September 2000 Issue | Leo Galland, MD

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Welcome to *Functional Medicine Update* for September 2000. You will receive an announcement this month about the availability of the audio tapes from the Seventh International Symposium on Functional Medicine. I want to alert you to the fact of their availability, however, since this month's Clinician of the Month is Dr. Leo Galland, winner of the Linus Pauling Functional Medicine Award at this year's Symposium. Dr. Galland's clinical presentation at the meeting was a highlight of the Symposium.

This month we will focus on the application of functional medicine in clinical practice, addressing "how to" questions that frequently come up in the practice of a busy clinician. First is nutritional therapies and whether we get what we are paying for. Are the diet or supplements we are providing to patients being utilized successfully?

The answer to that question depends on bioavailability. It is no longer enough to provide supplements just to prevent deficiency symptoms. Concern over vitamin-deficiency diseases of beri beri, scurvy, pellagra, xerophthalmia, and rickets has been replaced by questions of appropriate levels of nutrition to promote optimal health. "In this context," according to Dr. Maret G. Traber in a recent editorial titled "The Bioavailability Bugaboo" in the *American Journal of Clinical Nutrition*, "the term 'chronic disease' is invoked frequently." Epidemiological and clinical data are touted to show that diets high in fruit and vegetables are beneficial for reducing the risk of heart disease and cancer.

When single dietary components are tested in intervention trials using a pharmacological model, the results can be extraordinarily promising. They can also be adverse or neutral. Last year in *FMU*, for example, we described the 77 percent decrease in heart attacks in patients with coronary disease given vitamin E supplements. We also discussed the confounding 18 percent increase in lung cancer in smokers given beta carotene supplements in the Finnish Smokers' Trial. Results of other tests measuring the effectiveness of single nutrients in disease treatment were ambiguous and statistically inconclusive.

Measuring Vitamin C and Physiological Function

Reversal of deficiency symptoms was traditionally used to assess nutrient requirements. We have become much more skilled in biochemistry and molecular biology and its interrelationship with physiology. Therefore, the precise physiological roles of nutrients are now the standard for setting requirements for optimal nutrition. We can quantify the relationship between a certain nutrient or group of nutrients and certain physiological functions or endpoints for evaluation. We have moved away from measuring gross morphological signs of deficiency, to look at early warning signs and physiological function.

In his vitamin C physiological studies, for example, Dr. Mark Levine looked at *in situ* kinetics of vitamin C in ambulatory young male patients in metabolic wards. He found that the level of vitamin C needed for metabolic function was much greater than the Recommended Dietary Allowances. That conclusion led to the recent debate about new higher RDA or RDI level for vitamin C based on *in situ* performance kinetics, a biochemical marker.

Measuring Bioavailability of Fat-Soluble Nutrients

When one consumes a nutrient in a complex mixture in food, a multiple mixture in a nutritional supplement, or as a single-nutrient supplement, we cannot assume that nutrient will reach its point of action and will promote the desired physiological function. We need to determine bioavailability, which is defined as the plasma concentration of a water-soluble drug given orally compared with the concentration of the drug if given intravenously (IV). It is a comparison between equal amounts of IV and oral administration. The transfer of this concept from pharmacology to nutrition has been reasonably successful for most water-soluble nutrients, particularly vitamin C, for which extensive work has been done. It is less successful for the fat-soluble nutrients, including vitamins A, D, and E, and for essential fatty acids, vitamin K, and carotenoids. It is not possible to administer fat-soluble nutrients intravenously, so the partition coefficient is not easily determined.

Fat-soluble nutrients must be solubilized in micelles when they are digested, a process that depends on adequate bile and pancreatic secretions. Subsequently, the micelles transfer their contents to the intestinal cells, where these nutrients are packaged in chylomicrons and secreted into the lymph where the major absorption occurs, rather than into the hepatic circulation, and transported ultimately to the liver. Once the chylomicron remnant arrives at the liver, most fat-soluble nutrients then provide contrasting examples of nutrients to various transport proteins, and these results can vary, making this a much more complex process.

Comparing Vitamin A and E Transport Processes

In the example of vitamins A and E, significant differences exist in the way the transport proteins work. Vitamin A is bound to retinol-binding protein, which is secreted into the plasma where it acts as a plasma carrier protein for vitamin A. In contrast, vitamin E, or alpha-tocopherol, transfers in the liver to an alpha-tocopherol transfer protein. This activity occurs in the hepatocyte. Vitamin E is not secreted intact into the plasma. Rather, a subsequent transfer occurs from the transport protein of vitamin E in the liver to various lipoproteins. It is then transported in the plasma as a lipoprotein-bound vitamin E. Plasma correlation to the oral amount as a measure of bioavailability of fat-soluble nutrients, therefore, is a difficult and complex process.

Vitamin E bioavailability becomes difficult, for example, with genetic defect in the tocopherol transfer protein in the liver. People with this genetic polymorphism cannot transfer vitamin E effectively in the liver to the lipoprotein, so it doesn’t get into the plasma. This genetic defect leads to severe vitamin E deficiency at normal dietary intake levels of vitamin E, extremely low plasma and tissue vitamin E concentrations, and progressive peripheral neuropathy. This is one of the few examples where vitamin E tissue insufficiency has been associated with an overt pathology.

Overcoming Genetic Defect in Nutrient Bioavailability

One way to overcome this problem is to keep driving the mass action forward and overcoming the transport defect. When patients who have this tocopherol protein transport deficiency are given vitamin E orally in amounts 100 times the Recommended Dietary Allowance, they can maintain normal plasma and tissue vitamin E concentrations, and the neurological symptoms are reversed or halted.

Similarly, we can overcome the malabsorption of vitamin E by individuals with cystic fibrosis by using a more readily transportable form of the vitamin. The water-soluble polyethylene-glycomonosuccinate ester form of vitamin E seems to be better absorbed. It does not require the mycelization and uptake into the lymph and is more directly transported into the liver. A number of factors complicate the bioavailability of fat-soluble nutrients.

Dietary Fat and Absorption of Fat-Soluble Nutrients

Fat-soluble nutrients also require some fat for absorption. Fat tends to enjoy the company of fat. A recent paper in the *American Journal of Clinical Nutrition* is titled "Amount of Fat in the Diet Affects Bioavailability of Lutein Esters But Not of a -carotene, b -carotene and Vitamin E in Humans. The authors of this study, Roodenburg et al., attempted to determine how much fat is necessary to promote fat-soluble vitamin absorption. They studied the relative bioavailability of some carotenoids and vitamin E in humans and reported that the lutein esters, but not other fat-soluble nutrients, depend on a higher dietary fat content (36g compared with 3g) in a hot meal for increased relative bioavailability.

Study of bioavailability and nutrient interactions also needs to be extended beyond vitamin E and carotenoids to include flavonoids and other phytochemicals present in food. All of these factors interact to create different bioavailability partition coefficients. We are just beginning to understand this very complex topic. Despite the number of unanswered questions that remain about bioavailability, we can assume that bioavailability of specific nutrients is important in determining the amount of any given nutrient for optimal health. To establish optimal dietary levels, not just recommended dietary intakes, we must ask not only about the level of the nutrient, but also about absorption by the individual to promote physiological function, measured as one or a group of specific physiological endpoints. Because we have not yet answered all the bioavailability questions, we do not yet have optimal physiological doses of nutrients. It is a question of individualization. Dr. Galland will discuss the importance of individualization of therapy due to the wide diversity in genetic polymorphisms and how that impacts on nutrient uptake and utilization.

Osteoporosis and Vitamin K Intake

A current example of the problems presented by bioavailability is osteoporosis and vitamin K. Osteoporosis is a metabolic bone disease characterized by a defect in bone remodeling and the loss of normally mineralized bone. After age 40, the slow process of bone loss begins in both sexes and continues at a rate of about 0.5-1 percent per year until late in life. In women after menopause, the rate of bone loss accelerates to as much as 2 to 3 percent per year because of decreasing estrogen concentrations. Osteoporosis is responsible for about 1.2 million fractures in the United States annually and is considered a major cause of death in women because it contributes to fractures that ultimately lead to hospitalization and life-threatening post-fracture conditions.

Resistance to fracture depends on bone reserve. For most individuals, maintaining bone reserve above 1

g/cm^2 provides sufficient protection from the normal wear and tear of life to prevent bone fractures. If bone reserve falls below l g/cm^2, the individual is at increasing risk for fracture in the spontaneous movements of life. It is not the fall that causes an elderly woman to break her hip. It is the opposite. The elderly woman breaks her hip and falls down as a consequence of the twist, tension, and torsion on the bone.

Maintaining Bone Integrity

At peak bone density, individuals have between 1.4-1.6 g/cm^2. They are generally quite a bit above the threshold of bone fracture in their bone accretion maximum density years. As I mentioned, after the age of 40, there is a slow rate of loss or an accelerated loss in postmenopausal women that increases the risk for bone fracture.

Many nutrient factors are involved in maintaining bone integrity, both in osteogenesis or bone reformation, and in osteolysis or bone loss. Among these factors are total energy intake and the nutrients needed to promote synthesis of bone, including calcium, vitamin C, vitamin D, vitamin K, magnesium, boron, copper, manganese, and zinc. There are many genes required for bone synthesis and maintenance of integrity. Some are related to the metabolism of vitamin D. To be active as a hormone in stimulating calcium uptake and utilization in osteogenesis, vitamin D must be hydroxylated to 125-dihydroxy vitamin D. Vitamin D hormone receptors, estrogen receptors, transforming growth factor b , and interleukin-6 are also critical for normal bone metabolism. They show genetic polymorphism. Nutrients can have a range of different effects on individuals related to bone integrity, based on their genetic uniqueness.

Contributors to Osteoporosis

Sporadic factors that contribute to osteoporosis and increase the risk of bone loss include smoking, excess alcohol intake, physical inactivity, being overweight, possessing apolipoprotein e 4 genotype, and the use of certain medications such as anticonvulsant and anticoagulant drugs. Very high protein diets and excessive caffeine in the diet are also potential risk factors for increasing bone loss. Medical conditions that exacerbate bone loss include Cushing’s disease, hyperthyroidism, hyperparathyroidism, hypogonadism (because of ineffective steroid hormones related to anabolic effects on bone), and poor absorption of nutrients necessary for bone formation.

Vitamin K is another contributor to the relationship of genetic polymorphism and bone integrity. Vitamin K is required for the gamma-carboxylation of glutamate. It is very important with two proteins that are induced by vitamin D hormone in bone. One is osteocalcin, a 49-residue protein with 3 carboxyglutamic acid residues, which plays a very important role in adherence to bone mineral hydroxyapatite and secretion by the osteoblasts. In a 1989 paper Knapen et. al. found osteocalcin was under-carboxylated by 40 percent in postmenopausal women, compared with premenopausal women. The carboxylation of osteocalcin depends on vitamin K status. The postmenopausal women responded to phylloquinone supplementation with an increase in total and carboxylated osteocalcin and a decrease in urinary calcium and hydroxyproline, an indication of lowered bone loss in these postmenopausal women when they were supplemented with vitamin K.

Contributors to Hip Fractures

Szulc et. al. subsequently found the incidence of hip fractures in aged women correlated directly with the increase in under-carboxylated osteocalcin, and the bone mineral density correlated negatively with the rise in under-carboxylated osteocalcin.[7] In 1997 Shiraki et. al. found that postmenopausal women with an apo E4 phenotype had a lower bone mineral density than did those with the apo E2 or E3 phenotype. (The apo E4 genotype is also related to cardiovascular risk, the risk of dementia of Alzheimer's, and altered lipoprotein transport processes.) Some people call the double apo E4 the "death gene," because it is associated with a shortened life expectancy due to these effects related to biological aging. In addition, lowered vitamin K concentrations were found in patients with the apo E4 phenotype who had renal failure and were undergoing hemodialysis.

A recent paper in the *American Journal of Clinical Nutrition* follows up on this work. The paper, by Booth, Tucker, and Chen, is titled "Dietary Vitamin K Intakes Are Associated with Hip Fracture But Not with Bone Mineral Density in Elderly Men and Women." Mean bone mineral density in this study was 0.82 g/cm^2 in men and 0.62 g/cm^2 in women, both well below the 1 g/cm^2 density that represents the threshold to fractures. These are in the fracture range. Of the 44 hip fractures reported in this study, 8 occurred in men and 36 in women. This reminds us that osteoporosis is not solely a female problem. It can also relate to endocrine and metabolic dysfunctions in men.

Vitamin K and Retardation of Bone Loss

Absorption of nutrients, genetic polymorphism, and metabolic utilization of nutrients depends on a complex interaction, a symphony of different factors. We should not jump to simple conclusions about the cause-and-effect relationship between one nutrient and one outcome variable. Between the consumption of the nutrient and its ultimate effect on physiological function a number of factors participate in modifying the outcome of that function. Despite the limitations of the specific epidemiological studies related to vitamin K and osteoporosis specifically, they do support a very important role of vitamin K and the retardation of bone loss in elderly people. This is particularly true of postmenopausal women, who may be under-carboxylating glutamic acid in residues in osteocalcin and have altered bone metabolism and accretion.

Bioavailability is an important issue. Interaction of complex nutrients is also an important part of the story, and trying to determine optimal nutrition focused on the individual based upon his or her own genotype and not nutritional averages. As Roger Williams said, "Nutrition is for real people. Statistical humans are of little interest."

One area of genomic uniqueness about which we have spoken extensively in *FMU* is the detoxification profiles, specifically the polymorphisms as found in the phase I cytochrome P450 superfamily of monooxygenase detoxifying enzymes. A recent paper appeared recently in the *European Journal of Gastroenterology and Hepatology.* The article asks the question, "What should the clinician know about the cytochrome P450 system?" Ten years ago, a journal article would not ask this question. It was considered a question for clinical biochemists doing esoteric research. It never would have filtered into a paper for general practitioners in hepatology or gastroenterology.

Over the past five years we have increasingly recognized the genomic diversity of cytochromes P450. Their interaction with different drugs can give rise to untoward side effects as a consequence of cytochrome P450 2D6 polymorphisms, 1A2 polymorphisms, or CYP21 polymorphisms. These different

genetic types of detoxifiers may have vastly different effects in how they manage certain pharmacological agents and metabolize them by first-pass detoxification. According to the author of this paper:

> "The cytochromes P450 are a superfamily of enzymes which catalyze mono-oxidation, thus transforming fat-soluble toxins into water-soluble metabolites which are excreted in urine. Cytochromes P450 are mainly located in the liver; they play a major role in hepatotoxicity. The toxins (or the drugs) can be in part transformed into reactive metabolites (the so-called reactive intermediates) which destroy intrahepatocytic proteins (metabolite-related hepatotoxicity) or form an immune complex that induces immune reactions (immune-related hepatoxicity)."

Detoxification and Immune System Activation

The proper transport and handling of various substances to ensure their biotransformation, conjugation, and excretion can play an important role in lowering what the body might perceive as an antigenic burden due to these incorrectly metabolized substances. This misperception can then create immune reaction, immune complex formation, and liver injury. The relationship between the poor metabolism or detoxification of toxins and activation of the immune system may not be obvious to an individual who is unaware of the interrelationships among detoxification processes and antigenic production of these intermediary materials that are not completely detoxified.

Genetic polymorphism is a significant factor in the role of cytochrome P450s and their function in detoxifying chemicals in our internal and external environment. We may, for example, consume pharmacologically active agents that compete with metabolites from colonic bacteria that require the same enzyme systems for detoxification. Or we may have endogenously-produced steroid hormones that vie for detox enzymes in our liver which are responsible for the elimination/detoxification of exogenous toxins.

Genetic Polymorphism and "Atypical" Reactions

We now understand the role of genetic polymorphism in what were previously considered atypical reactions to drugs or the environment. Those reactions are not atypical at all. They are; in fact, typical and reproducible in that individual if we understand his or her unique genetic polymorphism. Understanding more, analyzing more, and evaluating more of these detox pathways, we now understand better how to promote a person’s healthy function to avoid immunologically active or oxidant-stress reactive materials as a consequence of incomplete detoxification.

Sickle Cell Anemia—50 Years of Progress toward a Nutritional Approach to Molecular Disease

Back in the 1950s both Roger Williams and Linus Pauling advanced the concept of molecular medicine and biochemical individuality. Dr. Pauling’s article, "Sickle Cell Anemia, a Molecular Disease," appeared in *Science* magazine in 1949 and is considered a landmark in this area. Some individuals carry the sickle cell gene for the single amino acid substitution in the beta globin heavy chain of the protein that ends up in the sickling process. We now understand we can modify this phenotype by administering agents that upregulate the expression of fetal hemoglobin. Clinical trials have found that both hydroxyurea and butyrate increase the production of fetal hemoglobin in individuals who carry the sickle

trait. Fetal hemoglobin, which is not sickled, dilutes out the sickled hemoglobin and prevents some of the packing problems of red cells that are found in the sickling crisis.

In his 1949 article Dr. Pauling also said the discovery of mechanisms of molecular disease would open up new vistas of opportunity for therapeutics. It has taken more than 50 years to get there. Another paper was just published in the same area. Some of the dysfunction that occurs as a consequence of the sickle crisis is the destruction of red cell membranes by oxidative stress. This oxidative damage to the red cell membrane produces cells that undergo a deformation, almost the echinocyte formation. One might wonder if it would be possible to modify the course of a sickle crisis through the administration of various kinds of oxido-reductive substances, so-called antioxidants. A paper in the *New York Academy of Science* in 1992, Dr. Charles Natta showed preliminary data indicating that antioxidant supplements seemed to reduce the severity and recurrence of crisis in individuals carrying the sickle characteristic in their genes.

Antioxidant Supplementation to Inhibit Formation of "Dense" Cells

A more detailed study of the same type recently appeared in the journal *Nutrition*. This research took place at the Philadelphia Biomedical Research Institute, Department of Biochemistry and Biophysics, University of Pennsylvania School of Medicine. A certain population of red blood cells in patients with sickle cell anemia has an elevated density and possesses an abnormal membrane as a consequence of oxidative damage.

These "dense cells" have a tendency to adhere to neutrophils, platelets, and vascular endothelial cells. Thus they are involved with the triggering of the vasocclusion and the subsequent painful crisis from which these patients suffer. By developing a laboratory method of preparing such dense cells, the researchers found that nutritional antioxidant supplements, given as a family to help quench hydroxyl radical formation and iron-binding agents, inhibits the formation of these dense cells *in vitro.*

Benefits of a Nutritional "Cocktail"

Similar effects are possible by administering nutritional supplements containing the same array of nutrients. Those nutrients include aged garlic extract, black tea extract with its catechins and polyphenols, green tea extract, pycnogenol, pine bark concentrate, vitamin E, coenzyme Q10 and, beta-carotene. This combination of nutrients produced an *in vitro* effect in lowering the damage to red cells to produce these dense cells. Both an *ex vivo* study and a pilot clinical trial demonstrated that a daily cocktail of 6 g of aged garlic extract, 4-6 g of vitamin C, and 800 to 1200 IU of vitamin E could help reduce the prevalence of sickle crisis and lower the dense cells circulating in patients’ plasma.

This preliminary study followed from an *in vitro* trial into an *ex vivo* study and then into a modest clinical pilot trial. It demonstrated, in individuals with sickle cell characteristic, that it is possible to modify the course of the dense cell formations associated with vascular adhesion by administering a complex mixture of antioxidants. This preliminary study represents only applied nutritional investigation looking at this modification of phenotype as a consequence of modifying the nutritional environment in individuals with unique genotypes. It represents utilizing nutrition at levels far different from that necessary to support individuals who do not have those specific genetic characteristics. This is the basis of what Dr. Pauling talked about as molecular medicine.

Bone integrity also plays a significant role in individuals who undergo orthopedic surgery. A paper on that topic, titled "Poor Bone Quality or Hip Structure as Risk Factors Affecting Survival of Total Hip Arthroplasty," appeared recently in the *Lancet.* Some individuals do not do well after hip replacement surgery. According to this paper, those individuals generally had poor bone quality to begin with.

Nutritional and/or lifestyle intervention to improve bone integrity *prior to surgery* may enhance the potential value of the surgery. The authors recommend assessing factors related to bone integrity and bone quality before surgery to ensure the durability of the replacement prosthesis and achieve the maximum success in surgery and employing biological initiatives to resolve problems related to poor bone integrity. Once again, functional/nutritional medicine can play a role in optimizing the outcome of a surgical procedure or perhaps even avoiding the need for some crisis interventions.

Diet is a powerful regulator of gene expression in many instances. Data published from this perspective leads to a whole different interpretation of the role of macro- and micronutrients and conditionally essential nutrients in phenotypic outcome. I recently reexamined the Dietary Approaches to Stop Hypertension (DASH) Study. The DASH Study, a dietary high blood pressure education program study, looked at how salt and such dietary nutrients as calcium, magnesium, and potassium influence blood pressure. On May 17, Dr. Claude Lenfant, director of the National Heart, Lung, and Blood Institute (NHLBI) declared the salt controversy was over. The results of the DASH-Sodium, the new follow-up of the DASH Study, found that although there salt restriction had some value, far and away the greater value in lowering blood pressure was a dietary intervention to improve potassium, calcium, and magnesium intake.

The results of this study strongly support the work of Dr. David McCarron at the Oregon Health Sciences University in Portland. For years he has talked about the importance of increasing calcium, magnesium, and potassium, not just focusing on sodium restriction to lower blood pressure. The control diet group reduced blood pressure in the DASH Study by 5.6 and 2.8 mmHg respectively, systolic/diastolic, which seems to be as effective as most first-generation antihypertensives. The suggestion is made that application of the DASH Study results may provide a blood pressure control remedy for nearly half of those suffering from essential hypertension. Long-term blood pressure management can be achieved when patients comply with a diet consistent with the DASH Study guidelines

Cardiovascular disease is an obvious outcome from elevated blood pressure and hypertension. Other extended risk factors for cardiovascular disease include inflammatory mediators, such as elevated levels of C-reactive protein (CRP) monitored with a high sensitivity screening method. If you are looking at CRP levels on a standard blood analysis to assess cardiovascular disease risk in your patients, you are probably looking at the wrong data on which to base a decision. Most laboratories still use low-sensitivity CRP as their standard CRP test. This measurement is not sufficiently sensitive to pick up early-stage markers for inflammatory connections to heart disease.

High-sensitivity CRP tests are now being developed. Four automated high-sensitivity CRP methods were recently compared in *Clinical Chemistry.* The authors of this paper point out that the four high-sensitivity CRP methods yielded different results for a healthy population. They recommend standardization to ensure high-sensitivity CRP results consistent with epidemiological studies showing that elevated CRP is associated with cardiovascular risk. A laboratory that provides data from high-sensitivity CRP should have good internal quality control and assurance data upon which to build clinical interpretation. Just

make sure your are getting high-sensitivity CRP measurements, and ask how the laboratory arrives at its normal ranges and values.

Inflammatory mediators associated with cardiovascular disease at the cell physiological level seem to be associated with increased levels of intercellular adhesion molecule 1, or ICAM-1, increased monocyte adhesion to the arterial endothelium, and transmigration of the white cell to the interior wall of the endothelium. The subsequent transformation leads to the oxidation of LDL and participates in the atherogenic process. Stickiness of white cells to arterial endothelium increases heart disease risk and is associated with increased inflammatory mediators.

Dr. Lester Packer and his colleagues at the University of California, Berkeley recently published a paper looking at pine bark extract pycnogenol and its influence on inducible intercellular adhesion molecule 1 expression. This study indicates pine bark pycnogenol downregulated interferon gamma-induced adhesion of T cells to human keratinocytes by inhibiting the production of the inducible form of ICAM. In other words, it downregulates the gene expression of ICAM-1. This is an example of the way a conditionally essential nutrient may influence gene expression and alter phenotype—in this case, adverse effects related to stickiness of white cells to endothelial surfaces.

This was an *in vitro* study, so we cannot immediately arrive at a clinical outcome conclusion. It does, however, seem to correlate with some observed effects noted clinically on individuals supplemented with pine bark pycnogenol. One such effect is related to peripheral vascular resistance and vascular circulatory problems in individuals with diabetes. Patients have experienced healing of aphthous ulcers with pycnogenol supplementation. Skin tone texture in extremities, particularly the feet in diabetics, improved significantly with pycnogenol supplementation, as did resistance to skin lesions. This *in vitro* study may help explain the physiological basis for these clinical observations. Although more work is needed, it indicates how pycnogenol may influence skin inflammatory process and aid in the healing process by reducing some vascular effects associated with inducible ICAM-1 expression.

Plasma homocysteine is another extended vascular risk factor. A number of recent papers indicate plasma homocysteine is a better marker than serum methylmalonic acid for early-stage, dementia-related problems and psychosocial performance difficulties in a geriatric population. One such paper appeared recently in *Clinical Chemistry*. If you are looking for B6, B12, and folate markers, methylmalonic acid may be secondary to plasma homocysteine.

Plasma homocysteine is also closely correlated with copper in patients with peripheral vascular disease. For years, Dr. Leslie Klevay at the USDA Grand Forks, North Dakota Research Station has talked about the copper connection to vascular disease. According to Dr. Klevay, hypercupremia is associated with heart disease risk. High copper also appears to be associated with high homocysteine, although a possible cause-and-effect relationship has not been fully determined. The findings in this study indicate that atherogenicity of homocysteine may be related to the copper-dependent interactions, and this may be another part of the story. There may be a relationship between high homocysteine and the release of copper from stores that induces oxidative stress. This study on homocysteine and elevated copper levels also appeared in *Clinical Chemistry.*

Individuals who consume a excessive amounts of distilled spirits and beer have increasing risk to vascular disease. A paper just published in the *Lancet* showed an inverse relationship between homocysteine levels

and vitamin B6 levels in individuals who consumed different kinds of alcoholic beverages. The higher the alcohol intake, the lower the B6 level and the higher the homocysteine level. That seems to suggest an interrelationship between vitamin depletion of certain nutrients necessary for metabolism of homocysteine, elevation of homocysteine, and the potential contribution of elevated homocysteine on atherogenic risk. Once again, one should look at patterns and interactions and not just jump to simple one-on-one conclusions. In this case, B6, B12, and folate may be interrelated with homocysteine as a consequence of alcohol consumption, which increases their metabolism and release from the body.

This is further confirmed in a review paper that appeared in *Nutrition.* The authors of this article, titled "Hyperhomocysteinemia in Chronic Alcoholism: Relation to Folic Acid and Vitamins B6 and B12 Status," show that increased heart disease risk in alcohol abusers may be associated with depletion of the B nutrients necessary for proper metabolism of homocysteine. The connection between alcohol and heart disease may be indirect through a hyperhomocysteinemia connection due to vitamin B depletion. If you want to determine vascular risk in a patient who consumes high levels of alcohol, you may look for elevated homocysteine levels as a marker for cardiovascular risk.

N-3 Fatty Acid Modulates the Progression of Arthritis

Other biological response-modifying nutrients that affect gene expression are the omega-3 fatty acids. In a paper published in 1985 in the *New England Journal of Medicine,* Elias Corey et al. from Harvard Graduate School, Department of Chemistry in the medical school, discussed the role of eicosapentaenoic acid (EPA) and its conversion to leukotrienes in monocytes and neutrophils. Activity of the 5-lipoxygenase enzyme was reduced, and numbers of these reactive intermediates declined in individuals supplemented with fish oils. The paper considered how that could influence potential inflammatory process. Patients were supplemented with daily doses of triglycerides containing 3.2 g of EPA acid and 2.2 g of docosahexaenoic acid (DHA). The outcome revealed increased range of motion, lowered pain and swelling, and lowered voluntary use of pain medication. We now recognize that omega-3 fatty acids may modulate the progression of certain forms of arthritis.

N-3 Fatty Acids and Arthritis

A more recent paper in the journal *Inform* is titled "N-3 Fatty Acids Modulate the Progression of Arthritis." Arthritis has always been a major chronic diseases in the United States. Approximately 15 percent of the population, or 40,000,000 people, have arthritis. The cost of treating this debilitating condition in those 65 years and older is estimated at about 65 billion dollars a year. The two most common forms of arthritis are osteoarthritis and rheumatoid arthritis. Both are associated with the release of inflammatory mediators from the leukotriene family and from other proinflammatory mediators that come through IL-1 and tumor necrosis factor alpha modulation and activation of the arachidonic acid cascade.

In previous issues of *FMU* we have discussed cyclooxygenase-1 and cyclooxygenase-2 and the new drugs that suppress cyclooxygenase-2 without influencing cyclooxygenase-1, and the relationship that has to changing the inflammatory process within the cell. We have talked less about modulating leukotrienes, some of which are proinflammatory mediators coming from arachidonic acid. In fact, this class of leukotrienes are about a thousand times more proinflammatory than histamine. We all know about antihistamines, but we don’t talk much about anti-leukotrienes. Omega-3 fatty acids behave as if they are

anti-leukotrienes. According to this article in *Inform*, they play an important role in providing beneficial outcome in patients with either osteo- or rheumatoid arthritis.

Benefits of EPA and DHA

EPA and DHA, the fish oil principles. have differential effects on serum lipids and lipoproteins. They can lower the levels of LDL cholesterol and triglycerides in certain individuals and influence insulin sensitivity. This appears to occur as a consequence of their modulation by the peroxisome-proliferated receptors alpha and gamma. The PPAR-γ family affects insulin sensitivity. The peroxisome is the organelle involved with the metabolism of very-long-chain fatty acids. The fish oils help sensitize and stabilize peroxisome metabolism and PPAR-γsensitivity. They are agonists of PPAR-γ . They play an effective role in management of triglycerides, cholesterol, and insulin, according to an article in the *American Journal of Clinical Nutrition*.

PPAR receptors and liver function are related in part to the dietary intake of various fats. Long-chain saturated fats are antagonists of PPAR-γ , and polyunsaturated omega-3 fatty acids are agonists that can help improve insulin sensitivity and lipid management. A number of papers describe this, including two in the *Journal of Lipid Research*, and another in *Carcinogenesis*. These papers all discuss the role of omega-3 fatty acids in lipid metabolism and insulin sensitivity and the difference between a PPAR-γ activator and a PPAR-α activator

INTERVIEW TRANSCRIPT

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Introduction

JB: This month we are fortunate to have as our Clinician of the Month the recipient of the sixth Linus Pauling Award in Functional Medicine, Dr. Leo Galland. Many of you know Dr. Galland personally and professionally from his contributions to functional medicine. He was our Clinician of the Month in November of 1993. Much has happened in the field of functional medicine in the years since Dr. Galland has appeared with us.

Leo Galland, MD, graduated from the New York University School of Medicine. He received his undergraduate degree at Harvard and served his internship at Bellevue Hospital in New York City and his residency at Bellevue, New York University Medical Center. He has been an instructor in clinical medicine at the Albert Einstein School of Medicine and an assistant professor in community medicine and family medicine at State University of New York, Stony Brook. He was also an assistant clinical professor of medicine at the University of Connecticut. He has been at the Gesell Institute and has been in private practice for many years. Dr. Galland is a founding member of the Institute for Functional

Medicine and a leader in nutritional medicine. He has published a great many articles and has written two best-selling books. The most recent, *The Four Pillars of Healing*, or *Power Healing*, is a scholarly book that raises the level of understanding of the field of integrative medicine. Dr. Leo Galland, thanks for being with us once again.

LG: It's always a pleasure to speak with you, Jeff.

Contributions on the Path to Perfectionism

JB: I have learned many things from you over the years. You taught me about parasitology in the Western World. We always thought parasites were a problem only in developing countries with poor sanitation and hygiene. You led us to understand parasitology and gut infection and recognize their clinical symptoms in developed countries of the world. You taught us about biological response agents like fatty acids. Years ago you collaborated with Dr. Don Rudin and David Horrobin to help us understand the precursors of fatty acids to the prostanoids. The relationship of gut permeability and gut ecology was brought into focus as a consequence of your education, writing, and clinical work. Cellular mediators and their activity at distant sites was an area you talked about early on. Immunonutrition was the focus of your first book, when you were dealing with pediatrics. You have done significant work with children's behavior. Those are only a few of the things we can attribute to Dr. Leo Galland.

How would you characterize the path you have taken from being an academic medical professional moving into this field of integrative medicine as a clinician?

LG: The way things started for me was through a kind of perfectionism. I didn't like the results I was getting in applying what I had been trained to do as an internist and through my residency. I started trying to figure out how I could be a more effective clinician. The first important lesson I learned was to try to understand the individuality of each patient. Of all of the principles that guide the field we are in, that's really the first—the recognition of the individuality of each patient, from a psychosocial perspective and, as Roger Williams taught us years ago, from a biological perspective.

That recognition requires two things we often don't speak about at our meetings. One is being present during the interview—giving the patient your attention and trying to understand who he or she is and what is going on with her/him. That has to happen independently of lab tests and medical diagnoses. Patients know when you're doing that, and they respond in a positive way to the process. That's a start, but it's not enough.

Illness and the Individual Patient

You have to acquire a database of information that you can apply to the recognition of the individuality of the person. In the late 1970s I started looking for scientifically based information that would help me understand each person as an individual. The task is a lot easier today. You have contributed to making it easier by pulling so much useful information together. Back around 1980, it was a wilderness out there. I probably spent as much time with my second medical education as I did with my first—going to meetings, reading books and journals, and trying to rethink the whole process of illness as it affects individuals.

Through that process I came up with the principles that went into the book, *Power Healing*, basically the

principles of *The Four Pillars of Healing.* Those principles are, first, establishing a good doctor/patient relationship, which begins with being present at the interview, listening carefully to patients. That is therapeutic on its own. Second is looking at nutrition. I have consistently found the nutritional principles to be very important, even in patients who have been to other nutritional physicians. I haven't found anything that displaces the recognition that people have different dietary requirements. There isn't one diet that fits everybody. Once you've pruned away all the junk food, which doesn't benefit any of us, you need to be tuned in to the fact that aside from food allergies, there are people who thrive on higher protein, lower carbohydrate intake, and people who thrive on totally the opposite.

Different Diets for Different Patients

I pay attention to the reports patients have given me about their experiences with food, what food has meant to them, how different dietary changes have affected them. By being very careful in my follow-up of patients and seeing how they've done with the recommendations I've given them, I have developed a way of individualizing general dietary advice. I have found that follow-up is really important. It is difficult to see somebody, do an evaluation, give him or her a program, and tell the patient to come back in three to six months to see how the patient is doing. This is especially true with the patients I see, who are pretty complex and have been ill for a long time.

Regular, frequent follow-ups to see how the person has done in response to the recommendations you've made are important for adjusting and fine-tuning the program, especially the nutritional program.

Key Nutrients

Certain specific nutrients, over and over again, wind up being very important. Essential fatty acids are a critical area. There aren't a whole lot of choices with regard to supplementation in this area. There are omega-3s and omega-6s. Statistically, the majority of people in the developed world have a shortfall of omega-3s because of food choices and food processing, but there are perhaps 15 percent of individuals who have difficulty utilizing the omega-6s. When I started researching this and lecturing about it around 1980, I had to explain what an essential fatty acid was. Today, there's so much information out there. It is gratifying to see the increased awareness of the importance of these fatty acids.

The second area, just as important, is calcium and magnesium balance, especially magnesium. There are fairly widespread deficits in magnesium, which are due not only to under-consumption, but also to the effects of stress on the body's magnesium economy. I have seen so many patients who have benefited from magnesium replacement that I couldn't begin to count them at this point.

Signs and Symptoms for Guiding Therapy

I have found certain symptoms and signs that are more helpful in guiding therapy than laboratory tests. With regard to the essential fatty acids, those include dry skin, soft or brittle nails, dry hair, excessive thirst, and rough skin (called follicular keratosis) on the backs of the arms and sometimes on the face. These are symptoms of an unmet need for essential fatty acids in the majority of people who have them. Even if my therapeutic intention in treating someone, let's say with a supplement of fish oils or flax oil, is to help control an inflammatory process, paying attention to how these relatively medically unimportant symptoms respond to the fatty acids has been helpful in making decisions about whether

they’re taking too much or the wrong kind.

For example, say someone with arthritis is taking fish oils. His arthritis isn’t getting particularly better, but his skin is getting excessively dry. That is an important sign. Although the literature says fish oils may symptomatically help rheumatoid arthritis or osteoarthritis, what is being accomplished with this pattern of dietary supplementation is really aggravating a problem with omega-6 metabolism. This may be someone who needs to add or switch to a source of gamma linolenic acid for control of arthritic symptoms. I have found that kind of balancing based upon an individual’s symptoms and physical findings has been really helpful. I also find that it works better than using fixed combinations that propose everybody has to have a certain amount of GLA in proportion to a certain amount of EPA. People aren’t all the same in their nutritional needs.

Magnesium and Calcium

It’s similar with magnesium and calcium. There are no good laboratory tests for calcium balance in the body. Magnesium in serum, red cells, hair, and white blood cells—all of those tissues handle magnesium differently. They don’t actually correlate well at all. Although I measure magnesium in serum and in red cells and occasionally in hair, I don’t find I can rely on those results as well as I can upon the clinical symptoms and the clinical response. Clinical symptoms that point to a shortfall of magnesium are difficulty falling asleep, irritability, sensitivity to loud noises, a tendency toward muscle twitches, cramps or spasms, or extreme anxiety. Another is palpitations, especially if there is no cardiovascular disease, hyperthyroidism, or some other condition which would produce the palpitations.

People with that constellation of symptoms, and there are many of them, usually respond well to magnesium supplementation—whatever the laboratory tests say. I’ve seen people with very low red cell magnesium who did not respond to magnesium supplements the way I would have liked at all. I find the symptom guide to be the first one to use. Then, it’s necessary to follow up with the person. There are people who have paradoxical reactions to nutrients given in a way that would seem to be appropriate. I have found that as a clinician, I need to know this. Someone whose cramping, for example, actually becomes worse when they’re supplementing with magnesium, may have a problem with calcium or potassium. Magnesium supplements, by lowering parathyroid hormone levels, which is generally beneficial, may be aggravating the calcium problem. I tried to incorporate these simple clinical decisions, which can have powerful effects in people, into the writing of *Power Healing.*

Antioxidants

Those are the nutritional areas I have found to have the most consistently important effects. In addition, of course, there is the extensive work that has been done with antioxidants of various types—the bioflavonoids and some of the newer phytochemicals. I think they show great promise for the development of useful therapies. I don’t feel we have developed a mastery of how they can be best used. I often find that the research literature promises better results than I find in clinical practice, but I use them considerably, especially among people who have allergic or inflammatory disorders and I sometimes find them very helpful. I may use them even if I don’t find a symptomatic improvement because I know these patients are under a lot of oxidant stress so I want to support the antioxidant defense system.

The Gastrointestinal Tract and Restoration of Health

In the course of working with nutritional supplements, originally I found patients who did not seem to respond to nutritional supplements and needed IV supplementation. In the early days, I was doing a fair amount of IV therapy and some IM nutritional therapy. Then I started investigating the role of the gastrointestinal tract in chronic illness. I found that if people were not responding to nutritional therapies, or if they had a whole separate constellation of symptoms that pointed to gut problems, if I treated the gut problems first, I didn't need to resort to parenteral nutrition to help those patients along. Consequently, over the past 11 or 12 years, most of the research and teaching I've done has focused on the important role of the GI tract in restoration of health. It's brought me back to some of the principles of the early naturopathic physicians.

Here again, when looking at GI problems, I've found that no program worked for everybody, and a good deal of individualization was necessary. Partly, individualization goes into recognizing food allergies and being able to eliminate allergenic foods. A more profound level of individualization is similar to the nutritional issue of looking at macronutrients. Some patients do better on high-protein diets and some do better on high-carbohydrate diets, whether it's complex carbohydrates or a diet that contains a lot of fruits and natural, simple carbohydrates.

Leaky Gut

When it comes to the gut, there are patients with chronic gastrointestinal symptoms and usually systemic systems, as well. The GI symptoms will include altered bowel habits—constipation or diarrhea, gas, bloating, distension, discomfort, possibly with reflux symptoms, and often with systemic symptoms that may include chronic fatigue, various musculoskeletal problems including frank arthritis, brain fog, and symptoms that affect the skin. For those individuals, it's important to try to develop a perception of what might be going on in the gut that's impacting on their overall health.

In reviewing the research literature and then looking at my clinical experience, I came up with a couple of concepts that continue to help me in clinical practice. The fundamental concept is intestinal toxicity. That can be divided into two parts. There's the whole notion of leaky gut and in my experience, clinical practitioners still don't really understand this very well. The leaky gut concept is a measurable increase in the permeability of the small intestine. That permits macromolecules and certain types of otherwise insoluble toxins to enter the body, with a number of different consequences. Not everybody who has chronic GI symptoms has a leaky gut. You can't necessarily make that diagnosis by clinical criteria.

Symbiosis/Dysbiosis

The other concept, equal or exceeding in importance, is dysbiosis. Symbiosis, which is the root word, is a Greek word that means "living with." We live with about 100 trillion bacteria in our gut and several thousands yeasts. Most people in the world live with one form of parasite or another. Actually, humans have lived with worms for a million years.

Symbiosis has many beneficial effects, or let's just say our gut immune systems have evolved in the context of this symbiosis. Dysbiosis, or dys-symbiosis, occurs when the symbiosis has negative effects on the person. A deficiency of beneficial bacteria, overgrowth of Candida, bacterial overgrowth, or the

wrong protozoa or metazoa growing in the gut for that individual are all part of the pattern of dysbiosis. It's not necessarily the same for everybody, and the symptoms are not specific. Many people can have more than one component of dysbiosis at a time.

Evaluating Dysbiosis

Evaluating dysbiosis is a real challenge. Stool testing using a really good laboratory, especially for parasites and secondarily for yeast, can be very helpful. Once again, however, the patient's history and clinical responses are more helpful. If someone has developed symptoms in the context of taking lots of antibiotics, that has one set of implications. If, on the other hand, antibiotics actually improved the symptoms, that has a different set of implications. Dietary requirements differ for people with these different forms of dysbiosis. I would say there are two dietary patterns that are widely used by nutrition-oriented physicians. One is the high-protein, low-carbohydrate pattern. Modifications of that will work very well for some people with dysbiosis due to excessive gut fermentation, which may involve either bacterial or yeast overgrowth in the small bowel, a condition that's very difficult to measure in the laboratory.

The other approach is the more naturopathic approach of high fiber—high complex carbohydrate diets. Those can actually be a disaster for people with excess of gut fermentation, but they work very well for people who have an excessive pattern of putrefaction in the colon. These individuals are producing large quantities of ammonia. Because of their previous high-protein diets, the bacteria have begun to increase their production of enzymes that alter amino acids and proteins. From a high-protein/high-fat Western diet, they've actually altered the bacterial population in the gut. For those patients, an increase in fiber and a decrease in fat and protein can be very beneficial.

There's not enough time for me to go into this in detail in our discussion today, but that has been one of the major challenges I've encountered in working with chronically ill patients. It is also one of the features of those patients that has tuned me in more and more to the importance of looking at how a patient responds to therapeutic interventions, rather than adhering to a single treatment protocol based upon an initial evaluation.

Beginning Clinical Approaches to Functional Medicine

JB: You now have 30 years of experience in this field. It may be overwhelming to the individual who has just moved into the field to think about how much you know and how far you've come. That person may wonder how to begin. You have talked about the need to retrain ourselves from what we learned in our formal training, and go on and take this other curriculum, one you sometimes must self-design and -implement. It may be daunting for clinicians who don't know how to start. When can a doctor act without having complete knowledge?

LG: I think there are a number of very simple, straightforward steps that can be taken, although it does start with the evaluation of the person. I would say that if we take the functional medicine perspective in particular, the first step is to find out what this person is eating and what nutritional supplements he or she is taking. For most people it involves cutting junk food out of their diet and eating a diet of higher nutritional density.

Next you begin to supplement that diet with a basic nutrient supplement package that includes about ten times the RDA of most of the B vitamins, 800 mcg of folic acid (which is not ten times the RDA), and some trace minerals. Check on their magnesium levels. Look through the symptoms of essential fatty acid deficiency, and have them supplement with some flax oil or fish oil. That's a reasonable way to begin with patients.

The Challenge: Patient Compliance

The challenge, of course, is compliance on the part of the patient. As you start doing this, you'll begin to attract patients because there's so much interest in nutritional medicine. Doctors who listen to their patients and are interested in their diets and the supplements they're taking, and who are willing to render even a simple nutritional prescription, will begin attracting patients who want this approach. The compliance of patients with recommendations will begin to go up as new patients come in.

The next thing is to make sure you see them within a relatively short period of time—two to four weeks—to see what changes they've made and what has happened to their symptoms. How do they feel having made these changes? I think that's something doctors don't need a lot of training to be able to do beyond their medical background.

Tracking Progress with Patients

The rewards of doing that will be enough to get you started. You learn from your problems. During the first year of doing this, you probably learn most from your successes, the people who come back and tell you they're feeling a lot better; this improved; that improved. Keep track of what it is that got better with this patient and what they did. You'll get a feeling for the patients you're treating in your population and what you do that really seems helpful to them, so you'll build on that knowledge.

After about a year, start paying more attention to the people who get worse or who don't get better—to the mistakes Then, at a more advanced level, people learn better from negative feedback. This didn't work; this was wrong. OK, what was wrong about it? Where can you go for information that helps you with that? *Functional Medicine Update* is a start on that. I am confident that over the next year or two, we're going to see the development of teaching sources for doctors that will guide practical treatment decisions in this area.

Patient-Centered Assessment

JB: One other thing you've contributed that is extraordinarily valuable to new practitioners in this field is the concept of how to evaluate the patient based on what you call patient-centered assessment. You look at antecedents, triggers, mediators, signs, and symptoms instead of focusing solely on diagnosis and medical taxonomy. That perspective provides a learning system for the doctor to evaluate the patient.

LG: Thanks for bringing that up. I would say that one of the most important questions you can ask any patient is "What was your health like before this illness?" Another is "When is the last time you felt really well?" Then you go to that period of time, which may or may not be closely related to the present illness. Ask what was happening in their lives before then. With people who are chronically ill, who are the main people seeking nutritional medicine and the integrated medicine approaches, nine times out of ten, there

are significant precipitating effects that preceded a change in their health status. If you can understand and address those things, you will be a more effective practitioner.

Linus Pauling Functional Medicine Award

JB: That's a wonderful closing statement to leave all of our listeners with. Once again, on behalf of your colleagues, I want to congratulate you for being the recipient of the year 2000 Linus Pauling Functional Medicine Award. You richly deserve that award for your years of contributions. Anyone who was not familiar with you before will be going out immediately and getting your book, *Power Healing*, to fill in the gaps in what they need to pick up from your vast contributions and clinical knowledge. Thanks very much. We will check back with you on the evolution of integrated functional medicine.

LG: I hope so, Jeff. It was a great honor to receive the Linus Pauling Award and to be interviewed today.

The Many Complex Health Factors Affected by Zinc Status

Dr. Galland brought up a number of interesting points. One I want to follow up on is his discussion about magnesium. Magnesium is a mineral that participates, along with other essential minerals, in modulation of many biochemical functions. It has been said that about 85 percent of the enzymes in the body require magnesium as a cofactor for their function. Other cofactors from the mineral, however, work synergistically with magnesium. One is zinc. We often forget about things that are very clinically valuable and important because we have moved on to new topics. We assume that everybody must still know about those things we were talking about 15 or 20 years ago. Zinc is a nutrient that deserves continued reinforcement in its clinical importance in our practices.

Zinc participates in more than 2000 enzymes as a cofactor. Dietary need for zinc, is comparable to iron—in the range of about 10 mg/day as a level of intake. Many foods are fortified with iron, but none are zinc-fortified. In fact, processing removes zinc from most foods. Zinc is found in the highest levels in lean muscle meats or in the exosperm in grains. As we have gotten into fattier diets and rendered diets, and moved to white flour/white sugar products, the zinc level in our diet has gone down.

Zinc's Many Roles

Zinc plays important roles that similarly match the physiological endpoint and benchmarks to that of the deficiency of magnesium and essential fatty acids that Dr. Galland was talking about. Skin problems, hair loss, increased allergic potential, digestive difficulties including chronic irritable bowel syndrome, vitamin A non-responsive night blindness, changes in taste perception, poor wound healing, immune dysfunctions—these are all signs and symptoms of chronic zinc insufficiency. One might also say those sound reminiscent in some respects to magnesium and essential fatty acid deficiencies. They go together.

A number of studies were done years ago looking at anorexia nervosa and zinc insufficiency. Hypothalamic function is dependent on zinc. In the lateral nucleus of the hypothalamus, the appetite control centers and their relationship to various hormone-modulating processes, hormone balance, and appetite are, zinc-related. This is a very complex nutrient with many influences on physiological function, some of which might be missed in the chronic state as markers of zinc insufficiency, if you were not familiar with this array of functions that zinc has in physiology.

Zinc-altered Immune Function

The results of a symposium on zinc nutrition and physiology were recently published in the *Journal of Nutrition* as a supplement (*Journal of Nutrition.* 2000;130[suppl]). It contains about 20 articles that describe the role of zinc in physiology. I will describe a few of the high points of these articles.

First is zinc-altered immune function and cytokine production. When an individual is zinc-insufficient his or her immune system is adversely influenced. Zinc induces cytokine production by isolated leukocytes. Zinc induces monocytes to produce interleukin-1, interleukin-6, and TNF alpha in peripheral blood mononuclear cells. When an individual is zinc-insufficient he or she cannot mount an appropriate immune response to an offending infectious agent or an initiator of potential injury. Zinc status must be taken into account whenever an individual with poor immune function, child or adult, demonstrates immune dysfunction.

Zinc Insufficiency in children

In children, one sign of zinc insufficiency is short stature for age and poor developmental progression. Zinc is an important nutrient. One of its functions is to participate as a central cofactor in the enzyme DNA-dependent RNA-polymerase, which involves the synthesis of messenger RNA. It is kind of the first step in getting the message off the genome and translating it into protein that's involved in the array of body functions. A child who has been raised on junk food and empty-calorie foods may have zinc insufficiency and may be adversely affected relative to growth and stature as a consequence. In children, zinc insufficiency alters taste perception, causing the tolerance for sweet to go way up.

Increasing sensitivity to the taste of sweet requires increased concentration of sucrose. The child is then driven to consume toward sweeter and sweeter beverages and foods, which are lower and lower in zinc. It's like a dog chasing its tail. The more zinc-insufficient the child is, the poorer the taste perception, and the more the interest in sweet, the lower the zinc, and so on.

Oral Zinc Tolerance Test

This is described very nicely in a variety of papers about zinc insufficiency as marked by taste perceptions to zinc. An individual who cannot taste a 0.1 percent zinc sulfate solution—it doesn't have a puckering or alum effect—may be zinc-insufficient. This is called the oral zinc tolerance test, or taste test. It's a very simple way to test zinc status. It's not a diagnostic determinant, but it is a useful prognostic screening tool that is easily done. The individual simply rinses his or her mouth with a small amount of zinc sulfate solution and then records the taste perception. If it tastes just like water, the person has no taste reaction to it at all. One can assume that person is likely to be zinc-insufficient and in need of zinc supplementation.

Zinc's influence on taste and appetite is reviewed in a paper in the *Journal of Nutrition.* This paper shows that zinc insufficiency alters taste perception and appetite regulatory mechanism. One of those altered taste perceptions is to zinc itself, making the oral zinc taste test a very useful assessment tool.

Zinc Status and Insulin Sensitivity

Zinc insufficiency reduces insulin sensitivity, as well. It may play a role in increasing the levels of insulin and ultimate diabetes, increasing then risk of oxidative stress in diabetics. This has been the result of a number of research papers over the past few years. Even mild zinc deficiency in animals results in increased oxidative injury, lowered insulin tolerance, and a tendency to shift toward hyperinsulinemia insulin resistance. Zinc should be included in a list of important nutrients for individuals who have clinically demonstrated insulin resistance, hyperinsulinemia, or diabetes. If they are low in zinc, they are at much higher risk of oxidative stress.

A three-week supplementation program in postmenopausal women with type II diabetes, using 30 mg/day of zinc as the glycine chelate, zinc glycinate, showed initially increased levels of zinc. Before these women got into the supplementation program, they had low plasma zinc levels. With supplementation, their zinc levels returned to normal range. The measurements of oxidative stress, looking at DNA damage markers, was significantly reduced after zinc supplementation.

Guidelines for Zinc Supplementation

Zinc supplementation should be kept within the upper limit of about 50 mg/day. As you get to 100 or more milligrams of elemental zinc per day, evidence suggests you run the risk of depressing HDL. One needs to be cognizant of the fact that a little is good, but too much may not be better. There is a curvilinear dose/response relationship. Up to 50 mg elemental zinc/day can be used safely in individuals to improve zinc status. When you get above that, one needs to look at lipoprotein patterns, particularly HDL to LDL ratios. Some therapeutic approaches use zinc supplementation as high as 220 mg of elemental zinc, but clinicians should follow the HDL/LDL ratio in cases of very high levels of zinc supplementation.

Zinc status is very important in individuals with HIV and consequent opportunistic infections of HIV. It can help improve immune function and lower the risk of opportunistic infections. The relationship of zinc to thymulin and thymus function is clearly identified. Extensive work has been done in France on the interrelationship among HIV, thymulin, thymus function, and zinc. One should be concerned about individuals who have an immune deficiency symptoms or syndrome and look at zinc status and replete zinc where necessary.

Zinc, Oxidative Stress, and Alzheimer’s Disease

Emerging evidence indicates that oxidative stress in connection with inappropriate zinc intake or status may also increase the risk of Alzheimer’s disease in genetically susceptible individuals. This new information suggests that b -amyloid protein undergoes scission that leads to these amyloid fragments that may correlate with Alzheimer’s disease as a consequence, in part, of poor zinc metabolism/zinc status and altered zinc economy in the body.

Zinc plays a variety of different very important roles to play in physiological function. Its status should be evaluated and supplementation considered along with magnesium and essential fatty acids.

Dr. Galland spoke about the important role of gut ecology. He was the first to use the term "dysbiosis" to describe the host of physiological things that are going on. One can improve gut ecology by dietary intervention. Favorable gut flora populations can reduce the relative risk of things like inflammatory

bowel disease. This fact was recently described in the *Journal of Parenteral and Enteral Nutrition.* According to the authors, recent evidence suggests the composition of colonic microflora plays a role in intestinal inflammation in conditions like IBD. If one can restore proper flora and resolve dysbiosis, one has a lowered immunopotentiation in the gut and lowered risk of IBD.

One can accomplish this by what we have commonly called the 4R Program™. That is the remove, replace, reinoculate, and repair program. A variety of nutritional agents, including prebiotics and probiotics, will improve gut flora disposition and help treat dysbiosis. Inulin is one nutritional substance that is coming up very quickly on the radar screen. A paper in the *Journal of Nutrition* discusses different molecular weight inulin fragments. These are the oligosaccharide fragments, as contrasted to FOS, which are shorter fragments. Inulin fragments are longer chain-link non-digestible fiber materials that then have a very powerful prebiotic effect and help to increase the formation of the friendly bacteria at the expense of getting rid of the unfriendly dysbiotic bacteria. Supplementation with acidophilus, bifidobacteria, and inulin simultaneously provides one component—the reinoculate portion—of the 4R Program™.

Once again, thank you for being with us. This month, we start back into a new academic year. It should be a very exciting autumn with regard to functional medicine.

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