December 2002 Issue | Mark C. Houston, MD, SCH, FACP, FAHA Associate Clinical Professor of Medicine

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Welcome to *Functional Medicine Update* for December 2002. For the past several months we have been following the theme of cardiovascular health. It is an increasingly complex picture, but new therapeutic options offer promise. In that spirit, we now raise a question: When should we say enough is enough? When do we have sufficient clinical evidence to move into practice and intervention?

We have been exploring the evidence supporting extended risk factors beyond cholesterol for cardiovascular disease. The question for cardiology now is, when is that proof sufficient? When will there be enough evidence of benefit to support incorporating nutrition and nutritional pharmacology into traditional cardiovascular disease management?

We will deal with that question this month in our Clinician of the Month interview with Dr. Mark Houston. A member of the clinical faculty at Vanderbilt University School of Medicine, Dr. Houston will help us understand aspects of endothelial dynamics with nutraceuticals and nutrition related to cardiovascular disease, in both risk management and treatment.

Let me start the story by going back to two interesting trials, the results of which have now been published. They are the DASH I and DASH II Trials. DASH stands for Dietary Approaches to Stop Hypertension. A report in the New England Journal of Medicine describes the effects on blood pressure of reducing sodium and increasing potassium, magnesium, calcium, and other phytonutrients by the application of the DASH Diet.[1]

The results, which were remarkable, followed previously published papers in the Journal of the American Medical Association and the Archives of Internal Medicine. A 1998 paper by Whelton et al. looked at the efficacy of sodium reduction and weight loss in the treatment of hypertension in older individuals.[2] This was the TONE Study. TONE stands for Trial of Non-Pharmacological Intervention in the Elderly for Hypertensive Disorders. The study was published in the Journal of the American Medical Association. Investigators reported that intervention in modestly hypertensive individuals with modest sodium restriction and a weight management program using diet and lifestyle, was a safe and effective intervention to reduce blood pressure without resorting to pharmacological agents.

Nutrition and Blood Pressure
In another report, published in 1999 in the Archives of Internal Medicine, Svetkey et al. looked at the effect of dietary patterns through the DASH approach on blood pressure and subgroup analysis of the

randomized clinical trial in DASH I. They focused less on sodium restriction than on increasing potassium and magnesium levels from a higher vegetable- and fruit-based diet. This intervention led to significant reductions in both systolic and diastolic blood pressure in modestly hypertensive individuals. The results were comparable to those achieved with common anti-hypertensive medications.[3] From the abstract it is not clear that this is really what they saw; they claim efficacy but no comparative data is cited.

When we saw the paper by Sacks et al. in the New England Journal of Medicine in 2001, we were not surprised to learn the DASH intervention demonstrated the kinds of results they reported in lowering blood pressure. Blood pressure is a large, global variable, however. A number of constituents at the physiological and biochemical levels contribute to the sphygmomanometer measure of blood pressure. What is really going on in the endothelium in arterial dynamics? What is happening in the venous blood system? How do these vasoactive reactive compounds influence the dynamics of tone we ultimately see as altered blood pressure? These questions are leading to new insights into the interface between nutrition and vascular diseases. We are beginning to explore the relationship between nutrients and gene expression and proteomic outcome that relates ultimately to a symptom or sign such as elevated blood pressure

Dr. Mark Houston is the principal author of a review paper titled "The Role of Vascular Biology, Nutrition and Nutraceuticals in the Prevention of Hypertension."[4] This paper outlines, through some 700 citations in the reference list, the advancing understanding of the role of nutrition in endothelial dynamics and, ultimately, hypertension. We discussed this theme with Dr. John Cooke in the November issue of *FMU* and with Nobel Prize winner Dr. Louis Ignarro in September of this year.

We are beginning to develop a complete understanding of the variables that ultimately control large-scale factors like cholesterol, blood sugar, and blood pressure. These factors ultimately are related, at the level of cellular physiology, to changes in endothelial dynamics. Large dietary intervention trials like the DASH studies reveal some of the effects that major changes in macro- and micronutrients can have at the cellular level.

Cumulative Effects/Sudden Outcome

As Dr. Houston points out in his review article, these influences are related in part to altered effects on gene expression and proteomic expression that regulates intercellular mediator molecules and causes functional changes to occur at the cell tissue and organ level. These changes ultimately shift the physiology into a state of alarm, inflammation, and activation. After years of progression we can diagnose this state of activation as vascular disease. It didn't start as a sudden event; it didn't begin with a heart attack in the absence of symptoms. It occurred following years of progressively increasing dysfunction that started off, perhaps, as benignly as a simple change in gene expression initiated by personal behavior related to diet, lifestyle, and exercise.

This paradigm shift is creating a new kind of medicine, based on fundamental physiological mechanisms that lead to ultimate pathologies. Declining steps of functional status within cells progress to tissues, organs, and organ systems. This issue of *FMU* will focus on the continued evolution of our understanding

In May of 2003 we will present our 10th International Symposium on Functional Medicine. The focus will be on "The Heart on Fire—Modifiable Factors beyond Cholesterol." This remarkable symposium will take

place in Tucson, Arizona, at the Westin La Paloma Resort. I encourage you to make plans to be with us May 25-28. In preparation for the symposium, I will be presenting a series of seminars on aspects of biotransformation and intercellular regulators. I have been presenting seminars for 25 years. The title of this year's seminar series is "Improving Health Outcomes through Nutritional Support for Metabolic Transformation." I think you will find this an exciting topic. You will have a chance to learn more about what biotransformation means in terms of chronic disease management, and how it relates to cardiovascular disease

Let me get back to our discussion of the DASH studies and a companion nutritional intervention study that is considered a classic, the Lyon Heart Study discussed in a recent commentary by Dr Alexander Leaf.[5] This study looked at the influence of the Mediterranean Diet on cardiovascular incidence and has been perceived as a strong indication that dietary factors do play a significant role in modifying and modulating the relative risk of vascular disease. One interesting feature of the Lyon Heart Study is the connection of fat amount and fat type to vascular disease.

The Lyon Study found that fat calorie percentage was not as closely tied to heart disease, as was the fatty acid composition of the diet. Risk of vascular disease decreased significantly with increasing levels of intake in the diet of a-linolenic acid, or ALA, which is the first of the members of the omega 3 fatty acid family.

Fat Type, Not Fat Amount
There is an interesting connection between increasing fat of a certain type and decreasing incidence of vascular disease. It seems counterintuitive to the way we have been thinking about dietary fat over the past decade. We have assumed that fat is bad, and that including it in the diet immediately increases atherogenic risk. Researchers have begun to study the type as well as the amount of fat. The Mediterranean Diet contains many complex carbohydrate sources, vegetable protein sources, fiber components, and phytonutrients from specific types of Mediterranean fruits, vegetables, and cereal grains.

When we start putting these components together, we see it is not a drug-like approach. We are not concentrating on a single agent. Instead, we focus on the interaction of a number of dietary variables with complex polymorphic genes to give rise to outcome patterns of health or disease. The key is the whole nutrient/diet relationship.

Diet and Vascular Disease
Dr. Brent Egan, a professor of pharmacology and medicine from the Medical University of South Carolina, comments on Dr. Mark Houston’s article (Reference 4) in which he argues that cellular transduction mechanisms are induced at the cellular and tissue level by various nutrients, and that this can ultimately lead either to cellular function that resists disease or cellular dysfunction that can contribute to disease.[6]

According to Dr. Egan, "There can be no doubt that what we eat impacts gene transcription, protein expression, and enzyme function that ultimately determine our cardiovascular health." This is a remarkable change in philosophy and basic set of assumptions about how diet may influence vascular health and vascular disease. It is beyond satiety; it is beyond the pleasurable aspect of food; it is beyond the prevention of nutrient deficiency diseases like scurvy, beri beri, pellagra, xeropthalmia, and rickets. It looks, instead, at the regulatory factors that appear in specific foods that modify gene expression,

ultimately controlling the function of cells, leading to healthy functional outcome or dysfunctional pathologies

We are beginning to understand why the DASH Study produced the results it did. We are starting to understand why cholesterol-lowering diets may have produced some of the results they did and why statin drug and other lipid-lowering drug trials have shown the value they have. We are beginning to understand why antioxidants may play a role in the prevention and perhaps even the management of dysfunction of the vasculature. We are beginning to understand homocysteine as a risk factor, why inflammation may play a role in vascular disease, and why cooking methods and the peroxidation of oils and cholesterol may produce an atherogenic outcome. We are beginning to understand why chronic infection with organisms like Helicobacter pylori or Chlamydia pneumoniae are increasing risk factors to vascular disease.

The list goes on and on, with literally thousands of independent points of observation for which an integrated theme was waiting to emerge. That theme is now emerging—an understandable mechanism by which we can start to use these observations to predict the success of therapies before they are even tried. This is what Dr. David Deutsch talks about in his book, The Fabric of Reality. When medicine becomes a science, it will allow us to predict from first principles, the success and outcome of specific therapies before they have even been subjected to trial. That goes from an empirically based protoscience to predictive science, which is ultimately where medicine may be headed once we have been able to understand the mechanisms of the diseases that afflict us and how they relate to the gene/environment interaction

In the November issue of *FMU* I discussed a molecule called asymmetrical dimethyl arginine, or ADMA. An understanding of the emerging role of ADMA in vascular biology will help us understand the field of vascular function. ADMA is an endogenous substance produced by normal metabolic processes. Arginine residues within specific proteins are often methylated. Normal turnover of these proteins releases ADMA, which can be converted to citrulline by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) or eliminated by excretion. It is typically found in very low levels in the body. Our concern is what happens as ADMA concentrations increase in the body.

The first reports of ADMA and its relationship to endothelial function in vascular medicine occurred in the 1990s, so it is a molecule whose role in vascular biology has only fairly recently emerged. In a 1998 paper in the journal *Circulation*, titled "Asymmetrical Dimethyl Arginine (ADMA): A Novel Risk Factor for Endothelial Dysfunction," Dr. John Cooke and his colleagues at Stanford reported that ADMA was elevated in young hypercholesterolemic individuals. That elevation, they stated, is associated with impaired endothelial-dependent vasodilation, and they also found reduced urinary nitrate excretion in these individuals.[7]

Urinary Nitrate

What is the role of urinary nitrate in this equation? Many years ago, Dr. Vernon Young at the Massachusetts Institute of Technology conducted feeding studies in adult males. The results of those studies, which were quite remarkable, were unexplained at the time. The men were placed on a protein-controlled diet, and their urinary output of various nitrogen metabolites was measured. Surprisingly, they began to show very high levels of urinary nitrate.

Nitrate was not known to be produced by normal human physiology, so Drs. Young and Riley wondered where it could have come from. Could it have been a contaminant in something these individuals were eating? During the course of this experiment, because it was the winter season, the men had all gotten the flu. During the time they were spilling high urinary nitrate, they were suffering from the flu. Dr. Riley made the connection between a viral-induced illness and increased urinary nitrate. That conclusion stood, interestingly enough, for approximately 20 years in the literature as an observation without explanation.

Nitric Oxide

Later, in the 1980s, a series of investigators started looking at cyclic guanine monophosphate (GMP), the GMP-modulated cascade, and its relationship to what was at that time called endothelial-relaxing factor (EDRF). They assumed there was this messenger substance that was produced by the endothelium that caused it to relax and dilate. This research, which occurred in three separate laboratories, led to a simultaneous discovery that resulted in all three of these investigators winning the Nobel Prize in Medicine and Physiology for their joint discovery that EDRF was actually a very small molecule called nitric oxide (NO). It was entirely unexpected that something as small as NO could have such a profound effect

Later studies revealed that NO was a modulator of function in the brain as neuronal NO, and in the immune system as immune-inducible NO and endothelial NO. It came to be understood as a central modulator of function ranging from neurotransmission to gene response second-signal messages.

NO, ADMA, and Urinary Nitrate Spill

Individuals who were producing higher levels of NO during upregulation of NO production were metabolizing NO by oxidative chemistry into nitrate, which is then spilled into the urine. That process explained the phenomenon Drs. Young and Riley had observed some 15 years earlier at MIT. Men on an isonitrogenous diet who had the flu suddenly began to spill higher urinary nitrate. The flu caused an upregulation of their immune systems. That upregulation led to more output of induced form of NO, which was converted into nitrate, and their nitrate levels went up.

With that historical context, let me go back to the paper on ADMA by Dr. Cooke and his colleagues. They found that an elevation of ADMA is also associated with reduced urinary nitrate excretion, meaning presumed lowered level of NO output. Reduced urinary nitrate with a nitrate-controlled diet means lowered NO production. This particular study assumed elevated ADMA and lowered NO. This was reported in 1998. The investigators in that study also made another observation in the modestly hypercholesterolemic males who had the elevated ADMA and reduced urinary nitrate. When these subjects were infused with 14g of L-arginine, urinary nitrate increased without affecting the level of ADMA .

Arginine’s Novel Role in Cellular Physiology

The observations in that study cover a number of interesting areas. We have vascular changes as a consequence of lowered endothelial production of NO. We have increasing levels of ADMA that somehow seem to be associated with lowered endothelial output of NO. And we have the potential role of dietary or supplemental arginine in modifying this dysfunction at the basic cellular physiological or biological level.

What novel role could arginine play in this process? In 1999 a paper appeared in the

journal *Circulation*, titled "Novel Mechanism for Endothelial Dysfunction—Dysregulation of Dimethylarguinine Dimethylaminohydrolase." The enzyme responsible for metabolizing ADMA.[8] Immune upregulation increases output of inflammatory mediators like tumor necrosis factor-a and/or an increasing level of oxidized cholesterol and other lipids, meaning increased lipid peroxidation such as cholesterol hydroperoxides. In this instance there is an accumulation of ADMA because the activity of DDAH decreased. There was however no change in the level of protein expression. Therefore, lipid peroxides and cholesterol hydroperoxides deactivate dimethylaminohydrolase. So do oxidized cholesterol, tumor necrosis factor-a, and other inflammatory cytokines.

The Inflammatory/Cholesterol Connection to Heart Disease

Now we have connected the inflammatory mechanism of heart disease and the cholesterol mechanism of heart disease to ADMA through the dysfunction of the detoxifying enzyme or biotransformational enzyme for ADMA, called dimethylarginine dimethylaminohydrolase. As the authors of the 1999 *Circulation* paper point out, the results suggest that endothelial vasodilator dysfunction, which is observed in hypercholesterolemia, may be due to the reduced degradation of ADMA, and this may contribute to increased blood pressure. I have now introduced hypertension into the equation as a sign that can be determined fairly simply with a sphygmomanometer cuff that may reflect these very subtle changes occurring at the vascular endothelium pertaining to ADMA metabolism and its role and effect on NO.

The Role of ADMA in Cardiovascular Disease Mortality

Now we move ahead to the year 2001 and a paper published in the *Lancet*, titled "Plasma Concentration of Asymmetrical Dimethylarginine and Mortality in Patients with End-Stage Renal Disease: a Prospective Study."[9] In this study, which was done in Italy, investigators evaluated the concentration of ADMA in individuals with various degrees of endothelial dysfunction. They examined the predictive power of ADMA for mortality to cardiovascular disease. The population they chose was hemodialysis patients who had renal threshold problems and whose plasma ADMA levels were very high.

Researchers in this study found that plasma ADMA was a very strong and independent predictor of overall mortality and cardiovascular outcome. The higher the level of ADMA in the blood, the higher the incidence of cardiovascular disease, and the greater the increase in overall mortality. The investigators concluded that findings support the hypothesis that accumulation of ADMA is an important risk factor for cardiovascular disease in chronic renal failure. They also stated that in chronic renal failure where there is poor exchange of ADMA, this may be a contributor of major proportion to the increased cardiovascular disease seen in kidney disease patients.

The Web of Variables in Heart Disease

That paper tells us a great deal about the web of interacting variables. This is particularly true if you add into the equation the previous discovery by Cooke and others that dietary arginine may play a role in altering ADMA accumulation and might lower the risk of endothelial injury associated with the accumulation of ADMA. Many questions remain to be answered in this particular story. I'll describe the way this story has evolved over time to 2002. As we have watched this story evolve, we have also seen the whole of cardiology and vascular disease move from a descriptive perspective to a mechanistic perspective. This is one example of the extraordinary transition that makes the field of cardiology much more scientific and gives it much higher predictive value.

The author of the editorial that follows the *Lancet* paper states that over the last 10 years, as NO has emerged as a vital signaling molecule in virtually every organ system, we have begun to recognize that substances that block, inhibit, or modulate NO production at the endothelium can have fairly profound effects on vascular dynamics and physiology.[10] Most interest has focused on the use of synthetic blocking agents of NO production in animal models. These agents include monomethyl-L-arginine, which is known to inhibit nitric oxide synthase (NOS) and block the production of NO. It was quite remarkable when it was found that not only synthetic molecules but a natural product that is produced in the body, ADMA, does the same thing. ADMA blocks endothelial production of NO, changes the dilator status of the vasculature, increases blood pressure, and is also associated with injury to the vasculature that can lead to atherosclerosis.

Insulin Resistance: The Web Expands

Another recent paper in *JAMA*, titled "Relationship between Insulin Resistance and an Endogenous Nitric Oxide Synthase Inhibitor," amplifies this same theme. [11] (The paper's authors include our November 2002 COM Dr. John Cooke, and a previous Linus Pauling Award in Functional Medicine winner, Dr. Gerald Reaven.) This collaborative study examined the relationship between insulin resistance and ADMA. In this study, investigators looked at the levels of ADMA and endothelial dysfunction in individuals with type-2 diabetes. These were people who had been given rosiglitazone medication as an insulin-sensitizing agent. Their ADMA levels were examined before and after insulin sensitization. Plasma ADMA concentrations were positively correlated in this study with impairment of insulin-mediated glucose disposal in non-diabetic normotensive subjects.

Consistent with syndrome X, ADMA levels were also positively correlated with fasting triglycerides, but not LDL cholesterol. Plasma ADMA concentrations were found to be increased in insulin-resistant subjects independent of hypertension. Pharmacological treatment improved insulin sensitivity and reduced mean plasma ADMA concentrations.

Now we have a connection with syndrome X, insulin resistance, hyperinsulinemia, and cardiovascular risk through ADMA. The web has many tendrils. As we start to understand the mechanisms, we can begin to understand how these seemingly independent variables actually depend on or interrelate with one another. Thus increases in plasma ADMA concentrations may contribute to the endothelial dysfunction observed in insulin resistant patients.

Connection Between Insulin Resistance/Hyperinsulinemia and Cardiovascular Disease

The editorial that follows the *JAMA* paper states that we have been looking for some time for a mechanistic connection between insulin resistance/hyperinsulinemia and cardiovascular disease.[12] Dr. Reaven has discussed the association between PAI-1 elevations, plasminogen activating inhibitor-1 elevations, and increased insulin resistance/hyperinsulinemia. That, in turn, is associated with increased incidence of vascular disease. Now it appears the swing molecule that may be connecting these two variables is the accumulation of ADMA and altered endothelial NO dynamics that is seen in insulin resistance and hyperinsulinemia.

The fact that an insulin-sensitizing agent was able to reduce plasma ADMA levels suggests that increasing ADMA levels may be the result rather than the cause of insulin resistance and that these are interacting variables. As we attempt to lower the risk of vascular disorders, we want to normalize insulin

levels and insulin sensitivity and the gene transcription mechanism that insulin is imparting. That mechanism interrelates with NO synthesis, ADMA levels, and the dimethylarginine enzyme for its detoxification, the biotransformation enzyme.

The Homocysteine Connection

Elevation of ADMA mediates endothelial dysfunction, not just by its influence on insulin resistance but by interaction with hyperhomocysteinemia as well. Homocysteine now enters into the story. A report in *Clinical Science* in 2001 showed a strong correlation between elevation of plasma homocysteine levels, impaired vascular endothelial function, and elevated concentrations of ADMA.[13] More significantly, the authors showed that the induction of hyperhomocysteinemia in humans increased the level of ADMA. Now we have homocysteine as well as inflammatory mediators and insulin resistance, all interrelated to the NO connection.

Homocysteine impairs the NO synthase pathway, and that increased ADMA causes vascular alteration.[14] It appears that homocysteine plays its role by inhibiting DDAH, the detoxification or biotransformation enzyme of ADMA that is the dimethylarginine/dimethylaminohydrolase. Homocysteine inactivates this enzyme, thereby lowering its ability to clear ADMA from the body.

Elevated levels of homocysteine and ADMA are seen in elderly stroke patients. A number of clinical trials now show how it impairs the NO synthase pathway. I refer to an article in*Atherosclerosis*, which showed that elevated plasma homocysteine correlated closely with ADMA in elderly patients who have had strokes.[15]

The Powerful Role of ADMA

We have diabetes connections, inflammation connections, homocysteine connections, chronic infection connections, hypercholesterolemia connections, and oxidative stress connections, all modulated through the ADMA NO vascular dynamic pathway. As NO is lowered and ADMA levels are elevated, there is a change in endothelial adhesiveness as well, with alterations in cell surface contact mediators such as ICAM-1 and VCAM-1, intercellular adhesion molecule-1, or endothelin. That increases the attachment adhesion of white cells to the endothelium and leads to its translocation so it can undergo transformation ultimately to foam cells, oxidizing LDL.

Now we get a feed-forward cycle. The very cycle that has been initiated now sets up a new functional state of physiology, and it feeds forward, replicating itself. It's like a snowball rolling downhill. It is picking up momentum, increasing oxidized cholesterol. That process further decreases the dimethylaminohydrolase enzyme activity, which further increases the amount ADMA, which further impairs endothlial NO, and so on. We get into an increasing replicative cascade. It is a different state of function of endothelial physiology. In a sense, it is a homeostasis of disease. Type 2 diabetes, hyperinsulinemia, insulin resistance, and inflammation all feed into this pathway, leading to increasingly adverse impact on vascular endothelial function.

ADMA and Type-2 Diabetes

This understanding is further supported in an additional series of papers that discuss increased plasma concentrations of ADMA in patients with type-2 diabetes and its correlation with a degree of impairment of insulin and management of insulin sensitivity.[16] Similarly, if you give Metformin to a type-2 diabetic

to improve insulin management and glucose regulation, it will lower ADMA concentrations and lower the incidence of risk to vascular disease.[17]

We are beginning to connect a number of variables—the oxidative stress model, the insulin/hyperinsulinemia model, the chronic infection model, the inflammatory model, the hypercholesterolemic model, the lipid peroxide model, and the free radical pathology model. All are modified through a complex interrelationship among genes, diet, environment, and regulators such as NO and ADMA.

INTERVIEW TRANSCRIPT

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JB: It is time once again for our Clinician of the Month interview. This month we are privileged to have a significant contributor, Dr. Mark Houston, an associate clinical professor of medicine at Vanderbilt University School of Medicine and Director of the Hypertensive Institute and Vascular Biology, whose career goes back to the 1970s. He has been one of the premier individuals to bring together knowledge from various disciplines to create an integrated view of vascular medicine. In this interview, we will focus on material from Dr. Houston's article, published in the Journal of Nutraceuticals last spring, titled "The Role of Vascular Biology, Nutrition, and Nutraceuticals in the Prevention and Treatment of Hypertension."

Career Evolution

JP: Welcome to FMU, Dr. Houston. What took you from a very traditional background in pharmacology and its relationship to vascular medicine, into looking at some of these nutritional variables?
MH: Jeff, thank you for the opportunity to be with you today. There are several things that brought me to this change in my philosophy of treating vascular disease and hypertension. One was patient request. Generally, patients want to be treated in an aggressive but natural way. They generally don't like to take prescription drugs unless there's no alternative. The other thing is that most people get a lot of side effects from pharmacological agents. Most of the time you are not going to get those side effects with natural products. If you understand when and where to use traditional pharmacologic agents, as opposed to the natural agents, and use the two together in the correct sequence, you can manage almost everyone with hypertension and have a good outcome.

Reception in the Medical Community

JB: How have your medical school colleagues responded to your work?
MH: I think in any traditional medical arena, you tend to raise a few eyebrows when you start talking about new concepts. Part of that is lack of knowledge of the topic. Most of us who were trained in traditional medicine received very little in the way of natural medicine in medical school. We learned it

on our own. That lack of knowledge most doctors have, and the skepticism toward the research involved, has created something of a schism in understanding the role of natural medications in vascular disease. But because I've been very careful to research everything that I say and do, perhaps the eyebrows are not going up as high, and they are seeing that it's working.

Patients are seeing that it's working. That fact has created credibility within the concept of using natural treatment for vascular disease, as well as pharmacologic treatment.

Applications of the DASH Studies

JB: Segueing into the research domain, which is a language that we hope produces some understanding if we can look at common mechanisms of action, we are impressed with the results of the DASH Study. How do you implement or integrate some of the DASH outcomes into your work with both macro- and micronutrients?

MH: The DASH I and DASH II Diets, which were published in the New England Journal of Medicine, were landmark studies. They clearly indicated, in controlled studies, that you could control blood pressure with diet to a level that was equal to or better than the use of one very effective pharmacologic agent for hypertension. The effects were fairly quick, they were sustained, and people had no side effects. When one looks at the composite results of DASH I and II, basically they used fruits and vegetables in very high amounts, 8 to 10 servings per day, along with a low-fat/dairy diet, and fiber.

The DASH II Diet added that to another dimension with sodium restriction. In all of those different mechanisms related to micro- and macronutrients, we then understood that by using the synergy of food and the right proportions of food we can have a dramatic impact on blood pressure. You can then take that information and try to segregate out what it is about those diets that works, and maybe supplement the DASH diet with additional components, both macro- and micronutrients, vitamins, minerals, and antioxidants, that complement that type of nutritional program.

Conclusions from the Lyon Heart Study and DASH

JB: Dr. Robert Lerman of our Functional Medicine Research Center has felt that one of the most profound nutritional intervention trials that has ever been done, and the one that convinced him about the importance of nutritional intervention, was the Lyon Heart Study. Would you describe the combined picture DASH and Lyon might provide?

MH: I think they have a common thread, and that is that the blood vessel has to be viewed as a very important organ that has the ability to control its destiny. An individual’s nutritional intake can have a significant impact in both preventing and intervening in vascular disease. The Lyon Heart Study looked at a group of patients related to cardiac death and myocardial infarctions (MIs). The DASH I and II Diets looked at blood pressure in a group of patients who were basically healthy. The common denominator in cardiovascular disease, MIs, strokes, renal disease, and high blood pressure, is basically vascular biology. Two components of vascular biology were affected by these two diets. One is endothelial dysfunction, and the other is the vascular compliance or the media of the muscle of the vascular tissue. By affecting those in a favorable fashion, a healthy blood vessel was created, and it therefore slowed down progression of atherosclerosis, reduced vasoconstriction, and thus promoted vascular health.

The French Paradox

JB: The Lyon Heart Study focused on the Mediterranean Diet principles, as contrasted to the way you

described DASH, which is related more to the general principles of adding fruits and vegetables. There are obvious interrelationships, in terms of both macro- and micronutrients. One thing that appeared to emerge, and one that has been discussed in the literature, is whether these relate to the so-called French paradox. According to the French paradox, there are certain phytonutrients present in these diets containing large amounts of unrefined fruits, vegetables, and whole grains that might have value beyond just the adjustment of fat, carbohydrate, and protein. Do you feel that is an emerging theme from this work?
MH: I do. I think one of the differences between those two diets was the increased use of monounsaturated fatty acids in the Mediterranean Diet. That was not a huge portion of the DASH Diet. Clearly, one contributor to the Mediterranean Diet was phenolic compounds, polyphenols in general, which are a major very much part of the red wine, are part of the fruits and vegetables, part of the monounsaturated fats. Another part of the story is the omega 3 fatty acids and how they fit into vascular disease. All those things, if they're instituted in the right proportions, in either the Mediterranean Diet or the DASH I and II Diets, add another level of vascular protection. I agree totally that those things need to be included in our diet.

Scientific Support for Dietary Changes
JB: For the sake of our clinician listeners, to distill down this complex topic, how would you describe the work that has been done, both clinically and in basic science that ties together hypertension, arterial sclerosis, and atherosclerosis to dietary influences?
MH: I like to think of the blood vessel as the primary organ of vascular disease. I am beginning to think of hypertension not as a disease of numbers, but one of blood vessels, or a disease of the arteries in particular. The disease is related to an inability to balance the vasodilator and anti-atherogenic components, which are primarily nitric oxide, bradykinin, and prostacyclins, against the vasoconstricting and atherogenic hormones for primarily angiotensin II, endothelium, plasminogen activator inhibitor 1, and other different components. It is good versus evil, so to speak, in the blood vessel. When one creates an imbalance of those two, you either create vascular health or you create vascular disease.

Vascular disease, once it starts, becomes a self-perpetuating process. You create endothelial activation, endothelial dysfunction, vascular smooth muscle disease, clotting, and oxidative stress, and then atherogenic processes go haywire.

All of this can be slowed or prevented, and sometimes there is even some regression of atherosclerosis, if you can turn back those negative impacts on the blood vessel, improve nitric oxide, improve vasodilators, reduce growth, reduce the oxidative stress, and reduce the clotting potential. There are ways you can do that, with natural things as well as with pharmacologic agents.

The Vascular Endothelium as a Major Organ
JB: In your review article you mention that there are about 14,000 sq. ft. of surface area, or approximately 6 1/2 tennis courts worth of surface area in the vascular endothelium, making it the largest endocrine organ of the body, perhaps the largest organ of the body. This is a dramatic concept for the person who has never thought about it, this huge metabolically, physiologically active barrier layer that is interfacing with the environment.
MH: Sir William Osler once said that a man is as old as his blood vessels. I think that's very true. If you have diseased arteries, you are going to have a shortened life expectancy and a lot of complications. The blood vessel becomes the primary impetus for prevention, certainly in Westernized countries where

coronary heart disease and stroke are still the leading causes of death.

Plasminogen Activator Inhibitor 1 and Insulin Resistance

JB: One of the factors you described as combining to determine vascular health is plasminogen activator inhibitor 1. Dr. Gerald Reaven has described PAI-1 as a variable associated with insulin resistance, hyperinsulinemia, and Syndrome x. Clearly, vascular biology is a complex endocrine-related function of which insulin is another mediator.

MH: Right. In fact, if you look at the hypertensive population, with either genetic or familial hypertension, you can demonstrate insulin resistance in probably 70 to 80 percent of the cases. Interestingly, you can see this before the patients become hypertensive. For example, if you have a hypertensive parent, or two parents, you can look at a child or a teenager and identify insulin resistance before his or her blood pressure ever goes up. Clinically, one of the best markers for insulin resistance is a high triglyceride, a low HDL and high LDL. Every clinician can measure those in his or her office.

If you want to go to other dimensions, you can get insulin levels and see peptides and all that sort of thing, but it's usually not necessary because you have a good family history and a very objective laboratory test that will identify insulin resistance. Once you've identified that, it's very important to start treating it aggressively with non-pharmacologic agents—weight loss, exercise, the right type of nutrition, micro- and macronutrients, antioxidants and whatever is available. These practices have good science and good research behind them, so they do, in fact, reduce the insulin resistance.

Creating a Clinical Management Program

JB: In your article you provided a number of figures and diagrams that summarize considerable information very clearly. One of those is a figure titled “Causes and Consequences of Endothelial Dysfunction.” In that figure you mention such things as advanced glycosylation endproducts that come from glucose-related non-enzymatic reactions with protein. You mention reperfusion injury, inflammatory injuries, estrogen deficiency, immune reactions, and oxidative stress reactions. As you start to see this complex, weblike interaction where the endothelium and the environment emerge, how do you distill it down into a clinical management program that is personalized to the patient but not so complicated that he or she can't comply?

MH: Let's go back and think about what you just said, which is a very astute observation. That is, the endothelium becomes inflamed. In essence, Virchow, the German pathologist, described arteritis inflamatans, meaning inflammatory arteritis, back in the 1850s and 1860s. It took us 140 years to figure out that he was correct in describing atherosclerosis as an inflammatory process. Having said that, and understanding that's been proven now in numerous studies, it becomes obvious that anything that gets in your blood has the potential to cause damage to the lining of the blood vessel. It can be an infection, bacteria, virus, traditional risk factors like diabetes, high blood pressure, high cholesterol, or it can be homocysteine. It can be any type of cardiovascular risk factor.

More than 400 coronary heart disease or cardiovascular risk factors have now been described. Every time I pick up a journal I find a new one described. What you have to do clinically is try to look at what the big ones are. Which ones really stand out that you can do something about that gives you perhaps 90 percent of the causes that are easily treatable. You try to get the blood pressure down to an acceptable range. We're looking at lower and lower numbers every day. The level may be as low as 110/70 now. We're looking at reducing LDL cholesterol now down to perhaps as low as 60 mg percent based on the Heart

Protection Study. We're looking at lowering fasting blood sugars clearly below 90, perhaps even down to 70, because of reducing of glycosylation products. The levels of homocysteine have been extremely high on laboratory testing, and the levels that are normal are not low enough. They were 15; they dropped to 12. Personally, 9 is the most I would accept, but I think there's a continuum of risk, not only with homocysteine, but everything else. There's a point at which you start to flatten out that risk. Clinically, I try to get all those things down to as low as I can go based on the scientific research that's out there that says you get clinical benefit from their reduction.

A Clinical Look at Oxidative Stress

JB: Is there a clinical way that you look at oxidative stress, or do you use the surrogate markers and map back against the potential for oxidative stress?

MH: I think you can make the general assumption that vascular disease and hypertension are oxidative stress models. Then if you want to, go ahead and document and measure that. Do a therapeutic intervention and determine whether or not you can change oxidative stress values. As you know, there are numerous things you can measure in blood, in urine, and in lipid peroxidation, that can tell you where that person is and whether your interventions have, in fact, improved the condition. I don't usually do that in a direct sense. I do it in the surrogate sense of looking at the obviously easy-to-measure things, with the assumption that if those things are returned to normal, and there are good data to back this up, that the oxidative stress and the vascular damage do, in fact, go back to normal.

I'll give you one clear example. A researcher at the University of Maryland, Dr. Robert Vogel, has actually shown in a human model that if you look at the nitric oxide production in the arterial system, it starts to decrease at an LDL level of 60 and up. With the same model, the blood pressure at 120/80 and up starts to reduce nitric oxide levels. So you have good evidence that those goals I previously mentioned clearly have an impact on nitric oxide. Then you can make a small jump to say that if NO levels are, in fact, going down, you're creating an atherogenic model because you're overbalancing with angiotensin II and other inflammatory cytokines.

Arginine As A Blocking Agent of Asymmetrical Dimethylarginine

JB: In our last clinician/researcher interview, we talked with Professor John Cooke at Stanford University Medical School, who is in the vascular biology research area. He talked about his work on arginine as a blocking agent for asymmetrical dimethyl arginine and the positive role it has on vascular endothelium in patients who have disruption or derangement of endothelial function. What you're now suggesting is that perhaps that derangement of function occurs at a much more benign level of variability in these markers than previously would be in the diagnostic area when we talk about blood pressure, LDL, or fasting glucose. That might suggest that things like arginine would be useful in certain people well before the presentation of pathology.

MH: Absolutely. One message I would like to make sure everyone understands is continuum of risk. There's no cutoff point at which you become diabetic, hypertensive, or dyslipidemic. There's a point at which your risk becomes flattened, but we don't know where those levels are for sure, although what I mentioned earlier gives us pretty good markers. For example, you mentioned ADMA, which is elevated in virtually anyone who has a vascular disease, whether it's diabetes, dyslipidemia, or hypertension. ADMA basically is just a competitive inhibitor for arginine, so you don't have the precursor for nitric oxide. If you can overload the system with arginine as the precursor, you might be able to competitively override the effects of ADMA and thus increase NO synthesis and improve vascular biology.

Taking the Message to the Patient

JB: Let's discuss how to take this complex information and design a program. Obviously, we've got the connection with the macronutrients; both the DASH I and II studies and the Lyon Heart Study helped us with some of the macronutrients. Then we have the micronutrients, and those are the phytochemicals and the traditional vitamin and mineral factors. Then we have the exercise component and the environmental/lifestyle component. When you sit down and describe these components to a patient, how you make this story understandable?

MH: I have a lot of help doing that. I have a full-time clinical nutritionist and a full-time educator. When a patient comes in with the family, they get at least a one- to two-hour nutritional consultation. We tell them not only what they need to do but why they need to do it and then how to get there. We have it done in small increments, trying to bite off a little bit at a time and not overwhelm them.

We have them come back frequently for re-education and questions. We have open-line discussions on the phone, on the internet, or by whatever means we have to make these people comply. The education component is very important.

Obviously, we start with the basics—nutrition, exercise, weight reduction, and ideal body weight. With patients whose levels of blood pressure need to be treated sooner rather than later, we may go ahead and institute a specific component, a special micronutrient, or a specific antioxidant early on.

Supplement Recommendations

For example, we may start someone on coenzyme Q10 early on because there's a huge amount of data showing its protective effects in cardiovascular disease, congestive heart failure, and coronary heart disease. Probably, if you look at the data, coenzyme Q10 is one of the best agents to help blood pressure in a control sense. That's one of the things we may start earlier. Increasing potassium in the diet is important, increasing magnesium, things that are very inexpensive and easy to do. Then we go through a systematic list of things that are synergistic in working with that initial basic foundation that we try to get the patient on.

Education about Dietary Fat

JB: A controversy exists in the area of dietary lipids, and that controversy has consumers confused about whether fat is good or bad. If it's bad, they wonder, how much should they cut out of their diet, and if it's not bad, what should they incorporate. How do you discuss the fat component of their diet with them?

MH: We have a lot of educational handouts they take home. In the office, though, we try to make it simple. We explain the different types of fat. We categorize them into the good ones and the bad ones in a simplistic sense, but we also make them realize there's balance. Just because something is called "bad" in one sense doesn't mean it might not have therapeutic or preventive effects in the body.

For example, we always think of saturated fats as bad. Well, not all saturated fats are bad; in fact, some of them are probably good. If you don't get enough saturated fat, there's been some indication in some Oriental studies that you may have more hemorrhagic strokes. We try to get the saturated fats down to a minimum, but also pick the right saturated fats and the right percentage. We increase the amount of monounsaturated fats, increase omega 3's, and try as best we can to eliminate trans fatty acids, which are in everything and not on the label yet.

ACE Inhibitors

JB: Would you tell us about the management of hypertension with ACE inhibitors and how that interfaces with some of the things you've described from a diet, nutrition, and lifestyle perspective?
MH: ACE inhibitors were originally described to inhibit the angiotensin-converting enzyme, which in turn was thought to increase bradykinin and therefore increase nitric oxide. As we learned more about ACE inhibitors, we've seen that they have a variety of effects on vascular biology. They increase angiotensin 1 through 7, which is a potent vasodilator that has effects almost identical to nitric oxide. The other interesting thing is that after about two months of treatment with an ACE inhibitor, the levels of angiotensin II actually go right back up to normal.

An ACE inhibitor is almost a misnomer today when you think about the mechanism. The real mechanism is through nitric oxide and angiotensin 1 through 7, at least that we now know about, but also they decrease PI-1 which in turn reduces thrombogenic risk. The ACE inhibitors reflect the same mechanistic action that I described earlier by overbalancing for the good with NO and underbalancing the bad with PI-1 and through other effects, the effects of angiotensin II.

Adding Accessory Nutrients
JB: As you start a person down the road toward improving vascular health, and you've educated him or her with your integrative team about the dietary variables, are there micronutrients or accessory nutrients or products you find useful? You mentioned coenzyme Q10, but I note from your article that you speak about many other phytonutrient concentrates that might be useful.
MH: Let's look at the macronutrients first. I tend to use a lot of hydrolyzed whey protein, which has a lot of good data on it. The important thing is that it has to be hydrolyzed; otherwise, it's not effective. It turns out that hydrolyzed whey protein is a very good natural ACE inhibitor. It probably has other effects, but the protein and amino acid sequence of whey protein is almost identical to that of some of the manufactured ACE inhibitors, and it's very cheap. There are other things you can use, but they're generally not well tolerated or they're not liked, like sardine muscle. And then adding some cold-water fish for the omega 3s.

As far as the micronutrients, there are some people who respond to calcium. It's not a general rule of thumb, but the so-called low-renin hypertensives which are low on calcium sometimes can respond to calcium intakes of 1000 to 1500 mg per day. We also use a combination of other foods like garlic, wakame seaweed, which is a seaweed available in Japan. Unfortunately, wakame is not available in this country yet. It is extremely effective in lowering blood pressure. Again, it's a natural ACE inhibitor. Eating celery, eating large amount of tomatoes and pink grapefruit, which are high in lycopene, have been shown to lower blood pressure. Then, if you look at specific antioxidants and vitamins— vitamin C, pyridoxine, vitamin B6, probably lipoic acid, L-arginine, and taurine are also very effective in lowering blood pressure, as well as carnitine. All these things are supported by good clinical studies, and you just have to decide when to use them based on the patient's response to your initial treatments.

The Future of Natural Therapies in Vascular Disease Treatment
JB: As a final question, what is your prediction regarding the integration of these natural therapies into the management of patients with vascular disease?
MH: I think about 50 percent of patients with hypertension can safely and effectively be treated initially with non-pharmacologic therapy or lifestyle changes. The impetus for integrating the natural with the traditional is going to be both scientific research and proof that validates a lot of these things we're doing. It will also be based on the patient's request and desire to be treated in a more holistic fashion. Patients

want us to treat their blood vessel as opposed to just treating their blood pressure and the numbers.

Clearly, a pharmacologic agent has a targeted role, whereas natural agents tend to have a broader, more universal range of effects. When you treat hypertension, for example, with any hypertensive drug, you may or may not have other effects that reduce vascular disease. With some of the natural products, it would appear that they have such a myriad of effects that you can actually reduce cardiovascular outcomes. In the next few years, as research becomes more available, I believe more people will start to use a combination of the natural approaches with the traditional approaches. I think we will have much better patient compliance and also improved cardiovascular outcomes.

JB: That's a very optimistic and hopeful note to end this discussion. We are pleased that you will be one of our plenary speakers at our 10th International Symposium on Functional Medicine next May in Tucson, Arizona. I know that will give us a greater opportunity to learn from you and to hear in a clinical setting how this might be applied. Thank you, Dr. Houston

I began this issue of *FMU* by asking how much is enough. When will we have enough information, enough data, enough clinical sense, enough studies, enough comprehensive understanding to act? That is a big question that would probably be answered in different ways by different individuals. Dr. Jan Basile, an associate professor of medicine, Division of General Internal Medicine/Geriatrics at the Medical University of South Carolina, recently wrote an editorial in which he talked about nutraceuticals and vascular biology. He asked if they are ready for Prime Time use.[18] According to Dr. Basile, “Until well-designed evidence-based trials evaluate these compounds in those with hypertension, nutraceuticals are not 'ready for prime-time' in those at risk for or being treated for hypertension, even though our patients may continue to believe so."

He goes on to say we need to know the exact dose and dose frequency of these agents that will provide clinical benefit, if there is real clinical benefit. He asks how homogeneous is the production of these products so that their bioavailability can be assured. Dr. Basile is serving as the nay sayer, stating that interesting information associations are provocative, but there has been no demonstrated proof, and it is certainly premature to act.

On the other side of the coin, however, we have an increasing number of blind studies in humans who have various well-defined vascular diseases who are demonstrating positive outcomes from specific intervention. Let me go back to one example we have been discussing in this issue of *FMU*. That is the ADMA connection to vascular endothelial dysfunction, to hypertension, to insulin resistance, and to vascular disease, arterial sclerosis and atherosclerosis. Are there ways of modulating the dysfunction of the vasculature's production of NO associated with increased levels of ADMA?

One of the molecules I described, which has been extensively evaluated, is the precursor to NO, the amino acid L-arginine. L-arginine, when given to individuals with optimal vascular function, has little or no effect in modulating NO dynamics. In those individuals, blood pressure does not drop and no remarkable change is seen. We might conclude that arginine is near saturation levels through normal intake of dietary protein, and increasing arginine levels will not increase NO production by driving more arginine through the NO synthase pathway. However, let's move beyond apparently healthy individuals and consider those who have dysfunction of their vascular endothelium.

Potential Benefit of Arginine Supplementation
Would these individuals possibly benefit from increased arginine that can alter and lower ADMA levels? That question is different from asking what would happen if everyone took arginine as a supplement. It is a consideration of finding the right dose for the right person with the right endpoint and outcome to be measured. It leads us to studies like the one that was published in the *Journal of Clinical Investigation* titled, "L-Arginine Improves Endothelium-dependent Vasodilation in Hypercholesterolemic Humans."[19]

In this trial, a supplemental dose of about 14 grams per day of arginine (infused at the rate of 10mg/kg/min for 20 minutes) was administered to hypercholesterolemic males, followed by observation of its effect on vascular function. The objective was to examine whether it had any effect on vascular reactivity. It was contrasted it to the placebo, D-arginine, which is not used by the enzyme NO synthase and therefore not converted into NO. Based on this comparison, the researchers concluded that endothelium-dependent vasodilation is impaired in hypercholesterolemic humans and that this abnormality can be improved by the intravenous administration of L-arginine, which appears to increase the production of NO.

L-Arginine and Coronary Endothelial Function in Cardiac Transplant Recipients
That is an interesting first-observation intervention. Now let's look at more recent studies like the one published in *Circulation* in 1994, titled "Effect of L-Arginine on Coronary Endothelial Function in Cardiac Transplant Recipients."[20] These are individuals who have had operations in which the coronary vasculature exhibits a generalized endothelial dysfunction. L-arginine infusion in these individuals improved endothelial function of both coronary microvasculature and epicardial coronary arteries. The authors state that the reversibility of epicardial endothelial dysfunction by L-arginine is more likely in vessels with normal wall morphology.

L-Arginine and Enhanced Endothelial Adhesiveness in Hypercholesterolemia
Let us look at the endothelial adhesiveness of white cells by L-arginine supplementation. This topic is covered in an interesting paper on an intervention trial in which the investigators gave supplemental L-arginine supplementation to New Zealand white rabbits (often used for arteriosclerosis research). Although administration of L-arginine in the diet did not necessarily lower cholesterol levels, it resulted in the reduction of white cell endothelial adhesiveness. The rabbits had more normal endothelial dynamics and more normal white cell rolling without adherence.

L-Arginine and Platelet Aggregation in Hypercholesterolemic Humans
Does L-arginine supplementation help reduce platelet adhesion in hypercholesterolemic humans? A double-blind, placebo-controlled study demonstrated that dietary supplementation with about 8g/d L-arginine modestly attenuated increased platelet reactivity in hypercholesterolemic patients.[21] This is well before you get into patent arterial dysfunction with significant symptoms.

L-Arginine Inhibits Lesion Formation after Balloon Angioplasty
Does administration of L-arginine enhance NO generation and inhibit lesion formation after balloon angioplasty? This was the topic of a paper in *Circulation* in 1997.[22] Investigators demonstrated that the intramural administration of L-arginine appeared to have a favorable effect on enhancing vascular NO generation and inhibiting lesion formation in New Zealand white rabbits.

L-Arginine and In-Stent Restenosis in Humans

A more recent study done this year and published in the *American Journal of Cardiology*looked at the effect of local delivery of L-arginine on in-stent restenosis in humans, showing a reduction of restenosis.[23] The results showed that local delivery of L-arginine reduced in-stent neointimal hyperplasia in humans, indicating that this may be a novel strategy to prevent in-stent restenosis.

We are beginning to witness results of clinical intervention trials in a variety of disease states associated with vascular disorders, and all of them have some relationship to hypertension, hypercholesterolemia, and neointimal thickening. Returning to what Dr. Houston said, we need to start examining new parameters for establishing optimal function, not just pathological levels. He talked about blood pressure and trying to achieve 110/70; LDL cholesterol not less than 120, but closer to 60 mg per deciliter; fasting glucose not less than 120, but closer to 70 or 80 mg per deciliter; hypohomocysteinemia or homocysteine in the blood not less than 12, but less than 9. Those are about the levels we've heard Kilmer McCully talk about. Eight or 9 should be the threshold, and HDL should not be less than 40. When we start to use these other biomarkers or surrogate markers for function rather than simply pathological dysfunctional markers, we can see that intervention may occur much earlier than we thought to improve vascular dynamics.

When is the Evidence Enough?

I return again to the question, how much do we need to know before we act? What are the relative decision-making points? If, in fact, the therapy, at worst, results in death, then clearly any decision requires understanding the risk/benefit relationship. If, however, at worst, the therapy produces no adverse influence and/or benign effects, then the decision becomes easier. Individuals with have functional impairment of the vascular endothelium, modest elevations of blood pressure, increased cholesterol, increased homocysteine, increased fasting sugars, and/or hyperinsulinemia may benefit from nutritional intervention. With these patients we may be encouraged to employ what Dr. Houston described to us and what we have learned from Drs. Ignarro and Cooke. Their studies open a new era of vascular biology associated with nutrition and nutraceuticals. It is the dawn of functional cardiology in the age of functional medicine.

Thanks for being with us. We look forward to seeing you at the start of 2003.

Bibliography

1 Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. New Engl J Med. 2001;344(1):3-10.

2 Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). JAMA. 1998;279(11):839-846.

3 Svetkey LP, Simons-Morton D, Vollmer WM, et al. Arch Intern Med. 1999;159(3):285-293.

4 Houston MC. The role of vascular biology, nutrition and nutraceuticals in the prevention and treatment of hypertension. J Am Nutraceutical Assn. 2002(suppl No. 1):5-71.

5 Leaf A. Dietary prevention of coronary heart disease: the Lyon Diet Heart Study. Circulation.

1999;99(6):733-735.

6 Egan BM. Commentary on “The Role of Vascular Biology, Nutrition, and Nutraceuticals in the Prevention and Treatment of Hypertension. JANA. 2002(suppl 1):1-2.

7 Boger RH,. Bode-Boger SM, Cooke JP, et al. Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction. Circulation. 1998;98:1842-1847.

8 Ito A, Tsao PS, Adimoolam S, Kimoto M, Ogawa T, Cooke JP. Novel mechanism for endothelial dysfunction. Dysregulation of dimethylarginine dimethylaminohydrolase. Circulation. 1999;99:3092-3095.

9 Zoiccali C, Bode-Boger SM, Mellamaci F, et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet. 2001;358:2113-2117.

10 Vallance P. Importance of asymmetrical dimethylarginine in cardiovascular risk. Lancet. 2001;358:2096-2097.

11 Stuhlinger MC, Cooke JP, Reaven GM, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA. 2002;287(11):1420-1426.

12 Nash DT. Insulin resistance, ADMA levels, and cardiovascular disease. JAMA. 1451-1452.

13 Boger RH, Lentz SR, Bode-Boger SM, Knapp HR, Haynes WG. Elevation of asymmetrical dimethylarginine may mediate endothelial dysfunction during experimental hyperhomocyst(e)inaemia in humans. Clin Sci. 2001;100:161-167.

14 Stuhlinger MC, Tsao PS, Her JH, Kimoto M. Balint RF, Cooke JP. Homocysteine impairs the nitric oxide synthase pathway. Role of asymmetric dimethylarginine. Circulation. 2001;104:2569-2575.

15 Yoo JH, Lee SC. Elevated levels of plasma homocyst(e)ine and asymmetric dimethylarginine in elderly patients with stroke. Atherosclerosis. 2001;158:425-430.

16 Abbasi F, Cooke JP, Reaven GM, et al. Plasma concentrations of asymmetric dimethylarginine are increased in patients with type 2 diabetes mellitus. Am J Cardiol. 2001;88:1201-1203.

17 Asagami T, Cooke JP, Reaven GM, et al. Metformin treatment lowers asymmetric dimethylarginine concentrations in patients with type 2 diabetes. Metabolism. 2002;51(7):843-846.

18 Basile J. Nutraceuticals and vascular biology: are they ready for prime time use? JANA. 2002;suppl 1:3-4.

19 Creager MA, Gallagher SJ, Girerd XJ, Coleman SM, Dzau VJ, Cooke JP. L-arginine improves endothelium-dependent vasodilation in hypercholesterolemic humans. J Clin Invest. 1992;90:1248-1253.

20 Drexler H, Fischell TA, Cooke JP, et al. Effect of L-arginine on coronary endothelial function in cardiac transplant recipients. Circulation. 1994;89:1615-1623.

21 Wolf A, Zalpour C, Cooke JP, et al. Dietary L-arginine supplementation normalizes platelet aggregation in hypercholesterolemic humans. J Am Coll Cardiol. 1997;29:479-485.

22 Schwarzacher SP, Lim TT, Cooke JP, et al. Local intramural delivery of L-arginine enhances nitric oxide generation and inhibits lesion formation after balloon angioplasty. Circulation. 197;95:1863-1869.

23 Suzuki T, Hayase M, Cooke JP, et al. Effect of local delivery of L-arginine on in-stent restenosis in humans. Am J Cardiol. 2002;89:363-367.p>