# May 2004 Issue |

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Welcome to *Functional Medicine Update* for May 2004. A number of themes were developed in preparation for the 11th International Symposium on Functional Medicine, held May 11-15 in Vancouver, British Columbia. I would like to summarize those themes in this issue of FMU. I want to talk about where we see medicine going and how it relates to the rising pandemic of metabolic syndrome and type 2 diabetes.

We are all hoping for a new medicine to emerge, one that is better able to address chronic, complex health problems. We have a sophisticated healthcare delivery system that, at the crisis care level, is quite adept at handling emergencies and life-threatening events requiring high technology for their successful remediation. It is when we extend some of the procedures that were developed for high-technology intervention and crisis care into the chronic care regime that we start to experience problems. Many of the medications that have been used successfully in the short-term for crisis care, when extended for long-term use, increase health risks and medical costs, drifting away from the benefit side of the equation. Things shift, resulting in adverse drug reactions and other long-term disabilities as a consequence of what have been called the iatrogenic effects of the treatments or procedures, and these begin to appear with greater frequency.

There is hope that medicine will deliver therapies to maintain health benefits and decrease risk to complications and adverse effects over decades of use. As Oliver Wendell Holmes said in 1847: “The key to living a long life is to have a chronic disease and take good care of it.” Most of us will probably not develop a disease that will immediately kill us, but we are likely to develop some condition that gets our attention and reminds us that we are mortal and need to work on our health care. We need to practice diligent maintenance of our health.

The biology of hope is an interesting topic. It interrelates with the mind/body field of medicine and the concept of complementary medicine. What is the biology of hope? It is an important part of the patient’s healing process. Sometimes it has been spoken of pejoratively as the “placebo effect.” If one has a hopeful and optimistic outlook, there is more likelihood of a positive outcome. From the work of Candace Pert in her book,*Molecules of Emotion,* we recognize that we can change our neurochemistry by the way we view our world and the sense we have of ourselves. We often want to mobilize the biology of hope in our patients; we want to create a milieu of molecules that will help to normalize the function of their neuroendocrineimmune system and give them optimal defense against disease.

I would also suggest that the biology of hope is equally applicable to the practitioner. If, in our work each day, we bring thoughts of despair about the state of medicine and our work within it, we have changed our own molecules of emotion in such a way as to create a different kind of outcome, both in ourselves and in our patients. I think it is important to recognize that concept is being applied every day in our

practices—sentient moments spent in the examination room with a patient on a one-to-one basis—that presents an important humanistic therapeutic encounter opportunity. If we ascribe to the biology of hope, it changes the dimension of our own neurochemistry and immune system, versus the biology of despair about the world in which we are working.

I am quoting from an interesting article that recently appeared in the journal, *ACUMEN*,written by Jerome Groopman, MD, titled "The Biology of Hope," in which he talks about the mind/body connection and the placebo effect.[1] Those of us who have been in this field for a while may recall Norman Cousins' wonderful paper in *The New England Journal of Medicine*titled "Anatomy of an Illness (as perceived by the patient)".[2] In that paper, he talked about laughter therapy, the biology of hope, and creating a healing opportunity.

There have been many papers published in this area since 1976. One of interest looks at catechol-O-methyltransferase (COMT) polymorphisms and how they relate to the production of neurotransmitters through the methylation pathway. We can speculate that the expression of the COMT enzyme can be influenced by an individual's mood, physical state, and psychological state. With different polymorphisms having different sensitivities to the environment, methylation patterns might be upregulated that would create a different symphonic orchestration of neurochemicals that are converted by methylation—the noradrenaline/adrenaline interconversion. There are some interesting manifestations of the mind/body connection related to biochemistry, neurochemistry, and immunology. There is a significant placebo effect regarding analgesic or hormonal research.

In our own clinical work, it has been fascinating to examine the symptoms of perimenopause and menopause. It is interesting to note the placebo effect accounts for upward of 50 percent of the change in hot flushes and night sweats in women. How they *believe* the outcome of their therapies will affect their physiology represents about 50 percent of the decrease in their symptoms. Similarly, work done on osteoarthritis has shown a significant placebo effect (about 50 percent) on pain. This confounds any kind of pharmacological intervention study. The placebo effect turns out to be a powerful therapeutic tool—the biology of hope, the belief of positive outcome. It extends from the patient to the provider and back again.

In a wonderful review article that appeared in *Scientific American* in 1998 titled, "The Placebo Effect," Dr. W.A. Brown talks about the extraordinary stratification of different kinds of patients into high-placebo responders versus low-placebo responders.[3] It could be that the high-placebo responders are individuals who can mobilize the biology of hope more effectively. The context of healing, the therapeutic encounter experienced between the practitioner and the patient, is one that is going to be determined, in part, by the definition of what the environment is. Is it one of hope or one of despair? We bring *a priori* assumptions and belief systems into the moment with the patient, and into our lives. How do we mobilize this positive part of the functional medicine arsenal—the biology of hope?

When we look at the state of medicine, which is primarily pharmacologically-based, there are reasons to despair. It appears that we are pushing the model beyond the point of diminishing returns, trying to squeeze out incremental value with the pharmacological model, in which every additional increment of value costs 10 to 100 times more, either in dollar expense, or in expense to potential risk. We have reached the point of diminishing returns.

That topic leads to an interesting review paper that recently appeared in *The New England Journal of*

*Medicine*, titled “The Pharmaceutical Industry versus Medicaid—Limits on State Initiatives to Control Prescription-Drug Costs.”[4] The authors of this paper state that escalating health care costs are closely tied to the escalating cost of medications and their increasing use, and that the healthcare system has not succeeded in controlling expenditures. The cost pressures resulting from technological advances and new drugs for use by an aging population are likely to exacerbate the problem of access and make the system even less cost-effective.

Examination of the cost of prescription drugs shows that Medicaid has been hard hit. Its spending on drugs soared from $4.8 billion in 1990 to $21.0 billion in 2000. In a single decade, that is more than a four-fold increase in expenditures for medications. What benefits have been realized as a result of these increases in expenditures? The authors discuss how some states are trying to find ways of reducing the costs of prescription drugs. This is a very complex equation. Much of it is tied to demand management and how patient interest in some of the new drugs is lowered, versus supply management, which is to prevent access to the medications. How is demand for these products reduced? That leads to the hope of a new kind of health care, one that would deliver better health to patients with complex chronic disease who have decades of living ahead during which certain medication regimes will be required.

Remember what Oliver Wendell Holmes said about having a chronic disease and taking good care of it as the secret to a long life. How does one take care of it? What is the least expensive way? What is the most cost-effective way? What is the most efficacious way, with the lowest incidence of adverse drug reactions? What conditions are we talking about—vascular insufficiencies, various types of chronic cardiovascular disease, autoimmune diseases, inflammatory disorders, neurodegenerative disorders like Parkinson’s, Alzheimer’s disease, and presenile dementia? What do we do about those?

These questions lead to asking whether the epidemic of obesity, insulin resistance, metabolic syndrome, and type 2 diabetes should be included. Shouldn’t we consider treatments for hypertensive disorders and their relationship to cerebral vascular disease and stroke? All of these diseases appear to have complex etiologies, not just a single cause as a result of a single gene that has mutated and can be taken care of with a single drug. These are functional disorders with multiple physiological factors across multiple genes unique to the individual, and interaction with each unique environment and lifestyle.

The question is, can we develop, at least theoretically, a preventive cocktail to be taken once per week, after which we instruct patients to call us when they turn 90 years of age? On the basis of the information that has been developed over the last 20 years on the etiology of complex chronic diseases, is there something that could be done that would result in a simple, safe, and effective strategy for reduction of risk to the major age-related chronic, complex diseases?

That leads to one of the more provocative papers I have read during the last year, written by Nicholas Wald and Malcolm Law, that appeared in the *British Medical Journal*, titled “A strategy to reduce cardiovascular disease by more than 80%.”[5] That is a pretty laudable objective. What treatment—surgical, radiochemical, or pharmaceutical—could lower a major disease (in this case, a major cause of death) by 80%? I do not know of a single treatment that could achieve that objective. Yet, these authors are presumptuous enough to suggest that there might be a simple strategy that could be implemented in people 55 years of age and older that would add 11 disease-free years to their life expectancy. That is pretty remarkable. According to statistics, people who have never smoked add 3 ½ to 4 years to their life span, on average, but the possibility of adding 11 years to one’s life is a pretty dramatic claim.

What is this claim built around? It is built around a preventive cocktail that would contain six different agents addressing the six most dominant contributors to age-related complex chronic diseases. What does the preventive cocktail contain? In a review of the article that appeared in the journal, *ACUMEN*, the authors talk about a "polypill," meaning that it contains six ingredients. That is the term Wald and Law used.[6] The authors suggest that this polypill, if implemented by people age 55 or older on a daily basis, could contribute significantly to the reduction of heart attacks and stroke in those with existing cardiovascular disease (statistically, more than an 80% reduction of the overall factors we know contribute to premature death from cardiovascular disease). What are the six different factors?

Regarding the mechanism that has emerged from our understanding of cardiovascular disease, cancer, and arthritis, what are the related themes? They are inflammation, oxidative stress, mitochondrial uncoupling, lipid infiltration, and cell signaling relating to proliferative cells. We have talked about those things as unifying mechanisms that underpin the principles and processes of functional medicine.

Let me discuss the six agents Wald and Law speak to. First of all, they talk about a statin, which would presumably handle lipid problems and also lower the arterial inflammatory process. Second is a folic acid-containing supplement to manage the homocysteine connection. According to Wald and Law, though vitamins B12 and B6 are significant, folate is by far the most important vitamin for managing the homocysteine connection to chronic health-related problems. Next are three types of blood pressure-modulating agents—a thiazide, a beta blocker, and an ace inhibitor given at half dose. They would be given under the radar screen for therapy, but more prophylactically to modulate the function of different systems (electrolyte management and angiotensin-converting enzymes)—interrelationships with angiotensin and angiotensinogen interconversion with renin and aldosterone. The beta blocker would lower the adrenergic drive in the cardiovascular system. The sixth agent would be an anti-platelet adhesion agent (low-dose aspirin or baby aspirin is suggested). Those are the six agents in the formulation—a statin at normal dose, a thiazide, a beta blocker, an angiotension-converting enzyme inhibitor at half dose, folic acid at a therapeutic dose, and an anti-platelet adhesion agent (aspirin or baby aspirin).

Could a lifestyle and diet be designed that would accomplish similar objectives for those six different agents? For instance, could a lifestyle and diet be designed that would lower serum lipids and arterial inflammatory potential; enhance folic acid intake and lower homocysteine; lower blood pressure and create a favorable effect on each of the three mechanisms of the antihypertensives that I described—the thiazide, the beta blocker, and the ace inhibitor? Last, could a lifestyle and diet be designed that would lower platelet adhesiveness and thromboxane production, such as one high in essential fatty acids from the omega 3 family?

If you were given that assignment, and had listened to FMU for the past 20 years, by going back and reviewing our summary cards you could probably pull up a strategy that would deliver the six agents in the proposed formulation. As David Deutsch said in his classic book, *The Fabric of Reality*, the future of medicine is to build on the predictive ability of first principles so that outcomes of therapies never before tried will be successful. That is when medicine becomes scientific and has a predictive, not just a historical, medical taxonomy perspective. That is a powerful example that comes out of the Wald and Law paper. In patients with individual risks in these categories, we might be able to develop a "polypill" or "polyprogram," personalized to the needs of each individual. Not everyone has the same risk in the six categories that I have just described.

That becomes a preventive cocktail, so to speak. If delivered effectively in people 55 years of age and older, statistically it could add 11 disease-free years to their lives and reduce cardiovascular disease by more than 80%. It is in the last 10 years of one's life that the majority of medical services are needed. That is when morbidity and mortality become much more real and medical service expenditures are extraordinarily increased.

Does that represent an alternative to the pharmaceutical model of intervention which leans toward fixing broken systems with increasingly expensive medications? I think the answer is yes. By the way, the six different agents I just mentioned are all generic and would be fairly inexpensive relative to some of the new third-generation drugs. This opens up a different strategic approach based upon understanding the origin of chronic complex age-related diseases.

Let us switch from a complex topic to a simple one. That is, what would happen if we simply got people to take a multivitamin and mineral supplement every day as they got older? Would that have any benefit? We should not assume that even a varied and moderate diet delivers all the nutrients needed for optimal function of various organ systems. What would happen if patients took out a nutritional insurance policy or program; for instance, one that included a high-potency multivitamin and multimineral? Results of a study on that issue—the Stockholm Heart Epidemiology Program (SHEEP)—have recently been published, and they are quite fascinating.

This study was related to the use of multivitamins and the risk of cardiovascular disease.[7]The investigators examined the association between the self-selected use of a daily multivitamin supplement and the incidence of myocardial infarction (MI) in a group of individuals from 45 to 70 years of age residing in Sweden. The study included 1296 cases, 910 men and 386 women, with a first non-fatal MI and 1685 controls, 1143 men and 542 women, frequency-matched to the cases by sex, age, and hospital catchment area. The odds ratios were calculated from the unconditional logistic regression models. Among controls, 57% of the women and 35% of the men used dietary supplements; corresponding figures for the cases were 42% and 27%, respectively. Of those taking supplements, 80% used multivitamin preparations. After adjustment for major cardiovascular risk factors to normalize variables, the odds ratio of MI, comparing regular users of supplements with nonusers, was 0.79 for men and 0.66 for women. This inverse association between increased intake of vitamin supplements and lowered incidence of cardiovascular disease was not modified by such healthy lifestyle habits as consumption of fruits and vegetables, increased intake of dietary fiber, smoking habits, and level of physical activity. The results of the study indicate that the use of low-dose daily multivitamin supplements may aid in the primary prevention of MI. This would be a very inexpensive first step in getting to a "preventive cocktail."

If we look at how this concept cuts across many disorders with differing ICD9 codes, does this strategy also relate to things like reduction of risk to type 2 diabetes, hypertensive disorders, arthritis, inflammatory bowel disease, or certain types of cancer? Is there a connection by way of a mechanism, rather than by a disease type? That is an interesting question that we are going to continue to explore in FMU. Perhaps if we can become masters of mechanisms, diseases will become less important.

Let us examine a couple of papers that might illustrate the importance of the mechanism connection, one of which appeared in the *Journal of the American Medical Association*, titled "C-Reactive Protein and the Risk of Developing Hypertension."[8] This is an interesting paper, and the authors of an editorial that follows it point out that the material in the paper demonstrates an interconnection between inflammation,

hypertension, and metabolic syndrome and its later connection with type 2 diabetes. These are not individual, independent disorders. They are interconnected disorders. Inflammatory disorders are connected to hypertensive disorders, which are connected to the metabolic syndrome, which is connected to type 2 diabetes, which is connected to vascular risk, and ultimately cardiovascular disease risk factors.

The original paper in *JAMA* was written by Dr. Paul Ridker and his colleagues who, for the last several years, have been actively involved with the connection of inflammation to a variety of chronic health problems. In this paper, the authors discuss a prospective cohort study that began in 1992 looking at 20,525 female U.S. health professionals, age 45 years or older, whose blood pressures were examined. They looked at high-sensitivity, C-reactive protein and found it to be significantly associated with an increased risk of developing hypertension in all pre-specified subgroups evaluated, including those with very low levels of baseline blood pressure. This suggests that inflammation has something to do with the etiology, and perhaps even the cause of increased blood pressure. The investigators conclude that C-reactive protein levels are associated with future development of hypertension, suggesting that hypertension is, in part, an inflammatory disorder. As discussed in an editorial that follows this paper by Dr. Scott Grundy, this association with inflammation connects hypertension to metabolic syndrome and atherogenesis, or to the origin of atherosclerosis.[9]

Vascular biologists are beginning to help us understand the mechanism that connects inflammation, endothelial dynamics, insulin resistance, metabolic syndrome, and atherogenesis. Therefore, possibly intervening with a program that deals with the reduction of inflammatory potential in a tissue-specific way, will help in the management or even the prevention of many diseases. It goes back to the Wald and Law polypill concept we were discussing earlier. If we hit the right mechanisms, perhaps many positive benefits will play out over decades of living.

Certain agents initiate inflammation, contribute to insulin resistance, affect the vascular system, and have adverse effects upon kidney function. This may lead to increased risk of nephropathy and problems with blood pressure control leading to hypertension, or possibly later-stage renal failure. That leads to an interesting series of questions that cut across the environment and the modification of things in that environment that affect function.

I want to focus on the concept of glycation. Let us quickly review what I mean by glycation and how it relates to inflammation, insulin resistance, metabolic syndrome, and nephropathic injury leading to renal failure. In following a patient with diabetes, we may measure an analyte in the blood called hemoglobin A1C, or glycosylated hemoglobin. Glycosylated hemoglobin is the heme protein which has undergone a non-enzymatic reaction with glucose in the blood called the Maillard Reaction. This reaction was first described in food chemistry. It is a glycosylation reaction where the aldose form of a reducing sugar, like glucose, reacts with the lysyl amino group of an amino acid and a protein to produce a Schiff’s base that rearranges to form a stable adduct called the Maillard product. That is a glycosylation product. In terms of a mental model, we might think of it as a crust of bread.

Glycosylation is to make crusty bread. When dough containing protein and sugar is baked in the oven after it has been yeast fermented in the warm spot of the interface between the oven temperature (the oxygen in the oven and the dough itself), there is an advanced glycosylation reaction. Sugar reacts with the animo groups of the protein to produce the Schiff’s base that becomes the crust of bread. In chemistry, glycosylation is to form crusts, or oxidation ofinjured proteins—a combination of lipids with

sugar or protein with sugar.

That particular reaction, which makes cosmetically attractive bread and also a different flavor in the crust than the dough of the bread, could also be used analogously to talk about what is going on in the plasma. Glucose reacts with proteins, such as plasma proteins, to induce glycosylation reactions. If they occur randomly and are not controlled by non-enzymatic processes under the agency of the Maillard Reaction, they form crusty proteins floating in the blood. These are called advanced glycation end products, or AGEs. Accumulation of a lot of AGEs is associated with biological aging in all animals that have been studied to date, including humans.

We want to prevent the disadvantageous random glycation of our proteins and the formation of AGEs. By the way, it has also been found that there are receptors for AGEs on various cells, such as the immune cells. What does that mean? It means RAGEs. A lot of AGE proteins results in the body becoming "enraged." RAGEs are activated by AGEs, and many crusty proteins in the body produce an enraged physiology (I am using those terms metaphorically) that upregulates inflammatory potential, oxidative injury, mitochondrial effects, and an immune system that is in a state of alarm.

Is there any connection between eating glycated proteins and activation of RAGEs? We assume that the foods we eat are broken down and metabolized by digestive enzymes, and that before they are absorbed across the brush border cells into the blood, they have been suitably detoxified and properly presented so there is no poor information still present in the food molecules that might lead to dysfunction. That is the line of thought in standard gastroenterology.

However, in terms of dietary AGEs, the molecules from cooking sugar-rich foods high in protein at high temperature, or carbohydrate/protein connections, AGEs occur when there is glycation of protein that produces a glycotoxin. Glycotoxins have recently been found to be absorbed into the blood to a small extent, which means they could place a burden on the body's immunological system. That is a whole new "aha" about how individuals might have different responses to cooked foods that are high in protein and high in sugar. Meringue is an interesting example. Egg protein and sugar is cooked to intentionally produce a browning reaction. That represents a huge amount of glycation. When you eat meringue, what does it do to your immune system? It is a new and foreign molecule that may incite the RAGEs to become enraged. That is the model.

Let's talk about an article in the *Proceedings of the National Academy of Science, USA* in 1997 that came out of the work of Dr. Helen Vlassara and her colleagues at the Laboratory of Diabetes and Aging in Manhasset, New York. It is titled "Orally absorbed reactive glycation products (i.e., glycotoxins): an environmental risk factor in diabetic nephropathy."[10] Renal excretion of orally absorbed AGEs is markedly suppressed in people with insulin resistance and hyperinsulinemia. It also demonstrates that daily influx of dietary AGEs, or glycotoxins, may constitute an added chronic risk factor for renal vascular injury, and that dietary restriction of AGE food intake may greatly reduce the burden of AGEs in diabetic patients and possibly improve their prognosis. I am quoting directly from the paper. Cooked foods high in sugar and protein may, in fact, enhance the relative age-related reactions associated with AGEs.

In animal studies, if exposure to AGE proteins in the diet is restricted, does that have any effect on kidney aging? The answer is yes. I am now quoting from a series of papers, one of which appeared in the *Journal*

*of American Society of Nephrology*.[11] Investigators showed that restriction of dietary intake of glycation products led to improved retention of kidney function in aged rats versus those intentionally fed certain amounts of AGE protein in their diet. This is very interesting. Using a dose/response relationship, the investigators showed how dietary AGEs could adversely influence kidney function.

An interesting example is discussed in another paper from Dr. Vlassara's group, titled "Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy."[12] In this paper, it was shown that in diabetes, environmental dietary AGEs promote inflammatory mediators leading to tissue injury, and that restriction of dietary AGEs can suppress their effects.

If we look at reviews published in 2001 and 2002 on this topic, it is interesting to see how the field is emerging. One is titled "Advanced glycation end-products: a review."[13] The authors explain that AGEs are a complex heterogeneous group of compounds that have been implicated in a variety of diabetes-related complications—ocular injury, neurologic injury, and nephropathic injury associated with oxidative upregulation of the immune system. These compounds may also lead to what is called protein carbonylation, another factor associated with immune reactions and oxidative stress that occurs during the upregulation of the immune system caused by exposure to AGEs.

It appears that agents used for the treatment of AGEs would be very useful in reducing the injury to tissues in individuals with metabolic syndrome/hyperinsulinemia. What are those agents? One class of substances is the aminoguanadines. They are probably the best studied of the pharmacological agents to reduce glycation. They are the metformin-like compounds. It is possible that one of the benefits of metformin beyond its glucose-regulating effect is its anti-glycation effect. The natural substance carnosine is an anti-glycation agent, as well. Carnosine has been shown in a variety of animal studies to be very helpful when given in supplementary doses for reduction of the combination of glucose with protein that forms AGEs.

Clearly, when blood sugar is inappropriately controlled, and when insulin regulation is disturbed, there is a strong increasing risk to the formation of AGEs. That relates to increased inflammatory potential, which ties together with increased cardiovascular risk, nephropathic risk, neurological injury, and ocular injury. It is part of an accumulative process of degenerative disease. Rather than putting people on medications once they get to the endpoint of damage, perhaps they should be put on an early-stage protector against AGEs, meaning a diet and lifestyle that could reduce glycation.

From a clinical management perspective, this might mean lowering a patient's glycosylated hemoglobin and not allowing it to reach the upper limits of normal. It might be well to manage their glycosylated hemoglobins in the low-normal range, not in the high-normal range, and use this as a marker over the life of the red cell (about 120 days). Any change made today may not result in significant changes in glycosylated hemoglobin for another three months, but it can be used as a marker for tracking some of the variables that associate diet and lifestyle with glycosylation and subsequently, with inflammation, hypertension, and metabolic syndrome. Again, it is a web of interacting variables. We are looking for a way to lower the incidence of later-stage, chronic, complex diseases which require cost-ineffective pharmacological intervention.

What other age-related problems might be approached from a similar strategy? That leads into a discussion about how AGEs and other factors initiate brain injury. We will talk about dementia,

Alzheimer's, Parkinson's, and neuroprotective therapy on Side 2.

Let us move from the mind/body association to some of the other principles emerging from neuroscience that, from a functional medicine perspective, might deliver on the objective of protecting the reserve of our cognitive and emotional function over time. In order to do that, I want to mobilize a nutritional component. There may be factors in our diet that play important roles in the neuroprotection pathway I have been describing. That brings back a term you have heard me use several times—nutrigenomics—the role that nutrition plays in gene expression.

What I am referring to is that no two people respond identically to the constituents of their diets. Based on genomic uniqueness, one may have differing sensitivities to environmental stimuli, different inflammatory potential, different oxidative stress potential, and different risk to neuronal injury. Nutrigenomics not only examines inflammatory disorders; it also looks at the role nutrition can play in inflammation.

Nutrigenomics implies both the role of macronutrients (fat, protein, carbohydrate and their forms), micronutrients (vitamins, minerals, and essential fatty acids), and conditionally essential phytonutrients. These could be plant-derived phenols or bioflavonoids, or nucleic acids. They could also include glucosinolates from cruciferous vegetables and their effects on detoxifying enzyme systems, as well as substances that activate synthesis of coenzyme Q10, taurine, carnitine, or intra-mitochondrial glutathione in the body, all of which have positive impact on neurological function. There may be a whole array of nutrients, both macro- and micronutrients, that may be important in modulating gene expression and proteomic outcome, and later metabolomic function, in a tissue-specific way that might be harnessed to deliver neuroprotection. That is the strategy the nutrigenomics model is focused on.

It is a long way from suggesting a nutrigenomic approach to delivering it in the clinic because of a wide variety of differences from person to person, assessment methods, and how programs would be personalized to the individual's need. But for the first time I can recall in my 30 years in this field, tools are becoming available to answer those questions. In the next few years, We may see multi-panel gene screens that will allow us to evaluate inflammatory genes that are most tracked against neurodegeneration. We may be able to mark their influence by different dietary effects on expression and how to "cool them off" so as to quench the flames of neurodegenerative fire (the "brain on fire," as it has been described).

I want to go over nutrigenomic goals and strategies. We have reviewed this in the past, but I want to revisit the wonderful paper that appeared in *Nature Reviews*, titled "Nutrigenomics: goals and strategies."[20] In this article, the authors specifically describe the use of various nutrients to modulate inflammatory signals in neurological function and brain aging.

Let me cut to the clinical takeway. That is discussed in a wonderful paper recently published in the *Journal of the American Medical Association*, titled "Neuroprotection in Parkinson Disease. Mysteries, Myths, and Misconceptions"[21] I want to focus on some of the features in this article because of their important clinical relevance.

The authors state that Parkinson's disease is an age-related neurodegenerative disease that affects approximately 1 million persons in the United States, and that its incidence is increasing as we become an

older-aged society. Current therapies, such as L-dopa Sinemet, provide effective control of symptoms, particularly in the early stages of the disease, but most patients develop motor complications with long-term treatment. Negative features develop, such as postural instability, falling, and dementia that are not adequately controlled with existing medications. This opens up an opportunity for a different augmented or accessory approach. Neuroprotective therapy might slow, stop, or even reverse disease progression, and we urgently need to find a way of both understanding what neuroprotective therapy for Parkinson's is and then delivering it more effectively.

In this paper about neuroprotection trials, there is a figure that represents a landmark. It is everything we have spoken to in the foundation of the philosophy of functional medicine for the past 20 years. The figure ties together genes and environment into a modification program focused, in this case, on the prevention of neurodegenerative disorders, i.e., Parkinson's disease. Let us go through the model that appears in Figure 1 on page 359 of this paper.

What is the emerging etiology for the neurodegeneration associated with Parkinson's disease? First, there are the genetic factors. These have been identified as specific genes that may be associated with poor detoxification, like single nucleotide polymorphisms (SNPs) of glutathione-S-transferase, catechol-methyltransferase, N-methyl-transferase, or the sulfation enzymes involved with detoxification of exogenous xenobiotics—foreign compounds capable of inducing neurological injury. Historical and epidemiological research has shown that Parkinson's disease is more common in individuals in workplace environments associated with exposure to toxins, such as farmers and agricultural workers, and those in the tanning, paint, and glue industries. Individuals in work environments that may be the most susceptible are those with genetic susceptibilities to the inability to effectively detoxify toxins. We have reviewed many papers on this topic, including Rosemary Waring's classic studies in England at Birmingham University Medical School in the Department of Neurology, showing that lower detoxification of sulfation, glucuronidation, and glutathione conjugation are associated with increased risk to neuronal injury. Those are the genetic factors.

Next are the environmental factors. What xenobiotics and endogenous chemicals are the genes exposed to that lead to a gene/environment interaction that presents as the etiology of Parkinson's disease? The answers to that question would be sought in the field of environmental medicine, e.g., in papers discussed above. If one has genes of high susceptibility, he or she should not be put into a high-risk environment. The environment needs to be tailored to the individual. That is what environmental medicine is all about—cleaning up the environment, pollution control, local eco-environmental control, the home, air, water, mold, toxins, etc.

Now, let's move from etiology to pathogenesis. What are the four mechanisms that have been postulated as being the causative agents for the cellular injury and death of the nigra striatum associated with Parkinson's disease? You have heard about all of them in FMU. They include oxidative stress, mitochondrial dysfunction, excitotoxicity (NMDA receptor activations and the hypothesis of endogenous excitotoxicity), and inflammation. If you have been a student in this field for some time, I am sure you would agree that all four of those mechanisms are interrelated. They are not independent etiological processes. Oxidative stress is interrelated with mitochondrial dysfunction, which is interrelated with inflammation, which is interrelated to excitotoxicity. These do not stand as independent contributors, but rather engage in crosstalk and messenger molecules that share pathways throughout the process.

How do we approach oxidative stress? What would we do to implement neuroprotective therapy to lower oxidative stress? The authors of the January 2004 *JAMA* article talk about antioxidant intervention with vitamin E, vitamin C, various antioxidants, and iron chelators to prevent free iron from becoming available in the nervous system that induces free radical oxidative injury through dismutation of superoxide. We want to enhance the redox potential of the brain (reduction/oxidation potential) by building power or reducing buffering capacity, a term often used with blood buffer and pH. We can consider redox buffering by enhancing these antioxidants.

Next is the area of mitochondrial dysfunction. What can be done to improve that? The authors talk about bioenergetic agents. What examples do they give? They discuss coenzyme Q10, lipoic acid, N-acetyl-carnitine, agents that enhance the control of electron transport and mitochondrial function, and lower oxidative leakage out of the mitochondria by mitochondrial uncoupling. These are some interesting examples of intervention with antioxidants. The intervention might also include things like N-acetylcysteine to enhance glutathione synthesis, and bioenergetic agents such coenzyme Q10 and lipoic acid.

Next is excitotoxicity. The authors talk about lowering activation of the NMDA receptors. Some new drugs are being explored that will be available on the market soon. They are anti-glutaminergic agents which will lower NMDA activity and stimulation of the receptors. There are dietary variables that will lower neuroexocitotoxicity, such as a clean diet, one that is lower in food chemicals, more basic in hypoallergenicity, and which may have a salutary effect on lowering neuroexocitotoxicity. Less exposure to mercury, lead, or cadmium may play a positive role, as well. These are environmental and dietary factors that may lead to lower excitotoxicity.

Last is inflammation. How do we lower that? First, we use antiinflammatories. We have talked about downregulating NFκB expression, managing and controlling cyclooxygenase and lipoxygenase activities, and trying to restore proper Th1 and Th2 balance in the immune system. Antiinflammatories might have important roles to play in regulating the expression of NFκB; in other words, liberating it from its inhibitor κB and the cytosol so it becomes available to the nuclear genome, resulting in a change in expression patterns. This is another important potential approach—stabilizing the NFκB complex and lowering its activity.

There are important things that relate to diet and lifestyle. We have talked about natural substances that modulate inflammation potential. There is a whole range of different dietary spices and phytochemicals that have antiinflammatory capability. What about the omega 3 fatty acids, DHA and EPA, and the role they play in some of the cyclooxygenase pathways?

What is emerging from the discussion in the JAMA article about neuroprotection in Parkinson's is a model that sounds very much like a functional medicine approach—evaluating antecedents, which they call genetic factors; looking at triggers, which they call environmental factors; and the interaction of triggers with antecedents resulting in a gene/environment interaction. Next, looking at the mediators that result from oxidative stress, mitochondrial dysfunction, excitotoxicity, and inflammation, and modulating those using differential approaches based on diet, lifestyle and, where necessary, pharmaceutical intervention. That ultimately results in improved protein handling, lowered loss of neuronal reserve, and lowered apoptotic cell death, which leads to what Dr. James Fries talked about—the loss of organ reserve and ultimately, increased dysfunction. The article in *JAMA* on neuroprotection in Parkinson's disease is a

model for so many things that we have talked about in functional medicine. It also addresses, in part, the "polypill concept" of reducing age-related, complex chronic diseases by the modulation of various pathways.

To take this to the next level, one might ask if there are any papers that have been published documenting the role that nutritional factors play in mitochondrial disorders or neurodegeneration, or is this all speculation? There is quite a large bibliography in that area, and I want to touch upon a couple of interesting papers.

Recently, in the *Journal of the American Dietetic Association*, a paper was published, titled "Nutritional Co-factor Treatment in Mitochondrial Disorders."[22] In this paper, it is shown that one of the most accepted ways of approaching the management of mitochondrial disorders is by augmentation of specific nutrients to restore proper mitochondrial oxidative function.The authors identify metabolic therapies have been reported to produce positive effects on mitochondrial degenerative disorders, including coenzyme Q10, ascorbic acid, vitamin E, lipoic acid, increased levels of riboflavin (vitamin B2), niacin and thiamin, vitamin K, creatine, and carnitine. A review of these supplements in mitochondrial disorders unfolds quite a large bibliography of supporting documents. In this article alone, there are over 80 citations on the use of various nutrients in the treatment of mitochondrial disorders. Generally, they are talking about inborn errors of mitochondrial dysfunction, but there are induced injuries to mitochondria in the somatic cells through oxidative stress, inflammatory upregulation, and mitochondrial uncoupling. It is not just inborn errors, but perhaps the mild, induced mitochondrial injuries where these particular interventions might prove useful. Coenzyme Q10, riboflavin, vitamin E, lipoic acid, N-acetylcarnitine, N-acetylcysteine, vitamin K, and creatine are all interesting nutrients in this emerging story. Coenzyme Q10 intake elevates mitochondrial and tissue levels of coenzyme Q10 and vitamin E in animals. This has recently been shown by Dr. Sohal and his colleagues at the University of Southern California.[23]

If there is mitochondrial injury due to oxidative stress reactions, it can modify cognition and increase age-related dementia. This has been shown in a variety of control studies in animals. A good paper was recently published in *Nature Genetics* looking at how mitochondrial DNA injuries can modify cognition and produce dysfunction at what is called the "intelligence level" in animals.[24]

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What nutrient has been found to be most useful for the protection of the mitochondrial processes that are so important for the maintenance of neuronal energy production and neuronal function, may ultimately control the production of neurotransmitters and neuromodulators, and may have significant effects on mood, mind, memory, and behavior? That is a question still being vigorously debated at both the laboratory and clinical levels. The nutrient I want to focus on (beyond the obvious coenzyme Q10) is vitamin E. The emerging vitamin E story is quite fascinating. It is a useful story as to how our understanding is evolving in the area of neuroprotective and other health-protective agents.

Vitamin E was first discovered in 1922. It was found to be a family of substances derived from vegetable oil and given the name "tocopherol" (Greek for "to give birth"). Research has shown that a lack of vitamin E results in fetal death in animals. Rats have a very convenient way of managing this; they resorb their fetuses. They do not miscarry; instead, the fetus is resorbed. In the absence of including this unusual fat-soluble factor of substances in the diet, the animals would become infertile, resulting in fetal resorption. Putting the substances back in the diet resulted in normal fertility and offspring. Because of that research, vitamin E gained the reputation of being a "fertility vitamin." Early lore about vitamin E described it as an aphrodisiac good for sexual vitality. That was a result of the research on its ability to prevent fetal resorption in animals and produce proper fertility and litters.

Since then, vitamin E has been the subject of much more research and discussion. It is now recognized as a member of different molecules in the family of tocopherols. It can be broken down into several different types of tocopherols based on the methylation patterns of the chroman ring, which is part of the structure of the vitamin E molecule. It can be an a, b, g, or dtocopherol. There are some derivatives of vitamin E that have unsaturated linkages in what are called the phytyl side chain of the vitamin E molecule, which makes them into what are called tocotrienols. There are a, b, g, or d tocotrienols, a family of different members that share similar chemical structure, but which may have different functions at the physiological level.

Different plant oils from which vitamin E is derived have different dispositions or ratios of a, b, g, or d tocopherols and tocotrienols. Depending upon what plant oil the vitamin E is extracted from, there may be differing amounts of the various family members. What has been considered the most active form of vitamin E? The literature over the past 50 years tells us that the natural form of vitamin E in the d-a form is the most active. It has 1.39 IU of activity per milligram, as contrasted to the synthetic vitamin E, the dl-a-tocopherol that has one unit per milligram. The natural form of d-a-tocopherol is about 30 to 40 percent more active per milligram.

How was that activity analyzed? What was the biomarker used for determining its higher activity? Why is the a form more active than the b, g, or d forms? That is a fascinating part of the story. In developing the bioassay, the best way of determining its activity in animals was to look at its ability to prevent rat fetal resorption. It was found that the most active form of vitamin E to prevent rat fetal resorption was the a form. Therefore, it was given the highest potency—1.39 IU per milligram.

How many people take vitamin E to prevent rat fetal resorption? The obvious answer is that no one does. They take it for other reasons—cardioprotection, immunological effects, mitochondrial defense, and neuroprotection. Does that relate directly to vitamin E's effect on the prevention of rat fetal resorption? That has been a big controversy. For years, we have assumed that the a form, the most active form for the prevention of rat fetal resorption, was also the most active form for the prevention of many other conditions in humans.

What research on vitamin E has emerged over the last few years? First, it has been found that the most common form of vitamin E in plant food oils is not the a form, but the g form. Therefore, the manufacturers of vitamin E often intentionally converted g to a to convert it into a "more active formulation," meaning higher IUs per milligram, or better in preventing rat fetal resorption. The a form is the most common form in human tissues as well, but is not the most "natural" in the diet. Gamma forms were intentionally moved to become a forms, but in a natural diet the major form is g-tocopherol. Vegetarians have been eating mostly the g form, but we have been supplementing mostly with the a forms. This is discussed in a paper published in the *American Journal of Clinical Nutrition*[25] that talks about g-tocopherol being the major form of vitamin E in the US diet.

Let us examine the role that g-tocopherol has, as contrasted to a-tocopherol, in the range of physiological function beyond rat fetal resorption. Gamma tocopherol produces a dramatic series of effects that do not appear to be as well shared with the a form, meaning there may be some benefits of g-tocopherol in human physiology that we have been missing for the last 10 years.

In 1978, I spoke at an international conference on vitamin E and raised a parenthetical question, not realizing what I was asking at the time, only that we had been doing research on vitamin E since 1971. I asked whether it might be possible that the major food form of vitamin E, g-tocopherol, had hitherto unexplained physiological effects, and that perhaps we were putting our eggs in the wrong basket, always focusing on a-tocopherol. That question ended up in an article on the proceedings of that conference presented in England in the late 1970s. Since then, many others have become interested in the g-tocopherol story, and research began to demonstrate that it has a profound influence on cytoprotection against certain free radical oxidants greater than that of a-tocopherol. This is described in a book on vitamin E that contains a chapter, titled "Beyond a-tocopherol: the role of the other tocopherols and tocotrienols,"[26] that includes its effect on signal transduction, platelet adhesion, and other processes.

Is g-tocopherol the new vitamin E? asks Maret Traber and Sridevi Devaraj in a recent paper in the *American Journal of Clinical Nutrition*.[27] The answer is no; it is not the *new* tocopherol; it has been around since time immemorial, but we are now reviewing its activity in a different way than before. It may be the preferable form of vitamin E to prevent nitrosation reactions and protect against peroxynitrite, the result of immune upregulation and inflammation. It may be preferable to defend against endothelial arterial injury. Perhaps g-tocopherol deserves a lot more attention than the a form in terms of its potency, as it relates to physiological protection against age-related chronic disease.

This is discussed in a number of research papers. For instance, recently in the *FASEB*Journal, a paper was published by Bruce Ames and his colleague, Qing Jhiang at the Division of Biochemistry and Molecular Biology, University of California, Berkeley and Children's Hospital Oakland Research Institute, Oakland, California. [28]In this paper, they discuss g-tocopherol (but not a-tocopherol), decreasing proinflammatory eicosanoids in animals—the cyclooxygenase and lipoxygenase-derived eicosanoids. They used a-tocopherol-supplemented corn oil and g-tocopherol-supplemented oil and showed that the g form had a much better ability to lower leukotriene B4 and cyclooxygenase-mediated eicosanoids. In this study, g-tocopherol appeared to be preferable in these functions. I want to emphasize that this was a study done in animals.

In another paper written by Bruce Ames and his colleagues that appeared in *Free Radical Biology and Medicine*, they talk about g-tocopherol supplementation inhibiting both protein nitration and ascorbate oxidation in animals in which inflammation had been promoted.[29]This suggests that g-tocopherol has preferable antiinflammatory effects. Gamma tocopherol, as contrasted to a-tocopherol, may directly inhibit cyclooxygenase activity in macrophages, one of the most important cell types involved in the production of inflammatory mediators. This work appeared in the *Proceedings of the National Academy of Science*.[30]

Supplementation of a, b, g, and d tocopherols, when studied in humans, showed enhanced function on endothelial NO synthase, and regulation of superoxide dismutase and protein kinase C activities in leukocytes of human subjects. These were 64 subjects randomized into three groups given either a-tocopherol, mixed tocopherols, or controls. A more salutary effect on endothelial constitutive NO synthase was observed with the use of the mixed tocopherols. This is work published in *Nutrition Research*.[31]

Mixed tocopherol preparations have been found to be superior to a-tocopherol against hypoxia-reoxygenation injury. This work was published in a paper in *Biochemical and Biophysical Research Communications.*[32]

There is a fairly broad body of literature indicating that the vitamin E family (e.g., g-tocopherol), with coenzyme Q10, and lipoic acid, appears to have beneficial effects in helping to lower oxidative injury, NO inflammatory effects, and peroxynitrite nitrosation reactions, and offer neuroprotection, as well. Obviously, there is much more to learn about the vitamin E story.

The Wald and Law article on the reduction of age-related chronic cardiovascular disease by way of a "polypill" has opened the door from a functional medicine perspective for more cost-effective medicine and delivering a biology of hope to our patients.

We will see you in June.

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