May 2000 Issue | Jeffrey Spencer, MA, DC

http://jeffreybland.com/knowledgebase/may-2000-issue-jeffrey-spencer-ma-dc/

DOWNLOAD AUDIO |

Welcome to *Functional Medicine Update* for May 2000. Our Seventh International Symposium on Functional Medicine will take place this month. I hope you plan to visit us in Scottsdale, Arizona for this event. If you cannot attend, you can order the tapes after the symposium to find out what went on there.

Every day, in dealing with patients, practitioners face challenges that are different from those they faced 10 or 20 years ago. Patients are asking questions not just about keeping alive, but about maintaining high-level function and improving basic performance. This issue of *FMU* is very timely, therefore, because it focuses on peak performance.

How do we define peak performance? What expectations do people have relative to peak performance? How do those expectations translate into comprehensive health care and personalized preventive medicine? How does that relate to the functional medicine perspective? We will address those questions during this month's *FMU,* and our Clinician of the Month will take us through his experience facilitating peak performance in sports medicine and sports nutrition.

A few months ago, the *New England Journal of Medicine* contained a retrospective on the millennium in medicine. The editors defined what they considered to be the principal discoveries of the past millennium.[1] They described the elucidation of human anatomy and physiology as a major breakthrough, when the workings of the body began to be better understood from a mechanistic point of view. The discovery of cells with van Leeuwenhoek's invention of the microscope opened up a new, previously invisible world. We began to see worlds within worlds and wheels within wheels as they give rise to the ecosystem, the biosphere, and individualized parts of individual cells in the human body.

Next came the discovery of the substructure of cells. The existence of organelles within cells reveal another level of organization. The structure/function relationships between the cellular organelles exhibit many of the characteristics of a macroscopic ecosystem.

All those developments were part of the breakthrough in the mechanistic understanding of body function. Next came the elucidation of the chemistry of life, the origin of the science of biochemistry in the 19th century. That science blossomed in the 20th century with Emil Fischer and the discovery of the structure of carbohydrate and with the synthesis of urea from isocyanate by Wohler, the boundary between organic and inorganic was eliminated. Scientists learned there was no life force present in organic chemicals, the molecules of life, that differentiated them from nonliving molecules, the inorganic world. It was the manner in which molecules were put together and assembled into super-molecular structures that led to the distinction between living and nonliving molecules.

The ability to assess the molecules of unhealthy living tissue or disease by pathophysiological determinations was next, and clinical chemistry was born. Scientists could look at the sugars or protein in urine to diagnose diabetes. They could examine chemical pathologies resulting from genetic metabolism diseases. These inborn errors of metabolism could be reflected in single molecular changes, later established in such diseases as sickle cell anemia. In this disorder, a single base mutation leads to an amino acid substitution on the heavy chain of hemoglobin, ultimately resulting in a complex disorder called sickle crisis. It affects not just a single organ, but the whole body, as the sickle cell cuts its way through the vasculature and causes damage to the body. In 1949 Linus Pauling introduced the concept of molecular medicine.

The Origin of Epidemeology

Another major breakthrough was the application of statistics to medicine. Epidemiology provide the ability to look back and apply the Karl Friedrich Gauss concepts of the bell-shaped curve and look at standard deviations from the mean. It gave us the ability to predict outcomes, based on retrospective analysis. Epidemiology was born as a science within the field of medicine. We now use biostatistics as a guide in clinical decision-making. The risk/benefit equation is built on statistical evaluation and probability statistics. Pascal helped people understand the nature of numbers and how statistics could be derived from numbers. The Pascal numbers concept was later applied to biomedical sciences through Gauss's concepts of random error.

One of the first people to use epidemiology and statistics in making a medical discovery was James Lind, the Scottish surgeon who discovered that scurvy was associated with the absence of citrus. From this discovery emerged the name "Limey" to describe a British sailor. Lind conducted detailed retrospective statistical analysis of the occurrence of scurvy in individuals in the British Navy in the absence of fresh citrus. We developed this effective backward-looking way of looking forward to learn to treat and prevent scurvy by providing a daily ration of lime juice for sailors. This interesting concept has changed medicine significantly.

Advent of Anesthesia and Antibiotics

Later came the development of anesthesia, which made it possible to perform surgery in the Western world. Anesthetic drugs, with their mechanism of action and control, opened up the interior of the body to surgical alteration. These changes led to the development of medicine as we know it.

In the late 19th and early 20th centuries, scientists discovered that disease could originate from microbial infection. Pasteur, Jenner, and Koch made contributions to the area we now term immunotherapy.

The major discoveries become more closely spaced as we get closer to the present time. They represent major paradigm shifts in the way we see the origin of disease and, ultimately, its treatment.

The development of antibiotics emanating from Alexander Fleming's discovery of penicillin ultimately led to the modern pharmaceutical industry as we know it. We could treat life-threatening diseases miraculously with these microbial metabolites called antibiotics, which could lead to overnight recovery of a patient with septic disease.

These are extraordinary chapters in the evolving model of medicine. The elucidation of the inheritance of genetics that occurred in the 20th century moved us beyond Mendel's laws into a new understanding of how inheritance is coded within the human genome and how it is related to the triplet code of the DNA molecules and our 23 pairs of chromosomes. Next came the understanding of inborn errors of metabolism and genetic plasticity, or polymorphism, and biochemical uniqueness. Roger Williams, a biochemist at the University of Texas and former president of the American Chemical Society, who discovered pantothenic acid, discussed biochemical individuality as a concept in the early 1950s.

The concept of biochemical individuality was enriched by the discovery by Watson and Crick of the double-helical structure of DNA, and then later the elucidation of the triplet code embedded in the ATGC pairs.

These are extraordinary chapters in the evolving model of medicine. The elucidation of the inheritance of genetics that occurred in the 20th century moved us beyond Mendel's laws into a new understanding of how inheritance is coded within the human genome and how it is related to the triplet code of the DNA molecules and our 23 pairs of chromosomes. Next came the understanding of inborn errors of metabolism and genetic plasticity, or polymorphism, and biochemical uniqueness. Roger Williams, a biochemist at the University of Texas and former president of the American Chemical Society, who discovered pantothenic acid, discussed biochemical individuality as a concept in the early 1950s.

The concept of biochemical individuality was enriched by the discovery by Watson and Crick of the double-helical structure of DNA, and then later the elucidation of the triplet code embedded in the ATGC pairs.

Knowledge of the immune system started to emerge at the end of the 19th century. The application of protein crystallography to the elucidation of antibody structure by Dr. Linus Pauling and his Cal Tech colleagues in the 1930s greatly accelerated our understanding of the immune system. The knowledge gained was central to our understanding of the antigen/antibody reaction and discovery of the structure/function relationships that comprise the modern view of the immune system, another instance in which Dr. Pauling made enormous contributions to the development of our modern paradigm of molecular medicine and biomedical thought.

The understanding of the immune system is a lot like particle physics. The more we look, the smaller units we see. We started with gross morphological features of the immune system, which led to sub-features and sub-sub-features. Now we are into the sub-sub-sub-features.

It is a differentiated artillery, infantry, and aerial system of protection, and offensive and defensive constituents are related to our defense against the exterior and interior environments and maintaining the integrity within our own native selves. Through HIV and other infectious disorders, various hepatitis outbreaks, and infectious diseases around the world, we have learned how lifestyle, diet, and environment influence the immune system.

The development of body imaging began with Madame Curie and her daughter, looking with X-radiography inside the body. This was a breakthrough as significant in changing our vision of human function as that of the microscope in looking at microbes and their relationship to health and disease.

Roentgen, the German physicist (1845-1923), discovered X-rays. The nature of X-radiography, with different contrast media, ultimately made it possible to observe the whole body. Radiology has evolved into a functional medicine field. The most citations in the medical literature of the past two years using the term functional medicine have been in areas of radiology and neurology. Radiology is becoming a functional assessment tool, with CT scanning and various noninvasive imagery that looks at function in the body, not just tissues in static presentation. With PET scanning we can examine metabolic functions of the body in real time.

The modern pharmaceutical industry is another major contributor to progress, with corticosteroid drugs, antimicrobial drugs, and antibiotics. Florey and Fleming, in their extraordinary work on the development of penicillin, led to a breakthrough that distinguished medical doctors from practitioners of other therapeutic modalities. With cortisone and antibiotics they had access to something that worked miraculously. These drugs were not available through any other traditional treatment. They provided medical doctors with the power of the prescription pad and the ability to give something quickly to make a patient feel better. As we have subsequently seen, however, the miracle-drug model does not extrapolate well to chronic conditions that are not of direct bacterial origin. The effects of the medication are not as successful in these conditions, and the side effects become more apparent with long-term administration. We are beginning to examine the risk/benefit tradeoff in that model.

With molecular pharmacotherapies we are now getting into more specific ways of manipulating function at the molecular level within cells, with H2 blocker drugs, proton pump inhibitors, or ACE inhibitors. We are starting to see more specific molecular interventions at specific enzyme levels or gene expression levels.

We are moving into the age of genomics, the most recent breakthrough, in which we are beginning to individualize treatment and personalize medicine based on the genomic uniqueness of the individual.

How does this translate to peak performance? Patients now say it is not enough not to be sick; they want to be truly well, to perform at high levels. They want to think well and act well. They want to live full, active lives for the extent of their years. The peak performance concept translates into getting the most from one’s genes. We want to squeeze out the highest phenotypic performance from our inherent limitations and the strengths of our genotype.

Dr. Ernst Wynder, who passed away last year, helped us, as both a scientist and an activist, to understand the genotype/phenotype/environment connection. Dr. Wynder was a prototype of what we consider a functional medicine investigator. In the 1950s he was one of the first to take on the cigarette industry and point out that cigarette smoking contributed to a variety of age-related illnesses and premature death.[2] He explained that prolonged use of tobacco, especially cigarettes, is a factor in the induction of all sorts of illnesses, particularly bronchogenic cancer.

Dr. Wynder devoted himself to unearthing the causes of cancer and persuading people to protect their health by modifying their environment to get the most from their genes in terms of their phenotype. He should be honored as a central figure in 20th century preventive medicine. Although he had a forceful personality, he was a very likeable person. I met him several times and felt his contributions were significant in style and intellectual commitment. He was able to get things done in the business community. He was a medical doctor, but he was also involved with basic research, including

epidemiology.

Dr. Wynder set up the American Health Foundation late in his professional career. He was influenced by observing an autopsy of a 42-year-old lung cancer patient who had smoked two packs of cigarettes per day. That led him to devise a questionnaire and interview patients with and without lung cancer. From the results, the association between cigarette smoking and disease became clear to him.

He received his MD degree from Washington University School of Medicine in the late 1940s. He served a one-year internship at Georgetown University Medical School in Washington DC and became an assistant resident at the Memorial Hospital for Cancer and Allied Diseases. A year later he became an assistant in the Sloan-Kettering Institute for Cancer Research in New York. He remained with both institutions in various capacities until 1999. He made us think about the gene-environment connection to our phenotype, focusing on smoking and cancer, and on food and phytonutrients and how they modulate cancer risk and influence function.

Interest in performance and the genotype/phenotype connection is being translated in the pharmaceutical industry into what are being called lifestyle drugs. The pharmaceutical industry is under great pressure.[3] Although the industry did well in 1999, it apparently was not good enough. A number of consolidations occurred as companies tried to appear more profitable and to realize greater returns on investment (ROIs) to shareholders. These companies want to continue to show the growth potential and capital base they have had over the last couple of decades.

"Lifestyle drugs" represent a major area of focus in R&D for pharmaceutical companies for the next few decades. These are drugs like finasteride for baldness, and sildenafil and celecoxib for inflammation. Although they may not treat life-threatening diseases, celecoxib and rofecoxib deal with the infirmity and pain of osteoarthritis and the disability of chronic pain. These medications are growing to be major place-holders in the portfolios of the pharmaceutical companies.

Lifestyle Drugs and Performance

These lifestyle drugs are positioned to meet the needs of consumers who are asking for ways to maintain peak performance or high-level function as they age. We are moving away from the development of drugs to treat crisis illness. Drug companies are spending more money in developing products to manage chronic infirmities and improve performance.

In the SSRI revolution, we have moved from the treatment of depression to the application of SSRIs to social anxiety disorders and other functional disorders related to performance. Examples are stage fright, agoraphobia, and anxiety about having to interact with a group with whom you are socially uncomfortable. You take an SSRI drug to make yourself perform at high levels in the social situation. This is a significant departure from the use of a medication to treat a crisis illness or an ICD9-definable pathology. Functional disorders are being given names. It is called the medicalization of symptoms. That transition is occurring as the aging Baby Boomers express their desire to maintain peak performance, or to even find peak performance as they move into their 50s, 60s, and 70s.

The nature versus nurture controversy may be about to be resolved. Our nature occurs as a consequence of our genes. When the sperm met the egg, we got what we got and we have been working with it ever

since. Nurture is important as well, in the way the environment acts upon the genes and how the genes are expressed to give rise to our phenotype or function. This function, which travels with us throughout life, is modifiable. The environment is modifiable.

This topic is nicely described in a recent article in *Scientific American,* titled "The End of Nature versus Nurture." The author states that yes, we are our genes, but our genes are very plastic and have a lot of different ways of being expressed.[4] They are pleomorphic as well as polymorphic. Therefore, the environment and the conditions in which the genes are exposed over the course of our lives, starting from the moment of conception, will give rise to how our phenotype outcome, or expression of function, is perceived.

The question that emerges is, if all these things aren't locked or hard-wired into our genes, can we postpone age-related diseases, or aging itself? That question is at the forefront of awareness of people who have started to talk about anti-aging medicine. Is there a form of medicine that will prevent aging? My particular bias is not to use the word anti-aging, because it tends to stigmatize aging as a negative process. Being an individual who, like you, is involved in that aging process, I don't find it necessarily a stigmatizing negative. I think it is desirable to gain wisdom as we travel through life and to feel we can find solutions to problems that we were unable to solve at a younger age through lack of experience. Love relationships become deep, warm, passionate, and less volatile. Is aging necessarily a bad thing?

I refer to youth as the period when one suffers from "small-molecule disease." One is driven by small steroid molecules to make decisions that are not always to one's evolutionary advantage. As you grow older, those molecules tend to smooth out, and you get a symphony of different regulatory processes. Therefore, anti-aging may be a term that is a little off the mark. We should be talking about healthy aging, modifying the expression of our genes to give rise to a phenotype of peak performance.

In a recent *Scientific American* article titled "Can Human Aging Be Postponed?" Michael Rose describes ongoing work aimed at rectangularizing the survival curve and extending the health span and life expectancy of individuals. Certain genes, he explains, code for rapid aging.[5] For most of us, the expression of age-related diseases is only about 25 percent determined by the genetic hard-wiring and about 75 percent by what we do and how we treat the genes over the course of our lives.

Early signs we see are functional changes of altered biological senescence, or aging and age-related diseases. These can be very subtle changes, like forgetting to stop at a stop sign, turning right when you should have turned left, slower reaction time, vision problems like photophobia with dim lights, impaired hearing, lower sensory perception to vibratory stimuli, or altered glucose tolerance. These changes precede what we might call age pathologies.

A recent issue of the *Lancet* featured an article titled "Might Olfactory Dysfunction Be a Marker of Early Alzheimer's Disease?"[6] The author explains that our nasopharynx and the nerves involved in olfaction are directly related to central regions of the brain that are influenced by the neurofibrillary tangles of Alzheimer's disease. Therefore, the early stage dysfunction seen with Alzheimer's could start with a change in olfaction and taste perception because smell and taste are so closely tied together in individuals. The gradual loss of the sense of taste and smell in aging individuals may indicate that other functional changes are going on in the brain associated with other neurological dysfunctions that would occur in later age.

If you have an apoE4 genotype and start losing your sense of taste and smell, that may be an early warning sign of things that are going on that need attention related to the maintenance of cortical function. This is a way of looking at functional analysis and how people are performing. One does not just examine for the presence of pathology. He or she looks for the presence or absence of function. It is a new way of assessment, to use Dr. Leo Galland's concept of patient-centered assessment. It is looking at antecedents that are worked upon by triggers to give rise to the mediators that ultimately relate to the signs and symptoms that people have and experience as it relates to aging.

An article titled "The Performance of a Lifetime: A Metaphor for the Phenotype" appeared in the Autumn 1999 issue of the journal *Perspectives in Biological Medicine*, published by the University of Chicago School of Medicine.[7] The author, Dr. Jeffrey Lewis, talks about the Human Genome Project. That project, which is taking molecular biology into the public eye, was first thought to discover how people were going to die by determining the imperfections in their genes that would give rise to the cause of death. Instead we are learning, as the article points out, not how people will die, but how they will live. What characteristics will make it possible for them to perform and function over decades of living? What can they do to their genotype to enable them to control its expression?

In the past we thought the genes were hard-wired and beyond our control. Now we realize this deterministic view of the genes is limiting and incorrect. Genes have pluripotentiality; the outcome is not predetermined. In the deterministic model, laws control everything. Using what was called Laplace's calculating demon, this model assumed you could define life by calculating all the laws of nature. We are moving toward the concepts of probability and pluripotentiality, Einstein's relativistic concept. The quantum concept is weaving itself into physiology. We recognize the genome defines the probabilities of function and the resultant pluripotentiality. We see discrete outcomes only as the genes are influenced by the environment of the host, starting with conception and moving on through life.

In this article, Dr. Lewis provides a profound philosophical construct for medicine and biology in the next century, as we realize we can do much more than we previously recognized in maintaining our health.

Certainly, some things are locked into our genome. We may possess certain characteristics with which, like biochemical Achilles' heels, we have to deal. One of these characteristics may be locked into the seat of our energy production within cells, the mitochondrion. Oxygen is consumed in the mitochondria, as food in some sense is combusted under the controlled conditions of respiration. The result is the production of high energy-reducing power (NADH) within the cell. Like a storage battery, the cell transforms this energy into ATP and transfers it to sites where it is needed, giving rise to function such as muscle contraction, nerve firing, secretion, immune function—all the things that are required to keep the body operating as an organized unit.

Until a decade ago, researchers paid scant attention to the mitochondrion. Now they have begun to see the more menacing side of these internal power plants. Mitochondria produce oxidants like the superoxide and hydroxyl radicals, as well as hydrogen peroxide. These high-energy oxidants can damage the cell, induce mitochondrial DNA mutations, peroxidize lipids within the mitochondrial membrane, and induce oxidative shifts in the redox potential of cells that alter gene expression by modifying cell-signaling. These products can initiate a set of well controlled biochemical reactions leading to premature cell death by a process called apoptosis. This condition is often triggered by an oxidative shift in the cell generated by the production of excessive mitochondrial oxidants.

Gerontologists have for some time discussed the possibility of a correlation between mitochondrial oxidants and age-related dysfunctions. Investigators like Dr. George Martin, a gerontologist at the University of Washington, have considered the correlations of oxidative stress and mitochondrial function to aging. Dr. Martin recently said there is no evidence that mitochondrial mutations functionally impair the cell or change the rate of mitochondrial replication. A paper that just appeared in *Science* magazine, however, has opened up this question for further consideration. This paper, from the Division of Biology, California Institute of Technology in Pasadena, California and the University of Milan, is titled "Aging-Dependent Large Accumulation of Point Mutations in the Human mtDNA Control Region for Replication."[8]

Although it does not prove exactly how mitochondria cause aging, it opens up the possibility of mitochondrial dysfunction and aging, and loss of performance. The authors state:

> "Progressive damage to mitochondrial DNA during life is thought to contribute to the aging processes. The idea has been difficult to reconcile with the small fraction of mtDNA so far found to be altered. Here, examination of mtDNA revealed high copy point mutations at specific positions in the control region for replication of human fibroblast mtDNA from normal old, but not young, individuals. Furthermore, in longitudinal studies, one or more mutations appeared in an individual only at an advanced age. Some mutations appeared in more than one individual."

This paper suggests these mitochondrial "hits" or mutations could, in specific regions of the mitochondrial genome, prevent mitochondria from replicating. That means the mitochondrion would pass on an inefficient energy production to the daughter cells, or to the cell, if it was in a resting state, and reduce energy efficiency. The effect would be seen as fatigue and low-energy performance. The energy of life is what maintains our structure/function, the negentropy against the tendency of the universe to randomize itself. If we lose biochemical energy and the energy of organization, we undergo the disorganization called aging.

This paper may be one of the first to take a step forward in confirming the mitochondrial hypothesis of aging and the oxidant stress connection. It explains how that relates, particularly in post-mitotic cells like the brain or heart of the muscle, to lowered function over time, which would result in low performance.

Like other cellular membranes, the mitochondrial membranes are made up of highly unsaturated fatty acids. Therefore, we recognize that polyunsaturated fatty acids provide more than calories. They may also be raw materials to construct the body and maintain its function. Lipid chemistry has been considered one of the least attractive disciplines in science. Now, however, like nucleic acid biochemistry, lipid biochemistry is coming to the forefront of a very dynamic field. We recognize these essential fatty acids and lipids play a central role not only in the structure of the organism, but also in cell signaling. We know that certain fatty acids are regulators of gene expression. We realize that certain fats influence the

expression of genes and can turn on or turn off certain characteristics of the genome. This is nicely reviewed in a paper in the *Journal of Nutrition.*[9]

Highly unsaturated omega-6 and omega-3 fats interact with various receptor nuclear receptor sites, or the orphan nuclear receptors, like the peroxisome proliferator activated receptors*alpha* and *gamma*, which influence genome expression and the phenotype of the organism. When you eat certain fats, you can influence the way your genes are being translated into messages that influence function, both at a morphological and a biochemical level. This is a profound change in our view of the role of fats in our diet and function.

Dietary polyunsaturated fatty acids, particularly the omega-3 family, have been associated with lowered risk of cancer in animals exposed to carcinogens. A recent paper in *Carcinogenesis* discusses this topic.[10] The authors describe the role of dietary polyunsaturated omega-3 fatty acids and breast and colorectal cancers and evidence showing that these omega-3 fats modulate gene expression related to oncogenes or chemical carcinogenesis. We are learning much about different types of fats, the amount of fat in our diet, and the influence of fats on the construction of membranes and membrane transport, and also on gene expression.

Effects of Different Ratios of ALA and LA on Visual Function and Growth of Term Infant
Omega-3 fatty acids play an important role in primates in ocular, retinal, and cortical brain development. Primates deprived of omega-3 fatty acids in infancy later develop ocular difficulties, may have immunochemical problems, and may experience learning disabilities. A paper published in the American Journal of Clinical Nutrition was titled "A Randomized Trial of Different Ratios of Linoleic to a -Linolenic Acid in the Diet of Term Infants: Effects on Visual Function and Growth."11 Investigators found that lowering the linoleic acid to a -linolenic acid in formulas (raising the a -linolenic omega-3 component in the formula by using the low-erucic acid canola oil rich in ALA), resulted in a modest increase in plasma DHA.

It had no effect on visual acuity or growth rate in these infants, but it did have a balancing effect on the function and structure of phospholipids, increasing the amount of the omega-3 fatty acids, presumably at the 2 position. ALA may not be the preferable fatty acid to offer in these children, however, because they may not be able to metabolize ALA into the 22-carbon atom polyunsaturated DHA very effectively, or the 20-carbon fatty acid EPA, eicosapentaenoic acid. Those are downstream metabolites by desaturation elongation from ALA. Perhaps giving ALA-enriched oil is not as effective as giving preformed EPA or DHA to children to provide more improvement in visual acuity.

Dark adaptation, motor skills, and learning can be influenced by deprivation of DHA. A paper in the *American Journal of Clinical Nutrition* looked at dyslexia, motor skills, dark adaptation, and DHA status.[12] DHA is the 22-carbon atom six double bond omega-3 fatty acid that is derived by two cycles of desaturation/elongation from ALA. Many children may not be able to synthesize DHA from ALA adequately. Therefore, flaxseed oil, which contains ALA, or low-erucic acid canola oil that is high in ALA, is not the same as preformed, algal-derived or fish oil-derived EPA/DHA.

The author of this study looked at DHA supplementation specifically. When considered with evidence from closely related conditions such as ADHD, for which reduced ability to elongate and desaturate the essential fatty acids linoleic acid and a -linolenic acid to arachidonic acid and DHA, respectively, has

been demonstrated, this study suggests possible interrelationships among dyslexia, poor dark adaptation, altered motor skills, and DHA insufficiency. We need to give the right fatty acid for the right functional effect.

A paper in the *Lancet* in the mid 1990s showed a correlation between what is analogous to IQ in infants and their red cell DHA level.[13] The higher the IQ, the higher the level of DHA in their red cells. We can't measure infant IQ specifically, but using psychometric indicators, we can measure the prognostic indicators of IQ for older children.

The hypothesis that long-chain polyunsaturated fatty acids play a role in modulating function in children with ADHD or dyslexia is still waiting for full confirmation. Evidence from double-blind, placebo-controlled trials, however, points to a benefit in supplementing these children, particularly boys. (Most available ADHD data concerns boys, as this condition afflicts boys more frequently than girls.) ADHD can be improved by administration of omega-3 fats in the preformed DHA or EPA states. A paper in the *American Journal of Clinical Nutrition* reviews studies that link omega-3 chain-elongated desaturated insufficiencies with ADHD.[14]

What other roles do these fatty acids play in modulating function and improving performance, such as in atopic disorders, allergy, and skin disorders? David Horrobin has been a significant contributor to our understanding in this field. He recently wrote a paper that appeared in the *American Journal of Clinical Nutrition.* In this paper, titled "Essential Fatty Acid Metabolism and Its Modification in Atopic Eczema," he discusses the use of *gamma*-linolenic acid, which is an omega-6 fatty acid. GLA is a fatty acid that is a precursor to the 1-series prostanoids, antiinflammatory, anti-self-proliferative, anti-platelet adhesive. In this paper, according to Dr. Horrobin, together with the omega-3 EPA and DHA, GLA provides a useful therapeutic tool for modulating atopic eczema.[15] The use of polyunsaturated fatty acids to promote skin integrity, immunochemical defense, and lowered inflammatory potential seems to be gaining credibility.

A number of basic research studies on this subject are now available. One is titled "Metabolism of Polyunsaturated Fatty Acids by Skin Epidermal Enzymes: Generation of Antiinflammatory and Antiproliferative Metabolites."[16] This study describes cell culture work in examining the role of omega-6 GLA and omega-3 EPA in modulating proinflammatory mediators. It shows that by giving an enriched level of these fatty acids, one can lower the level of inflammatory mediators and increase the level of antiinflammatory mediators and antiproliferative mediators associated with thickening of the dermis associated with disorders like psoriasis.

The role of these fatty acids can vary from person to person. The balance is generally two parts of the omega-3 to one part of the omega-6 GLA. The doses may be in the range of 6 to 10 grams per day of a complex mixture of EPA and 2 to 3 grams per day of the complex mixture of GLA.

Another fatty acid related to peak performance, improving gene expression, and getting the most out of our phenotype is conjugated linoleic acid (CLA). CLA was first discovered as a constituent of several isomers in butterfat, cream, and whole milk. It appears to have a modulatory effect on a variety of functions, particularly working as an agonist through the peroxisome proliferator activated receptor (PPAR) *gamma* binding site. It can improve insulin sensitivity, thermogenics, and certain aspects of immune function, and lower the risk of certain types of carcinogen-induced cancer. This association, discovered by Dr. Michael Pariza at the University of Wisconsin, has been extensively researched and

evaluated by other investigators, including Dr. Martha Belury at Purdue University.

Another review paper, which appeared in *Current Opinions and Clinical Nutrition Metabolism Care* in 1999,[17] discusses the role of CLA therapeutics in metabolic obesity, insulin resistance, and chemoprevention. Watch for further news of this new nutritional ingredient. When this fatty acid, as a mixture of CLA isomers, is given therapeutically at doses in the range of 5 to 6 grams per day, it may have some profound influence on type 2 diabetes and insulin resistance syndrome X, hyperinsulinemia.

Steroids, which are a type of complex lipid, also affect performance. Considerable discussion concerns the estrogen/progesterone/testosterone/cortisol connection, but particularly estrogen, progesterone, and testosterone. We will be speaking about this in greater detail this year in *FMU*.

A recent paper in the *Journal of Lipid Research* describes an animal study looking at the effect of. 17b -estradiol.[18] It found 17b -estradiol acted separately on LDL particles and reduced the accumulation of LDL in artery walls and atherogenesis by preventing the stickiness of white cells to the arterial wall. The experiment suggested that estradiol decreased endothelial layer permeability, and incorporation of estradiol into the LDL particle prevented binding of LDL to the artery wall. Certain steroid hormones in the estrogen family may have some profound relationship to cell signaling. Metabolites of estrogen in particular play very different roles in influencing function.

Effects of Estrogen Metabolites

Conjugation and ultimate excretion of estrone, estradiol (where estradiol is hydroxylated), and the subsequent steps to estriol become important parts of the molecular communication system. They can give rise to normal, optimal, or suboptimal function and increased risk of conditions such as cardiovascular disease and even estrogen receptor-positive induction of breast cancer.

Individuals have used soy isoflavones to try to modulate hormones in women. Phytoestrogens like genistein and daidzein in soy have been considered natural alternatives to estrogen replacement therapy. The authors of a commentary in a recent issue of the Lancet believe the genistein/daidzein connection should not be considered an alternative to the estrogen molecules.19 They have a different mode of action and a different effect on receptor sites, and do not have the same influence biochemically or physiologically. One should not jump to the conclusion that the modest change in flushing that occurs by increasing soy in the diet of a menopausal woman indicates she is getting the same effects on biochemical function as the natural hormones that a woman produces. These areas require further investigation and understanding.

INTERVIEW TRANSCRIPT

Clinician of the Month
May 2000

Jeffrey Spencer, MA, DC
2160 NW Vine Street
Grants Pass, OR 97526
541-474-6310

JB: This month, once again, we have a COM with a high level of expertise. Jeff Spencer, whom I have admired for many years, both professionally and personally, has many talents. He is a successful athlete in his own right, and is now a doctor of chiropractic with a postgraduate background in sports medicine and sports nutrition. Jeff is a leader in the field of integrated, structural, and nutritional medicine in the sports arena. He has worked with many leading athletes. I will have him tell you about them during the interview. Jeff, it is a pleasure to welcome you to Functional Medicine Update.

JS: Thank you, Jeff.

JB: How did you become an expert in sports medicine and sports nutrition?

JS: My background is in athletics. I was an Olympic cyclist in 1972, so I had my first introduction to what the body is all about during my practical experience as an athlete. One thing I found was that when I did get injured, the best thing I could do was to get back on my bike and get moving as quickly as possible. I didn't really know about the biochemistry of the body at that time. It was evident to me, however, that movement and function were the name of the game in minimizing down time from injury, as well as serving as a barometer for how my fitness was progressing.

Once I discontinued my competitive career, I enrolled as a graduate student at the University of Southern California to study sports science. The combination of academia and practical experience taught me that the lessons and the treatments athletes were getting were severely insufficient. The attitude was always "Let's-deal-with-it-once-it's-broke." The focus was not on defining parameters, developing strategies for optimizing performance, minimizing down time, and extending careers. Having been out of a formal learning setting for a while, I went back to chiropractic school because of my quest for a comprehensive approach to the management of athletes' health that would truly serve their needs. Because of my background in art, I loved working with my hands, so it was a natural for me to choose chiropractic. I used that springboard to create a system that met the comprehensive needs of the athlete, not only from a preparatory perspective, but also from a maintenance and management perspective.

JB: You have used the athlete as a metaphor for the spectrum of personalized, preventive care. Many people see the athlete as someone who has a small window of opportunity to make a name using his or her skills. Then the individual athlete burns out and we never hear of him or her again. The concept of extending productive performance life and allowing the athlete to continue at high levels of peak performance for a sustained period might be extrapolated to all of us who are not elite athletes. We are all trying to extend our health and vitality for decades of living. It seems as if you have used the athlete as a metaphor for generalized preventive, personalized health care.

JS: I would say that's true. The athletic environment is explosive and volatile. Time condensation gives fertile ground for putting in leading-edge technologies. The reality is that technologies used for the athlete are no different from what would be used for the average person. Clinicians who look at athletes and average patients as separate entities make a fatal mistake in discounting the capacity of average people for maintaining their health throughout their lifetime.

JB: How do you integrate the structural aspects of performance with the biomechanical, biochemical, and nutritional aspects? That is a unique feature of what you do with your athletes.

JS: That is the name of the game. When we look at the concept of optimal function, the benefits are certainly immediate performance enhancements. But there is also the reduced risk of injury and minimal down time if a person does get injured, as well as extended longevity of career. When we look at the body, both from the biomechanical and the biochemical aspects, then we are treating the comprehensive needs of the person, in this case, the athlete.

Traditionally, with athletes I get some very important historical background in terms of where they've been. That tells me where the gaps in the action have been. Where they fall down most frequently is in having previous injuries that have not healed correctly. Even when the pain goes away, the body is still not functioning the way it's designed to.

I have a series of functional biomechanical protocols that tell me exactly where the breakdown in the kinetic chain is happening. When I can determine the weak link in the system we can develop strategies for dealing with it. It is very much like the biochemical functional medicine model you have so appropriately researched over the last 20 years. We don't look at a person's pain as the nature of the problem. We look at pain as the body's cry that something is wrong and needs to be fixed. It doesn't tell us what it is or what to do about it. That demands a different type of look.

The functional biomechanical exam I do on patients comes from a couple of neurologists in Czechoslovakia who have devised this system over the last 50 years. It's a brilliant, energy- and time-efficient way of observing how the biomechanical system is working. In evaluating the biochemistry, through extensive history and diet analysis, it gives us information about what testing we need to do to look at the parameters that may be affecting the whole biochemical propulsion and body growth and repair systems. It's a combination of two approaches based on a biomechanical functional exam and doing the homework as far as the biochemical side goes.

I think that someone who looks at the body in terms of structure may be looking at irrelevant details. There is very little correlation between structure and function. Nachemson, the great Swedish researcher, said you can demonstrate, on imaging, a reason for a person's complaint only 85 percent of the time. Carel Lewit, the brilliant Czechoslovakian neurologist, said the doctor who only looks at pain is lost. Those are revealing statements in terms of how we need to look at the patient.

We not only need to look at the hardware—the muscles, bones, ligaments, and tendons—but also at the software package—the brain and peripheral nervous system and how it controls movement. If we don't do that, then we're not looking at the body in terms of its dynamics. We're only taking a snapshot of it in one instant of time, and that doesn't represent how the body is doing its job of life and function.

JB: After you complete this biomechanical analysis, do you develop a personalized strength and conditioning program as part of a therapeutic approach for your patients?

JS: We consider individual needs and create a personalized program. It generally involves several different areas. We need to make sure the articulation of the joints in the body is working correctly. If the accessory joint motions are not restored, the voluntary muscles that act on the joints cannot do their job correctly. So we assess and treat those factors. That is an in-office procedure.

We look at tight muscles, because tight muscles always inhibit their antagonists. When we have muscle

inhibition, there is always muscle substitution. All of a sudden, you have neuromuscular chaos that leads to energy-inefficient movement and strain on the body. So we develop a personalized stretching program for the patient. Then we develop strengthening protocols for those muscles that have been inhibited and the body has taken out of the movement equation, to reacquaint them with what they're supposed to do.

Once we've done that, we do some coordination exercises that reestablish proprioceptor pathways between the brain and the muscles to develop energy-efficient movement. It's a patient-based, active approach to care. It's not passive in any way. If you create the right environment, the body will upgrade to the level of function demanded of it. It's really a simple equation.

JB: That's a beautiful concept. As an artist you are gifted in terms of the way you see things, translate them into kinetics, and manipulate with your hands. I've seen some of your work. You have a talent most of us don't have. Can you teach this technique to others who may not possess the same gift you have?

JS: Absolutely. One of my greatest assets is my ability to communicate to people in a clinically friendly way. I teach them to look at a patient's neuromusculoskeletal system and develop strategies for resolving liabilities. Being a practicing clinician and not strictly an academician, I look at what I do and what I share through the eyes of the practicing clinicians. I've been doing this for about eight years.

I have taught seminars throughout the country to doctors who are interested in looking at clinically relevant and clinically friendly ways of implementing these procedures for their patients.

JB: Let's move from the biomechanical to the biochemical approach. Some people may not be familiar with chiropractic as a full-service discipline in health promotion, disease prevention, and therapeutics. They may not understand how a chiropractor would look at biochemistry. Would you explain how that becomes part of your overall program and assessment?

JS: The biomechanics are the nuts and bolts of how things get down, but if you don't have the biochemistry to provide for body growth and repair and energy production, then the whole mechanical system suffers accordingly. In my view, it's extremely important to look at the patient comprehensively if we are to create a system that leads to long-term health, productivity, and function. For me, it's essential to have some procedures in motion that allow us to screen for certain things that would affect the biochemistry.

A patient's overall health determines the rate at which he or she can improve musculoskeletal function. I look at areas that place physical demands on a person. If they are excessive, I look at the oxidative stress profile. Allergies are important in the biochemical assessment of athletes and the general population. Allergies, food- or airborne, are one of the quickest ways to consume a person's energy needlessly. Many people are also deficient in areas of essential fatty acids. A thorough weekly dietary summary gives clues about macro- and micronutrient balance and the role of EFAs in the biochemistry of the individual. Through the patient history we look at toxic load in terms of the environment, what the sport demands, and the individual's training systems, and choose our treatment accordingly.

JB: When talk to athletes about this integrative approach, do you find they understand intuitively, or do you have to spend quite a bit of time getting them to see this integration from their own perspective?

JS: People who excel at what they do usually do so because they are very intelligent. They get the connections. One of the beauties of working with athletes is that they are in touch with their bodies and they do understand performance, so it is very accessible. In today's athletic environment, a paradigm shift is happening that's actually being propelled by athletes, not so much by their administrative or medical staff. We look for ways to enhance performance, and in the medical control issues we're dealing with in sports today, this area is fertile ground for further exploration.

JB: In many professional sports there are some athletes who never miss a game or who compete at high levels for many years. When you look at their lifestyles, you see they sometimes march to a different drummer than most of their colleagues. Has anyone studied these athletes with extraordinarily healthy records who maintain high-level performance for many years compared to those who burn out quickly?

JS: Traditionally, that is overlooked in the health management systems of most professional teams. Professional teams spend millions of dollars on salaries but have no system in place to protect their investment by looking at the well-known factors that prematurely terminate careers. I believe this is where preparation needs to begin. I see some suggestions of that happening in the athletic community.

JB: In many professional sports there are some athletes who never miss a game or who compete at high levels for many years. When you look at their lifestyles, you see they sometimes march to a different drummer than most of their colleagues. Has anyone studied these athletes with extraordinarily healthy records who maintain high-level performance for many years compared to those who burn out quickly?

JS: Traditionally, that is overlooked in the health management systems of most professional teams. Professional teams spend millions of dollars on salaries but have no system in place to protect their investment by looking at the well-known factors that prematurely terminate careers. I believe this is where preparation needs to begin. I see some suggestions of that happening in the athletic community.

B: Could you describe some case histories of athletes with whom you have worked?

JS: A recent example with which many people are familiar was the 1999 Tour de France. I am Lance Armstrong's chiropractor. Lance's win last year is the greatest comeback in the history of sport. He fought his way back from testicular cancer that had metastasized to his lungs and his brain. He had undergone brain surgery and very aggressive chemotherapy, as well as other surgery. The demands of the Tour de France are excessive, to say the least. It is 21 days of racing on a bike in any type of climate conditions, at least 5 to 7 hours every day. We have to deal with sickness, overuse injury, and oxidative stress.

One interesting example on last year's tour happened to one of Lance's teammates. We do blood work every day on the team. We could see his hematocrit was dropping, so we knew he was on his way to getting sick even though he didn't have any symptomatology at that time. We could see him starting to get puffy, so there was a shift in intracellular/extracellular fluid, which is a key that things are happening. This person does have a history of asthma and allergy. In the off-season we did some comprehensive testing, an allergy profile, and we developed strategies in terms of antiinflammatory procedures using EPA/DHA and vitamin C, as well as some dietary changes, which really turned his whole off-season program completely around. That's one example.

During the tour, we used antioxidants to minimize oxidative stress on the body. The director of the team last year said he'd never seen anything like it. Generally, when athletes start to develop overuse strain injuries and their bodies start to fade in the tour, they slide off into oblivion. What actually happened last year is that the team came back stronger than ever. The director acknowledged to me that the nutritional protocols we had put in place through supplementation, in addition to the physical medicine things that I brought to the team, were essential and responsible for that phenomenon. It was very gratifying for me.

JB: Are there some general things you learned in your experience with Lance Armstrong that might be useful to other clinicians?

JS: I would say it's exactly the same for the Tour de France cyclists as it is for the average person. When you look at the things that are going to sabotage body chemistry and biomechanics, it's all the same. You need to look at past history. You need to look at things that were not addressed in a functional way during development or in dealing with previous injury. You need to develop strategies for supporting functional reserve and making up for functional deficits. The things I always do are based on the history.

When I feel clinical and testing protocols need to be done, I use Great Smokies Diagnostic Labs. For me, oxidative stress profile, essential fatty acids and amino acids profiles, comprehensive digestive stool analysis, and allergy profiles are extremely important for athletes and others I work with. That is generally one of the first lines of hidden breakdown in the body. Based on history, that would serve as our road map for making choices on the biomechanical side of things.

When we do a functional exam on a patient we realize that where a person hurts is generally not the problem. (That's usually where too much stress is going on because other things aren't working.) Then we do a series of functional tests that allow us to determine what key link is breaking down in the locomotor system. We support the person nutritionally from a foundational perspective (good macronutrient and micronutrient balancing and diet analysis), and deal with the individualized needs of the patient in terms of a dietary review and the results that come back from the testing protocols. It's a winner for everybody.

As far as I'm concerned, if we look at the concept of athletic careers or at people's lives, it's all a matter of looking through the lens of what's happening now as a preview of what is to come. If you wait for things to show up before deciding something is wrong, you have really missed the boat. It becomes a lot more difficult. In today's healthcare climate, 290,000,000 Americans all need some level of health care along the lines of function. There are enough patients to go around. It's our job, as clinicians, to create a system that brings a level of awareness to patients that the lives they lead can be greatly enhanced by taking an active role in their decision-making. The technology is there.

JB: Every day in the real world you see the concepts of biochemical individuality and genomic uniqueness. As you assess athletes in terms of performance and function, do you ever observe a competitor in one sport whose uniqueness might be better suited to a different sport? Do you ever have to tell them their repetitive injuries are the result of their doing something their bodies are not designed to do?

JS: I think a person's practical experience will dictate where he or she belongs, and the athlete usually gravitates toward that. The biggest problem, from the perspective of the athlete, administrator, trainer, or

medical staff, is that we look at what the body's doing, but we don't understand why it's happening.

When I was at the Olympic Training Center in Colorado Springs, for example, they were looking at a cyclist's pedal stroke and saw that his heel was not moving correctly. If he only dropped his heel, he would get more power out of his stroke. The recommendation was to drop his heel. To me, that was absurd. No one ever asked why that was happening. Technology has caused us to look at problems of performance and function in life through how we feel and what we do, not through what is causing us to behave the way we are and what our potential is. I think this view has to change if we're going to prolong a person's longevity in terms of their capacity for embracing life.

For me, the important criterion is that we are dealing with people's destinies and people's futures. We're not just dealing with sports performance. The greatest gift we can give is the knowledge and opportunity to have a long, productive life that extends beyond one's athletic career. The only way we can do that is to look at the reality of the biochemistry and biomechanics from the perspective of what is creating the three-dimensional reality we see. We've got to look behind the scenes. The technology is there, and everything you've done has contributed to the pioneering effort. We owe you a great debt of gratitude for that.

JB: We are both part of a team of evolving understanding. Chiropractic, like all fields of health care, is undergoing a transformation. Managed care has forced change. What do you see in terms of chiropractic as a profession in the future?

JS: I believe that right now we have the greatest opportunity in health care history for any practicing clinician, regardless of discipline. We have a population that is not responding and no longer willing to embrace traditional health care, whether it be chiropractic or traditional medicine, or any of the other disciplines. They're looking for reasonable alternatives that can be rationally explained, and they're willing to pay cash for it. Most people have already spent thousands of dollars spinning their wheels and going nowhere.

I feel this is a patient-driven process that has created an opportunity for us to create the practice we've always wanted to have. Patients know why they're coming to see us. They're willing to take an active role in their care. They're looking to us for reasonable and rational guidance. That leads to a level of credibility and accountability demanded of the professional, that I think is long overdue. It also allows the doctor and the patient to have a cooperative relationship. Through the doctor's guidance and the patient's participation and willingness to pay cash for service, they both embrace this thing called life and can have a lifetime relationship in a professional way that leads to the best of all worlds for both. There has never been a better time, Jeff.

JB: That's a beautiful way to close this discussion. Where can people follow up on what you're doing and some of the thoughts you have shared?

JS: They can contact me through my office at (541) 474-6310. I will be at that number for at least a couple of more months. I will be relocating after that time. When that new phone number becomes available, you'll be the first to get it.

JB: Thank you for spending time with us. It gives us an optimistic view of the horizon of health care.

Thanks for sharing your insight and clinical experience.

JS: You're welcome. The future has never been brighter. A great deal of credit goes to you for helping me solve the biochemical puzzle. That was the missing link. I look forward to the growth of our relationship in the future.

When we look at soy as an agent that manipulates performance and function, we should not consider it a substitute for natural estrogens produced by a woman or man. (Males, as well as females, produce essential amounts of estrogen). Instead, we should look at soy as a complex mixture of fibers, neutral plant sterols, isoflavones, and protein with a unique balance of amino acids. We know from James Anderson's paper published in the *New England Journal of Medicine* a few years ago (a meta-analysis of soy's role on cardiovascular disease), that a significant statistical correlation exists between increased soy in the diet and reduced incidence of cardiovascular disease. [20]

This association is further amplified in a review paper in the *Journal of Nutrition,* titled "Soy Protein, Isoflavones and Cardiovascular Disease Risk."[21] According to the authors of this paper, there is no better drug than soy for helping to reduce cardiovascular disease. It lowers the synthesis of cholesterol. It reduces the enterohepatic recirculation of cholesterol. It blocks the rate-limiting step HMG CoA reductase step as it relates to *de novo* cholesterol biosynthesis. It increases the conversion of cholesterol by 7 *alpha* cholesterol hydroxylase into bile salts, which is the major way the body gets rid of cholesterol. Soy and its constituents have a positive influence on the control of hypercholesterolemia and LDL elevations, a risk factor for heart disease.

Cardiovascular Disease—Advancements toward Health
Cardiology has become a more preventive medicine-focused discipline with the development of the statin drugs and the fibrates, drugs that influence cholesterol, cholesterol dynamics, and perhaps even inflammation associated with heart disease. A recent editorial in the Journal of the American Medical Association by Claude Lenfant, MD, a well-known cardiovascular investigator, asks how we can conquer cardiovascular disease. Is it more than just cholesterol management?22

In another paper in JAMA, titled "Preventing Coronary Artery Disease by Lowering Cholesterol Levels—Fifty Years From Bench to Bedside,"23 the authors explain the very strong encouragement for lowering elevated cholesterol because of the profound statistical reduction in risk for cardiovascular disease. However, many individuals with low cholesterol and LDL experience cardiovascular events by extended risk factors we are only now discovering.

Some of those extended risk factors include insulin resistance and hyperinsulinemia syndrome. This syndrome causes alterations in arterial dynamics; platelet adhesion and stickiness of white cells. Those factors are associated with alterations in intracellular adhesion molecules and vascular-associated adhesion molecules; stickiness of macrophages and later conversion to foam cells; LDL oxidation. We associate all of these things with the atherogenic process that may not be directly related to cholesterol, but that is related to inflammatory mediators and the promotion as a consequence of hyperinsulinemia. Thus insulin resistance appears to be a major cholesterol-independent risk factor to heart disease.

Modulation of the insulin resistance syndrome can occur in a number of ways. We have been doing research in our Functional Medicine Research Center on this issue for the past six years and have

improved our understanding of the modulation of this problem.

One simple therapy that should be introduced as a principal contributor to peak performance is exercise. We can apply it directly to the hyperinsulinemia syndrome. Exercise improves insulin sensitivity and glucose removal and transport. How much exercise is beneficial? That has always been the question.

A study published in *JAMA* discusses walking compared with vigorous physical exercise to normalize insulin and glucose levels in women.[24] The data suggest one can get substantial reduction in the risk of type 2 diabetes by moderate intensity exercise such as a regular walking program. I encourage every individual to find something to raise his or her aerobic potential into the training zone. Even if individuals cannot walk, isometric exercise can accomplish a lot. Strenuous exercise is not required in order to improve functions associated with glucose removal, glucose transport, and insulin sensitivity.

Hyperhomocysteinemia is another important extended risk factor for cardiovascular disease. It is related to a necessity for increased levels of vitamin B12, B6, and folate in individuals with a metabolic defect as a consequence of a gene polymorphism mutation at the gene called 5-10-methylene-tetrahydrofolate reductase. This enzyme is a common polymorphic mutation in humans. That block may require either very high doses of folate and B12 to push through the block, or one might use a downstream derivative of folic acid called 5-methyl-tetrahydrofolate, which avoids that genetic mutation and can stimulate the downstream metabolic processes related to the clearance and metabolism of homocysteine.

This situation is the topic of an article in the *American Journal of Clinical Nutrition*, which discussed serum concentrations of vitamin B12 and homocysteine, and their interrelationship to methylmalonic acid in an elderly population.[25] Elevations in methylmalonic acid are functional indicators of B12 and folate insufficiency. Even if a person seems to be getting adequate levels of these nutrients in their diet, elevations of methylmalonic acid indicate they are not getting adequate functional levels at the cell. Therefore, they need to increase or improve their folate, B12, and B6 status.

Another extended risk factor for heart disease is oxidation. It is connected to mitochondrial uncoupling and free radical oxidative shifts in redox potential within cells. The term "oxidant" is often loosely used. Reactive oxygen species and oxidative stress are terms we use generally, although they may have very specific definitions in the field of cell physiology. Oxidized low-density lipoprotein (LDL) cholesterol has a variety of components not present in native LDL. Data from *in vitro* cell culture systems, animal models, and even some retrospective human studies indicate oxidized LDL can participate in what might be called atherogenesis, or proatherogenic properties. It appears that numerous factors can contribute to oxidative shifts associated with atherogenesis.

The question of whether or not antioxidants be used to prevent that oxidative shift has been under great scrutiny and has generated a lot of research interest.[26] Therapy with a complex array of antioxidants may help balance these redox potentials within cells. Single antioxidants given at high doses may not be effective.

We can mark some of these oxidative shifts using various kinds of biochemical markers. The level of 8-hydroxydeoxyguanosine, or 8-OHDG, has recently received a lot of attention. 8-OHDG is an oxidative marker for damaged DNA that occurs in cells as a consequence of oxidative stress. A number of papers have discussed levels of 8-OHDG as a marker of DNA damage. One, which appeared in *Free Radical*

Biology & Medicine, indicates this is a fairly good indicator of damage that has occurred within the cell to the genetic material, as a consequence of oxidative shifts.[27] You might wonder, using this marker, if you can show it is altered when you put a person on a complex antioxidant diet.

A paper in *Carcinogenesis* describes a study to test the hypothesis that increased consumption of vegetables and fruits rich in complex antioxidants and polyphenolic substances could reduce the markers of oxidative stress assessed in either blood or urine.[28]In this study, 28 women participated in a 14-day dietary intervention. Researchers used 8-OHDG as the marker for DNA damage due to oxidative stress before, during, and after the dietary intervention. Subjects were free living and consumed a completely defined recipe-based diet that increased the average daily consumption of vegetables and fruits from 5.8 servings at baseline to 12 servings throughout the intervention.

Overall, the fruit and vegetable intervention reduced the level of 8-OHDG in the DNA isolated from the white blood cell lymphocytes and the level found in the urine. The malondealdyhyde (MDA) levels, which provide a measurement of lipid peroxides, were not altered, indicating that 8-OHDG may be a more sensitive indicator of oxidative damage than lipid peroxides. Curiously, analysis of 8-isoprostane F-2a , another marker of lipid oxidation, improved significantly.

Results of this study indicate that the consumption of fruits and vegetables, including lots of antioxidants in complex redox form, has a significant influence in reducing the markers of oxidative stress to DNA and, ultimately, to lipids. Therefore, the investigators say it is important to get a diverse number of botanical families containing these antioxidants. This complex matrix of redox-active substances plays a role that is different from that of single antioxidants given one at a time or even two or three at a time. I think the field is moving to recognize that single antioxidants in a pharmacological model are not nearly the same as complex antioxidants found in a food-based system that have been concentrated and delivered in their redox-active form.

How does that relate to the studies of the Shute brothers, which led us to believe there was a positive connection between vitamin E and heart disease? We cannot and should not conclude that single antioxidants have no value and vitamin E should never be given by itself. However, we are beginning to understand that antioxidants work best as a team to diffuse high-energy oxidants and uncouple them before they can create oxidative damage, to turn them into molecules with low oxidative potential, through a kind of step-wise form of redox chemistry.

An interesting paper that appeared in the *Journal of Nutrition* was titled "Vitamin E and Atherosclerosis."[29] It was one of the first papers in the true science literature (from the American Institute of Nutrition—some of the high-level nutrition research literature), that cited the discoveries made by the Shute brothers in London, Ontario. The author states:

> "Vitamin E was advocated as an effective treatment for heart disease by Dr. Evan Shute of London, Ontario more than 50 years ago. His pioneering claims, which were unacceptable to the medical community at large, have been confirmed by recent findings from epidemiologic studies and clinical trials."

The author of this review discusses vitamin E enrichment, the benefits of which have been proven. It retards LDL oxidation. It inhibits proliferation of smooth muscle cells, platelet adhesion and aggregation, and the expression and function of adhesion molecules such as ICAM and VCAM-1. It attenuates the synthesis of leukotrienes of proinflammatory mediators, which are the second-signal messengers. It potentiates the release of prostacyclin through upregulating the expression of cytosolic phospholipase A2 and cyclooxygenase, which help form the right balance of prostanoids of the antiinflammatory and proinflammatory families. We are developing an understanding of the biological mechanism for the action of vitamin E. I don't want to dismiss the importance of vitamin E and say it should never be taken as a single nutrient. I want to point out that it plays its role within the context of these other redox-active substances.

The Heart Outcomes Prevention Evaluation Study is described in a *New England Journal of Medicine* paper titled "Vitamin E Supplementation and Cardiovascular Events in High-Risk Patients."[30] In this study, patients at high risk for cardiovascular events were treated with vitamin E for a mean of 4.5 years. Vitamin E appeared to have no effect on cardiovascular outcomes.

One might wonder why 400 IU of vitamin E given daily, from natural sources, RRR tocopherol over 4.5 years, did not lead to any statistical improvement in secondary outcomes, including unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer. There were 772 of the of the 4761 patients assigned to vitamin E, and 739 of the 4780 assigned to placebo, in which outcome primary events were followed. Again, I emphasize one should not jump on a single nutrient bandwagon at the exclusion of looking at all the other variables.

Dr. William Pryor reviewed vitamin E and heart disease, basic science and clinical intervention trials, as senior editor of *Free Radical Biology & Medicine* journal.[31] The bibliography of this review contains 244 citations. According to Dr. Pryor, "…The scientific community must recognize that there never will be a time when the science is 'complete.' At some point, the weight of the scientific evidence must be judged adequate; although some may regard it as early to that judgement now, clearly we are very close. In view of the very low risk of reasonable supplementation with vitamin E, and the difficulty in obtaining more than about 30 IU/day from a balanced diet, some supplementation appears prudent now."

In looking at the complex nature of the evidence in the literature, I would not to try to dissuade anyone from using single antioxidant supplements such as vitamin E. I would look at it in the context of the whole.

A paper recently presented at the annual meeting of the American Cardiology Association describes vitamin C supplementation at 500 mg/day increasing arterial intimal thickening. It suggests vitamin C may be an atherogenic agent in some individuals, given at 500 mg/day. There are some very interesting questions about this study in terms of self-selection. It was not a randomized trial in the various aspects of the study protocol. Suffice it to say, however, that once again we are coming to recognize that complex mixtures of antioxidants at enhanced levels are more likely to give the right message to the genes to control things related to oxidative stress.

High doses of vitamin E have been used in treatment of disorders of the central nervous system in the aged. A recent paper in the A*merican Journal of Clinical Nutrition* described this work, which was done at Tufts University Medical School and the USDA Human Nutrition Center on Aging in Boston.[32] The

authors looked at experiences with very high doses of vitamin E—2000 IU daily. We have seen similar supplementation in the Stanley Fahn work on Parkinsonism.[33] Vatassery and colleagues conclude, "The safety and efficacy of supplemental vitamin E over periods of many years in the prevention of neurologic diseases has not been adequately explored." There are some presumptive conclusions that vitamin E has been of benefit in some individuals; for instance, those with Parkinsonism and it may even play a role in Alzheimer's disease.

Antioxidants are still on the frontier of further investigation. A paper in the *Lancet* last fall talked about the effect of antioxidants and the occurrence of pre-eclampsia in women at increased risk for that condition.[34] They used vitamin E and vitamin C supplements in this study—1000 mg/day of vitamin C, and 400 IU/day of vitamin E. They found supplementation with vitamins E and C was potentially beneficial in preventing pre-eclampsia in women at increased risk for this disease. The editorial that follows this study is titled "Is Oxidative Stress the Link in the Two-Stage Model of Pre-eclampsia?"[35] The authors describe how antioxidants could play a positive role in reducing the risk to eclampsia in these individuals.

Other antioxidants are also in the news. New indication of the antioxidant value of coenzyme Q10 is described in the *Journal of Nutritional & Environmental Medicine*.[36] Three case histories are described in which 120 mg/day of co-Q10 was prescribed for an individual with kidney disease; 180 mg/day for an individual with amyotrophic lateral sclerosis; and 120 mg/day for an individual with polymyositis. A clinical response was obtained with co-Q10 therapy alone in all three cases.

N-Acetyl-Cysteine Studies

Let us not forget N-acetyl-cysteine (NAC) as a precursor for glutathione and the regulation of glutathione intracellular levels. This is described in a case history in the Lancet,37 which demonstrated that a 10 percent solution of NAC in a water-in-oil emulsion applied topically lowered skin inflammation from ichthyosis.

Oral NAC has been used in the treatment of HIV-positive patients to improve immune function and lower oxidative stress. This is described in a paper published in Current Opinion in Clinical Nutrition and Metabolic Care.38

Much remains to be learned about antioxidants and their role in peak performance. In the future we will go beyond treatment of crisis disease to the area of peak performance, extension of health span, and functional improvement.

Join us in June in Functional Medicine Update for more information on these topics.

Bibliography

1. Looking back on the millennium in medicine. *N Engl J Med.* 2000;342(1):42-49.
2. Doll R. In memoriam. Ernst Wynder, 1923-1999. *Am J Public Health.*1999;89(12):1798-1799.
3. Rogers RS. Pharmaceuticals under pressure. *Chem Engineering News.*2000;78(3):21-22, 24, 26, 28, 31-32.
4. De Waal FB. The end of nature versus nurture. *Scientific American.* 1999;281(6):94-99.
5. Rose MR. Can human aging be postponed? *Scientific American.* 1999;281(6):106-111.

6. Burns A. Might olfactory dysfunction be a marker of early Alzheimer's disease?*Lancet.* 2000;355:84-85.
7. Lewis, J. The performance of a lifetime: a metaphor for the phenotype. *Perspectives Biol Med.* 1999;43(1):112-127.
8. Michikawa Y, Mazzucchelli F, Bresolin N, Scarlato G, Attardi G. Aging-dependent large accumulation of point mutations in the human mtDNA control region for replication. *Science.* 1999;286(5440):774-779.
9. Sessler AM, Ntambi JM. Polyunsaturated fatty acid regulation of gene expression. *J Nutr.* 1998;128:923-926.
10. Bartsch H, Nair J, Owen RW. Dietary polyunsaturated fatty acids and cancdrs of the breast and colorectum: emerging evidence for their role as risk modifiers. *Carcinogenesis.* 1999;20(12):2209-2218.
11. Makrides M, Neumann MA, Jeffrey B, Lien EL, Gibson RA. A randomized trial of different ratios of linoleic to α -linolenic acid in the diet of term infants: effects on visual function and growth. *Am J Clin Nutr.* 2000;71:120-129.
12. Stordy BJ. Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. *Am J Clin Nutr.* 2000;71(suppl):323S-326S.
13. Agostoni C, Riva E, Trojan S, Bellu R, Giovannini M. Docosahexaenoic acid status and develpmental quotient of healthy term infants. *Lancet.* 1995;346:638.
14. Burgess JR, Stevens L, Zhang W, Peck L. Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *Am J Clin Nutr.*2000;71(suppl):327S-330S.
15. Horrobin DF. Essential fatty acid metabolism and its modification in atopic eczema. *Am J Clin Nutr.* 2000;71(suppl):367S-372S.
16. Ziboh VA, Miller CC, Cho Y. Metabolism of polyunsaturated fatty acids by skin epidermal enzymes: generation of antiinflammatory and antiproliferative metabolites. *Am J Clin Nutr.* 2000;71(suppl):361S-366S.
17. Sebedio JL, Gnaedig S, Chardigny JM. Recent advances in conjugated linoleic acid research. *Curr Opin Clin Nutr Metab Care.* 1999;2(6):499-506.
18. Walsh BA, Mullick AE, Banka CE, Rutledge JC. 17β -Estradiol acts separately on the LDL particle and artery wall to reduce LDL accumulation. *J Lipid Res.* 2000;41:134-141.
19. Ginsburg J, Prelevic GM. Lack of significant hormonal effects and controlled trials of phyto-oestrogens. *Lancet.* 2000;355(9199):163-164.
20. Anderson J, Johnstone B, Cook-Newell M.. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med.* 1995;333(6):276-282.
21. Lichtenstein AH. Soy protein, isoflavones and cardiovascular disease risk. *J Nutr.*1998;128:1589-1592.
22. Lenfant C. Conquering cardiovascular disease. *JAMA.* 1999;282(21):2068-2070.
23. Steinberg D, Gotto AM. Preventing coronary artery disease by lowering cholesterol levels. Fifty years from bench to bedside. *JAMA.* 1999;282(21):2043-2050.
24. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women. *JAMA.* 1999;282(15):1433-1439.
25. Carmel R, Green R, Jacobsen DW, Rasmussen K, Florea M, Azen C. Serum cobalamin, homocysteine, and methylmalonic acid concentrations in a multiethnic elderly population: ethnic and sex differences in cobalamin and metabolite abnormalities. *Am J Clin Nutr.* 1999;70:904-910.
26. Parthasarathy S, Santanam N, Ramachadran S, Meilhac O. Oxidants and antioxidants in atherogenesis: an appraisal. *J Lipid Res.* 1999;40:2143-2157.

27. Lodovici M, Casalini C, Cariaggi R, Michelucci L, Dolara P. Levels of 8-hydroxydeoxyguanosine as a marker of DNA damage in human leukocytes. *Free Rad Biol Med.* 2000;28(1):13-17.
28. Thompson HJ, Heimendinger J, Haegele A, et al. Effect of increased vegetable and fruit consumption on markers of oxidative cellular damage. *Carcinogenesis.*1999;20(12):2261-2266.
29. Chan AC. Vitamin E and atherosclerosis. *J Nutr.* 1998;128:1593-1596.
30. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:154-160.
31. Pryor WA. Vitamin E and heart disease: basic science to clinical intervention trials.*Free Rad Biol Med.* 2000;28(1):141-164.
32. Vatassery GT, Bauer T, Dysken M. High doses of vitamin E in the treatment of disorders of the central nervous system in the aged. *Am J Clin Nutr.* 1999;70:793-801.
33. Fahn S. High-dose vitamin e and ascorbate in early Parkinson's disease. *Clin Nutr Rev.* 1993;13(3):216-217.
34. Chappell LC, Seed PT, Briley AL, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet.* 1999;354:810-816.
35. Roberts JM, Hubel CA. Is oxidative stress the link in the two-stage model of pre-eclampsia? *Lancet.* 1999;354:788-789.
36. Singh RB, singh MM. Effects of coenzyme Q10 in new indications with antioxidant vitamin deficiency. *J Nutr Environmental Med.* 1999;9:223-228.
37. Redondo P. topical N-acetylcysteine for lamellar ichthyosis. *Lancet.* 1999;354:1880.
38. Droge W, Breitkreutz R. N-acetyl-cysteine in the therapy of HIV-positive patients. *Curr Opin Clin Nutr Metab Care.* 1999;2:493-498.

p>