November 2002 Issue | John P. Cooke, MD, PhD Division of Cardiovascular Medicine

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Welcome to Functional Medicine Update for November 2002. The focus of this issue is on nutritional modulation of cardiovascular disease. We will continue to develop this important topic in discussions throughout the next several months as we prepare for our 10th International Symposium on Functional Medicine. The Symposium will take place May 21-25 at the five-star Westin La Paloma Resort in Tucson, Arizona. It will be our second visit to the Westin La Paloma. Those who attended the Sixth International Symposium on Functional Medicine thought it was a wonderful facility with great ambience and an enjoyable environment in which to learn while enjoying the high desert of Tucson, Arizona. The focus of the 2003 Symposium will be "The Heart on Fire: Modifiable Factors Beyond Cholesterol."

We have an impressive list of speakers for the 10th Symposium, including a winner of the Nobel Prize in Medicine and a series of clinicians and researchers who are internationally renowned in their respective fields. One speaker is Dr. John Cooke, our Clinician/Researcher of the Month in this issue of FMU. You will be receiving program and registration information soon. The 10th International Symposium on Functional Medicine will be a tremendous learning experience, with eight or more workshops to select from and a news-to-use format that will put you at the forefront in extended cardiovascular risk factor management

This month's *FMU* focuses on the evolving theme of the connections among genes, environment, and phenotype in relation to cardiovascular function and later-stage disease. A wonderful article by Dr. Richard Strohman appeared in *Science* magazine last spring.[1] The April issue of *Science* was titled "The Puzzle of Complex Diseases." In the past, we may have thought that individual diseases with individual disease codes, or ICD9s, came from individual mechanisms that were isolated and separate from other diseases. There was an insular line of thinking that each disease occurred as a consequence of its individual mechanism that was unique from any other disease, and an individual treatment would remediate or treat the particular condition.

That model originated in studies on the causes of communicable diseases and led ultimately to discovery of infectious agents, bacteria and viruses. Each disease had a specific etiology and would be sensitive to a specific antimicrobial agent. It was one agent, one disease, and one molecule to treat it. It was a simple concept that seemed to work wonderfully at the end of the 19th century and the beginning of the 20th century. We have tried to extend that concept into the dominant disorders in our population today, the chronic degenerative diseases-heart disease, cerebrovascular disease, maturity-onset diabetes, hypertensive disorders, rheumatoid arthritis, and other related autoimmune disorders, malignancies, and

neoplasias. We have found, however, that model is no longer applicable.

Complex Disorders, Multiple Pathways
We now recognize these chronic conditions are complex disorders with multiple pathways, each with the potential to give rise to similar outcomes in terms of physiology and pathology. Remediation of these conditions may require different and complex approaches and strategies rather than single molecules. That is the opinion Dr. Strohman expresses in his article, "Maneuvering the Complex Path from Genotype to Phenotype."

Except for rare mutational events, genotype is locked, when the sperm meet the egg, into the 46 chapters of our book of life, our chromosomes, one half of the chapters given by our biological mother, the other half from our biological father. In each of those chapters are thousands of stories. Those stories are our genes and they are not all read simultaneously. They are turned on and turned off, expressed and not expressed, based upon certain characteristics occurring with regard to our health status, environment, and age. The expression patterns of genes ultimately give rise to the formation of specific proteins in the cell (proteomics). That process, finally, controls metabolism, (metabolomics), which results in our phenotype- how we look, feel, act, and our overall health.

The New Model of Disease
The connection between genotype and phenotype goes through many environmental modulators according to the new model of disease, which takes us beyond the deterministic model of Mendel, which stated that if you had certain diseases in your genes, you would get them later in life. We are talking about modification of those genetic uniqueness by affecting their expression patterns.

Dr. Strohman states in his article that most human disease phenotypes, which ultimately give rise to what we would call our diagnostic codes, are characterized and controlled, not by individual genes but by a self-organizing network of interacting genes. They are not the product of a single gene working in isolation. There is not a single gene for cardiovascular disease, cancer, or any named disease you can select in the chronic, age-related degenerative disease family. Instead, there are networks of genes that are turned on and off to give rise to different physiological states, in essence locking them into a different state of homeostasis.

Homeostasis
We have often used the term "homeostasis" to imply the balance of good health-proper glucose, oxygen, electrolytes, and electrochemical potential. We think of homeostasis in association with good health, but you can be locked into an equilibrium state of alarm, which we would call a chronic inflammatory state. That state of health is not necessarily to the long-term advantage of the patient. It may be a short-term advantage for the patient to respond to a specific environmental threat, but if it is locked in for a long period of time, through some kind of feed-forward mechanism, it can become deleterious. We call that a chronic degenerative disease, and it has a complex etiology involving multiple genes that are turned on and off to give rise to the pattern we recognize as disease.

These networks range from metabolic pathways to signaling pathways that may include hormones. All of these signaling molecules, the interleukins, cytokines, prostaglandins, sex steroid hormones, neurotransmitters, intracellular adhesion molecules, and many more, are themselves the products of genes that in turn modulate the phenotype of the cell by regulating how it performs its function. Based on the

shift of these particular messenger molecules, the cell can be in a state of alarm, or hostility, or vigilance. It can even lead to cell suicide, apoptotic cell death, as it trims or prunes itself from the cellular network.

Network Dynamics
When perturbed, the networks alter their output of matter and energy, depending on the environmental context. This is the wild card in the whole schema-how environment, diet, lifestyle, thoughts, attitudes, beliefs, and exposure to air and water modulate gene expression. These factors combine to produce a pathologic or a normal phenotype. Study of the dynamics of these networks by approaches such as metabolic control analysis will provide new insights into the pathogenesis and treatment of these complex diseases. There is considerably more involved than a single agent producing a single disease for which a single molecule can provide treatment.

It has taken many years of work for thousands of highly intelligent men and women who are researchers, clinicians, observers, and implementation specialists to tease apart this particular story. This concept represents a paradigm shift. Many of you, because you are sensible, reasonable, and intuitive, may think, of course, that is the way disease results in the aging individual. But let me remind you this has not been the dominant textbook view of where disease comes from that has been taught over the past 50 years. This is a new concept. It is a revolutionary concept that is changing the way we see the inevitability of age-related diseases. It is changing how medicine views its responsibility, its conduct, and its relationship with patients. What is the responsibility of the physician in implementing the new disease plasticity model versus the disease deterministic model of the past?

The Environmental "Wild Card"
The answer to that question has not been fully answered. But I can assure you that the answer, as it emerges, will lead to a healthcare delivery system that is different from that which we have had for the past 50 years because of the relativism of disease as it pertains to the wild card called environment.

The study of nutrition will evolve from being considered an optional topic of esoteric interest in medical schools to become a dominant force by highlighting the fact that disease may result as a consequence of the imbalance of genes and environment, producing a phenotype of untoward outcome called pathology. It moves from an elective course to a central course of absolute requirement if you are going to improve healthcare efficiency and move from a disease-care system to a healthcare system.

Market-Driven Health Care
If altruism does not produce the drive for change, then it will come about through economics alone. The cost and efficiency of a system based on disease determinism and waiting for something to break before fixing it will bankrupt that system, as aging baby boomers ask for services equal to or greater than those their parents required. Dr. Regina Herzlinger at the Harvard School of Business addressed this topic in her remarkable book, *Market Driven Health Care*. In the COM interview we conducted with her on *FMU* in August of 1998, she said there has to be a consumer-driven alteration in the way health care is delivered, to meet the needs of the patient as he or she goes through states of disability toward pathology. In August of 1998, Dr. Herzlinger told us we were at the threshold of a paradigm shift in healthcare financing and healthcare delivery. It is four years later, and that shift is taking place.

I compliment Dr. Strohman for his article on the maneuvering in the complex path from genotype to phenotype. He reminds us that applied biochemistry and understanding the translation of genomics into

the phenotype, which may have appeared esoteric in the schools of metabolic diseases at certain medical schools, will move into the mainstream of our thinking as we define how to improve function in patients

Let me give you some interesting examples that illustrate this principle. Let's look at a patient who might present with the symptoms and signs of autoimmune thyroiditis. Traditionally, we would examine this patient and note he or she had a high titer of antibodies to his or her thyroid gland. The patient has altered thyroidal function in terms of symptoms. In acute thyroiditis the thyroid is enlarged and warm. When we examine the patient from a biochemical perspective, we see TSH and T4 levels that may be at the limits of the reference range or out of the normal reference range. When we put all this together, we arrive at a diagnosis, something like Hashimoto's thyroiditis.

What is the treatment once the diagnosis has been made? Historically, the treatment would be to tell the patient that because he has a specific problem related to being allergic to his thyroid gland, so to speak, we need to knock thyroid function down. We need to alter thyroid activity and somehow take control of this system. It may be through thyroid surgery, thyroid irradiation, or a thyroid-blocking medication. It may be thyroid alteration in terms of supplementation of certain synthetic or natural thyroid hormones. There may be a variety of pharmacological or surgical approaches used.

The Environmental Sentinel Gland

In light of what we are beginning to recognize regarding the genes/environment connection, however, we might ask, what is the thyroid gland? Metaphorically, we might say the thyroid is the environmental sentinel gland. It senses the outside environment in terms of various substances to which that organism is exposed. The activity of the thyroid gland depends, to some extent, on nutritional intake and adequate protein that delivers phenylalanine, which will go to tyrosine and then to thyroxin. It has to do with adequate iodine intake, so we don't get iodine-deficiency goiter. We know about those things.

More recently, we have begun to recognize that other elements in the diet are important for proper formation, activity, and sensitivity of thyroid hormones. One of these elements is selenium and its important role as part of the selenocysyeine containing deiodinase enzyme. This enzyme is found principally in the liver, but it is also found to some extent in brain tissue that deiodinates T4 to T3. T3 is approximately 100 times more active as a metabolic gene regulator than T4. We would consider T3 to be the bioactive thyroid hormone, but it is principally produced extra-thyroidally, outside the thyroid gland, by deiodinization.

Under-Conversion Hypothyroidism

In the early 1980s, when we decided to name these tapes *Metabolic Update*, I talked about under-conversion hypothyroidism, the inability of T4 to T3 to be manufactured properly or manifested, so the person would exhibit the signs of hypothyroidism or thyroid dysfunction. If you examined the individual from a biochemical perspective, however, it appeared that he or she had normal TSH or T4, and perhaps even normal total T3. At that point in the early 1980s, the concept of under-conversion hypothyroidism was on the minds of only a few. There were only a few investigators at that time who were interested in this topic. I would have been considered an outlier in this discussion.

Since then, however, over the past 20 years, the concept has become much better understood. Mainstream medicine now recognizes under-conversion hypothyroidism. But what is most interesting is the recognition that selenium insufficiency (not deficiency but insufficiency) can promote poor conversion of

T4 to T3 as a consequence of underactivity of the selenocysteine-containing deiodinase enzyme. Nutrition now plays a role in thyroid function. That was not known by anyone back in the early 1980s. That was a discovery made in the 1990s. Now we add selenium into the equation.

Selenium and Autoimmune Thyroiditis
Given this emerging concept and the gene/environment connection to the phenotype of outcome of the thyroid gland, is there any connection between selenium and autoimmune thyroiditis? We would extend this beyond frank hypothyroidism, possibly into thyroid dysfunction and immunological reactions against the thyroid gland.

A paper in the *Journal of Clinical Endocrinology and Metabolism* is titled "Selenium Supplementation in Patients with Autoimmune Thyroiditis Decreases Thyroid Peroxidase Antibodies Concentrations."[2] Investigators are finding that low selenium status appears to increase immune system reactivity to the deiodinase enzyme involved with the conversion of T4 to T3, thereby increasing thyroid reactivity and autoimmune thyroiditis.

Prospective Study of Thyroid Function
In this paper, the investigators point out that in places of the world where there is selenium deficiency in the soil, there is known to be a higher incidence of thyroiditis due to the decreased activity of the selenium-dependent glutathione peroxidase and also the deiodinaze enzyme. Selenium-dependent enzymes have several modifying effects on the immune system. Therefore, even mild selenium insufficiency may contribute to the development and maintenance of autoimmune thyroid disease.

As a consequence of these observations, investigators performed a blinded, placebo-controlled, prospective study in 70 female patients, mean age 47.5 +/- 0.7 years with autoimmune thyroiditis and thyroid peroxidase antibodies (TPOAb) above 350 IU/ml. The primary endpoint of the study was the change in the TPOAb concentrations, with secondary endpoints being changes in TSH and free thyroid hormone levels, as well as ultrasound patterns of the thyroid and the quality of life estimation. It was a combination of clinical and biochemical work, and some relationships to physiologic and anatomical function of the thyroid gland.

Patients were randomized into two age- and antibody- (TPOAb) matched groups; 36 patients received 200mg of sodium selenite a day, orally, for three months, and 34 patients received a placebo. All of the variables were maintained as constants. All patients were substituted with L-T(4) to maintain TSH within the normal range. The antibody-to-thyroperoxidase was studied over three months.

Study Results
The results were quite interesting. Nine patients in the selenium-treated group had completely normalized antibody concentrations in contrast to only two patients in the placebo group after the treatment protocol, with a P level of significant difference between the two groups less than 0.01. Ultrasound of the thyroid showed normalized echogenicity in the patients who had the normalized antibodies versus those in the placebo group for whom there was no lowering of antibodies, and who still had the abnormal echo study.

This would suggest a correlation between clinical symptoms, organ activity and structure, and a biochemical marker from selenium supplementation in patients who would traditionally be diagnosed as having Grave's disease, or perhaps Hashimoto's disease, as it relates to aspects of immune thyroiditis.

This opens up a more general topic. How many environmental modulators are there for this range of complex conditions that we try to codify with medical taxonomy into specific disease groups? Different pathways of physiological uniqueness lead to the phenotype of this disorder, so there is a genotype/phenotype connection through this environmental modulation, in this case, selenium.

Another interesting example is prostate cancer in individuals who are put on specific kinds of medication, such as flutamide. Flutamide is associated with a specific hepatotoxicity. Is there a difference among patients based on relative susceptibility to hepatotoxicity with this medication? First, in this study, the investigators knew that flutamide is metabolized principally through the cytochrome P450 phase I enzyme called CYP1A2. That turns out to be the principal isoform of P450 that metabolizes caffeine as well. The investigators asked if there was an association between altered caffeine clearance and relative susceptibility to hepatotoxicity in this drug in individuals who have prostate cancer.

We are starting to see this is as a pharmacogenomic approach, as a personalized medicine approach, asking not just what does this drug do in a generalized average prostate cancer patient, but what might it do in a specific patient who has a specific detoxification genotype. The caffeine test was used to measure the activity of cytochrome P450 in individuals who had prostate cancer who were given flutamide.

A recent paper described the application of this particular procedure of the use of the intervention with a caffeine clearance test. [3] The investigators were able to show that individuals given flutamide who subsequently had elevated liver enzyme profiles were those who had low caffeine clearance and increased residence of the drug without proper metabolism. We are looking at slow metabolizers, basically. This is an interesting application of personalized medicine concept. It involves knowing something about the patient before intervening with a medication that requires specific phase I and phase II.

Complex Mixtures Versus Single Molecules

One needs to be informed about the potentially broad array of influences a complex mixture of molecules may have on function. Their influences differ from those of single molecules against single endpoints. The effect of DES against a single endpoint may be quite different from that of a complex mixture. This is both good news and bad news. The good news is you may cover a lot more bases across the genotype/phenotype connection, the polygene or multigene connection, by using a complex mixture of the right composition and the right formulation. The bad news is it is difficult to know all the permutations and combinations.

It is hard enough to know the mechanism of just one substance. For instance, we used to think the statins worked only as HMG CoA reductase inhibitors. Those were highly studied. Now we find their effects on the inflammatory pathway may be even more profound than their role as HMG CoA reductase inhibitors. They may be working as antiinflammatories.

Positive/Negative Aspects of Understanding Complex Mixtures

Even understanding single molecules mechanistically can be complex and confusing. Mixtures become orders of magnitude more confusing and complex. We have to tie together clinical observations, safety information, cursory mechanistic understanding, and an integrated approach, and be willing to live with a bit of uncertainty about a possible positive clinical outcome. This is making way for a new approach, because our strategy in pharmacology has been focused on single agents, owning synthetic single molecules, and looking at single endpoint analysis.

The new medicine, based on multigenes and the gene/phenotype connection through the environment, is causing us to look at multigene/multiagent responses through various pathways that give rise to the phenotype we call pathology. Now we are looking at mixtures, and mixtures will create opportunities for exciting breakthroughs. They will also lead to more confusion, because we will not be able to define all the mechanisms of mixtures and the permutations and combinations as effectively as we can with single molecules. This concept has both positive and negative aspects.

We can apply this concept to cardiovascular disease, in preparation for our 10th International Symposium on Functional Medicine in May. We now recognize that atherosclerosis is more than a cholesterol disease. For years we made it as simple as we could, and in so doing may have thrown out the baby with the bath water by getting everyone to focus on saturated fats and cholesterol. Cholesterol is only part of a story that gives rise to different functions within the vasculature that ultimately arrive at some state of dysfunction and a named disease, a cardiopathology.

The primary person who helped me understand this complex story was Dr. Earl Benditt. Dr. Benditt, who was a professor of medicine in the school of pathology at the University of Washington, wrote a brilliant article that appeared in *Scientific American* in the 1980s. Titled "The Origin of Atherosclerosis," it described his work on monoclonal hyperplasia. [4]Unfortunately, Dr. Benditt passed away in 1996 at the age of 80. He made incredible contributions to our understanding of the weblike interactions of genes and environment to give rise to cardiopathology. It would be difficult to summarize his insights and contributions. He led us to understand that many cardiovascular risk factors-high cholesterol, smoking, alcohol-could be connected to a single potential mechanism. That mechanism is related to the concept, first proposed by German physiologist Rudolph Virchow in the 19th century, that atherosclerosis is an inflammatory condition.

Atherosclerosis and Inflammation

What Dr. Benditt found was that the lesion of an atheroma was initiated as a consequence of a monoclonal injury to a specific cell in the intima, causing it to undergo replicative growth. This would be similar to a benign tumor. It is not a malignancy as such; it doesn't have metastatic capability. It is more like a wart on the inside of the artery. As a consequence of the monoclonal hyperplasia or injury, to use the Virchow injury model of atherosclerosis, this particular lesion, as it grew, started to interrupt the laminar flow of the arterial system and induced eddy-diffusion. Eddy-diffusion produces a confused or chaotic system, which then activates white cells. Benditt's concept was that it led to later-stage infiltration of the lesion with immune cells releasing oxidants and producing their particular injurious effects on tissues until it later started to be "healed" or isolated from the body by infiltration with lipid and later calcium to form the sclerotic lesion.

Monoclonal Hyperplasia

The initial atherogenic process was the monoclonal hyperplasia. What initiates this, according to Benditt, are mutagens, including many of the traditional cardiovascular risk factors. These could be things that had mutagenic capability such as smoking, polynuclear aromatic hydrocarbons, oxidants in cigarette smoke, cholesterol oxides from fried foods containing cholesterol, or heat-injured cholesterol. All of these could create possible mutagenic upregulation of cell proliferation in the arterial intima.

Now we know that other inflammatory mediators, when produced in the blood, can also cause white cells to roll, to adhere, and to infiltrate the intima. These, too, can be potentially injurious mutagenic agents

when you have higher levels of inflammatory mediators like intracellular adhesion molecule 1 or interleukin-1 or -2. All of these may increase the risk to monoclonal hyperplastic conditions. Early on, Dr. Benditt got us thinking about an underlying mechanism that would incorporate many of the observable processes that are associated with cardiovascular disease.

Dr. Benditt's Biography

A look at Dr. Benditt's biography yields interesting information. [5] He was a graduate of Swarthmore, went to Harvard Medical School, and had an early interest in research. In his senior year, he worked on thiamin pyrophosphate and cardiopathies associated with B-vitamin insufficiency. That was in 1941, at the time of WWII. He understood the genes/environment connection well before it was fully explored. He continued in the 1950s with a series of studies on dietary effects on cirrhosis, looking at methionine and choline and the relationship to steatotic disorders. He explored the way dietary variables, through the folate cycle, reduced the risk of fatty infiltration of the liver and how that connects to homocysteine. It was a line of thought similar to that of Kilmer McCully.

From 1949 through the middle 1950s, Dr. Benditt became more interested in inflammation. He conducted experiments with Al Dorfman in various disorders, including rheumatoid arthritis and, later, cardiovascular disease. He started to understand the Virchow injury theory of atherosclerosis. You can see how intellectual lines of thought can merge from open-minded thinkers who think out of the box, and who are not willing to accept mental models without some deep reflection.

Thinking Outside the Box

From 1950 through 1990, Dr. Benditt and his colleagues were incredibly productive. They looked at the molecular connection to vascular disease and atherogenesis. If we looked at the 1960s, 1970s, and 1980s, we see the reaction-to-injury discussion. Dr. Benditt's work opened the field of atherosclerosis research and created a different environment for study of the multiple risk factors associated with heart disease.

I honor Dr. Benditt on many levels, not only for the monoclonal theory of hyperplasia, but more important, for opening up a construct from which we could start to construct a model predictive of cardiovascular disease beyond elevated LDL cholesterol

This discussion sets the tone for exploring many other variables that influence vascular endothelial dynamics and physiology, including hyperinsulinemia. What role does diet play in modulating insulin, and how does that interface with cardiovascular disease incidence? We might examine the glycemic index of foods. A lower-glycemic-index diet is associated with a more balanced insulin level and more significant insulin sensitivity. This result has been shown in a number of papers, including a recent article that appeared in *American Journal of Clinical Nutrition.* That article discussed glycemic index, glycemic load, and the relationship to insulin sensitivity. [6]

High glycemic diets are also associated with hyperinsulinemia, and the influence of elevated insulin on the adipocyte, which accumulates fat. There is an obesity connection with hyperinsulinemia and insulin resistance. High glycemic diets encourage hyperinsulinemia and increased insulin-driven fat accumulation, or obesity. That conclusion was recently described in the *American Journal of Clinical Nutrition*. [7] Stabilizing insulin levels occurs with a lower-glycemic index diet. Such a diet includes legumes, complex unrefined carbohydrate that is high in soluble and insoluble fiber, balanced protein/carbohydrate, less simple sugars, and less white starch products.

Soy isoflavones and soy itself play roles in the glycemic index in normalizing serum lipids, including the conversion of cholesterol to its damaged oxidized form, and in lowering of homocysteine. Some interesting studies demonstrate that soy has hypercholesterolemic effects, and that it also lowers oxidized forms of cholesterol in the blood and reduces homocysteine.

In one study investigators administered single daily doses of soybean phytosterols by adding them to ground beef. [8] Soy decreased serum total cholesterol and LDL cholesterol in young, mildly hypercholesterolemic individuals. These individuals were administered phytosterols like b-sitosterol, 2.7 grams per day, in all likelihood accompanied by milligram doses of soy isoflavones. The soybean has neutral plant sterols, b-sitosterol , campesterol, and stigmasterol that have a favorable influence on cholesterol dynamics.

When we look at the effects of soy isoflavones and soy protein on serum lipoproteins and total plasma homocysteine and oxidized cholesterol, we see that this combination also has a favorable effect on lowering cholesterol and homocysteine. This is another article in the *American Journal of Nutrition.* [9] Interesting research on cardiovascular risk factors may help manipulate the genotype into a favorable phenotype

Regarding hormones in postmenopausal women, we now find Premarin and Provera may not be the cardiac protectors we thought they were. Therefore, there may be other ways of achieving natural hormone balance through complex foods that contain natural phytosterols and phytoestrogens, genistein and daidzein. The results of the HERS Trial showed that cardiovascular disease outcomes were not so favorable 6.8 years after examining postmenopausal women who were supplemented with Premarin and Provera. [10]

We are starting to see that this is more than a single marker, cholesterol and heart disease. Extended variables tie together with vascular dynamics. That is an excellent segue to our Clinician/Researcher of the Month interview on Side II. Dr. John Cooke will tell us, from his perspective and 20 years of research, how this field has gone from empirical to experimental to clinic

INTERVIEW TRANSCRIPT

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JB: Our current Clinician/Researcher of the Month is a leader in the field of nutritional and functional medicine. With more than 20 years of experience, this researcher brings us a wellspring of information and news to use. It is a great pleasure to introduce Dr. John P. Cooke, a professor of cardiology at Stanford University Medical School. He has written more than 100 peer-reviewed papers as well as 100 other articles. I have read a number of those articles, and I can say without equivocation that Dr. Cooke

has set a standard in terms of the way we might view good science and good clinical work pertaining to nutritional medicine. Dr. Cooke has the kind of scientific and clinical background that can help us understand complex mechanisms as to how nutrients interface with physiological function.

Dr. Cooke, welcome to Functional Medicine Update. I am familiar with your work all the way back to 1982. I cited one of your papers from that period, in which you described the use of therapeutic doses of vitamin A in the management of ichthyosiform erythroderma. 11 Over the last 20 years, you have examined many variables. The one we are going to talk about extensively today is the connection of nutrition to nitric oxide (NO) modulation, vascular function, and the nutrient arginine.

Endothelial-Relaxing Factor

JB: In the late 1980s that you published a paper that talked about N-acetylcysteine potentiating platelet inhibition that was activated by endothelial-relaxing factor (EDRF). 12 It is interesting historically because EDRF was the precursor of what we now know to be nitric oxide so you were obviously in this field even before the discovery of the molecule that was responsible for vasoreactivity.

JC: That's right. First of all, Dr. Bland, thanks for inviting me to be on Functional Medicine Update. You have done a lot in terms of educating physicians about what we can do nutritionally to improve health. You're right about the fact that my focus for the last 20 years has been on how nutrition affects the endothelium, the lining of the blood vessel, and I've come to the conclusion that the healthy endothelium is really the cardiovascular cure. If we can improve endothelial health, we can prevent heart attack and stroke. We can prevent the development of atherosclerosis and halt it in its progression if we improve endothelial function.

In reference to that article you mentioned, in 1983 I started working in this area as a fellow in cardiovascular medicine at the Mayo Clinic. I had the opportunity to work with Paul Vanhoutte. At the time I walked into his laboratory, it was just a couple of years after Furchgott had made his discovery that the endothelium makes a very powerful relaxing factor. Furchgott won the Nobel Prize for that. He's a very bright fellow. The nature of EDRF evaded his analysis and that of many other capable scientists for about six years. In 1986, Ignarro, Furchgott and Moncada discovered that EDRF was nitric oxide.

When I walked into the laboratory we didn't know what it was. Now we know that this factor released from the endothelium is a very potent relaxer of blood vessels, but it also is our self-defense against heart attack and stroke.

L-Arginine Research

JB: In the early 1990s, you published papers, first in animal models, and then later in human trials, looking at the anti-atherogenic effects of the precursor to nitric oxide, L-arginine, and how it may relate to N-acetylcysteine and antioxidants. This is a fascinating, evolving story in which you have been involved, moving from the esoterica of biochemistry into the clinical arena.

JC: I started off at the Mayo Clinic. I went to Harvard, where I was an assistant professor. That's when we found that arginine, the precursor of NO, was in short supply for individuals who had high cholesterol or atherosclerosis. We began to investigate how we might enhance the production of this molecule by the vessel, this potent relaxer.

What we learned was that arginine was the precursor of NO, which is the EDRF. We were the first to show that in animals with impaired endothelial function due to high cholesterol, we could improve

endothelial function, endothelium-dependent vasodilation, simply by giving more of the precursor. We went on to show, in humans as well, that infusions and oral administration of arginine could actually improve endothelial function in hypercholesterolemic individuals.

Arginine and NO Synthesis
JB: From a biochemical perspective, as I recall, the Km value of NO synthase for arginine doesn't suggest that it is working considerably away from saturation. A traditional biochemist might say you can't give arginine and improve the synthesis of NO.
JC: But they did. When we came out with this finding, the scientific community was highly skeptical and for the good reason you just mentioned. The NO synthase should have plenty of arginine circulating for it to make NO. The Km value of NO synthase is in a micromolar range, as you mentioned, and the amount of arginine circulating in the blood is in a 20-50 micromolar range, so there should be sufficient amounts of L-arginine and you shouldn't need any more.

In fact, we showed that in hypercholesterolemic individuals, there was no reduction in arginine levels in the bloodstream. That was before we knew about asymmetrical dimethyl arginine (ADMA).

Asymmetrical Dimethyl Arginine
JB: Tell us about ADMA. That's a fascinating story.
JC: Other physicians and scientists reproduced our finding. It gave rise to something called the arginine paradox, because the pharmakinetic information and the in vitro data didn't fit with the in vivo data. There shouldn't be any rate limitation for arginine, but we were able to show that we could improve function with L-arginine administration. The explanation came later, when Patrick Vallance and Salvadore Moncada discovered ADMA, asymmetrical dimethylarginine, in human urine. This is an endogenous inhibitor of the NO synthase pathway, so it blocks arginine's conversion to NO by NO synthase.

ADMA and Endothelial Dysfunction
JB: As I recall, you were the principal author of a paper published around 1998, in which you described the relationship of ADMA to endothelial dysfunction. 13
JC: That's right. We took up the baton from Patrick Vallance and Salvadore Moncada and went on show that in individuals with risk factors-high cholesterol, high homocysteine levels, diabetes, insulin resistance-ADMA is elevated in the plasma. It inhibits the production of NO. Moreover, it can be overcome by nutritional intervention, and that intervention is arginine supplementation. We can restore the production of NO by administration of arginine to people who have risk factors.

iNOS
JB: How would you respond to an individuals who tells you that's all well and good in the endothelium, but what about the stimulation of inducible NO synthase through iNOS? If you get immune hyperstimulation of NO in combination with superoxide to form peroxynitrite, don't you have a benefit working against a disadvantage?
JC:You are referring to the fact that in certain types of inflammation, you can get the induction of another form of NO synthase, the inducible form of NO synthase. That enzyme is associated with inflammation and infection. This enzyme produces huge amounts of NO, and it's really another form of defense, a defense against foreign invaders It produces NO as well as superoxide anion, so you get formation of this very destructive free radical peroxynitrite anion, which you mentioned.

The body has this self-defense mechanism to destroy bacteria, to destroy invading cells. That pathway gets activated. Arginine is a precursor for NO in that pathway as well. It has led people to raise some concern about arginine supplementation in hypercholesterolemia and atherosclerosis. In atherosclerosis, particularly in the lesion, you have the induction of iNOS, so that's raised some concern.

Benefits of iNOS Induction

But in the last couple of years, we've been able to show in animal models that the induction of iNOS may actually be a good thing in terms of atherosclerotic plaque. By making NO, it can actually reduce the infiltration of monocytes and reduce the infiltration of inflammatory cells into the plaque. We were able to show that arginine supplementation in animals with pre-existing plaques actually reduced plaque size, caused plaque regression. That has now been documented by other investigators.

There is now less concern about iNOS as a bad guy. In fact, I think it's a good guy in terms of controlling inflammation in the vessel wall. There's now an iNOS knockout, so genetic or pharmacologic antagonism of iNOS actually accelerates atherosclerosis. In short, iNOS, in some situations, can actually be beneficial.

Effects of N-Acetylcysteine

JB: Your 1989 paper described N-acetylcysteine potentiating platelet inhibition by what was then called EDRF but what would now be called NO. If we examine that 1989 work from a 2002 perspective, might we find that N-acetylcysteine influences the formation of peroxynitrite? N-acetylcysteine is, in part, an antioxidant in that it affects intracellular redox potential. Could it have other effects that lead to a positive influence on the role of NO in endothelial function?

JC: I think that's right. N-acetylcysteine is an antioxidant. The NO synthase pathway takes two hits in our patients who have atherosclerosis. One hit is the ADMA, which reduces production of NO. The other hit is increased oxidative stress. When you have increased oxidative stress in the vessel wall, you get breakdown of NO into peroxynitrite anion, and that's not a good thing.

What we have found with arginine supplementation is that it not only increases NO production, but it also reduces superoxide anion production. There are multiple explanations for that, and. I won't be able to go into them in the context of this talk. There are a number of ways to improve vascular dysfunction in individuals with hypercholesterolemia or atherosclerosis. One way is to enhance NO production. Another way is to reduce its breakdown.

The Cardiovascular Cure

JB: I was able to get a prepublication copy of your new book, The Cardiovascular Cure, subtitled "How to Strengthen Your Self-Defense against Heart Attack and Stroke," which demythologizes for the reader a lot of the basic applied biochemistry and cardiac physiology. I understand this book has just been released and is available to the public.

JC: That's right. It's available widely. The premise of that book is that the cardiovascular cure is a healthy endothelium. There are many paths to a healthy endothelium. I talk about those in the book, practical things that patients can do to improve their endothelial function, including diet, nutrition, exercise, and nutritional supplements.

Arginine Deficiency in Vascular Disorders

JB: One paper you wrote was an editorial titled "Is Atherosclerosis an Arginine Deficiency Disease?" 14

In that editorial you pose some remarkable constructs that very few people have talked about. (Kruchevsky, whom I heard speak some 25 years ago about the arginine connection to hypercholesterolemia, was perhaps the precursor at the Wistar Institute to this whole field). Very few people have talked about arginine insufficiency as part of a vascular disorder. What kind of response did you get to that article?
JC: Initially, when we first proposed this idea, people were very skeptical. Now, with more work we and others have done, there is a good scientific foundation for the idea that in patients with atherosclerosis, arginine may actually be rate-limiting, and relative arginine deficiency may play a role in endothelial dysfunction and atherosclerosis. A number of investigators like ourselves have now shown that arginine supplementation not only improves endothelial function, but can also reduce the progression of atherosclerosis in animal models.

It has yet to be shown in humans that arginine supplementation can reduce the progression of atherosclerosis, but we have shown in humans (and others have confirmed) that we can improve endothelial function with arginine supplementation in individuals with high cholesterol and atherosclerosis. Moreover, that improvement in endothelial function is associated with improvements in symptoms. Several published papers from Mayo Clinic, from our group, and from others now show you can improve endothelial function.

You can see with improvements in walking distance, for example, in patients with coronary and peripheral arterial disease. Their exercise capacity is improved, their symptoms are reduced, and their quality of life is improved. These are all double-blind, placebo-controlled, randomized trials. They're small trials, but they are rigorous ones. It's my feeling that supplementation can be useful as a nutritional adjunct to our standard medical therapy.

Supplemental Arginine Levels
JB: You published two different papers on this topic, one in 1999 and one in 2000. One was titled "Dietary L-Arginine and Nitric Oxide." The other described the formulation of a delivery system for an arginine nutritional product in a bar form and its relationship to endothelial function. 15,16 What level of arginine was administered to subjects in these clinical trials?
JC: The arginine used in clinical trials has been in the range of 3 to 9 grams. In our normal Western diet, we get about 2 to 4 grams of arginine a day, so in most of the trials, the arginine supplementation was in the range of 3, 6, or even 9 grams. It represented a doubling or tripling of arginine intake. We just finished an NIH-funded dose-ranging study in patients with peripheral arterial disease, looking at the primary endpoint of treadmill exercise time.

In that study, we found that 3 grams a day had the optimal effect. In these patients we found about a 20 percent improvement in walking distance, which is modest but useful and certainly something that can be considered as a therapeutic adjunct. I would say, based on all the work that's available in the literature right now, somewhere in the range of 3 to 6 grams a day would probably be the right dose if you're trying to improve someone's endothelial function.

Effects on Cholesterol of Animal versus Vegetable Protein
JB: Dr. Kruchevsky discussed the difference between the effects of animal protein and vegetable protein on cholesterol levels. We've typically thought of cholesterol as a lipid problem, but he pointed out it can be a protein problem, and there is a difference between the cholesterol effects of animal and vegetable

protein. He postulated the difference was the arginine-to-lysine ratio in animal versus vegetable protein. As he explained, soy protein, for instance, is high in arginine and low in lysine relative to, say, casein milk protein, which has a higher ratio of lysine to arginine. He suggested, in the 1960s, that a cholesterol thermostat was somehow tied to arginine/lysine ratios. It seems, in light of your more recent work, that may be a different interpretation through the NO story, and our dietary protein selections may influence this as well.
JC: Right. One thing we have not observed in our studies is any change in cholesterol levels with arginine supplementation. The effect of arginine is not through a direct effect on cholesterol, but through a direct effect on the NO synthase pathway. There are other things to be said, though, about vegetable versus meat protein. I think vegetable protein is superior to meat protein for other reasons as well.

Vegetable protein contains less methionine. Of course, methionine gets converted to homocysteine, which is injurious to the endothelium, and there's more of that in red meat. Red meat contains more saturated fat, and it doesn't have all the beneficial fibers and phytochemicals that vegetable protein contains.

Phytochemicals and Vascular Disease
JB: You've published papers on soy isoflavones and their relationship to vascular disease. Do you think phytochemicals also influence some of these relationships?
JC: That's right. We did a study in which we looked at postmenopausal hypercholesterolemic women and sought to determine if we could improve their vessel function with isoflavone supplementation. 17 In that study, we provided 50 mg of a genistein and daidzein combination daily to the women, which is equivalent to about 50 grams of soy protein a day. The soy isoflavone supplementation was in the form of a pill.

As our primary endpoint, we looked at vascular function using duplex ultrasonography to study the brachial artery of the arm. We found, in comparison to placebo, that soy isoflavones improved flow-mediated vasodilation, but they also improved endothelium-independent vasodilation significantly, actually even more than the endothelium-mediated vasodilation. Isoflavones have a direct effect on the vascular smooth muscle. Our conclusion was that soy isoflavones improve vasodilation in postmenopausal hypercholesterolemic women. The mechanism in this case may be endothelium-independent.

Homocysteine and NO
JB: That connects to another observation you mentioned earlier in regard to the homocysteine atherogenic model. You recently published a paper about the connection between homocysteine and the NO component. Would you tell us about that?
JC: We just published an article in Circulation. 18 Our hypothesis is that homocysteine impairs blood vessels and accelerates atherosclerosis by directly impairing the NO synthase pathway. We worked out the mechanism by which it does so. We find homocysteine causes ADMA to accumulate in blood vessels in human patients and animal models. We found homocysteine directly interferes with the breakdown of ADMA. ADMA is not metabolized, and it accumulates and impairs NO synthesis.

Clinical Application
JB: You appear to be developing an integrated approach of functional cardiology. In the past, we have looked at cardiology in separate pieces rather than as an integrated model. You have presented this information to your colleagues and observed patients' response. Can you tell our listeners how they might

deliver this information to their patients?
JC: I think arginine supplementation is a nice adjunct to standard medical therapy. I am a believer in the traditional medications that we have, the statin ACE inhibitors, all of which improve endothelial function. And, of course, I believe in anti-platelet therapy for patients with cardiovascular disease. But we shouldn't ignore the very beneficial effects of nutrition. In my book, The Cardiovascular Cure, I talk about the right kind of diet. I'm recommending a modified Mediterranean Diet these days. Also, I talk about how that might be supplemented in some cases.

My own feeling is that if you're healthy and you have a healthy endothelium, you really don't need supplementation; you just need a good diet and exercise. However, if you have heart disease, you might benefit. You may have a relative arginine deficiency, and arginine supplementation may be useful. I'm currently using about 3 grams a day. I watch to see if the patient gets some benefit from that. I look to see if he or she has a reduction in angina if the individual has coronary disease. I look for an improvement in walking distance. If it's working for the patient, I continue that therapy. If not, I discontinue it and we try something else. It's just like any other medication.

Ginkgo biloba
JB: In your book, you speak about cardiovascular adjunctive nutrients, one of which is Ginkgo biloba. Could you give us some insight into how that fits into this array of nutrient modulators?
JC: I have an interest in peripheral arterial disease. I see a lot of patients with intermittent claudication. There is good data from Europe regarding Ginkgo biloba, small trials that suggest it's modestly useful to improve walking distance in patients with peripheral arterial disease. The data are sufficiently interesting that we were able to put together a proposal that was funded by the NIH to determine if Ginkgo biloba is useful in a large trial in peripheral arterial disease. That trial is underway.

We'd like to confirm the findings in Europe and see if Ginkgo is useful in peripheral arterial disease. There is a fair amount of data to support it. We want to confirm that and try to understand the mechanism. Again, we think the mechanism might be due to a beneficial effect on the endothelium, as Ginkgo biloba is an antioxidant and may preserve NO and improve blood flow in that manner.

Insulin and NO
JB: It sounds as though you are developing a strategy that can be readily implemented, a diet that's moderate in fat, higher in monounsaturates and essential fatty acids. This diet may contain more soy protein with the isoflavones, more fiber from unrefined carbohydrate. That ties us to the last link I know that you have been investigating, the insulin resistance/hyperinsulinemia connection. I notice you have written collaborative papers with Gerald Reaven. Could you tell us about the insulin connection to the NO story?
JC: Gerry Reaven moved into the cardiology division here at Stanford a couple of years ago and took an office right next to mine. That proximity led us to begin talking a bit. At the time, I had some data from the laboratory suggesting that ADMA, this endogenous inhibitor of the NO synthase pathway, was playing a role in endothelial dysfunction in hypercholesterolemia. Gerry, being interested in insulin resistance and being the father of the insulin resistance syndrome, asked me if I knew what would occur in that condition. I didn't know at the time. He does these very elegant characterizations of insulin sensitivity in his patients. We were able to get samples from his patients and look for a relationship between insulin resistance and ADMA.

We found there is a striking correlation between insulin resistance and ADMA levels. The more insulin resistance, the higher the ADMA levels. This may be one way in which insulin resistance causes or accelerates atherosclerosis, through this endothelial impairment. We have subsequently done a study with Gerry. It was a lot of fun to see if we could improve insulin sensitivity. If we can reduce insulin resistance, what effect would it have on ADMA? We did a study to show that Metformin could improve insulin sensitivity, and that was associated with the reduction in ADMA levels.

Arginine Supplementation in Insulin Resistance
JB: The next question I'm sure you're investigating is, does arginine supplementation in an insulin-resistant patient lower ADMA and improve vascular function?
JC: That's an interesting question and, as a matter of fact, we need to investigate that, but haven't started yet. We've got so many projects on our hands. It certainly would be interesting to look at that.

Conclusion
JB: Dr. Cooke, this has been a fascinating discussion. Your book, The Cardiovascular Cure, which fortunately is now available to readers, will help fill some of the gaps we just touched on in this discussion. Thank you for your 20 years of extraordinary work to open up this field and give us more tools to understand the web of cardiovascular function and its connection with the environment, particularly nutrition

I would like to talk about the modulation of inflammatory markers of risk to cardiovascular disease, which include elevated high-sensitivity C-reactive protein and serum amyloid A protein. Inflammatory markers of risk to cardiovascular disease include elevated high-sensitivity C-reactive protein and serum amyloid A protein.

A recent paper in the *American Journal of Clinical Nutrition* discusses the ability of fish oil, EPA omega-3 fatty acids, to suppress inflammatory mediators like TNF-a that are produced by peripheral blood mononuclear cells and associated with polymorphisms in the gene that codes for TNF-a production. [19] This study indicates that not all patients have the same response to supplementation with fish oils. It depends on their genetic uniqueness, the polymorphisms of sensitivity or selectivity. Omega-3 fatty acids have a dramatic effect on the production of inflammatory cytokines in some individuals, which may affect cardiovascular and other chronic disease risk. The same dose given to other individuals may have little or no influence on inflammatory mediators.

This study points out that the ability of fish oil to decrease TNF-a production is influenced by polymorphisms that relate to TNF production and activity. We should not see all patients as equal. That is part of the magic and confusion of functional medicine therapy in a personalized medicine concept. One must personalize treatment to the individual, recognizing that general principles exist but the results may not be identical. Giving 6-10 grams of fish oil per day to all patients will not bring the same response in their high-sensitivity CRP or their TNF-a levels.

Inflammation in Neurodegenerative Disease
It is not just vascular disease that is associated with inflammation, but also neurodegenerative disease. One mechanism may track against many ICD9 codes. Inflammatory conditions are involved in nearly all chronic, degenerative, age-related diseases.

We might consider a diet enriched in food or nutrients that are known to have antiinflammatory potential, not just the omega-3 fatty acids, but other substances such as vitamin C, vitamin E, and certain flavonoids. Researchers in a recent animal study gave Fischer 344 rats various types of food containing higher levels of nutrients that modulate inflammatory mediators. These might be considered antiinflammatory nutrients found in foods like apples, which contain many flavonoids, spiulina a unicellualr alga that provides chlorophyll and other antioxidants, or cucumbers that contain various types of polyphenols. While animals given spirulina or apples had a significant increase in antiinflammatory activity and a reversal in b adrenergic function, cucumber was without a significant effect. This result suggests we could retard some neurodegenerative changes in the biochemistry of the nervous system in these animals by administering concentrates of foods containing specific agents that promote proper inflammatory balance. This study appeared in the *Journal of Neuroscience*. [20]

It is obviously a big jump from an animal study in rats with neurodegeneration to humans. The model does, however, help us understand how these factors may work together in a complex environment in which people are making selections about what they eat, how they live, what they breathe, and what they drink every day. It depends on their workplace environments, their home environments, and their food selection habits, which are modifiable factors that interface with their genotype.

Effects of Arginine on Vascular Function

Dr. Cooke talked about arginine. A recently published paper looks at the effect of arginine on blood pressure and the incidence of acute coronary events in men in Finland. In this prospective cohort trial, investigators studied men who were free of prior coronary disease between 1984 and 1989 to see if dietary arginine levels had any influence on their vascular disease incidence. [21] They found arginine intake was not consistently associated with blood pressure and did not appear to be associated with risk of coronary events in these middle-aged men.

That result does not rule out what Dr. Cooke was telling us, because there are many other variables. Many genotypes underlie a Finnish population that may be different from another population. One might arrive at a different conclusion by evaluating dietary arginine intake versus intake of other amino acids in the Finnish diet and comparing the results to dietary arginine intake in other diets. Do you need to give therapeutic doses of isolated arginine, the 3-6 grams per day that Dr. Cooke referred to, in individuals with existing disease, to promote function?

Arginylated Protein

Arginine's role may be broader than just modulating nitric oxide or influencing unsymmetrical demethylarginine. A paper that appeared in *Science* magazine opens up another part of the story. [22] It seems arginine also can react with various proteins to undergo what's called arginylation. It can combine with specific proteins to form an arginylated protein. These N-terminal arginylated proteins may be related to different cardiovascular functions. That is emerging from this recent research.

Investigators in this study showed that the N-terminal cysteine, in contrast to N-terminal aspartate and glutamate, is oxidized before arginylation. This result suggests the arginylation branch of the pathway functions as an oxygen sensor and may have something to do with monitoring redox potential in the cell and the oxidation/reduction balance. The arginine story may be a lot more complicated than just

modulating NO synthase and the production of NO. Arginine may have other relationships in regard to its availability for arginylation and cell signaling and how that interrelates with the control of redox potential within the cell, the oxidant/antioxidant balance. Dr. Cooke's work in primates, other lower animals, and now in human clinical trials certainly demonstrates the potential benefits of therapeutic doses of arginine in individuals who have different kinds of vascular endothelial dysfunction.

Dr. Martin Pall, a former *FMU* Clinician/Researcher of the Month, wrote an interesting paper that appeared in *FASEB*[23]. Dr. Pall is from the School of Molecular Biosciences, Washington State University. In his FMU interview he discussed his work on chronic fatigue syndrome/fibromyalgia and multiple chemical sensitivity. He proposed an explanation for these disorders involving a feed-forward mechanism in the overproduction of NO and peroxynitrite in relation to immune hypersensitivity reactions. This overproduction is driven through some hypothalamus/pituitary central factor in the brain by exposure to an activating agent or series of agents. Those agents could be toxins, allergens, or infectious agents, which lock a person in a feed-forward cycle toward immune dysfunction and excessive production of peroxynitrite.

Dr. Pall moved to the next level in this elegant paper that appeared in the *FASEB Journal*. The title of this paper is "NMDA Sensitization and Stimulation by Peroxynitrite, Nitric Oxide, and Organic Solvents as the Mechanism of Chemical Sensitivity in Multiple Chemical Sensitivity." In this paper he examines the root origins of some complex disorders, going back to Dr. Strohman's work that I talked about earlier.

Origins of MCS

Dr. Pall points out that multiple chemical sensitivity (MCS) is a condition in which previous exposure to hydrophobic organic solvents or pesticides appears to render an individual hypersensitive to a wide range of chemicals, including organic solvents. The mechanism has never been fully understood, because when you take away the exposure the person continues to have the symptoms. The hypersensitivity is often exquisite, with MCS individuals showing sensitivity that appears to be at least two orders of magnitude greater to the same chemical exposure than that of normal individuals. These are the "yellow canaries."

In this work, Dr. Pall argues that interacting mechanisms that explain this heightened sensitivity based on his earlier theory with MCS and the relationship to CFS and fibromyalgia. It has to do with the sensitivity of the NMDA receptor sites, the excitotoxic receptor sites in the nervous system, and their relationship to peroxynitrite production through feed-forward cycles. It has been demonstrated NO-mediated stimulation of neurotransmitter release, peroxy-mediated ATP depletion, and consequent hypersensitivity of the NMDA receptors. The suggestion is that a centrally mediated neuronal component is translated into the immune system to cause a feed-forward of continued oxidative stress, peroxynitrite-induced injury, neuronal hypersensitivity, and depletion of ATP stores that leads to the fatigue.

MCS Treatment of Choice

The treatment of choice, to use a euphemism, would be detoxification, repletion of mitochondria, which we call mitochondrial resuscitation. Nutrients used include coenzyme Q10, N-acetylcarnitine, N-acetylcysteine, vitamin E, and selenium. We would also try to rebuild cellular membranes and immune system activity. Essential fatty acids may also play an important role, along with those nutrients of the B-complex vitamin family in therapeutic doses that help repair and support proper mitochondrial metabolism. This might be a place where high-dose niacinamide might be very useful; doses in the 1500 mg-per-day or greater level.

Dr. Pall is beginning to develop a concept that integrates much of what we have learned about these complex disorders, integrating the gene/phenotype connection in a logical potential therapeutic manner. What we will ultimately see emerge from this type of research are predictive strategies for the management of complex personalized illnesses, even though we have not yet done the double-blind, placebo-controlled trials. This is an exciting chapter, and we thank Dr. Cooke for his contribution over 20 years to our emerging insight.

We will see you in December.

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