a potent antioxidant, it also enhances the effect of two other well-known antioxidant vitamins, C and E. When combined with L-carnitine, it was reported to put the spark back into aging rats, and might do the same for aging baby boomers, according to a study at the *University of California, Berkeley*, and Children's Hospital Oakland Research Institute.

Acetyl-L-carnitine (ALC) has demonstrated some positive effects in Alzheimer's patients and may improve depression, Parkinson's disease and stroke *(PDR Health, Physicians Desk Reference)*. L-carnitine shuttles acetyl groups and fatty acids into the mitochondria. Fatty acids are essential for energy production. It is reported that, in addition to neuroprotective activity, supplemental acetyl-L-carnitine may have cardioprotective activity. The *Journal of Child Adolescence Psychopharmacol*. Dec:17(6):791-802 reports Acetyl-L-carnitine (ALC) is a metabolite necessary for energy metabolism and essential fatty acid anabolism. *Neuromolecular Medicine.* 2007;9(3):264-9 reports that combined administration of N-acetyl-cysteine and alpha lipoic acid enhances activity of acetyl -L-carnitine.

Phosphatidylcholine is made from phospholipidsis and is the protective barrier (membrane) around every cell in the body. In order to repair the structural damage caused by free radicals, pathogens, and toxins, the body requires a constant supply of phospholipids. Many of the structures inside each cell are also made from phospholipids. One of the most common sources of phospholipids is lecithin, which appears naturally in foods like egg yolks, soy beans, sunflower seeds, and grapeseeds. Levels of n-3 fatty acids are depressed in vegetarians due to prolonged consumption of the high linoleic and oleic acid components *(fatty acid composition of erythrocyte, platelet, and serum lipids in strict vegans. Lipids. 1995 Apr;30(4):365-9).* Important as they are, cell membranes are also exceedingly thin and delicate structures which are particularly vulnerable to damage from common dangers of the cellular world (like drugs, toxins, and oxygen free radicals). Any

(Continued on page 106)

Vital Nutrients

The Key Company

The Legacy Continues

Dr. Jay Kessinger

by A. Jay Kessinger IV, DC, ND, DABCI

In addition to our annual educational license renewal requirements (which all professions have), *boundary training* was added to our state's agenda.

Boundary Training!! …… I often thought that rather than have the focus only on anti-sexual doctor-patient education, there is more to the boundaries of practice than sexuality. Our boundaries are not only set in moral and legal stone, but our boundaries as doctors are defined by our personal fortitude, based on our knowledge, and desire.

Sexual prowess has no place in professional service. It is unethical behavior and should not be tolerated. This narrow scope of boundary training is important in clarifying what "it" means, and what is meant by sexual innuendo. I've heard this presentation several years and it doesn't seem to vary. I think I've got it: keep your hands to yourself in any kind of sexually suggestive manner, and when you are treating any member of the opposite sex (yin/yang) always have a staff member present to remove any doubt of inappropriateness or mal -intent.

Some of the boundaries/limitations set forth toward our ability to provide for our patients, with no further ado in regards to sex and other inappropriate professional behavior include cancer, infectious disease, inflam-matory disease, and emergency situations. These are listed in the order of which they came to mind. There are probably more, but it is my hope that these and their subsets will serve to point out and guide toward enlightened personal goals. As Grandad, Dr. A. J. Kessinger so aptly said, "You can do whatever you're big enough to do."

Cancer treatment is legally a medical bailiwick; however, the diagnosis of the likelihood for, and the treatment of, the sequelae of cancer is well within the scope of chiropractic. Such endeavors should be of paramount stature within the chiropractic physician's mind's eye, whether with direct personal involvement or indirect application, via a surrogate chiropractic internist utilizing DABCI principles and protocols The services offered by the orthodox medical oncology department is, at best, lacking. To take up the slack in an intelligent attempt to provide individually optimal health care, even to those with "terminal disease," it would behoove us to strive toward their allowance of necessary nutrients essential to ramp up their recuperative capabilities to the max. It is not humane to allow patients and their family members to suffer the mal-effects of palliative treatments with the misunderstanding that there is nothing else that can be done. When was the last time anyone recalls an orthodox oncology department recommending, much less acknowledging an alternative form of treatment even when theirs is of admitted no hope? This is a void in the world of oncology; an absence of ability or willingness to look outside the accepted scope of tradition to solve a life threatening conundrum with increased quality of life; that chiropractic is not only suited for, in its holistic DABCI form, but was created to provide.

Treatment of infectious disease is another topic for analysis. An infectious disease is a disease caused by bacterial, viral, fungal, or protozoan infection. Though some infectious diseases are not contagious, others may be transmitted from animal to person (bird flu and cat scratch disease) or from person to person (MRSA, STDs, etc.). Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. As a portal of entry into the professional health care delivery system, a physician must be able to define the severity, or the potential severity, of their patient's condition, and provide a reasonable and informed decision of treatment options from which the patients or their representative may choose.

Although the main emphasis in our clinic is to provide a good offense i.e., prevention is the best medicine there are many times in which a patient presents with an infectious condition that can be successfully treated with natural methods. A positive streptococcus pharyngeal screen in a child doesn't dictate antibiotic usage, but it does require a doctor's supervision to evaluate the successful eradication of a potential cardiologic path-ogen. Pneumonia doesn't require emergency medical care unless the natural means of treatment fail to provide ample oxygenation and recuperation. By monitoring and maintaining an individual healthy im-mune system and utilizing a conservative chiropractic approach, optimal health most often can be restored and maintained without the use of pharmaceutical intervention. However, it is wonderful that we live in the day and age of advanced emergency medicine. If natural means fail to achieve set goals of recovery in a specific period of

(Continued on next page)

time, as noted by diligent testing and retesting, then advanced emergency medical care will have ample time to render its desired effect. If, on the other hand, the patient with the infectious disease is one who always succumbs initially to unscrupulous antibiotic therapy, there will most likely become a time when his friendly bacteria will rebel against the antibacterial onslaught, and metamorph into a pathogenic resistant bacteria potentially resulting in impetigo or MRSA-like infection.

Inflammatory disease and emergency situations, such as appendicitis, heel spurs, and car accidents bring the boundary lines of practice to mind in similar yet diverse manners. In the case of appendicitis, a condition thought to be an emergency medical bailiwick, hospitalization is not always necessary initially; however, I've always found solace in the fact there's an emergency room right around the corner. I've successfully treated several of these, but the one I didn't inform of the diagnosis went to the hospital where the surgeon said, "You got here in the nick of time, because it was ready to explode." Heel spurs seem to always be amendable to natural means, but this is not to say that I haven't had patients that sought surgical intervention before my treatment protocol was fully implemented. Sometimes the only thing you can do with people is just love them, because you are not in control of anyone but yourself. But you should always act with informed consent, and the only way to keep your patient informed is to be informed. In the last mentioned situation, I treat a lot of car accident victims. I haven't seen any of them in my office while they were still visibly bleeding; however, I like to perform a complete blood test to ascertain if there are any internal blood loss. If I'm in a car wreck I want to go to the hospital, if I am bleeding. Medicine's greatest benefit is keeping its patients alive; however, its greatest weakness is its refusal to look outside of itself to prevent people from needing its services. That almost makes sense too.

These are but a few boundaries in which we need to consider expanding. Bubba's line, "It depends on what you mean by "it" still doesn't hold water. There are some boundaries that are never to be crossed, much less to even get near, while there are others that we need to expand for the benefit of those we serve.

You don't have to do things the way they have always been done just because they've always been done that way. In the 1800's tomatoes were considered poisonous in America while Europeans routinely consumed them.

Don't let the tomato effect hold you down. ◆

LONG
CREEK
HERBS

Latest Findings on Essential Fatty Acids and Cardiovascular Health

by Mark Houston, MD, MS, FACP FAHA
and William Sparks, BS

The epidemiological studies by Bang and Dyer[1] in the mid-1970s of the Greenland Inuits established a low prevalence of age-adjusted mortality from myocardial infarction in that population as compared to Danes or North Americans. The striking difference between diets was the presence of 5-10 g of the long-chain n-3 polyunsaturated fatty eicosapentaenoic acid (C20:5n-3) and docosahexaenoic acid (C22:6n-3) per day. Lower coronary heart disease has been established in at least three prospective epidemiological studies with men who ate at least some fish weekly as compared to men that ate none.[2] Men who consume 35 g or more of fish daily compared with those who consumed none had a relative risk of death from CHD of 0.62 and a relative risk of non-sudden death from MI of 0.33.

Harris[3] has proposed that an omega-3 fatty acid biomarker, the omega-3 index (erythrocyte EPA+DHA), be considered at least a biomarker, if not a risk factor, for coronary heart disease, especially sudden cardiac death. The largest (11,000 plus patients) and most well-controlled study[4] with small intakes of omega-3 and CHD disease in high risk patients examined the randomized effects of one capsule of 850 mg (EPA+DHA) as compared to usual care. After following the patients for 3.5 years, the patients that received the omega-3 capsule had a reduction of 20% for risk of death and 45% for sudden death.

The American Heart Association[5] acknowledges the beneficial effects of omega-3 fatty acids in those at high risk of, or who have, cardiovascular disease. Patients without documented coronary heart disease are recommended to eat a variety of fish at least twice a week. Patients with documented CHD are recommended to consume about 1 g of EPA+DHA per day. The FDA ruled in 1997[6] that intakes of up to 3 g per day of marine omega-3 fatty acids are generally recognized as safe (GRAS) for the inclusion in the diet. The ruling included specific considerations of the reported effects of omega-3 fatty acids on glycemic control in diabetic patients, on bleeding tendencies, and on LDL cholesterol.

The enrichment of membrane phospholipids by omega-3 fatty acids influences the mechanisms by which many of the beneficial properties of omega-3 fatty acids are observed. Because of their highly unsaturated nature they alter membrane fluidity. The omega-3 fatty acids displace arachidonic acid (AA). Omega-3 fatty acids compete with AA for enzymes responsible for the production of inflammatory mediators, such as eicosanoids and platelet-activating factor (PAF). Increasing the ratio of EPA to AA enhances the formation of prostaglandin E3 (PGE-3) which can block inflammation.

Intracellular omega-3 FA are able to serve as ligands for a variety of nuclear receptors. Omega-3 FA are observed to alter the expression of genes responsible for production of TNF-alpha, interleukin-1 as well as modulate the expression of genes controlling both systemic and tissue-specific lipid homeostasis.[7] In addition, omega-3 fatty acids can regulate the activation of transcription factors including NF-kappa B, which induces many of the genes in response to inflammatory stimulation.

Inflammation plays a key role in coronary artery disease and other manifestations of atherosclerosis.[8] Immune cells dominate the early atherosclerotic lesions, and their effector molecules accelerate the progression of the lesions. The infiltration and retention of LDL in the arterial intima initiate an inflammatory response in the artery wall. The balance between inflammatory and anti-inflammatory activities can control the progression of atherosclerosis. Omega-3 FA, as modulators of the inflammatory process, are natural agents that have also been reported to be beneficial for other inflammatory processes.

Maroon[9] treated 250 patients who had been seen by a neurosurgeon and were found to have non-surgical neck or back pain with 1,200 mg per day of omega-3 FA. After taking the omega-3 FA for 30 days, 59% of the patients discontinued taking their prescription NSAID medications for pain. Sixty percent stated their overall pain was improved, and 60% that their joint pain had improved. Eighty percent said that they were satisfied with their improvement, and 88% that they would continue to take the omega-3 FA supplement. Maroon noted that "the literature reviewing rheumatoid and osteoarthritis, both chronic inflammatory conditions, consistently reports improvements in joint pain and function using omega-3 EFA."

The modern western diet which contains corn, sunflower, and safflower oils supplies large amounts of li-

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noleic acid (LA) and omega-6 FA (C18:2n6). Vasquez[10] notes that two omega-6 fatty acids in particular, LA and arachidonic acid (AA) (C20:4n6) should be reduced or eliminated from the diet to the extent possible. Linoleic acid increases inflammation by several mechanisms, one of which is the activation of NK-kappa B. The increased omega-6/omega-3 ratio most likely contributes to an increased incidence of cardiovascular disease and inflammatory disorder.[11] The earlier hunter-gatherer diet provided an omega-6 to omega-3 ratio between 1:1 and 4:1. These ratios were maintained until the industrial revolution but are now estimated at between 16:1 and 20:1. In order to obtain a dietary fat intake that more closely resembles what our genomic code is based upon, a reduction of omega-6 oils and an increase of omega-3 oils is necessary in the human diet. These dietary suggestions do not take into consideration the effects of trans fats, oxidized fats, and saturated fats that have occurred with industrial food supplies.

To obtain 1 g of omega-3 FA per day from fish an individual would have to consume 2-3 ounces of salmon, sardines or mackerel per day or consume dietary supplements containing fish oil. A potential issue arises from the fact that some fish may contain relatively high amounts of heavy metals, such as mercury and/or organic pollutants such as polychlorinated biphenyls and dioxins. Since July 2002, the US Food and Drug Administration (FDA) has tested over 3,400 cans of tuna as well as 227 samples of various fish. Large carnivorous fish that are high in the food chain were found to have the highest levels of mercury. Swordfish may have 1 µg/g. Tuna was found to have an intermediate level of mercury (0.1-0.5 µg/gm).[12] The mean daily intake of mercury is 3.5 µg per day in the United States. Because of concerns of mercury contamination in the food supply, women of childbearing age are recommended by the FDA to eat no more than one or two portions of oily fish per week (about 0.4-0.8 g/day of omega-3 fats).[13]

In 1997, the US Environmental Protection Agency (EPA) recommended the value of 0.1 µg/kg body weight per day as a lifetime safe daily intake of mercury (methyl mercury). For a 60 kg woman the EPA maximum safe dose of mercury per day would be 6 µg. This level would result in the consumption of 7 ounces of canned tuna per week equaling or exceeding the EPA safe limits for mercury. The FDA has reviewed the data on mercury and proposed a reference dose of 0.5 µg/kg of body weight per day (NRC, 2000).[14]

To provide a diet of 1 g omega-3 FA per day, supplementation with omega-3 fatty acid capsules becomes the only non-toxic remedy available. There are many sources of omega-3 FA in the market place. The food standards agency for the UK published in 2005[15] the total mercury as measured in 100 samples of fish oil dietary supplements. The level of detection, minimal amount that can be measured, was reported as <0.0014 mg/kg. That level is the same as 1.4 µg/g. The consumption of six fish oil capsules could be acceptable by their own testing methods and could also result in a potential consumption of (6 x 1.4 µg) 8.2 µg of mercury from the fish oil capsules. The European guidelines for mercury are based upon the provisional tolerable weekly intakes set by the joint expert committee on food additives as set forth by the United Nations and World Health Organization. For mercury the European guidelines are 0.005 mg/kg body weight per day for which no more than two-thirds should be from organic mercury (methyl mercury). For a 60-kg person, consumption of less than 20 µg per day of mercury from fish would be considered safe under their guidelines.

Due to contaminants, fish, such as tuna, swordfish, or cod, are recommended not to be consumed on a regular basis. Cod oil was the original sourcing for omega-3 FA capsules. Freezing the oil provided a rich fraction of omega-3 FA. Concerns over heavy metals , dioxins, and polychlorinated biphenyls (PCBs) lead to methods of purification, such as clay and silica filtration, and reduced the contaminants in the oils. Refiners of fish oil now rely on sourcing fish that have lower levels of toxic exposure to produce omega-3 oils low in toxins. Harvesting of fish, such as Peruvian achoveta and sardines off the north and south poles, combined with established refining methods, allows the production of high purity fish oils. The high purity fish oils used in the manufacturing of high purity omega-3 FA will typically assay at less than 0.01 µg of mercury per gram of oil (<10 ppb, parts per billion).

Because we cannot synthesize omega-3 or omega-6 FA, they must be obtained from the diet and therefore are essential nutrients. Both omega-3 and omega-6 are structural components of all cell membranes. These fatty acids affect membrane properties such as fluidity and permeability, in addition to the activity of membrane bound enzymes. The adequate daily intake (AI) for adults of omega-3 FA (as EPA+DHA) is 0.65 g. Found in flax seed, canola, soybeans, walnuts and dark green leaves, the omega-3 FA alpha-linolenic acid (LNA) (C18:3n-3) has an AI of 2.22 g. LNA is a plant derived fatty acid and can be elongated to EPA and DHA by the enzymes delta-6-desaturase, elongase, and delta-5-desaturase. The process of conversion of LNA to EPA and DHA requires essential vitamins (vitamin c, pyri-

(Continued on next page)

doxine) and minerals (zinc, magnesium, iron). This process is inhibited by catecholamines (stress), thyroxine, glucagons, trans fats, saturated fatty acids, alcohol, smoking, elevated blood glucose and aging.[16,17,19] Functionally, the omega-3 FA EPA and DHA should be considered essential nutrients in many individuals. Siguel reports that essential fatty acid insufficiency (EFAI) is one of the most prevalent nutritional deficiencies, occurring in >10% of samples in the Framingham Offspring study. Siguel states, "We believe that EFAI is associated with significant disease states and may underlie many of the chronic diseases prevalent in Western societies. We have shown in patients with angiographically documented coronary artery disease that indicators of EFAI are highly predictive of coronary artery disease."[23]

Omega-6

The AI for the omega-6 FA linoleic acid (LA) (C18:2n-6) is 4.44 g/day. Western industrialized countries rely on corn, safflower, and soybean oils as sources of omega-6 FA. There is an overabundance of omega-6 FA in that food supply. Most American consumers obtain more than 15 g/day of LA. To be fully utilized by the body, LA must be metabolized to a range of other substances.[18] The first step in this process requires the enzyme delta-6-desaturase and produces gamma linolenic acid (GLA). This enzymatic step is slow and rated "limited," especially in humans.

GLA is present only in small amounts in the oils commonly used in the Western diet but is found in high amounts in plant oils — borage seed (23%), blackcurrant seed (18%), and evening primrose (9%). GLA is rapidly converted by the enzyme elongase to dihomo-gamma-linolenic acid (DGLA) (C20:3n6). Increased dietary intakes of GLA or DGLA have been shown to increase prostaglandin E-1 (PGE-1) which suppresses PGE-2 production. PGE-2, produced from arachidonic acid (AA), is pro-inflammatory and suppresses T-cell function. Both GLA and AA compete for the same cyclooxygenase enzyme. GLA down regulates the production of pro-inflammatory cytokines by competing with AA.

PGE-1 increases intracellular cyclic AMP, and it is this increase in polymorphonuclear leukocyte cyclic AMP that reduces the release of lysosomal enzymes, reduces polymorphonuclear leukocyte chemotaxis, and reduces the margination and adherence of leucocytes to the blood vessels.[20] By a similar fashion, PGE-1 inhibits the inflammatory responses mediated by lymphocytes. PGE-1 is also a potent inhibitor of vascular smooth muscle cell proliferation.[23] The interplay of these eicosanoids, PGE-1 and PGE-2, influences a wide range of physiological and pathological processes, including inflammation, immunity, hemostasis, blood pressure, and atherosclerosis. This balance is thought to be regulated by the complex interaction between DGLA, AA, and EPA.[21]

The administration of GLA, which rapidly converts to DGLA, has been shown to reduce joint swelling and tenderness in patients with autoimmune diseases such as rheumatoid arthritis (RA). The dosage of GLA required for effectiveness is not well established. Studies using less than 500 mg/day of GLA for periods of less than six months typically fail to show benefit in the treatment of RA. In a 24 week trail, using 1.4 g/day of GLA, Leventhal showed clinical improvement in RA patients. GLA reduced the number of tender joints by 36% and swollen joint count by 28%, whereas the placebo did not provide improvements.[24]

The reduced capacity to convert LA to GLA has been associated with a variety of other pathophysiological states including aging, diabetes, alcoholism, atopic dermatitis, premenstrual syndrome, cancer, and cardiovascular disease.[25] The decline in delta-6-desaturase activity that occurs with aging is greater in women than in men.[26] DGLA also exerts its effects on cytokine activity independent of its effect on COX enzymes. DGLA is present in cells as a free fatty acid, and has been shown to regulate gene function.[27] Das[28] proposes that a functional deficiency in delta-6-desaturase underlies the origins of the inflammation that leads to the initiation and progression of atherosclerosis. Provided adequate antioxidant status, increased levels of essential PUFA, GLA, and DGLA are capable of suppressing inflammation and expression of various adhesion molecules on the surface of endothelial cells.

Combined Effects of Omega-3 and Omega-6

The enzyme elongase rapidly converts GLA into DGLA. The enzyme delta-5-desaturase can convert DGLA to AA. *In vitro* and *in vivo* studies have shown that inflammatory cells, such as neutrophils, contain elongase but not the delta-5-desaturase activity. Because of this, dietary supplementation of GLA will increase only DGLA and not AA in cells such as neutrophils. Serum levels of AA may be increased with dietary GLA. Since AA has been shown to enhance the formation of platelet-aggregating endoperoxides and thromboxanes, platelet aggregation can be enhanced by dietary supplementation with GLA. EPA and DHA block the activity of delta-5-desaturase. The combination of EPA with GLA prevents the increase of serum AA. Barham[29] was able to show that an equal amount of EPA added to GLA prevented an increase of AA *in vivo*. The addition of EPA not did inhibit the conversion of GLA to DGLA in neutrophils.

(Continued on next page)

Laidlaw and Holub[30] examined the effects of supplementation with fish oil n-3 fatty acid and GLA on circulating plasma lipid and fatty acid profiles in women. The objective of the study was to determine the effects of different levels of GLA supplementation together with a constant intake of EPA and DHA on the reduction of triglycerides (triacylglycerol) and fatty acid patterns of serum phospholipids. Four grams of EPA+DHA were supplied to 31 healthy women who were assigned to one of four groups. The groups received no GLA, 1 g of GLA, 2 g of GLA, or 4 g of GLA daily for 28 days. The group that received 4 g of EPA+DHA and 2 g of GLA had the largest mean reduction in non-HDL-cholesterol concentrations (14.4%). The DGLA increased only when the ratio of EPA+DHA to GLA was 4:2 or 4:4. The one-gram, two-gram and four-gram GLA groups had decreases in LDL cholesterol and improved LDL:HDL ratios. Overall, the mixture of 4 g EPA+DHA and 2 g GLA (2:1 ratio) provided the greatest reduction, 43%, in the 10-year myocardial infarction risk as measured by the PROCAM program (which takes into account LDL, HDL, and triglyceride concentrations). The one-gram GLA group had a 33% reduction in risk, and the four-gram GLA group had a 24% reduction in risk.

Vitamin E Required with EFA Supplementation

PUFA supplementation increases the daily requirement for vitamin E. Concentrations of alpha tocopherol in plasma decrease significantly with fish oil supplementation. Kramer[31] observed a reduction of plasma alpha tocopheryl of 20% in patients supplemented with 7.5 g EPA+DHA. In healthy elderly patients, vitamin E supplementation has been found to increase immune responses such as lymphocyte proliferation.[32] The immuno-enhancing effect of vitamin E in the elderly has been shown to be dampened when it is consumed with fish oil. In subjects consuming 2.5 g of EPA+DHA, 200 mg of vitamin E as dl-alpha tocopherol was able to increase plasma vitamin E levels by 25%.[33] Natural d-alpha tocopherol has a bioavailability of almost three times that of synthetic dl-alpha tocopheryl acetate.[36] An optimal dose of natural alpha tocopherol would be 67 units per 2.5 g of EPA+DHA.

Vitamin E as a lipid soluble antioxidant inhibits the proliferation of smooth muscle cells, reduces platelet adhesion and aggregation, and prevents monocyte-endothelial interactions. All of these actions are increased in the development of the atherosclerotic process. Clinical trials have demonstrated a linear decrease in oxidative stress markers in patients supplemented with vitamin E.[34] Plants produce eight different molecules with vitamin E activity (alpha, beta, delta and gamma tocopherols and the four corresponding tocotrienols). Alpha tocopherol is the major form of vitamin E found in human tissues. Gamma tocopherol is the major form found in the US diet. Gamma tocopherol has been demonstrated to be more powerful in trapping many reactive oxidative species and displays a broader anti-inflammatory profile than alpha tocopherol. Compared to alpha tocopherol, gamma tocopherol is a more potent inhibitor of COX activity and is more effective for the inhibition of key mediators of inflammation such as TNF-alpha, nitric oxide an inflammatory eicosanoid production. Clinical evaluation of individuals suffering from coronary heart disease has shown decreased levels of gamma-tocopherol but not alpha-tocopherol.[35]

Omega-3, Omega-6 & Vitamin E

To obtain the optimal omega-3 index, supplementation with omega-3 FA is necessary. To obtain the optimal PUFA supplementation, the addition of GLA with omega-3 FA is necessary. The 2:1 mixture of omega-3 to GLA has been shown to provide the greatest supplemental benefit to patients. The addition of a high gamma tocopherol vitamin E to a 2:1 omega-3:GLA is necessary to ensure healthy antioxidant status. Natural mixed tocopherols, as found in many whole foods, provide 20% alpha tocpherol, 60% gamma tocopherol, and 24% delta tocopherol. The optimal dose of natural mixed tocopherols for 1.5 g of EPA+DHA would contain 215 mg gamma, 86 mg delta and 50 IU of alpha tocopherol. All these factors must considered when choosing a supplement that contains omega-3, GLA, and or vitamin E.

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Nutritional Management of Celiac Disease - An Individual Case Study

by Robert A. Duca, Jr. DC, DABCI, DACBN, DACBSP, FIAMA

Introduction

Celiac disease is a digestive system disease that damages the small intestine and interferes with absorption of nutrients from food. It is also known as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy. Patients with celiac disease cannot tolerate the protein gluten. These proteins are found in all forms of wheat, such as durum, semolina, and similar grains such as rye, barley, and triticale**.** Damage to the villi[1] of the mucosal surface of the small intestine is caused by an immunologically toxic reaction to the ingestion of gluten which results in interference with the absorption of nutrients. Celiac disease is an autoimmune disease and it is often accompanied by other autoimmune processes such as Sjorgen's syndrome, type 2 diabetes, thyroid disease, SLE, and RA.

New data suggests that stress can provoke the development of celiac disease. Recent studies demonstrate that celiac disease is relatively common.[1,3-5] These findings estimate approximately 2 million people in the US have celiac disease.[2] It is a genetic disease and individuals that have one blood member of the family with the disease have a 1:22 chance of developing it. Common symptoms of the disease are abdominal gas, bloating, abdominal pain, diarrhea, anemia, dermatitis herpetiformis, apthous ulcers, osteoporosis or osteopenia, weight loss or gain, and amenorrhea in females. Complicating the diagnosis of the disease is the fact that a significant portion of celiac patients may be asymptomatic. Celiac disease is diagnosed via the anti-tissue transglutaminase antibody (tTG), or antigliadin antibodies (AGA), IgG, and IgA. Gastro-esophageal endoscopy and subsequent tissue biopsies are often done to confirm the diagnosis.

Our patient was a 38-year-old Caucasian female athlete. She was single and worked as a computer consultant. She was an elite level kayak and canoe paddler and trained extensively throughout the year.

***Chief Complaint*:** Over a period of six weeks, the patient began to develop abdominal bloating, pain, and rectal bleeding. She had no prior history of gastrointestinal symptoms or disease. The patient estimated a loss of approximately one teaspoon of blood every other day while cleaning herself after going to the bathroom. The abdominal pain and bloating occurred daily. Her symptoms did not appear related to the ingestion of foods or alcohol.

***Medications*:** The patient has taken oral birth control pills for the previous 10 years. She took NSAIDs on an infrequent basis for the relief of aches and pains related to minor sports injuries. She had been prescribed multiple rounds of antibiotics in the last four months for a recurrent folliculitis. She was not taking any vitamin, herbal remedy, or any type of ergonomic aid. The patient had never had any major surgery, history of drug use, eating disorder, or psychologic and/or emotional disease. She did have a history of significant musculoskeletal injuries suffered in various sports endeavors. She listed the injuries as multiple sprained ankles, hamstring tears, back and neck injuries, and a dislocated right shoulder.

***Family Medical History*:** The patient's family medical history was deemed non-contributory. The patient stated that the father is in excellent health. The mother had a CVA. The patient has one brother in good health. She had no knowledge of celiac or autoimmune disease in her extended family.[2]

***Lifestyle*:** The patient had traveled overseas on two occasions in the last year for paddling competitions. She did not use tobacco products. She drank alcoholic beverages very infrequently, perhaps one to two servings monthly. The patient trains diligently for her paddling sports and estimated that she jogs 5-6 miles three times/week, bicycles 60 miles weekly, and lifts weights and does stretching exercises 30 minutes/day. She paddles her kayak and canoe for 1-3 hours/day. She competes in sprint kayaking and open water outrigger endurance racing, entering events 1-3 weekends each month. She hydrates 2 liters of water and eats three full meals daily. In between meals she snacks on fresh fruits and vegetables. She adamantly proclaims that her diet is nutritious and free of low biologic value foods. She does not eat fast food, fried food, or refined carbohydrates. The majority of her meals are prepared fresh at home.

She provided me with a 3-day food diary. Analysis of the dietary diary revealed a balanced diet that averaged 3,000 kcal/day. Her diet was approximately 65% complex carbohydrate, 20% protein and 15% fat. She ate

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seven servings of fruit and vegetables daily. She ate fish, poultry, and beans frequently.

***Review of Systems*:** The patient denied headache, fever, sore throat, or vertigo. She stated that her weight had fluctuated up and down by 10-20 lbs over the course of the last year. She denied esophageal reflux, heartburn, or indigestion. She had intermittent bouts of diarrhea, 3-4 times monthly and noticed "greasy" stools with some "white material" on them. She had three episodes of melena, but denied hematuria, frequent UTIs, or nephrolisthiasis. She did develop a pruritic rash on her buttocks which resolved in one month with an over-the-counter topical cortisone cream. She was treated for folliculitis with three courses of antibiotics in the last eight months. She denied a previous history of hepatitis, parasitic disease, or positive TB tests. She was gravida X 1. She has not had a menstrual period in over eight years. She denied insomnia, but had felt fatigued in the last few months. She denied polyarthralgias. She had two large tattoos — one on her right thigh and the other on the lumbar spine. She stated that they were done under sterile conditions. She denied any food allergy or allergy to medications but suspected that she might have had an allergy to pollen, household dust, and weeds in the spring and fall in Virginia.

***Physical Examination*:** The patient's appearance was physically consistent with her chronologic age. She was pleasant and cooperative throughout the history and physical. Her height was 66 inches and her weight was 154 lbs. Her ideal body weight was 130 lbs. +/- 10 lbs. Her right wrist measured 16 cm in circumference. She was a mesomorphic body type. Her body fat percentage was calculated to be 24.5% using a bio-impedance device. Her BMI was 24.9. The waist to hip ratio was .82. The patient's seated BP was 120/82, ear temperature was 98.4° F, pulse 58 bpm, respirations 14, and pp02 was 99%. The ENT examination was unremarkable. The thyroid palpated normal size with no evidence of nodules. Heart[3] and lung auscultation and percussion were unremarkable. She was normoreflexic and had no major muscle paresis. The nail beds of five different digits on both hands had koilonychias and white spots commonly identified with zinc and iron deficiencies. The abdominal examination was remarkable for left and right lower quadrant pain with mild palpation. There was no rebound tenderness. There was no peritoneal mass or ascites. There was no evidence of organomegaly. The patient developed wheal reactions on the integument of the thigh and buttock when stimulated with a Wartenberg pinwheel. There was evidence of dermatitis herpetiformis on the posterior right biceps femoris and right buttock. The anoscopic exam revealed proctitis with evidence of *candida albicans* perianally. There was no evidence of anal fissures or *condyloma latum*.

***Diagnostic Impression*:** It was decided to order lab testing to rule out Crohn's disease, ulcerative colitis, and celiac disease. A strong suspicion of iron deficient anemia was noted. Included in the differential diagnosis were diverticular bowel disease, bowel carcinoma, bowel polyps, amoebic colitis, parasitic infestation, *candida albicans*, and gastrointestinal dysbiosis. Zinc, calcium, folic acid, vitamin K, vitamin A, and magnesium nutrient deficiencies were suspected.

***Laboratory Testing*:** A CBC reported in May 2006 showed a low RBC count at 3.7 x 10E6/µL and a low Hgb at 12.0 g/dL. There was eosinophilia at 10.2 X10E3/µL. The TIBC was elevated at 500 µg/dL. The blood chemistry was remarkable for low serum calcium at 8.0 mg/dL, low alkaline phosphatase 24 IU/L, low serum phosphorus 2.5 mg/dL, and an elevated fasting glucose of 110 mg/dL. A blood test for 25-OH vitamin D total was depressed at 11.0 ng/dL. ANA and uric acid tests were normal. The urinalysis was normal. A stool culture for yeast and fungi was 3+ for *candida albicans*. A gastrointestinal stool profile was negative for *clostridium dificile*, giardia, cryptosporidium, *amoeba histolytica*, roundworm, and tapeworm. The total intestinal stool SIgA was low at 104 mg% dry weight. Milk, soy, egg, and gliadin antibodies of SIgA were all positive. The tTG, AGA, IgG and IgA were positive confirming the diagnosis of celiac disease.

In June 2006 the patient was referred for a DEXA bone scan, upper endoscopy, and a colonoscopy. The DEXA bone densitometry was normal. The colonoscopy detected a tubal adenoma which was resected while the colonoscopy was being performed. There was no evidence of granulomatous disease. The upper endoscopy detected gastritis in the body and fundus of the stomach, candidal plaques of the esophagus, and duodenitis. Biopsy of the duodenum revealed moderate villous atrophy with increased chronic inflammatory cells in the lamina propria, blunting of the villi, and intra-epithelial lymphocytes. The gastroenterologist also ordered a CT scan of the upper abdomen which revealed thickening of the third portion of the duodenum. A 96 food IgG ELISA allergy panel was significant for strong allergic reactivity to cow's milk, pineapple, white potato, tomato, wheat, gluten, egg white and egg yolk, and barley.

A working diagnosis of celiac disease, iron deficient anemia, systemic candidiasis, and vitamin D deficiency was documented. Although not detected with blood

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laboratory tests, a high suspicion for zinc, calcium, folic acid, vitamin K, vitamin A and magnesium[4] nutrient deficiencies remained. After the completion of all diagnostic testing, the patient returned to our facility for nutritional therapy and counseling.

***Nutritional Therapy*:** The patient was immediately placed on a wheat and gluten-free diet. She was also instructed to eliminate from the diet all foods for which she reacted strongly on the IgG food allergy test. She was specifically instructed not to eat spelt, triticale, oat kamut, rye, and barley. She was advised to avoid most grains, pastas, cereals, and many processed foods. The patient was frustrated because she felt she had a very limited choice of foods to consume. She was assured that she could eat a well-balanced diet with a variety of foods, including gluten-free bread and pasta. She was advised to use rice, corn, amaranth, quinoa, buckwheat, and bean flour instead of wheat flour. She was given a list of stores where should could buy gluten-free bread, pasta, and other products. She was referred to the American Celiac Society website which had a plethora of gluten-free food alternative suggestions and locations where they could be purchased.

The patient was placed on an anti-inflammatory diet.[6] This was a diet rich in antioxidants, fruits and vegetables rich in natural enzymes, and essential fatty acids from fish oil, olive oil, borage oil, and flaxseed. She was advised to consider stopping her BCP medication because of the evidence suggesting its adverse effects on intestinal villi and depletion of the nutrients vitamin C, folic acid, and vitamin B6.[7] The diet prescribed for the patient was 35% protein, 45% carbohydrate and 20% fat. She was placed on a 2,400 kcal diet based on the Mifflin equation. A consideration of calculating her RMR using the Mifflin equation was her extremely high level of physical exercise. She was instructed to eat foods that were most easily absorbed into her stomach and intestines. It was recommended that she consume nut butters, soups, and foods with baby food consistency. She was instructed to purchase a food processor and a blender in order to make vegetable juices and purees. Because of her diagnosis of candidiasis she was advised to avoid all fruit sugars, alcoholic beverages, processed foods, and refined carbohydrates.

The patient was prescribed nutritional supplementation as follows:

- Zinc 50 mg qd — Zinc plays a fundamental role in cellular immunity, glucose metabolism, and wound healing.[8] Zinc deficiency is commonly associated with inflammatory bowel disease.
- Vitamin A 25,000 IU — Vitamin A has essential antibacterial and antiviral functions and is essential for healthy epithelial tissues.
- L-Glutamine 1,000 mg tid — L-glutamine is a conditionally essential amino acid which may benefit pathologic villi changes associated with celiac disease.[9]
- Non-yeast vitamin B complex — Because the best food sources of B vitamins are grains[5] and cereals, the patient was supplemented to avoid any potential deficiency. Folic acid deficiency is common with celiac disease.
- A hypoallergenic multivitamin/mineral.
- Iron dysglycinate 25 mg tid — Current literature indicates the dysglycinate form of iron is more readily absorbable than ferrous sulfate.
- A broad spectrum enteric coated probiotic which did not contain dairy ingredients, 12 billion CFU tid.
- Ascorbic acid 1-2 g/day to bowel tolerance.
- Vitamin D 5,000 IU/day.
- Calcium citrate 1,200 mg/day.
- Magnesium 500 mg/day — The depletion of zinc, vitamin K, vitamin D, folic acid, vitamin A, magnesium, iron, and calcium stores are commonly encountered with celiac disease.[10]

The patient returned for a follow-up appointment six weeks after the onset of nutritional therapy. She demonstrated diligence in her compliance to the diet that had been recommended. She provided a 7-day food diary. The diary was analyzed, and it was determined she was averaging 2,500 kcal/day. She consumed an average of 32% protein, 48% carbohydrate, and 20% fat daily. She was eating significant amounts of fish, beans, and fresh vegetable juices. She was eating gluten-free pastas and breads. She eliminated all fruit juices and high natural sugar foods from her diet. She stated that she felt less abdominal pain and virtually no bloating. She noted that her rectal bleeding and pruritis had stopped entirely.

Eight weeks after the start of nutritional therapy, a repeat stool yeast and fungi culture was taken. This test reported no detectable level of *candida albicans*. At 12 weeks post-nutritional therapy repeat blood testing was ordered. The results were as follows:

- The CBC reported in May 2006 which showed a low RBC count 3.7 x 10E6/uL but was now nor-

(Continued on next page)

mal at 5.0 10E6/µL.

- The previously low Hgb 12.0 g/dL was 16.3 g/dL and normal.
- The eosinophil count was normal.
- The TIBC was normal at 225 µg/dL.
- Serum calcium improved from 8.0 mg/dL to 9.8 mg/dL.
- Alkaline phosphatase improved from 24 IU/L to 80 IU/L.
- Serum phosphorus improved from 2.5 mg/dL to 3.9 mg/dL.
- Serum glucose normalilzed to 78 mg/dL.
- 25-OH vitamin D total improved from 11.0 ng/dL to 40 ng/dL.

The patient continued to adhere to her regimented diet and continued supplementing the diet with the zinc 50 mg qd, vitamin A 25,000 IU qd, L-Glutamine 1,000 mg tid, non-yeast vitamin B complex, a hypoallergenic multivitamin/mineral, iron dysglycinate 25 mg qd, and probiotics.[6]

In March 2007, a repeat upper endoscopy with biopsy was performed. The results of the test and biopsies were entirely normal. The upper endoscopy detected no evidence of gastritis in the body or the fundus of the stomach. There was no evidence of candidal plaques of the esophagus. Duodenitis was no longer visible. The histology report of the biopsy showed normal villi in the lamina propria.

Fifteen months after the onset of nutritional therapy the patient continues to remain symptom-free while maintaining a strict diet and taking nutrient supplementation. She continues to be monitored for nutrient deficiencies and food allergies.

***Discussion*:** Eight months after the onset of nutritional therapy this clinician discussed the results of the endoscopic findings with the consulting female gastroenterologist. She stated that it was rare when she observed improvement in inflammatory gastric and duodenal tissues and/or histologic pathology after a patient has been diagnosed with celiac disease. She acknowledged that most patients are referred to a registered dietician for dietary control and managed symptomatically with various anti-inflammatory medications. We feel that this case study suggests the potential benefit of nutritional supplementation, allergy avoidance diet, and a diet that mediates intestinal inflammation as an adjunct to simple avoidance of gluten containing foods as treatment.

***Conclusion*:** Celiac disease is more common than once thought and can be difficult to diagnose because a significant portion of patients have no symptoms. Our patient was diagnosed relatively easily which afforded us the opportunity to implement a therapeutic program immediately after her symptoms led to her diagnosis. Conventional medical management of celiac patients is simply a wheat and gluten avoidance diet. Symptomatic and palliative treatment is rendered for disease sequalae such as *dermatitis herpetiformis*, apthous ulcers, weight loss, and fatigue. It is our contention that addressing the underlying nutritional deficiencies through supplementation, food allergy avoidance, and educating the patient in proper alimentation is a superior therapeutic methodology. Further research to support our hypothesis is needed.

About the Author

Dr. Robert A. Duca, Jr is a graduate of the National University of Health Sciences amd has been in private practice for 22 years. He is a diplomate of the American Board of Chiropractic Internists, the American Board of Clinical Nutrition, the American Board of Chiropractic Sprorts Physicians, and a fellow of the International Academy of Medical Acupuncture.

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Facts about Iodine and Autoimmune Thyroiditis

by Guy E. Abraham, MD

Since the 2006 publication by Tang, *et al*,[1] reporting a positive association between iodization of salt in China and autoimmune thyroiditis (AIT), I have received a lot of calls and e-mails questioning the use of iodine in patients with autoimmune thyroiditis. Iodophobes were elated with this publication, which vindicated their iodophobic viewpoint. However, a year later in 2007, the same authors, using the same data[2] retracted their original statement and concluded that: "Chronic iodine excess does not apparently increase the risk of autoimmune thyroiditis."

I will present some facts about iodine and autoimmune thyroiditis.

In 1912, pathologist H. Hashimoto published in a German medical journal,[3] his histological findings in four thyroid glands removed at surgery: numerous lymphoid follicles; extensive connective tissue formation; diffuse round cell infiltration; and significant changes of the acinar epithelium. He called this pathology of the thyroid "struma lymphomatosa", but it became popular under the name "Hashimoto thyroiditis". At the time of Hashimoto's publication, autoimmune thyroiditis was not observed in the US population until the iodization of salt. Hashimoto's thyroiditis is now classified as goitrous AIT because the gland is enlarged, in distinction to atrophic AIT where atrophy and fibrosis are predominant. Both conditions are chronic, progressing over time to hypothyroidism in a significant percentage of patients.[4]

In several communities worldwide, an increased incidence of AIT was reported following implementation of iodization of sodium chloride.[5] In areas of the US where this relationship has been studied, mainly in the Great Lakes Region, a similar trend was reported. In 1966 and 1968, Weaver, *et al*,[6,7] from Ann Arbor, Michigan reported: "The salient histopathological feature of the thyroid glands, removed at operation in a five-year period before iodine prophylaxis (1915-1920), was the *paucity* of lymphocytes in their parenchyma and, more importantly, the *absence* of thyroiditis of any form … It should be emphasized that the thyroid glands prior to the use of iodized salt were devoid of lymphocytes, and nodular colloid goiters with dense lymphocytic infiltrates were found after the introduction of iodized salt in 1924."

Furszyfer, *et al*,[8] from the Mayo Clinic, studied the average annual incidence of Hashimoto's thyroiditis among women of Olmsted County, Minnesota, during three consecutive periods covering 33 years of observation, from 1935 to 1967. They found the incidence to be higher in women 40 years and older versus women 39 years and younger. However, in both groups, there was a progressive increase in the incidence of Hashimoto's thyroiditis over time. During the three periods evaluated — 1935-1944; 1945-1954; 1955-1967 — the average annual incidence of Hashimoto's per 100,000 population were 2.1, 17.9, and 54.1 for women 39 years and less. For women 40 years and older, the average annual incidence over the same three periods were 16.4, 27.4, and 94.1.

It is important to point out that the Mayo Clinic study started 10-15 years after implementation of iodization of salt in the area. Therefore, even during the first decade of observation, the prevalence of AIT was already significant. Again, it must be emphasized that prior to the implementation of iodized salt as observed by Weaver, *et al*,[6,7] this pathology of the thyroid gland was not reported in the US, even though Lugol solution and potassium iodide were used extensively in medical practice at that time in daily amounts two orders of magnitude greater than the average intake of iodide from table salt.[4] This suggests that inadequate iodide intake aggravated by goitrogens, not excess iodide, was the cause of this condition. To be discussed later, AIT cannot be induced by inorganic iodide in laboratory animals unless combined with goitrogens, therefore inducing iodine deficiency.

The pathophysiology of AIT is poorly understood. Experimentally induced autoimmune thyroiditis in laboratory animals by acutely administered iodide required the use of antithyroid drugs, essentially goitrogens, to produce these effects.[9-12] These goitrogens induced thyroid hyperplasia and iodide deficiency. Antioxidants either reduced or prevented the acute iodide-induced thyroiditis in chicks[13] and mice.[14] Bagchi, *et al*,[13] and Many, *et al*,[14] proposed that the thyroid injury induced by the combined use of iodide and goitrogens occurs through the generation of reactive oxygen species.

We have previously proposed a mechanism for the oxidative damage caused by low levels of iodide combined

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with antithyroid drugs:[2] Inadequate iodide supply to the thyroid gland, aggravated by goitrogens, activates the thyroid peroxydase (TPO) system through elevated TSH, low levels of iodinated lipids, and high cytosolic free calcium, resulting in excess production of H_2O_2. The excess H_2O_2 production is evidenced by the fact that antioxidants used in Bagchi's experiments did not interfere with the oxidation and organification of iodide and therefore neutralized only the excess oxidant.[11] This H_2O_2 production is above normal due to a deficient feedback system, caused by high cytosolic calcium due to magnesium deficiency and low levels of iodinated lipids which requires for their synthesis iodide levels two orders of magnitude greater than the RDA for iodine.[4] Once the low iodide supply is depleted, TPO in the presence of H_2O_2 and organic substrate reverts to its peroxydase function, which is the primary function of haloperoxydases, causing oxidative damage to molecules nearest to the site of action: TPO and the substrate thyroglobulin (Tg). Oxidized TPO and Tg elicit an autoimmune reaction with production of antibodies against these altered proteins with subsequent damage to the apical membrane of the thyroid cells, resulting in the lymphocytic infiltration and in the clinical manifestations of Hashimoto's thyroiditis. Eventually, the oxidative damage to the TPO results in deficient H_2O_2 production. Hypothyroidism occurs in AIT when oxidation and organification of iodide in the thyroid gland become deficient enough to affect synthesis of thyroid hormones.

In vitro studies with purified fractions of calf thyroid glands by De Groot, *et al*,[15] gave compelling evidence that iodide at 10^{-5} molar confers protection to TPO against oxidative damage. To achieve peripheral levels of 10^{-5} molar iodide, a human adult needs a daily amount of 50-100 mg. DeGroot's findings can be summarized as follows:

- TPO is inactivated by H_2O_2.
- KI at 10^{-5} molar protects TPO from oxidative damage.
- Potassium bromide and potassium fluoride do not share this protective effect of KI.
- The protective effect of KI is not due to the covalent binding of iodine to TPO but due to the presence of KI itself in the incubation media.

The concentrations of iodine measured in the thyroid of patients with AIT are the lowest observed. Further, AIT patients with hypothyroidism have significantly lower iodine levels in the thyroid gland than AIT patients with normal thyroid function. For the US population, Okerlund[16] reported a mean value of around 10 mg iodine/thyroid, with a range of 4-19 mg. In 56 patients suffering from autoimmune thyroiditis, but with normal thyroid function, a mean value of 4.8 mg/thyroid was reported. In 13 patients with autoimmune thyroiditis and hypothyroidism, the mean value was 2.3 mg/thyroid.

Based on the above facts, it is obvious that iodine deficiency, not excess, is the cause of AIT.

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The Bioavailability of Iodine Applied to the Skin

by Guy E. Abraham, MD

I have often been asked a couple questions:

1) Is the application of iodine to the skin an acceptable way to supplement iodine?
2) Are there any data confirming the validity of the iodine skin patch test to assess body sufficiency for iodine?

The iodine skin patch test consists of applying iodine solution to a small area of the arm, leg, or abdomen. The faster the yellow color of iodine disappears from the skin, the more iodine deficient the person tested; and vise versa, if the yellow color lingers, the more sufficient in iodine the person tested.

Over 100 years ago, the application of iodine to the skin was used extensively for iodine supplementation. In 1932, Nyiri and Jannitti[1] from the Rutgers University College of Pharmacy wrote: "Iodine is being used extensively as a prophylactic and therapeutic agent by application to the outer integument, (for the reader's information, that is the skin) and has maintained its place in medicine for many decades. Its use by external application is merely on an empirical basis; very little proof of its efficacy has been obtained by experimental work. The main question as to whether or not iodine passes through the unbroken human and animal skin has not been conclusively answered."

In order to assess the bioavailability of iodine applied to the skin, these investigators used 44 rabbits and six dogs, but no human subject.

"Although the question of iodine penetration has been studied extensively especially during the second half of the last century, no satisfactory conclusion has been reached because the techniques of the various experiments were not fully reliable. Considering the increasing biological significance of the outer integument (Klose (30), Unna (31), Vollmer (32), Urbach (33)) and the widespread medicinal use of iodine on the skin, we made a series of experiments about the fate of iodine applied to the skin; thereby studying the possibility of penetration of free iodine, its fate in the body, its elimination, and its conditions of evaporation for the surface. We carried out the experiments on six dogs and forty-four rabbits."

To summarize the results of their experiments:

1) Free iodine penetrates through the unbroken skin.
2) Approximately 88% of the iodine evaporates from the skin within three days.
3) Colloidal iodine evaporates somewhat more quickly than tincture of iodine; Lugol's solution is more stable than either of them.
4) The influence of ambient temperature on the evaporation of iodine is significant. Within the first minute, the losses of iodine by evaporation are 10-15% at 9° C; 18-25% at 24° C; and 35% at 37° C.
5) The remaining iodine on the skin following evaporation of 88% of the total iodine, approximately 12%, penetrates through the skin. The bioavailability of the remaining 12% of the skin iodine is very gradual.
6) The fate of iodine in all above experiments is the same whether iodine is applied to the skin in the form of an alcoholic solution or in colloidal suspension. (For the reader's information, the alcoholic solution is tincture of iodine and the colloidal suspension is a saturated aqueous solution of diatomic iodine, I_2).

The authors concluded:[1] "Our quantitative determinations prove that iodine which penetrates through the skin is removed only slowly from within this area into the body, thus forming an iodine depot in the skin for several days. In this prolonged retention of iodine within the skin, we see a favorable condition for a possible local prophylactic and therapeutic action."

The above conclusions apply to rabbits and dogs, but not to human subjects. The best study of the bioavailability of iodine applied to the skin in normal human subjects was reported by Miller, *et al*, in 1989.[2] The purpose of Miller's study was to assess the effectiveness of skin application of iodine in blocking radioiodide uptake by the thyroid gland. The subjects used in this study were 24 adult male volunteers aged from 21 to 51 years. These subjects were divided into four groups of six subjects each. One group served as control and did not receive stable iodine. The other subjects in the remaining three groups received respectively 130 mg KI orally equivalent to approximately 100 mg iodide; 80 mg iodine (tincture) on the skin; and 160 mg iodine on the

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skin. All 24 subjects ingested 131I labeled NaI and radioiodide thyroid uptake was measured at 2 hours, 6 hours, and 24 hours post-ingestion of radioactive iodide. Serum inorganic iodide levels were measured at time zero, 2 hours, 6 hours and 24 hours post intervention. Twenty-four-hour radioiodide uptake by the thyroid gland as percent of dose administered was used to assess the effectiveness of iodine in blocking radioiodide uptake by the thyroid. The 24-hour percent radioiodide uptake by the thyroid gland were:

- Control: 10.9 ± 2.9% (SD)
- Oral KI: 0.34 ± 0.26%
- Skin 80 mg iodine: 7.0 ± 5.5%
- Skin 160 mg iodine: 2.0 ± 2.5%

Prior to administration of stable iodine, the mean serum iodide in the three intervention groups were 0.024 mg/L, 0.033 mg/L, and 0.02 mg/L. The mean of the three mean values is 0.026 mg/L.

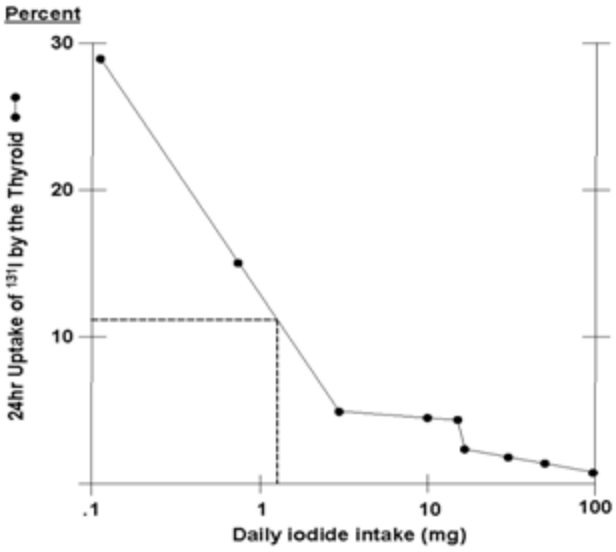
Under steady state conditions, the computed daily intake of iodine based on serum iodide is equal to the product of serum iodide times 43.5 L/day, which is the renal clearance of iodide.[3] The estimated average daily intake of iodine by this group of men is 0.026 mg/L × 43.5 L/day = 1.13 mg/day. This daily intake may be due to the iodization of bread in the 1960s and 1970s and in some states in the 1980s. The estimated daily intake of iodine during that time in the US was 1 mg.[4] This computed daily intake in Miller's subjects is in agreement with the mean percent radioiodide uptake by the thyroid gland in this group of subjects with a mean of 10.9. By interpolation on Figure 2 of Reference 5, 10.9% uptake corresponds to an average intake of approximately 1.5 mg iodine (See Figure 1).

The two questions mentioned previously can now be answered.

To answer the first question, we will use the data in the six subjects who were exposed to 160 mg iodine via cutaneous application, because the mean serum iodide levels were relatively constant over the 24-hour period: 0.27 mg/L at 2 hours; 0.2 mg/L at 6 hours; and 0.24 mg/L at 24 hours post-intervention. The mean value of the three means is 0.24 mg/L iodide. The average amount of iodine bioavailable in these six subjects would be the product of the serum iodide levels by the renal clearance of iodide — 0.24 mg iodide/L × 43.5 L/day = 10.4 mg. The percent of bioavailable iodine from 160 mg applied to the skin is 6.5% (10.4 x 100/160). If the data reported by Nyiri and Jannitti[1] in dogs can be extrapolated to humans, (that is 12% of the applied iodine was available for utilization by the body), then some 50% of the remaining skin depot of iodine was available during the first 24 hours following skin exposure to iodine. One can conclude that skin application of iodine is an effective, if not efficient and practical, way for supplementation of iodine with an expected bioavailability of 6-12% of the total iodine applied to the skin. The serum iodide levels were 10 times higher at 2 hours post-intervention with oral ingestion of 100 mg iodide than with 160 mg iodine applied to the skin (Figure 2).

Figure 1

Percent 24-hour Uptake of Radioiodide following Intake of Increasing Amount of Iodide†



The dotted line represents the percent uptake by Miller's subjects and the estimated average daily intake in this group of subjects.

† Modified from Reference 5 (Abraham, et al. *The Original Internist*, 2002; 9(4):30-41).

To answer the second question, the skin iodine patch test is not a reliable method to assess whole body sufficiency for iodine. Many factors play a role in the disappearance of the yellow color of iodine from the surface of the skin. For example, if iodine is reduced to iodide by the skin, the yellow color of iodine will disappear because iodide is white. In order to regenerate iodine on the skin, one needs to apply an oxidant such as hydrogen peroxide, complicating the test further. The evaporation of iodine from the skin increases with increased ambient temperatures and decreased atmospheric pressure. For example, the yellow color of iodine will disappear much

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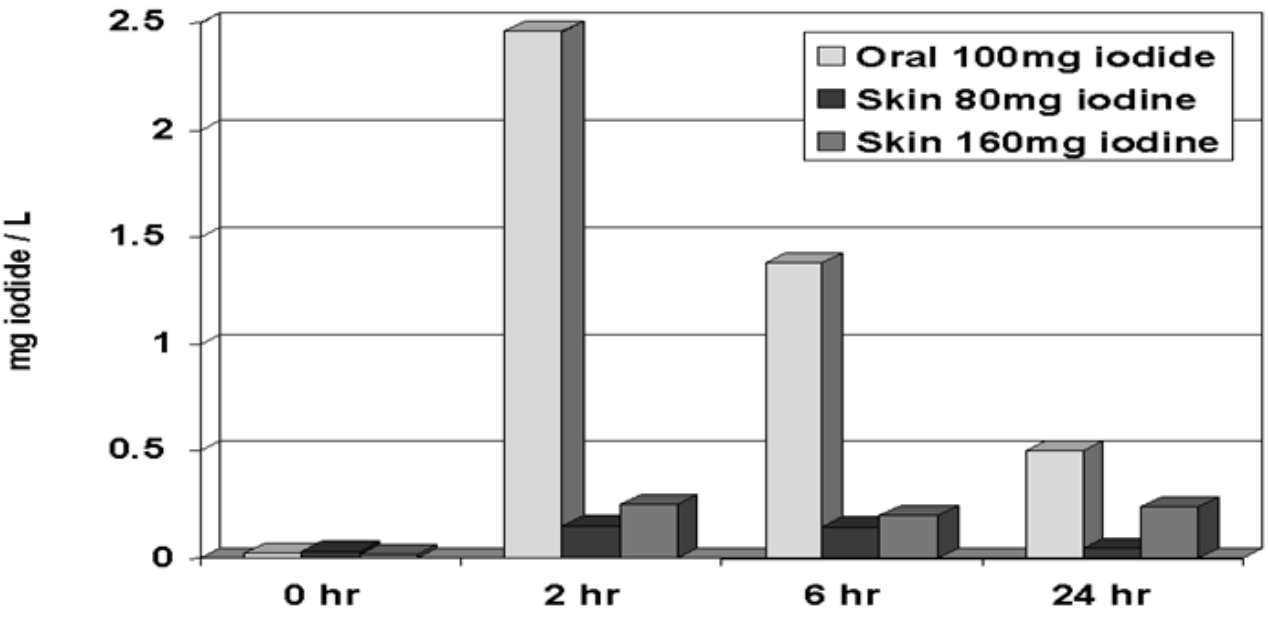
Figure 2

Serum Iodide Levels following Oral Ingestion of 100 mg Iodide and Skin Application of 80 and 160 mg Iodine††



Each bar represents the mean of six subjects.

†† Compiled from Reference 2 (Miller, et al. *Health Physics*, 1989; 56:911-914).

faster in Denver, Colorado at 5,000 feet above sea level than in Los Angeles, California at sea level, irrespective of the amount of bioavailable iodine. The iodine/iodide loading test[4] is much more accurate, and it is now available from three laboratories participating in the proficiency testing of Optimox Corporation: FFP Laboratories in Hendersonville, North Carolina; Hakala Research in Lakewood, Colorado; and Labrix Clinical Services Inc. in Oregon City, Oregon.

About the Author

Guy E. Abraham, MD, is a former Professor of Obstetrics, Gynecology, and Endocrinology at the UCLA School of Medicine. Some 35 years ago, he pioneered the development of assays to measure minute quantities of steroid hormones in biological fluids. He has been honored as follows: General Diagnostic Award from the Canadian Association of Clinical Chemists, 1974; the Medaille d'Honneur from the University of Liege, Belgium, 1976; the Senior Investigator Award of Pharmacia, Sweden, 1980. The applications of Dr. Abraham's techniques to a variety of female disorders have brought a notable improvement to the understanding and management of these disorders.

Twenty-five years ago, Dr. Abraham developed nutritional programs for women with premenstrual tension syndrome and post-menopausal osteoporosis. They are now the most commonly used dietary programs by American obstetricians and gynecologists. Dr. Abraham's current research interests include the development of assays for the measurement of iodide and the other halides in biological fluids and their applications to the implementation of orthoiodosupplementation in medical practice.

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ALLETESS

BLACK AND WHITE

Pick up from December issue
Of 2007 OI

Mobilization of human $CD34^+CD133^+$ and $CD34^+CD133^-$ stem cells in vivo by consumption of an extract from Aphanizomenon flosaquae — related to modulation of CXCR4 expression by an L-selectin ligand?

by : Gitte S. Jensen, Aaron N. Hart, Lue A.M. Zaske, Christian Drapeau, Niraj Gupta, David J. Schaeffer, and J. Alex Cruickshank

This article was originally printed in the Cardiovascular Revascularization Medicine Journal.

Introduction

Much recent research has focused on the role of selectins and their ligands in mobilization of bone marrow stem cells. L-selectin belongs to the selectin family of cell adhesion molecules involved in cellular migration during normal immunosurveillance and inflammatory conditions.

L-selectin is best known as a homing molecule for recirculating lymphocytes to recognize high endothelial venules during the process of extravasation[1-3] and for leukocytes to recognize and home to inflamed tissues.[4-8] However, L-selectin plays significant roles in other physiological cell adhesion processes as well, including the retention versus release of bone marrow stem cells into the blood circulation.[9-11]

Of special importance are findings that engagement of L -selectin by some ligands will modulate the expression of the CXCR4 chemokine receptor.[12] The CXCR4 receptor specifically recognizes the chemokine stromal derived factor 1 (SDF-1), which acts as a potent chemoattractant for stem cells and assists in retaining stem cells within the bone marrow environment.[13-16] The chemoattractant properties of SDF-1 on stem cells were shown *in vitro*[17] as well as *in vivo* to be directly associated with recruitment of stem cells into kidney[18] and liver.[19] The mobilization of recruitment of stem cells is associated with repair of the central nervous system,[20,21] heart,[22,23] and other tissues.[24] Stem cell mobilization and homing involve a series of G-protein-coupled receptors that can interact with each other as well as with adhesion molecules.[25,26] It is proposed that loss of responsiveness towards CXCR4 may be one of several contributing mechanisms that allow some bone marrow stem cells to detach and leave the bone marrow as part of the mobilization process.[27,28]

The use of selectin ligands has been proposed as a mechanism for stem cell mobilization.[29] Some L-selectin ligands (LSLs), including fucoidan and sulfatide, have a proven effect on stem cell mobilization.[29,30] The mobilization appears to happen in selectin-dependent and -independent mechanisms in tandem. As an example, the sulfated polysaccharide fucoidan can act as an LSL and up-regulate the chemokine receptor CXCR4, a receptor for SDF-1. However, fucoidan also assists stem cell detachment within the marrow by binding to another adhesion receptor, CD11b, during stem cell mobilization.[30]

The objective of this study was to evaluate the effects on human stem cells *in vitro* and *in vivo* of an extract from Aphanizomenon flos-aquae (AFA), enriched for a novel ligand for human L-selectin. We report here that a novel compound from the blue-green algae AFA binds to the ligand-binding area of human L-selectin. The effect of this compound was tested in various *in vitro* assays as well as on stem cell mobilization in humans.

Materials and Methods

Buffers and Media: For cell cultures, freshly isolated human marrow cells, as well as the KG1a and K562 cell lines, were resuspended and cultured in RPMI-1640 with 10% fetal calf serum (Gibco, Grand Island, New York), 1% penicillin and streptomycin, and L-glutamine. For immunostaining, cells were washed, resuspended, and stained in phosphate-buffered saline (PBS) containing 0.02% azide and 1% fetal calf serum or bovine serum albumin.

Cyanobacterial Extracts: Dried powder of the freshwater blue-green algae AFA was obtained from Desert Lake Technologies (Keno, Oregon). Dried powder of *Spirulina platensis* was obtained from Healthforce Nutritionals (Escondido, California). One gram of dried algal material was resuspended in 10 ml PBS and incubated for one hour at 4° C and protected from light. The resulting slush was mixed by repeated inversion of the vial and centrifuged at 400 g for 10 minutes. The bright blue supernatant was decanted and sterile filtered using a 0.22-mm filter. This filtrate of AFA water extract, AFA-W, was stored cold and dark and used within the same day of preparation.

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Monoclonal Antibodies: The CD62L monoclonal antibody TQ1 (specific for the ligand-binding area of the L-selectin molecule) linked to phycoerythrin (PE) was purchased from Coulter (Hialeah, Florida). CD45-PerCP, CD11b-PE, CD14-PE, and isotype control antibodies were obtained from Becton-Dickinson (San Jose, California). Monoclonal antibodies for CXCR4 (clone 12G5) and CCR9 were obtained from R&D Systems (Minneapolis, Minnesota).

Capturing of Ligand Using Dynabeads and Chimera Proteins: In order to identify the molecular weight of the L-selectin binding compound, we used a cell-free method in which Dynabeads (Dynal Biotech, Lake Success, New York) coated with protein G were incubated with an L-selectin chimera protein (R&D Systems). The chimera protein is a fusion of the extracellular domain of human L-selectin with the Fc portion of human immunoglobulin G (IgG), thereby facilitating binding to protein G. The chimera protein was captured and subsequently covalently linked to the protein G-coated Dynabeads using the protocol recommended by the manufacturer. Beads were incubated for one hour in a freshly made 5.4-mg/ml solution of dimethyl pimelimidate x 2HCl (Sigma Aldrich, St. Louis, Missouri) in 0.2 M triethanolamine buffer (pH 8.0) (Sigma Aldrich). The cross-linking was stopped by removing the beads from the cross-linking solution and resuspending them in 50 mM TRIS buffer (pH 7.5) (Sigma Aldrich) for 15 minutes. Unbound chimera was eluted off the beads by two washes in citrate/citric acid buffer (pH 2.8). The beads were then washed several times in PBS (pH 7.4), and added to a freshly made AFA water extract. Bound material from the AFA water extract was eluted in one of three ways: (1) boiling in Laemmli buffer containing betamercaptoethanol; (2) pH 12.5; or (3) competition for the LSL binding site using heparin. In parallel experiments, beads coated with recombinant human L-selectin/IgG1 fusion protein were used to see whether a similar water extract from another blue-green algae, *S. platensis*, contained a similar selectin-binding compound.

Electrophoresis: Samples of elutant from the Dynabead affinity method were prepared for gel electrophoresis by mixing 1:1 v/v in Laemmli sample buffer (BioRad cat# 161-0737) with mercaptoethanol. Sodium dodecyl sulfate (SDS) gel electrophoresis was performed on 4-15% gels (BioRad) in TRIS/ glycine/SDS buffer (Biorad cat# 161-0732) for one hour at 120 V. Electrophoresis for native protein was performed with SDS-free reagents, using native sample buffer (BioRad cat# 161-0738) for loading and TRIS/glycine buffer (BioRad cat# 161-0734) for electrophoresis.

***Human Subjects*:** Peripheral venous blood samples were obtained from healthy human volunteers between 20 and 45 years of age upon informed consent. Freshly drawn marrow was obtained upon informed consent, approved by the Merle West Medical Center Institutional Review Board (FWA 00002603). Blood and bone marrow samples were obtained under aseptic conditions and processed immediately.

***Immunostaining for L-selectin**:* Polymorph-nucleated (PMN) cells were purified by gradient centrifugation, washed twice in PBS, and distributed into wells in a V-bottom 96-well microtiter plate at the concentration of 105 cells per well. Serial dilutions of freshly prepared AFA-W were added to the cells in the presence of sodium azide to inhibit cytoskeletal movement and block L-selectin shedding. Cells were incubated at room temperature and in the dark for 20 minutes. Cells were washed twice and resuspended in a volume of 50 Al PBS containing 1% fetal calf serum and 0.05% azide. Staining was performed with the TQ1-RD monoclonal antibody for 10 minutes; cells were washed, resuspended in 50 Al buffer, and fixed in 1% formalin. Samples were kept cold and dark until acquisition by flow cytometry. Acquisition was performed within 24 hours of fixation.

***Immunostaining for CXCR4 Expression on Different Types of Progenitor Cells*:** The binding of fucoidan to L -selectin results in externalization of premade CXCR4 onto the cell surface. This is followed by internalization, creating a window of time for responsiveness to chemotactic factors. We used this system to examine whether AFA-W would compete with fucoidan for binding to L-selectin on the leukocyte cell surface and to assess whether it would block the externalization of CXCR4 triggered by fucoidan. To do so, freshly purified human bone marrow peripheral blood mononuclear cells (PBMC), as well as KG1a and K562 cells, were resuspended in RPMI at 106 cells per milliliter and distributed in a series of round-bottom microwells. Fucoidan was added to one series of wells, AFA-W to another series, and a mixture of fucoidan and AFA-W to the third series of wells. At different time points (1, 10, 20, 30, 40, 60 minutes), PBS containing sodium azide was added to wells in order to stop cytoskeletal movements and thereby stop the recycling of CXCR4. This allowed us to stain for CXCR4 expressed at the cell surface at each time point. Cells were washed in PBS containing sodium azide, stained with CXCR4-PE and CD34-fluorescein isothiocyanate (FITC) using the staining protocol described above,

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fixed in formalin, and acquired by flow cytometry. Analysis was performed by gating on the lymphocyte population using the forward and side scatter properties, then gating on the $CD34^+$ cells and analyzing the $CD34^+$ bone marrow-derived stem cells (BMSC) for their mean fluorescence intensity, which is proportional to their CXCR4 expression.

***Induction of CXCR4 Expression on Various Types of Stem and Progenitor-Type Cells*:** Using the same method as described above for BMSC, we evaluated the effects of fucoidan and AFA-W on the two cell lines KG1a and K562, both obtained from American Type Culture Collection (Manassas, Virginia). The KG1a cell line is strongly positive for the stem cell marker CD34 and is phenotypically and functionally less mature than the parent cell line KG-1. KG1a is characterized as a promyeloblast cell line but does not spontaneously differentiate into more mature myeloid cells. The K562 cell line is also characterized as a highly undifferentiated, multipotential hematopoietic cell line but is negative for CD34 and does spontaneously differentiate into progenitors for erythrocytoid and myeloid cell types. Both cell lines were maintained in log phase, washed in PBS, resuspended in RPMI-1640, and used in the CXCR4 expression assay.

***Study Design for in Vivo Testing of Consumption of an LSL-Rich Fraction of AFA*:** Two consumables were tested: StemEnhance (StemTech HealthSciences, San Clemente, California) and placebo. StemEnhance is a proprietary blend of the cytoplasmic and cell wall-rich fractions of the whole plant biomass, enriched approximately fivefold in content of the LSL compared to the raw AFA biomass. One gram of StemEnhance or placebo was given to volunteers with 4-6 ounces of water. The appearance of the placebo was identical to that of the StemEnhance and consisted of green-dyed, finely ground potato flakes encapsulated in vegetable capsules. The following exclusion criteria were used: under 20 or over 65 years of age, pregnancy, severe asthma and allergies requiring daily medication, any known chronic illness or previous/current venereal disease, frequent recreational drug use, and impaired digestive function (including previous major gastrointestinal surgery). Twelve volunteers were scheduled on two study days one week apart. Testing was always performed at the same time of the day (8-11 a.m.) to minimize the effect of circadian fluctuations. Due to the interference from stress with the release versus homing of other types of lymphocytes,[31] effort was taken to minimize any physical and mental stress during testing. In addition, on each study day, volunteers were instructed to complete a questionnaire aimed at determining any exceptional stress-related circumstances that might affect the person on that particular study day. Predetermined criteria for exclusion from final analysis included significant lack of sleep and severe anxiety. After completing the questionnaire, volunteers were instructed to remain quiescent for three hours, comfortably seated in a chair. After the first hour, the baseline blood sample was drawn. Immediately after drawing the baseline sample, a consumable was provided. Blood samples were later drawn 30, 60 and 120 minutes after ingestion of the consumable. At each time point, 5 ml of blood was drawn into heparin, and 2 ml blood was drawn into EDTA. The blood vials were placed on a rocking plate until use. The blood drawn into EDTA was used for obtaining a complete blood count (CBC) with differential, using a Coulter counter (Micro Diff II, Beckman Coulter). All CBCs were performed within an hour of drawing the sample and in triplicate. The heparinized blood was used for purification of the PBMC fraction by gradient centrifugation and processed for immunostaining and flow cytometry. The stem cell markers CD34-FITC (clone 8G12, BD BioSciences, San Jose, California) and CD133-PE (Miltenyi Biotech, Auburn, California) were used for two-color immunofluorescence. Staining of all samples with CD34-FITC/CD133-PE was performed in triplicate. IgG1-FITC and IgG1-PE isotype controls (BD BioSciences) were used in parallel samples. Separate, positive control samples for each donor included CD45-FITC and CD14-PE. Stained PBMC were fixed in 1% formalin and acquired by flow cytometry immediately. Files of 200,000 events were collected on each triplicate sample. The percent $CD34^+$ $CD133^-$, $CD34^+$ $CD133^+$, and the $CD34^-$ $CD133^+$ subsets were analyzed separately and were analyzed again after multiplying with the lymphocyte cell counts, as obtained from the average of the triplicate lymphocyte counts obtained by the CBC differential count.

***Statistical analysis*:** Flow cytometry data from the *in vitro* analysis of phenotypical and functional changes were analyzed by CellQuest Pro (BD BioSciences) and FlowJo (Tree Star, Ashland, Oregon). These data were exported to Microsoft Excel for further analysis, including Student's *t* test. Data were considered significant at $P<.05$. In the human *in vivo* assay, for each volunteer, the time 0 (preingestion) level of $CD34^+$ cells for a given treatment (placebo or StemEnhance) was subtracted from the levels of $CD34^+$ cells in the samples collected at 30, 60 and 120 minutes post-ingestion. Thus, the data used for analysis are normalized to each person's baseline. These data are repeated measures on a person, as well as repeated

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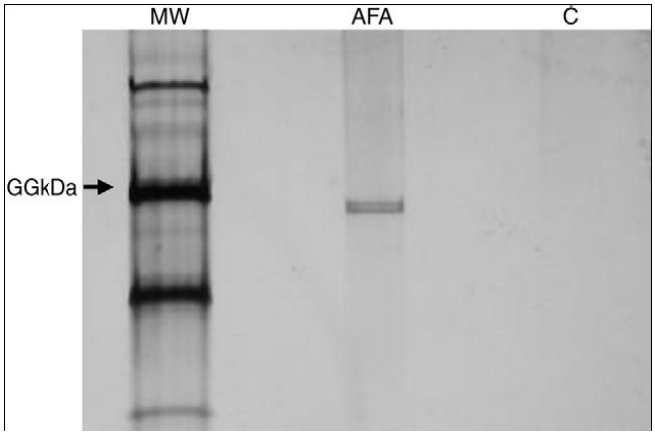
Figure 1



SDS gel electrophoresis on eluted material after immunoprecipitation of an LSL from AFA is shown in the center lane labeled bAFA.Q This ligand was affinity-purified from AFA-W by paramagnetic Dynabeads covalently linked with the fusion protein rHuL-selectin/IgG Fc chimera and eluted from the beads by alkaline treatment at pH 12. The eluted material was subjected to SDS gel electrophoresis under reducing conditions. The negative control, as shown in the lane labeled bC,Q was prepared by incubating the Dynabeads coated with the fusion protein rHuL-selectin/IgG Fc chimera with PBS instead of AFA-extract. The molecular weight standards included bovine serum albumin with a molecular weight at 66 kDa, as indicated by the arrow in the lane labeled bMW.Q Two bands are seen with apparent molecular weight of 57 and 54 kDa, respectively. The data shown are representative of 12 independent experiments.

measures for treatment and time. The two trial factors were volunteer ID (number code) and analysis replicate. Normality of the dependent data was determined by the Shapiro-Wilk test. The data were analyzed using repeated measures analysis of variance, followed by contrast tests to compare placebo and StemEnhance at 30, 60 and 120 minutes. Significance was declared at $P<.05$. Analyses were carried out using Systat 11.01 (Systat, Richmond, California).

Results

***AFA Contains a Ligand for Human L-selectin (CD62L)*:** Using a cell-free affinity purification system in which paramagnetic Dynabeads were coated with a human L-selectin/IgG1 Fc fusion protein, we captured an L-selectin binding compound from the AFA water extract (AFA-W). Under reducing conditions, this compound showed a distinct double band. Two proteins had apparent molecular weights at 57 and 54 kDa, respectively (Figure 1). The native protein is larger and estimated to be of an approximate molecular weight of 160-180 kDa. Comparing band density to SDS gel electrophoresis of a standard curve of known amounts of bovine serum albumin, we estimated that the ligand is present at 0.2 Ag/g of dried AFA biomass (data not shown). The molecular weights of the two subunits of the AFA-LSL were present in equal amounts, as estimated using scanned gels from a series of experiments.

***AFA-W Specifically Reduces TQ1 Immunostaining of L-selectin on Human PMN Cells*:** The incubation of PMN with AFA-W resulted in reduction of immunostaining with the TQ1 anti-human L-selectin monoclonal antibody, which is known to be specific for the ligand-binding area of L-selectin.[32] On PMN, an approximate 50-fold reduction in TQ1 staining was seen when cells were preincubated with AFA-W (Figure 2). The AFA-W-mediated reduction of TQ1 staining was strongest on lymphocytes and PMN but was also observed on monocytes (data not shown). The expression of CD11b was slightly up-regulated, while no significant changes were observed for other adhesion markers (CD11a, CD18, CD29, CD49d, CD49e and CD44; data not shown). Formalin-fixed peripheral blood lymphocytes were incubated in the absence or presence of serial dilutions of AFA-W. Staining of lymphocytes with the TQ1 antibody showed a dose-dependent reduction in TQ1 binding to L-selectin with increasing concentrations of AFA-W. As the effect was seen also on the formalin-fixed lymphocytes, the reduced staining could not be due to shedding of L-selectin but was indeed a result of a direct binding to the ligand-binding area.

***AFA-W Inhibits the Fucoidan-Induced CXCR4 Expression on $CD34^+$ Cells from Bone Marrow and on the KG1a $CD34^{bright}$ Cell Line but Not on the $CD34^-$ Cell Line K562*:** CXCR4 expression was evaluated on $CD34^+$ cells from human bone marrow. The $CD34^+$ cells from bone marrow responded to fucoidan by increasing the expression of CXCR4 from intracellular stores (Figure 3A, right column of histograms). Fucoidan-induced expression of CXCR4 receptors was partially inhibited by AFA-W.

In addition to the $CD34^+$ BMSC, the two primitive cell lines KG1a and K562 were compared in terms of responsiveness to L-selectin ligation by fucoidan and the ability of AFA-W to inhibit this response. Both cell lines are brightly positive for L-selectin, as evaluated by staining with the TQ1 monoclonal antibody. KG1a is brightly positive for CD34, whereas K562 is further differentiated; it is negative for CD34 and positive for GlyA due to its commitment to the erythromyeloid lineages. Both cell lines contain intracellular reservoirs

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of the CXCR4 chemokine receptor, as revealed by intracellular staining for CXCR4 (data not shown), but only the KG1a cell line responds to L-selectin ligation by externalizing this receptor (Figure 3A, left and center columns). AFA-water extract is able to block the fucoidan-mediated effect on CXCR4 expression on KG1a.

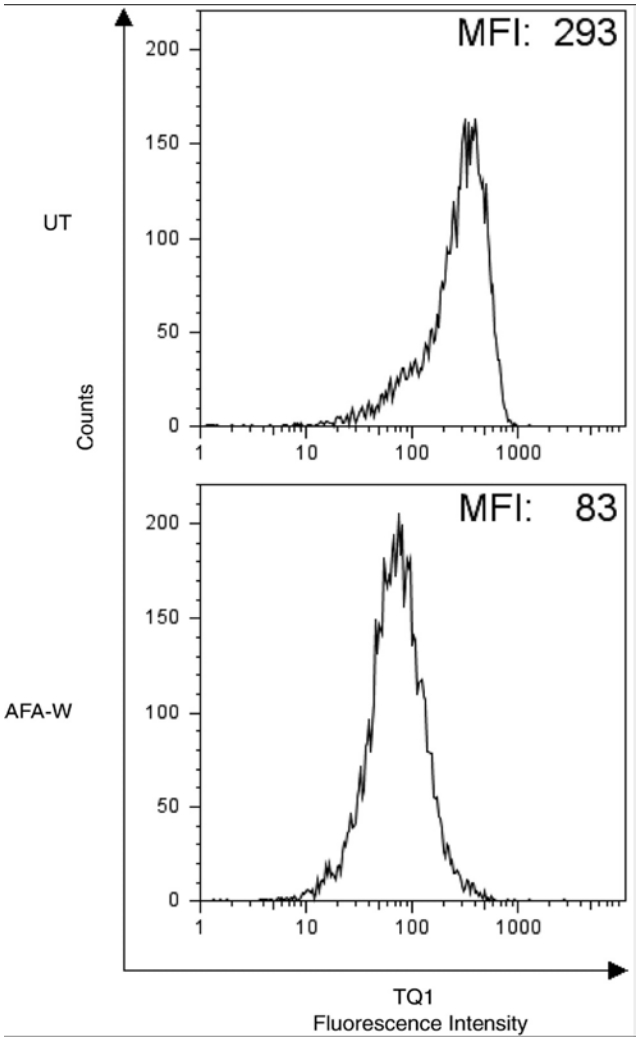
The time course for the fucoidan-induced CXCR4 expression on KG1a and K562 is shown in Figure 4. The inhibition of CXCR4 expression by AFA-W was effective across the time course and was statistically significant ($P_{15\ min} < .02$).

***In Vivo: Consumption of an AFA Extract Rich in AFA-LSL Resulted in a Transient Increase of Circulating CD34$^+$ Cells*:** The level of circulating CD34$^+$ stem cells was compared before and after ingestion of 1 g of the AFA-LSL-rich extract StemEnhance or placebo. The staining included both CD34-FITC and CD133-PE on the PBMC, and analysis was performed on CD34$^+$ overall in parallel to CD34$^+$ CD133$^-$, CD34$^+$ CD133$^+$ and CD34$^-$ CD133$^+$. The change in percent CD34$^+$ lymphocytes from T0 to 60 minutes after consumption (T60) of either StemEnhance or placebo are shown for one out of the 12 study participants (Figure 5).

Only the analysis of CD34$^+$ showed a significant difference upon consumption of StemEnhance. The relative distribution of CD34 vs. CD133 on the lymphocyte population, gated to exclude any cell that did not express either stem cell marker, is shown in Figure 6. The proportion of CD34$^+$ CD133$^+$ versus CD34$^+$ CD133$^-$ cells remained constant, indicating that the mobilized progenitor cells included cells of both phenotypes.

When including all volunteers, ingestion of StemEnhance resulted in an 18±3% increase in the number of circulating CD34$^+$ cells, maximizing around 60 minutes after ingestion ($P < .0003$). This was in contrast to placebo, which resulted in only minor fluctuations of the levels of CD34$^+$ cells in the blood circulation over 2 hours. Questionnaires completed by the volunteers on every experimental day revealed that three of the volunteers met criteria for exclusion (e.g., significant lack of sleep, severe anxiety) on at least one experimental day. Exclusion of these volunteers in the analysis resulted in a 25±1% increase in the number of circulating stem cells at 60 minutes ($P < .0001$) (Figure 7). As expected *a priori*, effects for people (ID), the interaction between people (ID), and the interactions between people and treatment type (StemEnhance or placebo) and people and time differed significantly.

Figure 2



Competition for the LSL binding site between the monoclonal antibody TQ1 against the compound from AFA. The top histogram shows the fluorescence intensity of TQ1 staining of PMN in the absence of competition for L-selectin binding (UT, untreated). The bottom histogram shows the reduction in TQ1 binding in the presence of AFA-W extract. The mean fluorescence intensity (MFI) of TQ1 staining on the PMN is shown for each histogram. The data are representative of five separate experiments.

There was no significant difference between replicate analyses, nor the interactions between replicate analyses and treatment type (StemEnhance or placebo) and replicate analysis and time. That is, the analytical variability was similar across people, treatment types, and times. Also, overall analysis on normalized data for each study participant showed significance.

In order to test the repeatability of the effect of consumption of StemEnhance on the levels of CD34$^+$ cells in the peripheral blood, 16 separate experiments

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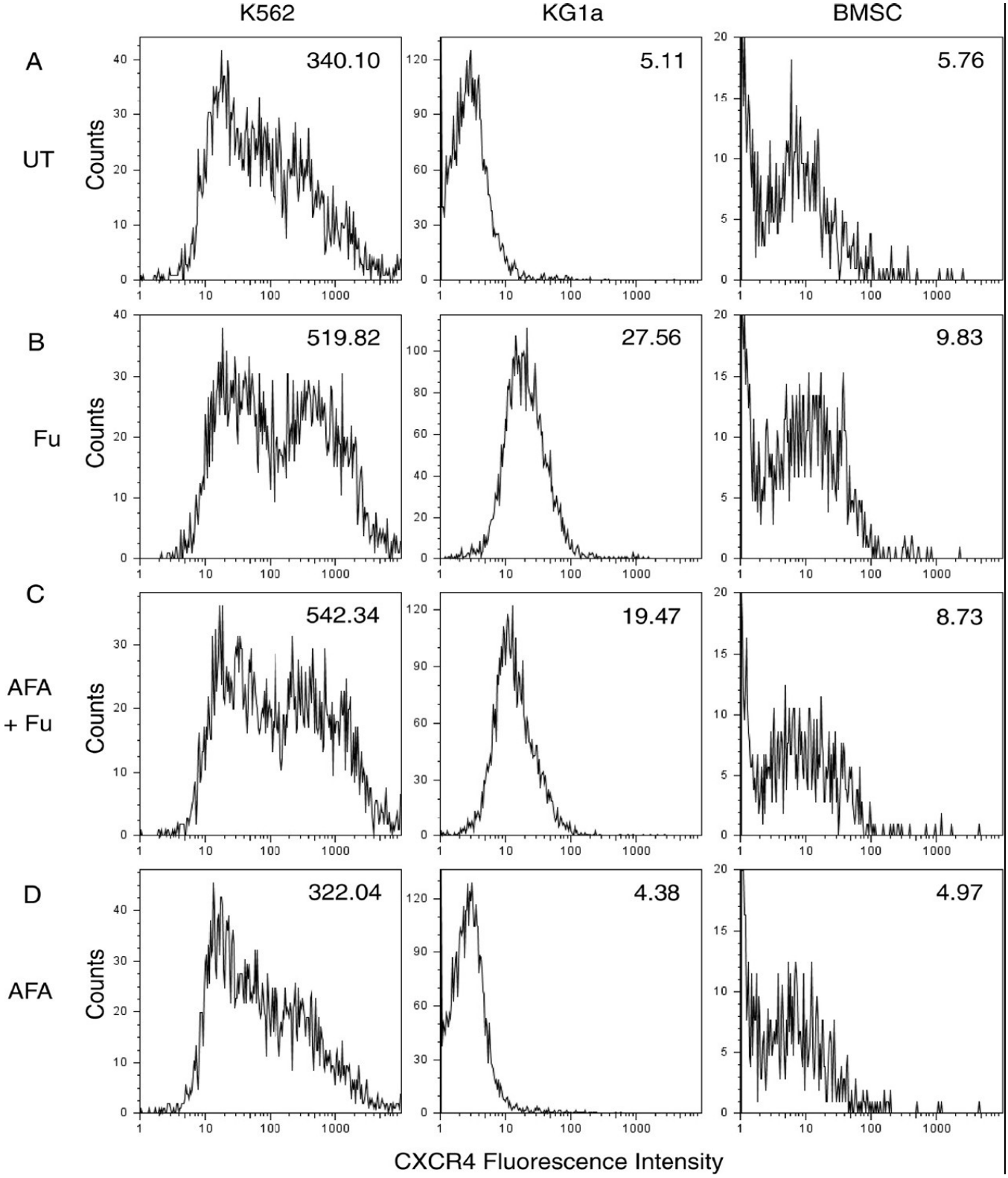
Figure 3



Treatment of BMSC and the cell lines KG1a and K562 with the LSL fucoidan (Fu) resulted in rapid externalization of the chemokine receptor CXCR4, as measured by immunostaining and flow cytometry. Row A shows the baseline expression of CXCR4 on UT cells. Row B shows the level of CXCR4 expression after treatment with Fu. Row C shows the inhibition of CXCR4 expression on KG1a and $CD34^+$ BMSC cells where both Fu and AFA-W were added simultaneously. Row C also shows that the effect did not extend to the $CD34^-$ cell line K562. The last row D shows that AFA-W alone did not trigger CXCR4 expression on the cell surface. The data shown are representative of testing involving three different bone marrow samples and three separate experiments involving the two cell lines.

were performed on one volunteer. The average increase in the number of circulating stem cells was 53±16%, with a median of 36% and a highest and lowest increase of 233% and -4%, respectively (Figure 8).

No statistically significant changes were observed when comparing numbers of total leukocytes or lymphocytes between the two treatments (StemEnhance versus placebo) (Table 1).

Discussion

Dietary strategies for supporting stem cell biology represent an emerging field of nutritional medicine. The understanding of the effect of nutrition on stem cells needs to include stem cell viability, proliferation, mobilization, and tissue-specific homing. It has been reported that Spirulina consumption may increase erythropoiesis in a mouse model.[33] In addition, antioxidant-rich blueberry and green tea extracts have been reported to increase stem cell life span and proliferation *in vitro*,[34] which may provide a better understanding of some aspects of antioxidant therapy in aging.

This study involving human stem cell mobilization was triggered by a few cases of empirical evidence that consumption of an extract from AFA, enriched for the LSL, resulted in an unexpected extent of recovery after traumatic injuries to the central nervous system. The mobilization of stem cells is complex but involves two key features: interference with the adhesion of stem cells to the bone marrow via L-selectin and a reduction of the chemotactic response to SDF-1 via the CXCR4 chemokine receptor. We found that the cyanobacterium AFA contains a novel compound that specifically binds to the ligand binding area of human L-selectin. It is composed of two subunits with apparent molecular weight around 54-57 kDa under reducing conditions. This compound differs from the 100,000 kDa polysaccharide from AFA previously described.[35] This ligand for human L-selectin, precipitated from AFA-W, was able to modulate the functional response on human lymphocytes *in vitro* and interfered with the up-regulation of CXCR4 when bone marrow stem cells were exposed to another LSL, fucoidan. In parallel to human bone marrow stem cells, the primitive $CD34^{bright}$ KG1a cell line was responsive to L-selectin-mediated up -regulation of CXCR4, possibly due to its stage of differentiation being comparative to a subset of bone marrow-resident stem cells. The ability of AFA-W to down-regulate the expression of CXCR4 on BMSC and KG1a, but not K562, suggests that this ligand could play a role in stem cell mobilization from the bone marrow. This may specifically have relevance for mobilization of stem cells from marrow into the circulation, as it has previously been shown that interference with the SDF-1/ CXCR4 axis is a primary mechanism of stem cell mobilization from the bone marrow.[11] The LSL may also have a direct effect on stem cell release, as LSLs have been proposed as a therapeutic method for stem cell release and increase of the number of circulating stem cells.[29]

A double-blinded, placebo-controlled crossover study involving 12 healthy subjects showed that consumption of an AFA extract enriched in this ligand (StemEnhance) resulted in a small, but significant, increase in the number of circulating $CD34^+$ stem cells, peaking at one hour after consumption. The effect was statistically significant ($P<.0001$). When tested on one individual on many occasions, the increase in the number of circulating stem cells after consumption of StemEnhance averaged 52±16% and varied greatly from 96% to 333% of baseline value. Interestingly, the average response in the one individual tested repeatedly on 16 different study days, and the average response to StemEnhance in the double-blind randomized study involving 12 people was similar, with an increase in $CD34^+$ cells at 153% versus 125%, respectively. The hypothesis that StemEnhance transiently increases the levels of circulating $CD34^+$ cells is supported by significance for the difference between the two treatments and the interactions of this difference with person and time. This suggests a significant consistency in the response, despite day-to-day fluctuations, which may have contributed to an underestimation of the response to StemEnhance in the double-blind study.

The increase in the number of circulating $CD34^+$ cells peaked within one hour after consumption of StemEnhance. This is in contrast with the response time seen with the known mobilizer granulocyte colony-stimulating factor (G-CSF), the response of which peaks after a few days of injection.[36,37] It is believed that G-CSF triggers stem cell mobilization by activating proteolytic activity in the marrow, which degrades SDF-1, interfering with the SDF-1/CXCR4 axis.[11] More comparable to StemEnhance is the response to the CXCR4 antagonist AMD3100 that peaks around six hours after injection.[38] This supports the view that the effect of StemEnhance on stem cell mobilization may be caused by its LSL, down-regulating the expression of CXCR4. The magnitude of the mobilization obtained with StemEnhance (18-25%) is much smaller than what is seen with G-CSF and AMD3100 (20- to 200-fold).[36,37] Recent studies using G-CSF and AMD3100 have added

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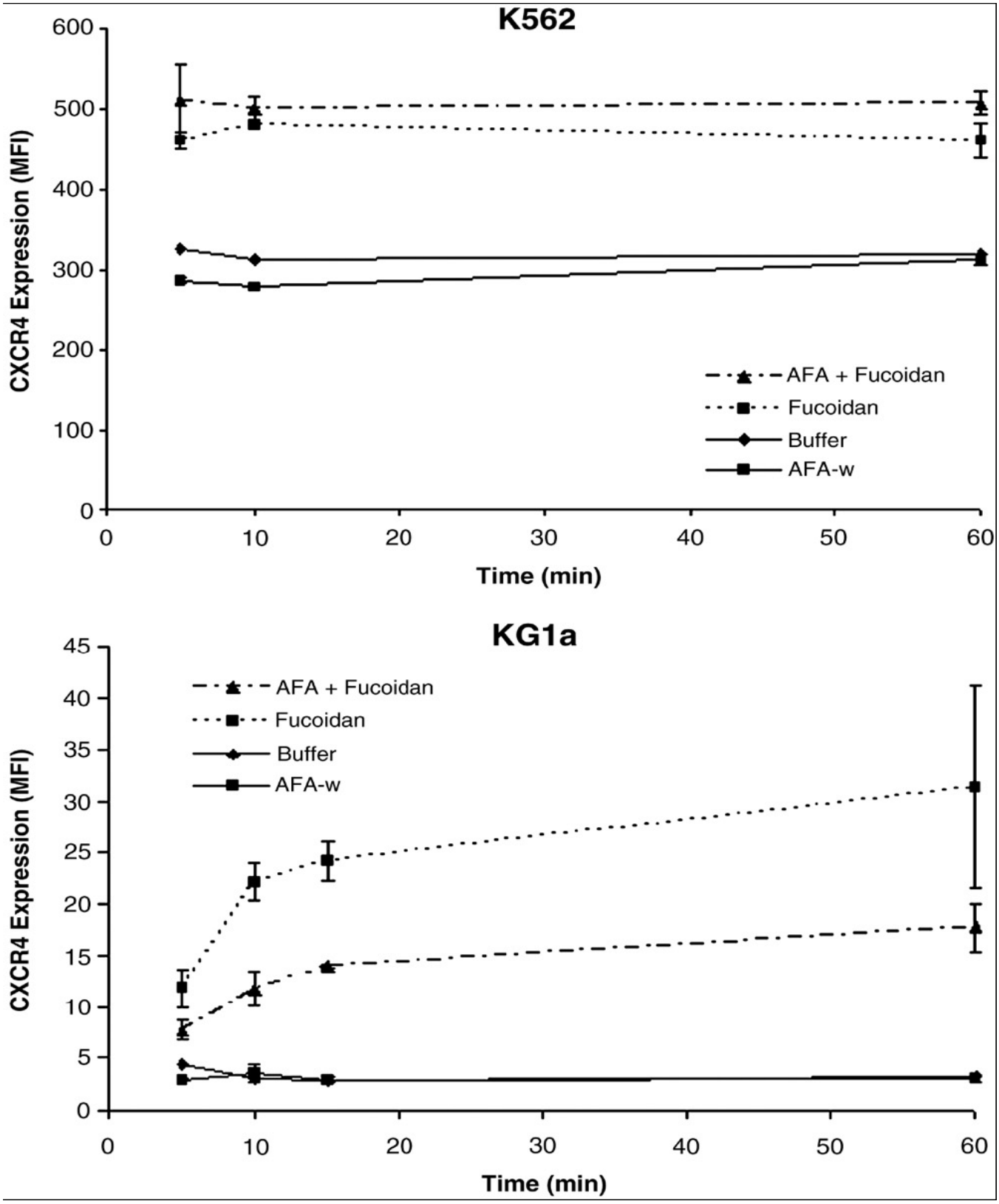
Figure 4

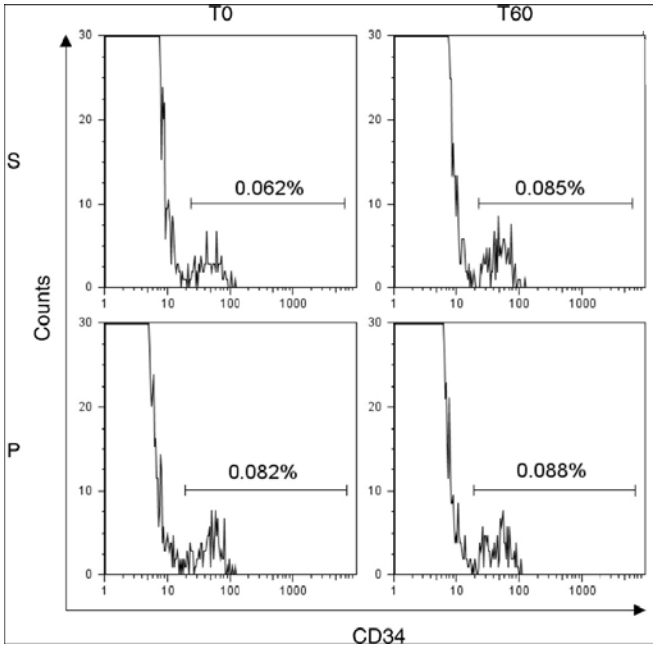


Time course evaluation of CXCR4 expression on K562 and KG1a cells was performed by immunostaining and flow cytometry after the cells were treated with Fu, AFA-W, or a mixture of both Fu and AFA-W. Treatment with Fu led to an immediate (5 min) and sustained (1 h) increase in CXCR4 expression on both cell types. Incubation of the cells with a mixture of Fu and AFA-W resulted in a significant reduction of CXCR4 expression on the KG1A, but not K562, cells, indicating a competition between Fu and the AFA-derived LSL on KG1a cells.

evidence for the potential role of stem cell mobilizers in the mitigation of various diseases such as cardiomyopathies,[39,40] kidney failure,[41] multiple sclerosis,[42] stroke,[43,44] and wound healing[45] as well as many other health conditions.[46] Such compounds, however, can only be used for short periods of time due to severe side effects.[28] However, such an extreme increase in the number of circulating stem cells may not be required to achieve health benefits. Tomoda and Aoki[47] quantified the level of circulating stem cells in victims of acute myocardial infarction and reported that individuals with more stem cells showed greater recovery of ejection fraction six months after the incident. Werner, *et al*,[48] related the levels of circulating stem cells with the risk of cardiovascular incidents in 519 patients with coronary artery disease and concluded that the level of circulating $CD34^+$ endothelial progenitor cells predicted the occurrence of cardiovascular events and death from cardiovascular causes.

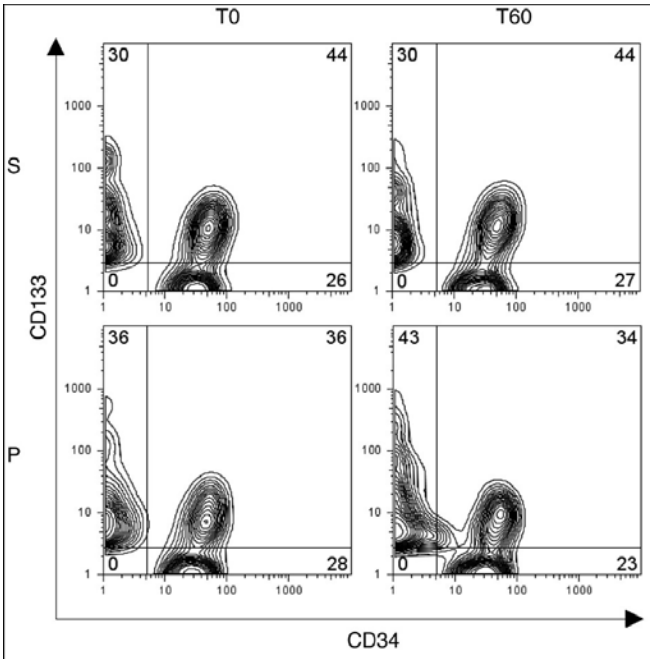
Two recent publications have further confirmed the association between G-CSF-mediated stem cell mobilization after acute myocardial infarction (AMI) and improved cardiac repair. The degenerative remodeling of the heart often seen over time after AMI was prevented by G-CSF treatment, as long as

Figure 5



Histograms showing the percent CD34+ lymphocytes immediately before consumption (T0) and at 60 min after consumption (T60) of either StemEnhance (S) or placebo (P). The data shown represent one of the 12 study participants.

Figure 6



Contour plots showing the relative distribution of $CD34^+$ $CD133^-$, $CD34^+$ $CD133^+$, and $CD34^-$ $CD133^+$ cells immediately before consumption (T0) and at 60 min after consumption (T60) of either StemEnhance (S) or placebo (P). The data shown are representative of one of the 12 study participants.

percutaneous coronary intervention (PCI) was performed early rather than late.[49] G-CSF treatment provided a significant increase in the short-term myocardial perfusion.[50] The conclusions presented from these two trials are different from a Korean study in which G-CSF-mediated mobilization alone had little effect on increased cardiovascular output.[51] The Korean study found greater effect when intracoronary injection with stem cells was performed in conjunction with G-CSF treatment. It is important to note the different timing of G-CSF treatment in relationship to the PCI procedure when comparing these two studies. In the German study protocol, the PCI was performed first and then followed by G-CSF injections, and the G-CSF injections were started within 90 minutes after PCI. In the Korean study protocol, an initial 4-day course of G-CSF injections were followed by the PCI, and no further G-CSF treatment was given after the PCI procedure was completed. The relative simplicity of G-CSF injections as a singular treatment option makes this an attractive option if proven to provide significant benefit to the patients. In addition to further understanding the consequences from the two different study protocols, it would also be interesting to further evaluate whether geographical differences exist in the underlying causes

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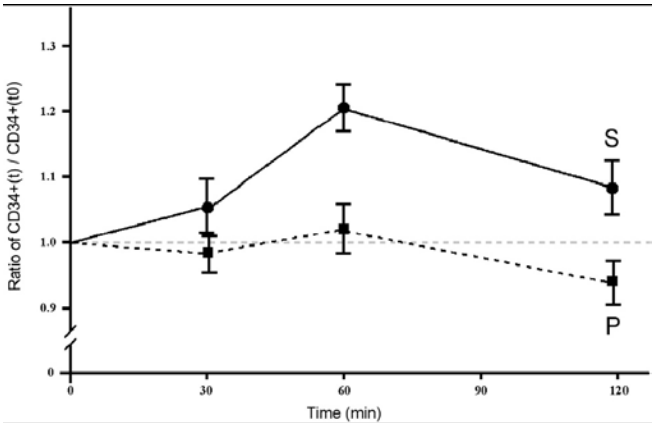
Figure 7



Consumption of StemEnhance triggered a transient increase in the number of circulating CD34+ cells that peaked at 60 min after consumption (25F1%). The data shown are the averages of changes within each group and were calculated in the following manner: the actual numbers of CD34+ cells were calculated by multiplying the percent CD34+ cells, based on immunostaining and flow cytometry on triplicate samples from each sampling time point, by the number of lymphocytes, as obtained by CBC, also performed in triplicate for each sampling time point, normalized to the value 1.0 at time 0 (immediately prior to consumption). The lines connecting each data set do not indicate a linear function but only serve to indicate which data sets belong to each treatment.

of cardiac function, including diet- and stress-related factors, as well as additional differences in medical management of cardiac disease prior to and during myocardial infarct between studies.

At this point, the effect of a massive but transient increase in the number of circulating stem cells, as induced by G-CSF injection, has not been compared to the effect of a mild but daily increase in the number of circulating stem cells, such as what is seen after consumption of StemEnhance. The 25% increase in the number of circulating stem cells occurring after ingestion of 1 g of StemEnhance may have positive effects on various health conditions and, when triggered daily for several weeks or months, might contribute to cardiac tissue regeneration. Studies should be conducted to investigate the potential of such approach for therapeutic purposes.

The observation that the mobilized progenitor cells included cells of both the $CD34^+$ $CD133^+$ and $CD34^+$ $CD133^-$ phenotypes may indicate that a broader range of different types of progenitor cells are affected, instead of a single type or developmental stage of stem cells. Circulating $CD133^+$ cells are reported to include endothelial progenitor cells, which play a role in endothelial repair. The study by Engelmann, *et al*,[50] showed that the phenotypes of G-CSF-mobilized stem cells contributing to this improvement included $CD31^+$ $CD34^+$ $CD117^+$ $CD133^+$ cells. In patients with coronary heart disease, a reduced number of circulating $CD133^+$ cells has been proposed as an independent risk factor for erectile dysfunction.[52] In particular, our data raises the question as to whether daily consumption of StemEnhance may counteract the reduced number of

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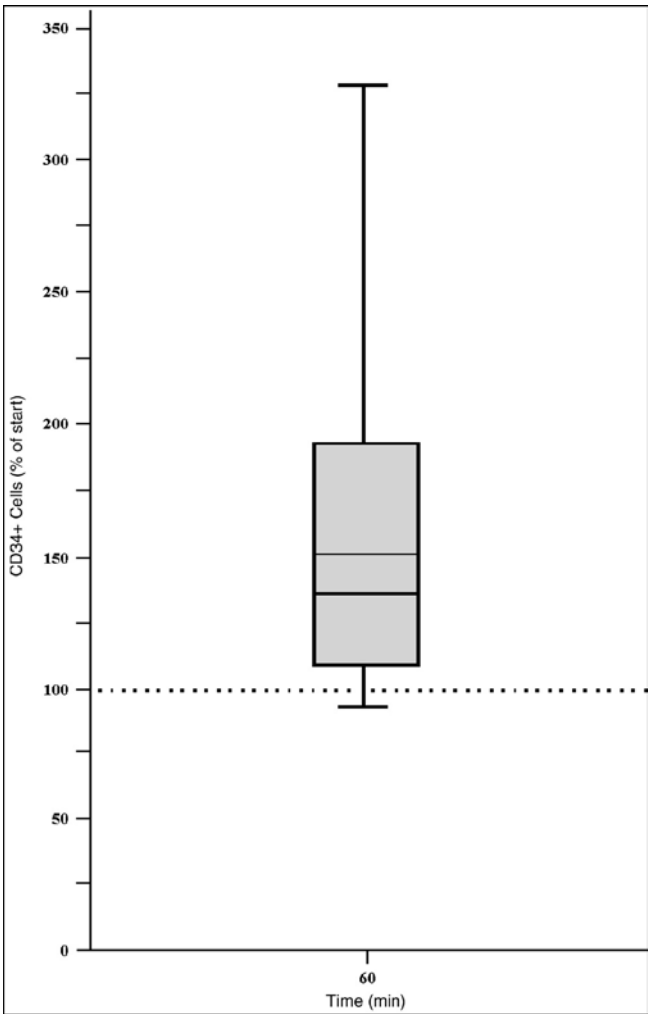
Figure 8



Multiple testing on one individual on 16 different test days revealed a similar response to StemEnhance on different test days. However, the magnitude of the response varied between tests. The box plot shows the 25 –75% spread of the results, the median (M), the average (A), and the lowest and highest response.

$CD133^+$ cells in the circulation of patients with cardiovascular disease linked to endothelial dysfunction, including erectile dysfunction. Empirical observations suggest that consumption of StemEnhance for longer periods of time might indeed bring significant improvement in various health conditions, including specific neurodegenerative diseases, chronic obstructive pulmonary disease, kidney insufficiency, and other degenerative problems. However, rigorous studies are necessary to examine the effects of StemEnhance on specific degenerative diseases.

In conclusion, our data presents the observation that consumption of an herbal extract can significantly alter the proportion of stem cells in circulation. The novel LSL isolated from AFA has complex biological activities *in vitro* that could explain the increase in circulating stem cells observed after consumption of the AFA extract StemEnhance *in vivo*. The extent to which this LSL may be responsible for the *in vivo* effect on stem cell mobilization and the effect of such mobilization on various health conditions are currently subject for further study.

Acknowledgments

We are grateful to Kelly M. Patterson and Amber R. Coaty for technical assistance.

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(Continued on next page)

Table 1
Lack of Effect of StemEnhance on the Level of White Blood Cells and the Lymphocyte Subset

	StemEnhance				Placebo			
Time (min)	**0**	**30**	**60**	**120**	**0**	**30**	**60**	**120**
White Blood Cells	100	104±1	104±1	109±5	100	107±3	104±3	111±4
Lymphocytes	100	107±2	108±2	118±5	100	109±3	109±3	124±5

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Cell Membrane Health
Your Door to Health

by: Rachel Olivier, MS, ND, PhD

Biological cell membranes are fluid membranes as depicted by the fluid mosaic model of phospholipids and proteins. They possess amphipathic (polar and nonpolar) characteristics, which enables them to spontaneously form bilayers, with the hydrophilic portions facing the aqueous side, and the hydrophobic (water repelling) core on the inner side. As a chief component of these membranes, essential fatty acids play a major role in both membrane structure and function. As summarized by Mead, their actions fall into three major classes. The first class is depicted by their involvement in the "homeoviscous control of the membrane bilayer." In this capacity they serve to regulate intrinsic membrane enzymes and proteins, both of which are critical for the structural integrity of the membrane. Secondly, they are required as precursors to the eicosanoids, which includes various end products such as prostaglandins, leukotrienes, and thromboxanes, all of which profoundly influence cellular reactions. Finally, they serve to regulate the transport processes across the cell membrane. An additional critical function of essential fatty acids not mentioned by Mead is their action in the modulation of gene expression.[1]

As one of the classes of essential fatty acids, omega-3 (ω-3) fatty acids serve a number of basic biological roles, including: their involvement in the structure and function of biological membranes; and their importance as both cellular signals and hormone precursors. They are also vital to the cellular metabolism, acting as an aide in the regulation of nutrient uptake and excretion. Diets deficient in essential fatty acids have the potential to result in enormous consequences, both on body metabolism and function. Additionally, it is currently estimated that the typical North American diet contains a much greater percentage of omega-6 fatty acids, outnumbering the intake of omega-3 fatty acids by a factor of twenty. Symptoms of fatty acid deficiency are numerous and comprise skin problems, including eczema, psoriasis, and dry skin, inflammatory arthritis, learning problems, attention deficit, irritability, melancholy, fatigue, frequent infections and an increased synthesis of triglycerides. Numerous studies have correlated ω-3 fatty acid intake with beneficial attributes for a wide range of these physiological situations, and recent research has associated their intake with the modulation of gene expression.

The most active and beneficial derivatives of marine-derived ω-3 fatty acids are eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA). Both the brain and nervous system are higher in DHA, as compared to the rest of the body. Low brain serotonin levels have been linked to low levels of DHA, resulting in an increased tendency towards despair, suicide, and violence. Additionally, based on observations in animals, it has been hypothesized that high levels of DHA in the brain may enhance neuronal survival. Low levels of ω-3 fatty acids have been associated with behavioral issues and learning problems in children with attention shortfalls, including behavior and learning problems. Seafood, cold-water fish in particular, is known to be an excellent source of ω-3 fatty acids. Thus it is not surprising that seafood consumption during pregnancy was correlated to the child's verbal intelligence quotient (IQ), noting that low maternal seafood intake (<340g per week) increased the risk of children ranking in the lowest quartile of IQ scoring, compared to those mothers who consumed a higher quantity of seafood (> 340 g per week). In addition, low maternal seafood intake was correlated to suboptimal social development, with lower indices in social behavior, fine motor, communication, and social development scores.

A reduction in inflammatory markers, including C-reactive protein, IL-6, COX and lipoxygenase (LOX), has been correlated with a high intake of polyunsaturated fatty acids (PUFAs). Numerous studies have documented the beneficial effects of diets high in ω-3 PUFAs. Consequently, an increased intake of ω-3 PUFAs has been associated with a reduction in cardiovascular events and other related complications, and in many populations the risk of cardiovascular illness has been inversely correlated with the dietary intake of ω-3 PUFAs. Conversely, a diet high in ω-6 EFAs, such as the Standard American Diet, results in the production of inflammatory prostaglandins, thromboxanes, leukotrienes, and other metabolites of arachidonic acid (AA; 20:5n-3), which, in turn, contributes to the formation of thrombi and atheromas, allergic and inflammatory consequences, and cellular proliferation. EPA-derived eicosanoids have established effectiveness in blocking the production of series-2 prostaglandins, for example PGE2 and PGF2-α, which when elevated ensues in an anti-inflammatory response. Additionally, an increase in ω-3 fatty acids has demonstrated a diminishing effect on the level of proinflammatory markers, including IL-6, high density lipoprotein, TNF-α and C-reactive protein, along with a corresponding elevation in anti-inflammatory markers, in-

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cluding soluble IL-6 receptor and IL-10. Accordingly, a fitting dietary change for cardiovascular health benefits is to emphasize an increase in the dietary amounts of ω-3 fatty acids, including the fish oil constituents EPA and DHA, while simultaneously decreasing the dietary content ω-6 fatty acids. Conservative estimates indicate that to balance this ratio, there would have to be a four-fold increase in fish consumption. Alternately, supplemental forms of ω-3 fatty acids could be incorporated into the diet to achieve adequate EFA intake.

In addition to its benefit in inflammation, ω-3 fatty acids have also demonstrated beneficial therapeutical effects for persons with symptoms of depression. It is well known that the essential fatty acids play a central part in both the development and function of the central nervous system. Epidemiological evidence has correlated the intake of fish/seafood with a lower occurrence of these symptoms. In addition to general melancholy symptoms, a high intake of fish/seafood has also been correlated to protection against symptoms of melancholy following pregnancy, unbalanced/mood instability and seasonal sadness. A random sampling study confirmed the benefits of frequent fish consumption, indicating that it was significantly associated with a decreased frequency of melancholy and suicidal contemplation. A cross-sectional study also established a correlation between fish consumption and mental health, as a result of a higher self-reported mental health status. In a separate study, depressive symptoms were correlated to a higher ω-6: ω-3 ratio, which as indicated above enhances the production of pro-inflammatory cytokines, confirmed by elevated levels of TNF-α and IL-6.

Published trials utilizing ω-3 fatty acids have correlated a broad range of benefits to its use. For example randomized controlled trials with diabetic individuals having elevated levels of triglycerides indicated that supplementation with ω-3 significantly lowered serum triglycerides in these individuals, thus demonstrating the effectiveness of ω-3 fatty acids in reducing plasma triglycerides and platelet reactivity in these patients. In two large studies, positive correlations were associated with an increase in ω-3 fatty acid intake and a decreased risk of cerebrovascular events, implicating a significantly lower risk of thrombotic or ischemic events with an increased intake of omega-3 fatty acids. Omega-3 polyunsaturated fatty acids were also shown to benefit cardiac arrhythmia (abnormal heart rhythm). Since abnormal heart rhythm is correlated to an increased risk of cerebrovascular events, ω-3 fatty acids should provide benefit in these populations.

The average North American population's daily intake of EPA and DHA is currently estimated at 130 mg. The minimal EPA and DHA intake, as proposed by an international panel of lipid experts, is 650 mg/day, suggesting that daily consumption should be increased **five-fold**. Considering the many benefits of increased intake, it is reasonable to recommend increased consumption for all, thus subsequently offsetting the dominance of the inflammatory mediating omega-6 fatty acids. Be it that contamination issues, particularly that of heavy metals, are of concern with an increased consumption of dietary EPA/DHA from fish, a favorable method of increasing the daily allowance is via supplementation. Quality fish oil, specifically one that is assayed for and known to be harvested free of contaminants so as not to require distillation, thus remaining fully functional (biologically active*),* is a smart choice for all.

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Memo from ABCI

To All DABCIs: Recertification is going on at this time and must be completed by June 30, 2008. If you are a DABCI and have not received your Recertification Packet, please contact Dr. Todd Smith at vp@dabci.org as soon as possible. Also, remember as a part of your recertification requirements, hours must be obtained at the CDID sponsored Symposium at least every other year. So, don't forget to register for Symposium 2008.

ABCI Examination Announcement: ABCI written examinations for Part I and Part II will be given in Cincinnati at the Symposium 2008 on Friday. Anyone interested in sitting for the written boards needs to contact Dr. Boudro at secretary@dabci.org.

Re-Takes: If you would like to retake any of Part I or Part II at the Symposium 2008 please submit a letter stating which parts you would like to retake plus a check for $75.00/per test. Please submit the to Dr. Anderson at 4082 River Ridge Lane, Sandwich, IL 60548.

ABCI Examination for fall is October 18-19. Deadline for application is September 1, 2008. Contact Dr. Boudro at secretary@dabci.org for an application packet.

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Memo from ACA CDID Clinical Message Board

The council on Diagnosis and Internal Disorders of the ACA has established a clinical message board for DABCI's, DABCI students and practitioners of functional medicine. We invite all interested parties to participate. Our clinical message board will be in a new Yahoo! Group format.

Topics of discussion will include:

- Diagnostic questions
- Case Studies
- Current Research
- Post-graduate seminars
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ABSTRACTS OF INTEREST

Submitted by Emerson Ecologics

Pelargonium sidoides Extract Shortens the Duration of the Common Cold

Author: Donald Brown, ND

Reference: Lizogub VG, Riley DS, Heger M. Efficacy of a *Pelargonium sidoides* preparation in patients with the common cold: A randomized, double-blind, placebo-controlled clinical trial. *Explore* 2007;3:573–84.

Design: Randomized, double blind, parallel-group, placebo-controlled trial

Participants: 103 adult patients (18–55 years old) with at least two major and one minor or with one major and three minor cold symptoms for 24 to 48 hours. Major cold symptoms included nasal discharge and sore throat and minor symptoms included nasal congestion, sneezing, scratchy throat, hoarseness, cough, headache, muscle aches, and fever.

Study Medication and Dosage: Liquid extract (1:8–10; ethanol 11% [wt/wt]) from the roots of *Pelargonium sidoides* *; (Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) or placebo – 30 drops t.i.d.

Duration: 10 days

Outcome Measures: Following enrollment, patients were seen on days 3, 5, and 10. The primary outcome measure was the sum of symptom intensity differences (SSID) of the cold intensity score (CIS) from day 1 to day 5. The CIS consists of 10 symptoms considered to be associated with the common cold and are designated as major or minor (see above). At each patient visit, all symptoms except fever were rated according to a five-point verbal rating scale with zero meaning no symptoms to four being very severe. The maximum CIS score was 40 points. Secondary outcome criteria included diverse response according to the total CIS, changes of individual symptoms of the CIS, changes of further cold-related symptoms, ability to work, activity level, general well-being, health-related quality of life, time until onset of treatment effect, treatment outcome according to an integrative medicine outcome scale, and satisfaction with treatment according to the integrative medicine scale.

Key Findings: From baseline to day 5, the mean SSID improved by 14.6 ± 5.3 points in the *Pelargonium sidoides* group compared with 7.6 ± 7.5 points in the placebo group ($p < 0.0001$). The mean CIS decreased by 10.4 ± 3.0 points and 5.6 ± 4.3 point in the *Pelargonium sidoides* and placebo groups, respectively. After 10 days, 78.8% of the *Pelargonium sidoides* group were clinically cured (CIS equal to zero points or complete resolution of all but a maximum of one cold symptom) compared to 31.4% in the placebo group ($p < 0.0001$). The mean duration of inability to work was significantly lower in the *Pelargonium sidoides* group (6.9 ± 1.8 days) compared to the placebo group (8.2 ± 2.1 days; $p = 0.0003$). Adverse events occurred in three of 103 patients (2.9%)—two in the *Pelargonium sidoides* group and one on the placebo group. All events were assessed as being minor.

Practice Implications: As noted in earlier reviews in this column, *Pelargonium sidoides* (also designated as EPs 7630) has been shown to safely and effectively treat acute bronchitis in both adults[1,2,3] and children[4] as well as tonsillopharyngitis in children.[5] This new trial adds the common cold to the list of potential treatments for *Pelargonium sidoides,* demonstrating a significant reduction in the severity and duration of symptoms in those using the herbal extract. With new attention being paid to the danger of OTC cold medications in children, it would be nice to see a future pediatric common cold study with *Pelargonium sidoides*. It should be noted, however, that a large phase IV trial with patients ranging in age from 2 months to 93 years old found no significant adverse events in children under the age of 6 years using *Pelargonium sidoides*.[4]

***Note:** The *Pelargonium sidoides* used in this study is the active ingredient in Umcka® Cold Care (Nature's Way/MMS Pro, Springville, Utah).

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Korean Red Ginseng Improves Glucose and Insulin Regulation in Type 2 Diabetics

Author: Donald Brown, ND

Reference: Vuksan V, Sung M, Sievenpiper JL, et al. Korean red ginseng (*Panax ginseng*) improves glucose and insulin regulation in well-controlled, type 2 diabetes: Results of a randomized, double-blind, placebo-controlled study of efficacy and safety. *Nutrition Metabol Cardiovasc Dis* 2008;18:46–56.

Design: Randomized, double-blind, placebo-controlled, crossover clinical trial

Participants: 19 participants (mean age 64 ± 2 years old, BMI: 28.9 ± 1.4 kg/m^2, and HbA_{1c}: 6.5%) with well-controlled type 2 diabetes.

Study Medication and Dosage: Following a 4-week placebo run-in phase, participants were randomized to receive either 2 g of a Korean red ginseng (*Panax ginseng*) rootlet preparation (KRG; Korea Ginseng Manufacturing Plant, National Agricultural Cooperative Federation, Chung-buk, Korea) or a placebo 40 minutes before each meal, three times per day (total dose of 6 g/day). This was followed by another 4-week washout phase and then randomization to the alternate treatment for the second phase of the study.

Duration: 12-week treatment phase

Outcome Measures: Outcome measures included the primary endpoint HBA_{1c}, as well as fasting and 75-g oral glucose tolerance test, plasma glucose, plasma insulin and insulin-sensitivity indices. Safety measures included markers of hepatic (AST, ALT), renal (serum urea, serum creatinine, 24 hour creatinine clearance), and hemostatic (prothrombin time, activated partial thromboplastin time, and blood pressure). During each treatment phase, participants were seen at the clinic every 6 weeks. They were asked to submit 7-day dietary records during the last week of each treatment period. At weeks 0 and 12 of each treatment phase, a 75 g oral glucose tolerance test with venous samples obtained at 0, 30, 60, 90, and 120 minutes and a 24-hour ambulatory blood pressure monitoring study were conducted.

Key Findings: There was no significant change on the HbA_{1c} during the study. However, the participants HbA_{1c} remained well controlled throughout the study (HbA_{1c} = 6.5%). KRG treatment decreased 75g-oral glucose tolerance test plasma glucose indices by 8-11%, and fasting-plasma insulin and the 75g-oral glucose tolerance test plasma insulin indices by 33-38%, and increased fasting-insulin sensitivity and 75g - insulin sensitivity indices by 33%, compared with placebo ($p < 0.05$ for all measures). Safety measures remained unchanged during the study.

Practice Implications: Led by Dr. Vladimir Vuksan of the University of Toronto, this study suggests that 6 g/day of Korean Red Ginseng rootlets helps maintain glycemic control and improves plasma glucose and plasma insulin regulation. It is important to note that the treatment did not improve the primary endpoint HbA_{1c}. The batch and dose for this study were selected based on extensive acute screening studies.[1] These results are in contrast to earlier work done by Dr. Vuksan's group which suggest that American ginseng (*Panax quinquefolius*) was effective in improving glycemic control over a 12-week period.[2] Hopefully, future studies by this group will look at larger populations of type 2 diabetics and compare the efficacy of the two different ginseng species for improving glycemic control.

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Enteric-Coated Peppermint Oil Once Again Found to Successfully Treat Irritable Bowel Syndrome

Author: Donald Brown, ND

Reference: Cappello G, Spezzaferro M, Grossi L, et al. Peppermint oil (Mintoil®) in the treatment of irritable bowel síndrome: A prospective, double-blind, placebo-controlled, randomized trial. Digestive Liver Dis 2007;39:530-6.

Design: Randomized, double-blind, placebo-controlled trial

Participants: Fifty-seven patients (18 - 80 years old) with symptoms indicative of irritable bowel syndrome (IBS) according to the Rome II criteria. Patients were required to have normal lactose and lactulose breath tests and negative antibody screening for celiac disease for inclusion.

Study Medication and Dosage: Patients were randomized to receive either 225 mg of enteric-coated peppermint oil (Mintoil®, Cadigroup, Rome, Italy) or placebo b.i.d. The capsules were administered one hour before meals.

Duration: 4 weeks

Outcome Measures: The primary outcome measure was the change in total IBS symptoms score before and after treatment of 1.0 or greater points. The symptoms score evaluated the following symptoms on a severity scale from 0 (absent) to 4 (unbearable) as well as frequency scale from 0 (absent) to 4 (≥ three times per week): ab-

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dominal bloating or distension, abdominal pain or discomfort, diarrhea (> 3 watery bowel movements/day), constipation (< 3 stools/week), pain at evacuation, and passage of gas or mucus. A total IBS symptoms score was calculated as follows: 1) a mean score for each symptom was obtained for each patient adding the relative intensity and frequency scores and halving this value; 2) the mean scores of the eight symptoms were summed for each patient and divided by 8, obtaining a total IBS mean score for each patient. The collection of symptoms occurred at baseline (T0), at the end of treatment (T4) and 4 weeks after the end of treatment (T8). Remission of IBS symptoms was defined as a ≥ 50% improvement of the overall IBS symptoms score from T0 to T4 and T8.

Key Findings: Data from 50 patients was available at T8. Six patients (three in each group) were lost to follow-up and one patient in the peppermint oil group withdrew due to intense heartburn after taking the medication. At T4, 75% of patients in the peppermint oil group had a ≥ 50% reduction in mean total IBS symptom score compared to 38% for the placebo group. At T8 this difference was 54% vs, 11%, respectively. In the peppermint oil group, there was a significant improvement in total IBS symptoms score at T4 ($p < 0.01$), persisting at T8 ($p < 0.05$) as well. Although there was a significant decrease in diarrhea and pain and bloating in the placebo group at T4 compared to baseline, between groups analysis found that the peppermint oil decreased all individuals' symptoms significantly greater than placebo at T4 ($p < 0.05$ for all symptoms).

Practice Implications: This new clinical trial again demonstrates the safety and efficacy of enteric-coated peppermint oil for the relief of symptoms associated with IBS. It's interesting to note that symptom relief continued for an additional four weeks after treatment was stopped. It should be noted that as opposed to two earlier peppermint oil trials that found overall symptom relief but no effect on abdominal distension and gas in both adult and pediatric IBS patients1,2, this study was careful to exclude those patients with lactose intolerance and small intestinal bowel overgrowth. While the symptom relief found with enteric-coated peppermint oil offers potential symptom relief, readers should keep in mind the potential of probiotics for the long-term treatment of IBS.

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Folic Acid Improves Cognition in Healthy Older Adults with Slightly Elevated Homocysteine Levels

Author: Steve Austin, N.D.

Reference: Durga J, Van Boxtel MPJ, et al. What can we learn from the FACIT trial: a randomized, double-blind, controlled trial. J Nutr Health Aging 2007;11;320-4.

Design: Double-blind randomized intervention trial

Participants: 818 adults aged 50 to 70 with total homocysteine (tHcy) level >13 μmol/L (73rd percentile of those screened) were included in the trial. Thus, only those in the top 27% of tHcy were included. Subjects whose tHcy appeared elevated due to low serum vitamin B12 levels were excluded.

Study Medication and Dosage: 800 mcg/day of folic acid (FA) given for 3 years

Outcome Measures: Standard measures of performance that track global cognition, memory, sensorimotor speed, "complex speed," information processing speed, and word fluency

Key Findings: tHcy declined 26%. FA supplementation led to a memory level 4.7 years younger than reported in those given placebo (P=0.01), 1.7 years younger for sensorimotor speed (p=0.055), 2.1 years younger for information processing speed (p<0.02), and 1.5 years younger for global cognitive function (P=0.03).

Practice Implications: tHcy has been reported to be elevated in association with heart disease and age-related cognitive impairment. FA has been proven to lower tHcy without reducing the risk of heart disease. However, the clinical effects of FA-induced tHcy-lowering in patients with impaired cognition remain in debate, with some previous trials also reporting efficacy, others coming up empty-handed, and at least two trials producing findings that suggest FA supplementation might slightly impair memory. The authors of the new report suspect their results bested those of most previous trials because they limited their pool of subjects to people with higher than optimal tHcy levels, which probably means their subjects were consuming suboptimal levels of dietary folate. Also, their large study population was followed for a full three years. The authors note that shorter trials may have ended prematurely before improvement in cognition would have reached measurable levels.

As measured by the Mini-Mental State Examination, baseline incidence of dementia in this group appeared to be quite low. Thus, these findings may not apply to more impaired elderly subjects. Indeed, the authors note that FA may be useless after a certain level of impairment has already ensued, which might also account for the

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poor showing reported by several previous research groups that studied more impaired subjects.

Honey: The First Scientifically Supported Nocturnal Cough Suppressant

Author: Steve Austin, N.D.

Reference: Paul IM, Beiler J, McMonagle A, et al. Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Arch Pediatr Adolesc Med* 2007;161:1140–6.

Design: Double-blind randomized intervention trial

Participants: 105 children 2 to 18 years of age, with upper respiratory tract infections (URI), nocturnal cough, and illness duration of no longer than one week completed the trial.

Study Medication and Dosage: A single "nocturnal dose" of buckwheat honey, 17 mg/5 ml dextromethorphan (DM) that has been altered to artificially taste like honey, or no treatment was administered to subjects. Given that DM had previously been shown to be no more effective than inert placebo, DM was used in this trial as the placebo.

The precise dosage of honey was not stated in the trial, but a recent interview with the principal investigator (P.I.) stated that the following doses are considered appropriate: for children under 1 year, no honey (due to fear of botulism); for those between 1 and 5 years, ½ teaspoon (tsp); for those who are 6 to 11, 1 tsp; and for those who are 12 or older, 2 tsp per dose. Doses may be administered "every 3–4 hours as needed" though in the actual trial, doses were limited to once per evening.

Main Outcome Measures: Cough frequency and severity, and sleep quality of both child and parent as assessed by graded (7-point scale) surveys completed by parents

Key Findings: These researchers used a wide variety of 7-point indices (with "zero" equaling no symptom and "6" indicating a severe symptom) to measure aspects of cough or sleep quality. On most of these indices, honey produced better results than did the DM placebo, which in turn did better than no treatment. For most symptoms, honey scored approximately 15 to 39% better than did DM. Compared with no treatment, honey faired even better, with the difference between those 2 groups achieving statistical significance for cough frequency and combined symptom score. Nonsignificant trends favored honey over no treatment regarding child sleep, cough severity, and parent sleep quality. While differences between honey and DM did not achieve statistical significance, most indices favored the honey over DM. DM was not more effective than no treatment in any parameter that was measured.

Practice Implications: DM is found in most over-the-counter (OTC) cough medicines used by children and adults despite the fact that it has been linked to a long list of side effects and has never been proven effective. In 2004 the same research group found that DM along with diphenhydramine—another common OTC cough suppressant—was no more effective than placebo. Yet, they remain in common use.

The P.I. of this trial, Ian Paul, was aware that the World Health organization recommends honey as an anti-tussive. Noting that no published clinical trials had tested its efficacy, he decided to investigate.

Honey has antimicrobial and antioxidant effects. The latter are partly due to the phenolic compounds found in honey. Buckwheat honey was chosen because, like other dark honeys, its phenolic compound content is relatively high. Whether similar results could be obtained with lighter-colored honeys remains unknown, though the P.I. has acknowledged that possibility. In addition, any sweet substance, honey included of course, stimulates saliva production, which may in turn have a demulcent effect.

Clinical experience has told most practitioners who work with botanical medicine that a variety of plant extracts traditionally used to reduce URI-related cough severity and frequency do help. Generally, however, these herbal medicines are put into a syrup, often sweetened by honey. While we now have reason to accept honey as a valid therapeutic agent, we now need research to validate (or not) the efficacy of horehound, wild cherry bark, coltsfoot, or other traditional anti-tussive botanicals.

Soft Drinks are Linked with Gout Risk and Fructose Appears the Culprit

Author: Steve Austin, N.D.

Reference: Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 2008;336:309–12.

Design: Observational prospective study

Participants: 46,393 men with no history of gout at baseline

Primary Outcome Measures: Food frequency questionnaires given at baseline were used to assess soft drink and total fructose intake. These data were paired against the risk of gout as a function of the 755 incident cases of gout that developed during the 12 years of follow up.

Key Findings: Compared with men consuming soft drinks rarely if at all, men consuming 5 to 6 servings per week had a 29% increased risk of gout. For those con-

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suming one serving per day, the risk was 45% higher than those who essentially abstained, and for those consuming at least 2 servings per day, the risk was 85% higher (p=0.002). In contrast, diet soft drink consumption was not associated with risk in any way.

The relative risk for gout also went up progressively with each quintile of total fructose intake, with the second through fifth ascending quintiles of fructose consumption exhibiting relative risks 29%, 41%, 84%, and 102% greater risk respectively than those in the bottom quintile (p for trend<0.001). Consumption of major contributors to total fructose intake besides soft drinks was also associated with increased risk (e.g., fruit juices, apples, and oranges). All findings were independent of alcohol consumption, body mass index (BMI), or other potential confounders.

Practice Implications: The authors of the new report remind us that incidence of gout has been rising sharply in the U.S. and this rise has coincided with the increase in soft drink consumption. Per capita consumption of high-fructose corn syrup has increased from zero intake in 1967 to 64 pounds per year.

Fructose is known to increase uric acid levels and recent epidemiologic data have reported a positive association between fructose consumption and risk of gout. Moreover the effect of dietary fructose in increasing uric acid levels has previously been shown to be greater in people with gout than in the general population. The primary mechanism, increasing ATP degradation to AMP (which is a precursor to uric acid) is much the same as it is with alcohol. Most estimates for increased risks associated with moderate (up to 3 drinks per day) alcohol consumption, and daily meat consumption are actually *lower* than the risks now being associated with sugared soft drink consumption. Only being overweight (BMI ≥25) when compared with being slim (BMI <23) has been reported to correlate with a higher risk of gout than the risk now associated with soft drink consumption. The fact that fruit juice consumption also correlated strongly with an increased risk of gout suggests that fructose is the culprit, and not simply a marker for either something else found in soft drinks *or* with something else in the diet of people consuming more soft drinks. Diet soda pop, which contains no fructose but otherwise contains everything else found in sugary soda pop (except glucose), did not correlate with risk in this large study.

Depending upon the preparation, high-fructose corn syrup, the primary sugar used to sweeten soft drinks in the U.S., contains between 42% and 90% fructose, the remainder consisting of glucose. When we eat table sugar (sucrose), disaccharidases in the gut break down that disaccharide into equal parts of fructose and glucose. Thus, even though the current study did not investigate sucrose intake, there is little reason to assume that sucrose consumption would not have related troublesome effects upon uric acid metabolism.

Finally, the authors of this report remind us that fructose consumption increases insulin resistance, and given that most gout sufferers have metabolic syndrome and are overweight, the consequences of a high fructose diet might be even more extensive than the association with gout risk reported here.

What are clinicians to do with this information? Gout and elevated serum uric acid levels have been linked with an increased risk of cardiovascular disease, yet fruit consumption is believed to lower risk. It is not time to advise patients to reduce their fruit intake. Yet if fruit is protective against heart disease, it's likely that the cholesterol-lowering effect of the soluble fiber found in whole fruit is the primary protective agent. Unlike whole fruit, fruit *juice* lacks this fiber. And of course there is nothing to recommend consumption of sugary soft drinks.

Therefore, it is now time to tell current gout sufferers, those with a personal history of gout, and those with asymptomatic high serum uric acid levels, to switch from sugary soft drinks to water or at least diet pop, and also to switch from fruit juice consumption to eating whole fruit. Even though the latter still contains fructose, it's much harder to eat six apples than to drink them. Thus, switching to whole fruit doesn't simply increase soluble fiber input, it also is likely to reduce consumption of fructose.◆

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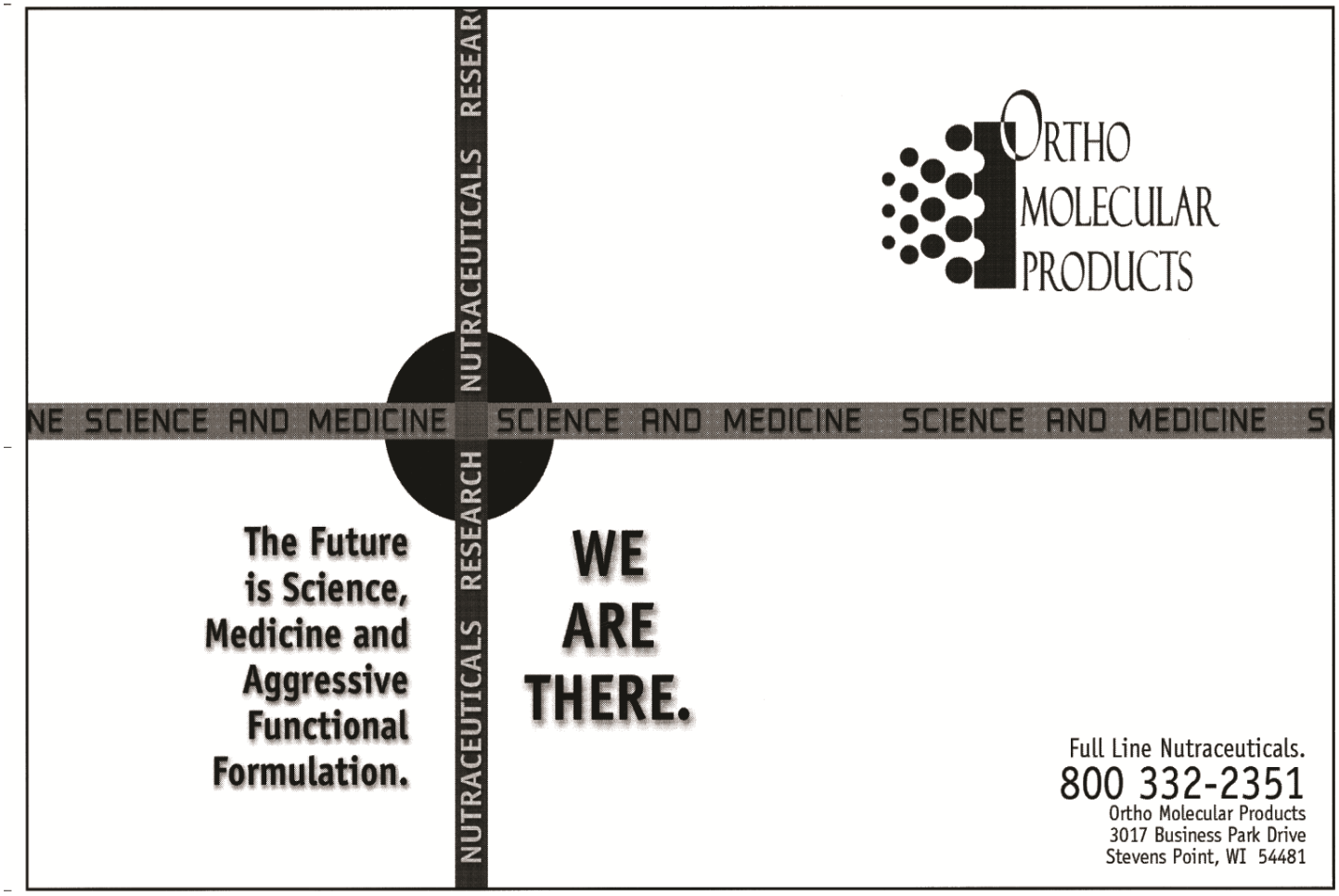

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EDITOR: *continued from page 60*

phospholipid damage that makes the membrane more porous endangers the life of the cell. The most vulnerable tissues are those marked by a rapid turnover of cells. Key among these are the skin, GI tract, lungs, kidneys, heart and blood vessels, and especially the liver. If cells are going to survive, damaged phospholipids must be quickly replaced; and if tissues are going to survive, damaged or dying cells must also be replaced in a timely manner. Many people, including older folks, have a diet deficient in nutrients necessary to produce these essential phospholipids.

Vitamin D has recently become the focus of several studies. Vitamin D has long been recognized as essential for promoting calcium absorption in the gut and maintaining adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts *(van den Berg H. Bioavailability of vitamin D. Eur J Clin Nutr 1997;51:S76-9* and *Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes: Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. Washington, DC: National Academy Press, 1997 and Cranney C, Horsely T, O'Donnell S, Weiler H, Ooi D, Atkinson S, et al. Effectiveness and safety of vitamin D. Evidence Report/Technology Assessment No. 158 prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-02.0021.* and *AHRQ Publication No. 07-E013. Rockville, MD: Agency for Healthcare Research and Quality, 2007)*. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults *(DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80:1689S -96S)*. Together with calcium, vitamin D also helps protect older adults from osteoporosis. Vitamin D has other roles in human health, including modulation of neuromuscular and immune function and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D *(Hayes CE, Hashold FE, Spach KM, Pederson LB. The immunological functions of the vitamin D endocrine system. Cell Mol Biol 2003;49:277-300).* Vitamin D deficiencies are being recognized as widespread in all stages of life, even in sunny climates *(J Clin Endocrinol Metab 2001;86:1212-1221).*

N-acetylcysteine (NAC) is the acetylated precursor of both the amino acid L-cysteine and reduced glutathione (GSH). More recently, animal and human studies of NAC have shown it to be a powerful antioxidant and a potential therapeutic agent in the treatment of cancer, heart disease, HIV infection, heavy metal toxicity, and other diseases characterized by free radical, oxidant damage. NAC has also been shown to be of some value in treating Sjogren's syndrome, smoking cessation, influenza, hepatitis C, and myoclonus epilepsy. It has lowered lipoprotein (a) levels to a degree not previously achieved by either drugs or diet *(PDR for Nutritional Supplements).*

Glutathione is an antioxidant enzyme often referred to as the body's "master antioxidant" due to its central role in protecting the body's cells from free radical damage. Glutathione is synthesized from three amino acids cysteine, glutamine and glycine and is concentrated in the liver, although it carries out its work throughout the body. This important enzyme is involved in protecting cells from environmental toxins, drugs and alcohol as well as toxins produced by the body itself as a result of normal metabolism. It is so important to health that it's depletion leads to cell death. The liver and lungs are the primary sites of glutathione synthesis. Glycine and glutamic acid are plentiful in cells, so it is the availability of cysteine that controls the reaction rate.

Cysteine is a nonessential amino acid (protein building block), meaning that cysteine can be made in the human body. Cysteine is one of the few amino acids that contain sulfer. This allows cysteine to bond in a special way and maintain the structure of proteins in the body. Cysteine is a component of the antioxidant glutathione. The body also uses cysteine to produce taurine, another amino acid. Cysteine can also be converted into glucose and used as a source of energy. Cysteine strengthens the protective lining of the stomach and intestines, which may help prevent damage caused by aspirin and similar drugs. In addition, cysteine may play an important role in the communication between immune system cells.

The body can synthesize cysteine from the amino acid methonine but is also found in high protein foods such as poultry, wheat, broccoli and eggs as well as garlic, onions and red peppers. Cysteine is rarely used as a dietary supplement. N-acetylcysteinewhich contains cysteine, is more commonly used as a supplement.

By implementing a few simple and visionary steps, the chiropractic and naturopathic professions can become the undisputed leaders in this newly developing health care parade.

The demand for all things natural provides both challenges and untold opportunities, and with visionary leaders, alternative providers can lead this parade.

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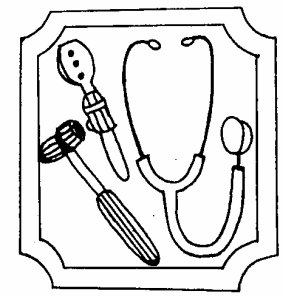

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