June 2005 Issue | Erminia M. Guarneri, MD, FACC Scripps Clinic

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Welcome to *Functional Medicine Update* for June 2005. One of the themes we have followed over the years in FMU is the relationship of dysfunction to chronic disease. As we have said on many occasions, the burden is shifting from acute disease to chronic disease. That is represented beautifully in a paper that appeared in the *Journal of the American Medical Association,* titled "The global burden of chronic diseases. Overcoming impediments to prevention and control."[1] This is a manifesto to the need for a better solution for management of chronic disease, which now accounts for 78 percent of healthcare expenditures. We need to manage chronic disease with a prevention and functional medicine-based strategy.

In this article, the authors state:

"Chronic diseases are the largest cause of death in the world. In 2002, the leading chronic diseases-cardiovascular disease, cancer, chronic respiratory disease, and diabetes-caused 29 million deaths world-wide. Despite growing evidence of epidemiological and economic impact, the global response to the problem remains inadequate."

We still do not have a healthcare system that is focused on delivering appropriate services to individuals in various stages of chronic, age-related diseases.

This article calls for a more concerted strategic and multi-sectorial policy approach, underpinned by solid research in the area of chronic diseases, which is essential to help reverse the negative trends in their global incidence. That has been the major focus and impetus between where we started the functional medicine movement and how far it has evolved in 2005. We would like to think that functional medicine plays a role in providing an epistemology, or a methodology for the evaluation and management of chronic disease at a more cost-effective level, focusing on the origin of disease at the mechanistic level rather than the treatment of disease at the symptomatic level.

There are many markers of concern about chronic disease in our society. The economic markers are certainly one indicator, but there are also the indicators of human suffering. There is no better example of that than the rising prevalence of age-related, chronic diseases that used to be relegated to older age, but which are now being seen in adolescents, and even younger children. The obesity epidemic, its relationship to type 2 diabetes, and even early-age vascular autoimmune diseases, are starting to appear with greater frequency in children and adolescents. This was relatively unheard of when I was being trained in biochemistry in the late 1960s. Now, it has become a much more common theme in clinics

around the world, and certainly here in the industrialized United States.

We wonder how this could happen at a time when we are spending twice as much per capita on health care than any other country; yet, statistically, we are 11th in healthcare outcomes. We also wonder how this could happen in light of all the new pharmacological, diagnostic, and surgical technologies that allow us to treat so many diseases that were previously considered untreatable. Yet, what we find is that the answer to many of these chronic diseases is not found in crisis treatment, but rather in better understanding the early origins of the mechanism of the dysfunctions, and correcting them before the system is broken, or in a state of pathology.

That comes through in hundreds of articles that are published in top-tier journals, but yet still sits languishing for lack of proper application.

We see that as we look at the incidence of metabolic syndrome and type 2 diabetes in children and adolescents. One only needs to read the article in *The New England Journal of Medicine*, titled "Obesity and Metabolic Syndrome in Children and Adolescents."[2] The prevalence of metabolic syndrome has increased significantly over the last decade and a half, and the prevalence of type 2 diabetes and cardiovascular disease has followed it, particularly in the adolescent population. In this article, the authors point out that the prevalence of the metabolic syndrome is high among obese children and adolescents and increases with worsening obesity. Biomarkers of an increased risk of adverse cardiovascular outcomes are already present in these youngsters, indicating that as they move into their 20s and 30s, they are likely to be high users of medical services because they will have complications of type 2 diabetes and cardiovascular disease at a much younger age than ever before.

This is reminiscent of what Rudolph Virchow talked about in the 19th century. In 1847, he wrote about the origins of vascular disease, calling it an "inflammatory disorder." However, it was so uncommon in the 19th century that it was almost an esoteric sidebar and not seen with any level of frequency. Perhaps it was even overlooked to some extent. As we moved into the 20th century, vascular disease became more and more prevalent, as did cancer, and it became the watchword of support for medical centers, with development of coronary artery bypass surgery. This is a profitable surgery, with many drugs and procedures involved, such as stenting and various types of technologies used to manage heart-related dysfunction. We are starting to see a similar trend in the 21st century, as these conditions begin to penetrate into the younger-age population. From the standpoint of economics, this trend is capable of bankrupting the disease-care system.

Recently, in *The New England Journal of Medicine,* there was an article discussing that for the first time in the recorded history of the human species in the Western world, based on mean average demographic trends, it appears that children born today may have a lowered life expectancy than that of their parents.[3] That trend has never been seen before. In regard to Medicare benefits for the children of today, the older-age individuals of the future, they are in peril because the system may be bankrupt by the time they need the services. There is an increasing rise in the prevalence of chronic disease at a younger age, and decreasing financial support for its management. That is definitely an economic motivator for change. We are at the place right now where change has to occur, either by altruism and forthright thinking, or by absolute economic requirement.

We are reminded of that when looking at a particular case history published in *The New England Journal*

of Medicine.[4] . This type of case has become much more common in today's clinics. The patient is a 49-year-old woman with a panoply of health-related problems. At presentation, she is obese, with a body mass index of 52 kg/m^2. She has elevated blood pressure and diabetes. She has apparent ischemia and a number of other problems common to severe obesity, including narrowing of disk spaces in her vertebrae and intermittent leg pain, hyperlipidemia, and episodes of depression. This woman has many accompanying problems as a consequence of all her difficulties. She is on eight different medications, some of which could be interacting with one another.

What does one do about this patient? In our technology-minded society, we consider gastric bypass surgery, which may be the treatment of choice for someone who is in this serious a state of impairment. In this case, the patient has gone from chronic into acute. The reason why gastric bypass surgery was recommended is because it does not seem to result in the same degree of protein/calorie malabsorption as some of the other procedures. It does appear to induce neurohumoral effects that result in the decrease of appetite, accelerated postprandial satiety, and diminished emotion-based or reward-based eating.

This calls into question to what degree the gut is the seat of emotion. When a portion of the gut messaging system is remove, (it is part of the neuroendocrineimmune system), the connection between the gut hormones and the brain hormones is modified. In his book, *The Second Brain*, Dr. Gershon explained how these regulatory compounds or triggering molecules travel back and forth from the brain to the gut. By disconnecting the signaling of the gut, some of what is called emotion-based, or reward-based eating habits are disconnected. I find this fascinating because people often talk about eating as being totally controlled by the lateral nucleus of the hypothalamus, meaning centrally-mediated. It seems more likely, if we are to learn something from gastric bypass surgery, that there is also something happening at the gastric-hormonal-neuroendocrine level. From a functional medicine perspective, it reminds us of the web of interaction of the gut hormones with the beta cells of the endocrine pancreas, with the effects of adipocyte signaling, adipocytokines, central mediation, muscle cell physiology, and the important metabolic role the liver plays in managing calories or energy economy through lipids and sugar.

It is the web of interacting messages that gives rise to a person eating when he or she should not be doing so. That brings up the question, why do people with many extra stored calories in their body fat (about 3500 calories per pound of fat) always seem to be hungry and need to eat more? It is as if the body is saying it does not have enough energy. There seems to be something paradoxical related to the signaling molecules that regulate nutrient sensing, metabolic function, and ultimately the appetite. We have a lot to learn. Case histories of gastric bypass surgery patients should help guide us in understanding that just dealing with simple calorie restriction, putting people on psychological adjustment programs, and trying to cut down their calories, is not the total answer to the problem.

In people who have had gastric bypass surgery, we need to be cautious about problems related to selective nutrient difficulties, particularly some of the micronutrients that become commonly insufficient after this procedure. Some at the top of the list include iron, calcium, vitamin B12, vitamin D, and vitamin K. There are significant indications of deficiency in those nutrients after undergoing a bypass surgery procedure. Vitamin D is very important for the regulation of calcium phosphate levels in the blood and parathyroid gland function. Generally, people should be supplemented with vitamin D because more than 60 percent of gastric bypass patients have secondary hyperparathyroidism from malabsorption of calcium and vitamin D. Vitamin B12 deficiency is also very common in gastric bypass surgery patients.

Supplementation with B12, folic acid, and calcium should be considered.

Complex signaling mechanisms interrelate with environmental triggers, nutritional status, exercise patterns, stress-related function, and signals through gene expression patterns to what evolves as metabolic obesity, type 2 diabetes, insulin resistance, and ultimately, lipid abnormalities and coronary heart disease.

A pharmacological approach to this situation that has been suggested is outlined in an article I reviewed previously by Wald and Law, titled "A strategy to reduce cardiovascular disease by more than 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}," that appeared in the *British Medical Journal* in 2003.[5] It was an interesting and controversial article in which the authors proposed that cardiovascular disease could be reduced by more than 80 percent in people 55 years of age and older by giving them a pill that contained six different ingredients. It would not be necessary to go through the complex process of lifestyle adjustment, nutrigenomic signaling alteration, or exercise repatterning. The pill would contain six ingredients, including a statin, folic acid (for homocysteine), a baby aspirin (for its anti-platelet effect), and half strengths of a beta blocker, an ACE inhibitor, and a diuretic. All six ingredients in one pill, the authors hypothesized, would result in a good formulation for people age 55 and older, and would reduce the relative incidence of vascular disease by more than 80 percent.

Rather than accept that as a hypothesis, let us look at the model that underlies the rationale for the polypill, which is that lowering lipids and homocysteine, managing platelet and renal function, and stress-related hormones and their interrelationship with insulin sensitivity, is an important part of an overall prevention program. I would call it a functional medicine-based program for improving health outcome and lowering the burden of chronic disease. Rather than getting caught up with six molecules in the polypill, perhaps we should get caught up in the six *mechanisms* they are describing.

As I mentioned previously, in the December 2004 issue of the *British Medical Journal*, there was a good article, titled "The Polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}."[6] The authors of that paper described that one could achieve the same benefit as a polypill by designing the dietary intake correctly to send the right nutrigenomic signaling messages to improve function associated with the etiology of CAD by similar mechanisms, if not identical, to those of the five synthetic molecules in the polypill (folic acid is considered a natural substance). This is a different strategy for reducing the burden of chronic, degenerative disease.

A very elegant screening approach for lipoproteinsthat includes lipoprotein subtyping has been developed over the years, and is available from laboratories such as Berkeley Heart Labs or Atherotech. The laboratories are also developing various ways of screening lipoprotein subparticles for atherogenecity. The relationship between apolipoprotein concentration and risk to future CAD has been shown in many different studies. It has been concluded that apolipoprotein(a) predicts risk of angina and that this risk is substantially increased with high concomitant LDL cholesterol. Small apo(a) size predicts angina with greater strength and is more independent than other types of lipid parameters. Presumably, it gives more specificity to the evaluation of vascular risk. These are called extended cardiovascular risk factors, getting into lipoprotein fractionation analyses. I am reporting from an article that appeared in *Clinical*

Chemistry.[7] This comes from work being done at Harvard on extended cardiovascular risk factors.

Intervention with lipid-lowering agents, such as statins, modifies lipoproteins, reducing various small-particle size atherogenic proteins, and alters serum triglycerides. Depending upon the statin used and the individuals taking it, there are different degrees of response. Primary prevention of CVD with statins in patients with elevated triglycerides and low HDL (meaning they are candidates for type 2 diabetes) is improved. This is all on the basis of randomized multicenter trials showing that intervention with statins in people with that risk factor-dense LDL particles with increased triglycerides and lowered HDL-improvement of serum lipid patterns and be achieved and reduce cardiovascular risk. Now, physicians are going beyond gross cholesterol/HDL ratios into lipoprotein profiling, looking at things like surrogate markers for type 2 diabetes and metabolic syndrome, which is the triglyceride-to-HDL ratio. That is becoming part of a profile called the extended risk factors for vascular disease. The trial I just mentioned is a multicenter trial on patients with an elevated triglyceride/low HDL complex, and its relationship to vascular disease. The paper appeared in *The Lancet*.[8]

The takeaway from this discussion is that we went from gross serum lipid analysis to lipid fractionation into the LDL, HDL, and VLDL families, and now into subfractionation into apo(a) and apo(b), looking at apo(e) isoforms such as apoE1, 2, 3, and 4, and eventually developing a better atherogenic risk profile based on these lipid particle sizes. Aggressive statin therapy in people with lipid abnormalities lowers atherogenic lipoproteins and is clinically correlated with reduced incidence of CVD. The question that has been raised is whether we are treating with statins the cause or the effect. Perhaps the statins, which have been found to be pleotrophic, (meaning having multiple functions other than blocking HMG CoA reductase, the cholesterol rate-limiting enzyme in the liver), also influence inflammatory parameters and inflammation of the artery wall. Perhaps the effect of statins is, in part, through their antiinflammatory effects, or perhaps the antiinflammatory effects have a clinical correlation with the cholesterol-lowering effects. Perhaps they are mechanistically connected. That is where the research is just starting to open up a potential connection.

The connection has the potential of being related to the topology of the membrane. As cholesterol is removed from the blood and enters into the lipid environment of the cell's membrane, its structure is changed. Therefore, the membrane-bound receptors that sit on the surface of the cell, an endothelial cell for example, pick up different signals from the composition of their membranes, which is influenced by what is in the blood around them. They may be picking up different inflammatory messages based upon the cholesterol composition in their membranes. Or, it is possible that inflammatory message signals at far different sites can alter cholesterol synthesis, resulting in changes in blood cholesterol concentration and, eventually, in the lipid bilayers of membranes, which alter the cell's structure and function. Whether it is inflammatory mediators that cause the cholesterol changes, or the cholesterol changes that alter the inflammatory sensitivity and mediators, is still open for discussion. There is clearly some degree of interrelationship between the two, even though inflammation and serum lipids are partially independent processes.

Let me move to the subject of folic acid. The homocysteine argument has continued to emerge since Kilmer McCully first brought it to our attention nearly 40 years ago. Now, there is generally a more widespread understanding that elevated homocysteine is an atherosclerosis and cerebrovascular risk factor. An interesting paper published out of the prospective Kuopio Ischaemic Heart Disease Risk Factor Study that investigated the relationship between serum folate, homocysteine, and the incidence of acute

coronary events, found that the hypothesis that high circulating homocysteine was a risk factor for acute coronary events in male populations free of heart disease, does not seem to be true.[9] However, the investigators found that moderate to high serum folate concentrations are associated with a greatly reduced incidence of acute coronary events.

This raises the question, is there something about folate beyond the issue of homocysteine that is related to cardioprotection? That is an interesting theme that I have been talking about for some years. In 2004, I discussed a paper that appeared in the *Journal of the American Medical Association* that indicated that women with higher dietary folate intake, as menstruating younger women, have lower blood pressure than women of the same age with reduced folate intake. This did not appear to be related to homocysteine. The mechanisms of these observations are starting to be seen as a consequence of better understanding of the physiology of the endothelium and its relationship to vascular smooth muscle tone in the artery system. As there is an alteration in endothelial function, there is an alteration in smooth muscle tone-it is more constricted, less dilated, and the pressures increase.

What is the connection between folate and endothelial function that would indirectly relate to the modulation of blood pressure? That is a good question, and the answer seems to be emerging through a better understanding of how folate regulates endothelial nitric oxide synthase (eNOS) activity. I will be discussing that in greater detail in this issue of FMU, but eNOS is the enzyme responsible for converting arginine in the endothelium into the amino acid citrulline, and producing nitric oxide (NO) as a byproduct. NO used to be thought of as the elusive endothelial relaxing factor. It is secreted into the adjacent smooth musculature of the arterial system, thereby causing muscle relaxation and lowering blood pressure. This work won the Nobel Prize in Medicine in 1998 for Ignarro, Murad, and Furchgott. The discovery of the role of NO in human physiology has now revolutionized our thinking about small molecules and the influence they have on a wide range of tissue function, in this case, endothelial function specifically.

Tetrahydrobiopterin
It turns out that the cofactor for the conversion of arginine to citrulline in the production of NO is tetrahydrobiopterin. Tetrahydrobiopterin is a folate-requiring cofactor in cellular physiology. It is found in high levels in endothelial cells in the conversion of arginine to NO through eNOS. Therefore, it is possible from studies that have been published, that enhanced levels of folate have a direct effect on vascular tone through their influence on eNOS activity and the production of more NO. Here is a non-homocysteine-mediated effect on vascular function that may help to explain why folate and vitamin B12 have been found useful in lowering the incidence of heart disease, even in the absence of elevated homocysteine. I come back to the Finnish study that did not show a correlation between homocysteine and sudden coronary events, but did show a correlation with folate.

We are bearing here slightly on an interface between vascular biology, serum lipids, and the concept of immune function and inflammation. It is a somewhat swirling pattern that is emerging when we talk about the reduction of risk and incidence of cerebrovascular and cardiovascular disease. Clearly, the arterial garbage collector that picks up a lot of this lipid and may modify the inflammatory potential is the lipoprotein called high density lipoprotein (HDL). Most individuals would say that HDL is a "good cholesterol" because it is able to remove lipid from circulation that may be atherogenic. It is a reverse flow of potential atherogenic lipid. Individuals with low HDL levels are those who have been found to have higher incidence of CVD. Conversely, people with high HDLs have lower incidence of CVD.

HDL exists in several isoforms, some of which may be more atherogenic than others. We probably should not just talk about generic HDL. Before we get into the specific isoforms of HDL, I want to talk about HDL modification. HDL is a good cholesterol, until it has been potentially chemically modified in the vasculature by undergoing oxidative modification. What is it that oxidizes HDL? It is an enzyme called myeloperoxidase. Myeloperoxidase is a white-cell enzyme involved in the Klebanoff reaction, the reaction that produces hypochlorite, or bleach, that is part of the chemical warfare armamentarium that our bodies use to kill foreign invading cells. When white cells are activated, they produce higher levels of activity of myeloperoxidase, which increases hypochlorite production. Myeloperoxidase activity also increases the conversion of HDL to damaged HDL. It has recently been found that oxidative injury to HDL changes "good cholesterol" into "bad cholesterol," meaning it converts friendly HDL to unfriendly HDL.

This is an interesting new twist on the story because it connects the inflammatory mechanism with the lipid mechanism through the HDL modification pathway. An antiinflammatory apoA1, when converted into a proinflammatory form by myeloperoxidase, results in injury to HDL, which becomes atherogenic. This is a fairly remarkable new discovery. I am now citing one of a series of papers in *Nature Medicine* that talks about the atherogenecity of oxidatively injured HDL. [10] People are now starting to look at myeloperoxidase levels. In fact, we cited a paper that appeared in the *Journal of the American Medical Association* in 2004 that showed a close correlation between the relative incidence of CVD and myeloperoxidase activity levels, potentially a new prognostic marker, another one of the extended risk factor markers. If we think of myeloperoxidase as being an indirect inflammatory marker, then this connects inflammation to serum lipids to atherogenecity.

Metabolic control of serum lipids is very important. Control of the status of lipids so they do not undergo oxidative injury is important. Lowered inflammation is important. Proper vascular biology related to eNOS is important, and increasing HDL levels is favorable. How can that be done?

There are different protein hydrolysates that have been shown to increase HDL levels. There have been some interesting studies showing that fish protein hydrolysates and certain soy proteins can actually increase HDL levels. I am now quoting from the *Journal of Nutrition*.[11]There are certain dietary signals that are more than just protein, carbohydrate, and fat, but specific types of molecules in our diet that may have a favorable effect on elevating gene expression of the HDL lipoprotein, or apolipoprotein.

That raises the question as to whether there are specific types of foods that contain elements that can speak to the genes in such a way as to activate favorable cardioprotective outcomes. It is more than just restricting calories, and it is more than just restricting fat and increasing protein, or decreasing carbohydrate. There is something about the messenger molecules, the dietary signals we are sending from specific foods, that relate to the outcome we call relative disease risk

If we marry this to recent data on statins, it opens up some interesting questions. If we look at statin research, we know that aggressive or intensive intervention with statins has been demonstrated to lower acute coronary syndromes. This is discussed in one of a series of papers that appeared in *The New England Journal of Medicine*, in which intensive statin therapy was called a "sea change" in cardiovascular prevention, trying to get LDL levels lower than 100 mg per deciliter.[12] ,[13] When LDL is around 70, the risk or incidence of cardiovascular disease is reduced even more. However, in more recent studies published in 2005, it has been demonstrated that intensive statin therapy results in greater

reductions in both lipids and high sensitivity C-reactive protein (hsCRP). In addition, the decreases in lipids and CRP is associated with reduced progression of atherosclerosis. It is not as simple as looking solely at LDL cholesterol, but it is also necessary to look at serum inflammatory markers. I am citing here from a *The New England Journal of Medicine*, 2005.[14]

It is not just lipid levels. As we see more and more evidence being published, there is something pleotrophic about the mechanism of action of statins. They may affect the lipids and endothelial inflammation in some people. I am now quoting from a review that appeared in the *Journal of the American Medical Association*, titled "High-dose statins in acute coronary syndromes. Not just lipid levels," in which the authors talk about the dual responsibility, or effects of statins.[15]

C-reactive protein, as a measurement of inflammation, is not only an inflammatory marker, but could also be a direct agent that relates to relative risk of injury to the arterial endothelium. We think of intracellular adhesion molecules as being indicative of injury. We think of proinflammatory cytokines, such as IL-6. We think of myeloperoxidase and we think of hsCRP. As has been pointed out, hsCRP is not the be-all and end-all for cardiovascular risk due to inflammation, but it is a good screening tool. Values chronically elevated (above 1.5 mg/dL) may suggest an increasing relative risk to vascular disease. Levels of hsCRP can be elevated solely by a cold, the flu, or running a marathon, but they will usually come back to normal after recovery. It is when there is a consistent elevation of hsCRP over time that we talk about the "arteries on fire," and their relationship to cardiovascular disease. A discussion of this topic can be found in *Medical Hypotheses*.[16]

There is a distribution of elevated C-reactive protein in the population at large. This is discussed in a study in *Clinical Chemistry*, in which the authors talk about the fact that people with more insulin resistance, metabolic syndrome, and high triglycerides/lower HDL also generally have increased hsCRP levels.[17] It is a bell-shaped, non-parametric distribution of hsCRP in our population, skewed to the higher level, meaning we are already a culture in inflammation associated with the increasing risk of CVD.

Coxibs and Cardiovascular Disease

How does the use of the selective coxib drugs relate to this? As they were being used for the treatment of osteoarthritis, in some people they actually increased coronary events, because by blocking all COX-2 enzymes, they also block favorable enzymes that produce friendly eicosanoids in terms of the control over blood flow parameters. In this case, the selective COX-2 inhibitors, such as rofecoxib, and even celecoxib, have been associated with increased vascular events, due to blocking production of prostacyclin (PGI2) in the endothelium. As Garret FitzGerald recently discussed in *The New England Journal of Medicine*, coxibs are associated with cardiovascular disease because of the non-tissue-specific inhibition of regulatory substances from arachidonic acid, which are prostaglandins associated with housekeeping functions, like PGI2 from the vascular endothelium.[18]

In a further editorial in *The New England Journal of Medicine*, author Eric Topol contends that the drug companies were failing the public health by not bringing to light the fact that these anti-arthritic drugs were also having adverse cardiovascular effects due to blocking important prostanoids in an untenable fashion.[19]

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician/Researcher of the Month. Last month, we had the pleasure of interviewing Dr. Mehmet Oz from Columbia University, and we were all rewarded by the comments he made concerning how he sees medicine evolving. On this theme, we couldn't be more pleased to have cardiologist and internist, Dr. Mimi Guarneri as our guest this month. In 1999, she founded, and is now Director of, the Scripps Center for Integrative Medicine. Dr. Guarneri received her Bachelor's Degree in English Literature from New York University, a Master's in Bioengineering from The Polytechnic Institute of New York, and MD from SUNY Downstate. She is also board certified in holistic medicine, and an assistant clinical professor of medicine at the University of California/San Diego. In addition to her many accomplishments, she is a remarkable person, and I have had the privilege of getting to know her over the last few years.

To elaborate on her background somewhat, Dr. Guarneri is co-author of a paper published in the American Journal of Cardiology (1999), titled "Quantitative angiographic analysis of stent restenosis in the Scripps Coronary Radiation to Inhibit Intimal Proliferation Post-Stenting (SCRIPPS) Trial." Another of her papers was published in 2003 in the American Journal of Cardiology, titled "Improvement in medical risk factors and quality of life in women and men with coronary disease in the Multicenter Lifestyle Demonstration Project." She also has a paper currently in press on how biofeedback increases heart rate variability in patients with known coronary artery disease. Heart rate variability is a very important function of heart health-the more variable, the more degrees of freedom, the more degrees of entropic freedom, the healthier the heart. All these things demonstrate Dr. Guarneri's wide range of interests.

Mimi, it's a privilege to have you on FMU. The first question I want to ask is, how do you get to cardiology from an undergraduate degree in English literature and a Master's Degree in bioengineering?

MG: Thank you for that wonderful introduction, and that's a great question. Literature has always been a love of mine, and when one goes to college, there are many opportunities. Most of the other premed students were majoring in biology and chemistry, which are certainly important. I was always fascinated with those subjects, as well as reading Shakespeare and Homer's poetry. I've always worn two different hats. The bioengineering was a wild card, because for a short period of time, I thought I could make a difference by devoting myself to the research side. Then I realized that medicine is my love, because people are my love. I decided to go to medical school and the rest is history.

JB: I understand from Dr. Bonakdar, your colleague at Scripps, that you recently decided, for reasons you will probably share with us, that you needed to go back and focus on a Board certification in nuclear cardiology. Is that correct?

MG: Yes. One of the things we learned here at the Integrative Medicine Center is that the more we can bring into the center that blends Western medicine with alternative medicine, the more well-rounded we are. To that endeavor, because one of my passions is prevention of disease and to be able to detect disease

early, we put a significant amount of resources and energy into creating what's called an early detection center. That includes quite a bit of technology, with CT imaging and PET, which stands for Positron Emission Tomography imaging, for the heart. To be prolific and able to read these scans, one needs to be Board certified in nuclear cardiology. My ultimate goal with all of this is not only to identify disease early so as to prevent it, but to test some alternative modalities and integrative interventions utilizing this technology.

JB: Well, congratulations. Dr. Bonakdar also told me I should have great respect for anyone who has accomplished this goal, because nuclear cardiology is known to be one of the more difficult Board certifications, requiring a lot of study. Some people need to take this exam a couple of times. You passed it with flying colors on the first time through, while still overseeing the directorship of the Integrative Medicine Center and all of your other responsibilities. It's another measure of you as a person, and we are all in awe. It's pretty impressive.

MG: Thank you.

JB: With your background and broad range of interests, how did you ultimately become the founder of the Scripps Integrative Medicine Center? That might be somewhat risky with your background. What led you down that path?

Initiation of the Scripps Integrative Medicine Clinic

MG: I don't think it's risky. I came to Scripps to put stents in coronary arteries. I was doing what I call advanced plumbing-fixing vessels that already had evidence of narrowing from cardiovascular disease (CVD). I would put in seven to ten stents a day. Then I would go up to the ICU to see my patients and they would be eating roast beef sandwiches or beef stroganoff. They would go home the next day with absolutely no instruction about lifestyle changes, proper nutrition, nutraceuticals, or stress management. After you do this for a while, you begin to realize the old Chinese saying about what insanity is-doing the same thing over and over and expecting a different result. That rings true in cardiology. The more we were stenting and sending people home, the more they were coming back. Not only were they coming back with re-stenosis or lesions within their stents, but they were coming back with new lesions. A lot of that is because we weren't taking the time 0o turn the faucet off, literally. After watching this year in and year out, I started to realize that we needed to do something radically different for our heart patients. That's where we began-with the heart patients. Ironically, of course, in the beginning, ten years ago, teaching heart patients about nutrition and exercise was considered alternative medicine.

JB: As I recall, you originally started with Dr. Dean Ornish's program at the center. We have had the privilege of interviewing Dr. Ornish on FMU. Clearly, that's evolved as you've gained experience and have seen what works and what doesn't related to developing the best approach to the personalized needs of the patient. Tell us about how you started down this path, from your mission to its implementation.

Scripps and Dean Ornish's Research

MG: It's an interesting story. I came out of the cath lab one day and Dean Ornish was talking to one of my colleagues. He introduced himself and said he wanted us to be a site for his research. I asked him what the focus of his research was, and he explained that it was a low-fat, vegetarian diet; yoga; meditation; exercise; and group support for heart patients. I looked at him as if he was a little bit crazy because my whole paradigm was one of stenting and doing the high technology piece. Long story short, I said I would

be happy to be the principal investigator for Scripps, because I'll do just about anything for research-and off we went.

The first thing I had to do was to get trained myself, so I enrolled in one of Ornish's retreats in northern California. I went to the retreat with a cholesterol of 320, a type triple A personality, and enormous amounts of stress in my daily life. I began to do the retreat as a heart patient. I came out one week later and I was a vegetarian. I was doing yoga two hours a day and, more importantly, I had learned an enormous amount from the patients who were there. I started to see people's lives change, just in one week of intensive intervention. By that, I mean insulin levels were being cut in half, and chest pain was going away. I thought this research needed to be taken seriously. That's how we went forward in the beginning-being part of what's called the Multicenter Lifestyle Heart Trial, of which Scripps was one of the research sites.

JB: With your mechanical mind, as well as your broad-based humanistic perspective, did you feel that there would be ways of putting this into an institutional setting and making it work? That's always been a challenge-going from conceptualization to practice.

Incorporating Integrative Medicine into Cardiology

MG: Absolutely. I looked at what we were doing inside the research program. When the research was over, I thought that we couldn't let it go. At that time, people were randomized to go into the lifestyle change program or have a stent or a bypass. So, it was randomization of lifestyle change versus stenting and bypass. Ronnie King and I looked at this and agreed that we needed to do both. That's when we embraced the term, "integrative medicine." We thought that's what we were really about. It's OK to have a stent if you need one. It's OK if you need a bypass. But why should we stop there? We decided to combine the lifestyle changes with the intervention and birth an integrative medicine center. We went forward with that concept and it was embraced on some level by the physicians because we called it integrative medicine. Quite frankly, the term alternative medicine in a conservative healthcare institution has some negative stigma to it. We called it integrative medicine and said we were going to start from the heart, because that's what we do best. We began to do what we like to refer to as a more personalized medicine approach-not one diet fits all, not one group of nutraceuticals fits all, and not one exercise program fits all. We began to slowly, but steadily build a program to incorporate heart patients who had surgery or stenting and, of course, people who wanted to prevent any of these situations who were at high risk.

Incorporating A Pain Management Program

About three years into the program, we looked back again. We were exercising people and what did they have? They had joint pain, muscle pain, aches, and arthritis, and I didn't want any of my heart patients on excess amounts of pain relievers. At that time, I was concerned about blood pressure and GI side effects from non-steroidals. Many of my patients have renal insufficiency. There are drugs that can affect their GI tract. That's when we thought that in addition to doing lifestyle changes with heart patients, we needed a pain management program. That's when Dr. Bonakdar came aboard to lead the way in that arena. Slowly, but surely, the pain management program has grown. We have incorporated many of the technological pieces into the integrative center that we were previously sending out. For example, we decided we wanted to be "high tech/high touch." Frankly, in a hospital system, you can be as high touch as you want, but it doesn't pay the bills. This is getting down to the brass tacks of being successful. Medicine considers success financial success, as well as the success of helping someone. Without

financial success, we would not be able to exist. We decided to do everything under one roof, including the best of technology, CT, PET imaging, stress testing-all of the things we would do at the hospital-along with acupuncture, yoga, meditation, tai chi, nutrition counseling, herbal medicine and so on. And that's where we are today.

JB: For those listeners who haven't had the privilege of visiting your facility, it's an amazing blooming of right/left brain hemispheres, of east and west, of cultural and ethnic diversity, and with a very remarkable laboratory demonstrating that these things can live in harmony. It has a wonderful feeling to it.

Debates are ongoing as to what the real versus perceived benefits of integrated cardiology are. We might believe that certain things are good, but our colleagues might ask us to show them the reality, the facts, and the evidence base. In any field, there are points of exaggeration where things don't measure up under scrutiny. What would you say the real versus perceived dilemma, or dialectic, is right now in integrative cardiology?

Issues in Integrative Cardiology

MG: There is a lot of data in good medical journals. Looking back at the early research of Dean Ornish, for example, he was able to demonstrate that in certain populations of patients, the progression of vascular disease can be halted. More importantly, 91 percent of the patients in the Ornish research studies became angina free. Their endothelial function improved because of stress management, a low-fat diet, and the benefits of exercise. If you look at nutraceuticals, the area in which you are an expert, Jeff, no one can dispute the fact that certain supplements have good data for the heart. For example, if I want to raise someone's good cholesterol (HDL), there's nothing out there. Maybe there's some research on synthetics going on right now, but there's nothing out there better than niacin to achieve that goal, in my opinion as a cardiologist. If I want to lower homocysteine levels, I think the data is good for the use of B vitamins. If we need to, we can certainly pull out data on anything we do here at Scripps and justify it; for example, even exercise in heart patients. Half the number of hospital readmissions are patients who are doing cardiac rehab, and yet almost every hospital in the country cuts cardiac rehab programs because they don't make money.

The Need for a Paradigm Shift

What we need is a paradigm shift. We need a paradigm shift to the point where physicians get compensated for keeping people well. That's the big issue. Physicians don't get compensated for that. They get compensated for putting in devices and doing surgery, which I'm not against, but there's more to medicine than that. Any area you can think of, whether it's exercise, stress management, biofeedback, or nutraceuticals, we can quote you good literature as it applies to the heart, and there's no cardiologist in the country who would say that nutrition, lifestyle changes, managing stress, anxiety and worry, and exercise, or dealing with someone's diabetes, is not going to improve cardiovascular outcome. Most physicians don't do it because they don't have the resources that allow them to do it.

JB: I often hear from people who are not ready for change that they are fearful of liabilities and, in our society, if one is not Board-certified and in the stream of their peer service organization, it's too much of a liability. What about the liability issues?

The Issue of Liability

MG: It doesn't matter what kind of medicine you are practicing. You need to do what's within your scope of practice, knowledge, and understanding. If there's research behind it, then it's just medicine. It's not

integrative medicine; it's not alternative medicine; it's not Western medicine; it's just medicine. If it's been demonstrated to work, then you use it. As a physician, for me personally, I could not sleep at night if I was doing something that I was even remotely concerned about regarding liability issues. Then, I'm doing something that is out of scope, perhaps of good judgment, or so on. That's not what's going on here, at least at Scripps. And that's how I choose to practice. For example, if I'm giving someone magnesium for the prevention of cardiac arrhythmia, there's research to support that. I don't really worry about liability. Maybe I don't worry about it because I'm not doing anything that I consider radical.

JB: That's well said. I've had a couple of conversations with very well respected cardiologists who said they don't think there's anything to the inflammation/atherogenesis story and that they don't worry about things like hsCRP or inflammation. What's your position on that?

Inflammation and Atherogenesis

MG: I'd be shocked, because I go to the big meetings and inflammation is the buzzword. Most cardiologists in academic circles are talking about inflammation. I'll give you a good example. Within the last year, we had two major lipid studies published. One is called "Reversal;" the other was called "Prove It." In the lipid study, "Prove It," they took high-risk people with cardiovascular disease and randomized them to two different types of statin therapy-one was a high dose of Lipitor and the other a dose of Pravachol. What they found at the end of the day was that both drugs reduced the HDL the same amount. For example, if you take people who had a 40 percent reduction with Pravachol and people who had a 40 percent reduction with Lipitor, for some reason, the people who took the Lipitor had more plaque regression. The question is, why? Is LDL so smart that it knows the difference between two statins? I don't think so. When they examined the data more closely, they found Lipitor had a much more profound effect on hsCRP. I point this out because here's a perfect example of LDL-lowering with different clinical outcomes that can only be pointed to based on hsCRP. You know better than anyone, and certainly better than I do, that this is just one small tip of the iceberg marker for inflammation. We now know, and I believe this, that on every level of atherosclerotic plaque, when LDL comes into the subendothelial space, it becomes oxidized. That turns on inflammatory cytokines that lead to adhesion molecules pulling in white blood cells. We know now that inflammation is involved in every step along the way. I would challenge almost any cardiologist who has been in practice for at least a few years, that they will have patients with cholesterols of 120 and 130 with coronary disease, and the only risk factor is inflammation. We know there is a very high risk for CVD in patients with rheumatoid arthritis (RA). Inflammatory diseases are associated with a very high risk of vascular disease. I don't think we can throw inflammation out. As a matter of fact, we've been focusing on LDL for a long time, and maybe we've been missing the boat.

JB: The reimbursement issue is another area that is responsible for why people don't change to integrative approaches. Patients can't get reimbursement.

The issue of Reimbursement

MG: As healthcare consumers, we have to take health care more into our own hands. What I encourage people to do is get medical savings accounts. You can put aside a piece of your earnings, or a piece of your salary so you can use it in a way that you and your physician deem you need. You may determine you cannot go to a program because you don't meet the criteria. For example, let's say you want to attend a cardiac rehab program. You have to have had a heart attack or a stent or an angioplasty or surgery before you can get into a cardiac rehab program. There has to be some sort of devastating event or, more

importantly, a nutrition consultation. I would challenge most people to call their insurance company tomorrow and tell them they've put on some weight, and that they just want to learn how to eat healthy. Ask if they will pay for seeing a nutrition counselor. Invariably, the answer will be, "only if you have diabetes." I encourage my patients to set aside a portion of their salary so they can choose to spend it in a medical savings account the way they want to spend it. If they think acupuncture is what they need for their muscle spasms, or tennis elbow, or back pain, then at least there's money they can pull from. We have to be more creative because we are all healthcare consumers. We have to be savvy about this kind of thing. As the old joke goes, should I go into a lifestyle change program or have a bypass? Oh, I think I'll have the bypass because that's what my insurance covers. We need to get people out of that mindset.

JB: You interface at the integrative medical center with the other departments at Scripps. You have conversations with colleagues across multi-disciplines of specialty. How do you deal with some of the political and communication-related issues? Is it just information? Is it opening up the opportunity for discovery? How do you handle those complicated interfaces?

Political and Communication Issues

MG: We're in a 320+ physician group. Integrative medicine is a separate division, which we're proud of, the same as cardiology and rheumatology are separate divisions. Just like anywhere else, when you forge change, there will be people who embrace it and those who fear it. Fear is what brings about opposition. The more we can be mainstream with the other physicians, the more they know we're there to help the patients. The more they trust that what we're doing is evidence-based and has research behind it, the more we build bridges. For example, in the department of neurology, many, but not all, of the neurologists have embraced the pain management program, and they will send us complicated patients who can benefit from biofeedback or massage, particularly for headaches. We get rheumatology patients, patients with fibromyalgia, and we get cardiology patients, of course, because I'm a cardiologist. Slowly, but surely, you have to work within your system.

It's very important to have physicians who are not afraid to be on boards like the IRB. Dr. Bonakdar is on the Scripps Pain Management Board. We're working with everyone else. That's how you deal with a lot of the potential politics and opposition. Not to say it's perfect, but our goal is one of education. Believe me, we have been branded by people who don't come and visit us because they don't know who we are at this alternative center. They think we're doing all sorts of things that we don't do at all. We always invite people to come, see what we're doing, and spend some time with us. We have a very active teaching program for interns, residents, and Fellows so we can get the word out in a meaningful way.

JB: One last question. It strikes me in getting to know you, Dr. Oz, and others in your field, that you are quite remarkable people. You're semi-fearless, very intelligent, well schooled, tireless workers, and you take on a lot more responsibility than the average person does. It raises the question that a lot of people coming into this field might ask, and that's whether it is expecting too much of the average doctor to make this transition. Are we saying that you have to know everything and be everything to be successful? I want to raise that question because clearly, you are a very exceptional person. Is there still room for people who don't necessarily have all the necessary background skills and commitments that you have?

Making the Transition to Integrative Care

MG: You don't have to know everything. You can always surround yourself with people who are more knowledgeable in a particular area than you are. One of our pharmacists is far more knowledgeable than I

am, for example. You can educate yourself and get to the best of the knowledge. Any physician can do that. The real challenge is being able to stand up to the system, look at your patients and ask what you can do differently for them. In other words, how can I make it better? For me, that came with an integrative medicine attachment to it. I looked at my heart patients and realized we didn't have exercise programs, proper nutrition or nutraceutical counseling, stress management, or a pain management program. How can I be the change that I want to see (to use the words of Ghandi)? That's where the courage comes from-standing up and saying you're not happy with the way it is, and that you want something different for your patients. That's really what it takes from a physician to get something like this going. It takes the willingness to run against the herd, or away from the herd, and realize that the way you're doing it is good, but you can do it a little bit better.

JB: That is such an aspiration of what we're trying to create in our vision and mission. Thank you very much on every level, both technically and philosophically, for sharing time with us. We're all motivated by vision. All of us sometimes need to draw from our colleagues who are pulling the oars and moving in the same direction. You've given us a tremendous resource to draw from. Thank you so much and keep up the tremendous work.

MG: Thank you, Jeff.

Regulation of Nitric Oxide Synthase and Cardiobiology

Following up on some of Dr. Guarneri's comments, I would like to embellish a couple of concepts that we were discussing during the first part of this month's issue of FMU. They have to do with the regulation of eNOS and its relationship to cardiobiology. This is a fascinating area in which we are developing an ever-increasing understanding. It is becoming clear that individuals with deranged endothelial function due to insulin resistance, hyperinsulinemia, oxidative stress, or inflammatory activity, may also benefit from enhancement of eNOS activity through the use of supplemental arginine and antioxidants, and 5-methyltetrahydrofolate, or folic acid. The combination of those nutrients helps to regulate eNOS output, causing vascular smooth muscle to relax, improving vascular tone, improving insulin sensitivity and lowering inflammatory potential, because it lowers the uncoupling of eNOS and its production of oxidants. There is a variety of positive influences in people with damaged endothelial function by supplementing with the amino acid arginine and various antioxidants, including polyphenols, vitamin E, vitamin C, and 5-methyltetrahydrofolate, or folic acid.

According to Dr. Ignarro, one of the 1998 Nobel Prize winners, the doses I am talking about are in the range 6 to 9 grams a day of arginine and 2 mg of folic acid (that could be 2 to 5 mg, depending upon the degree of endothelial dysfunction). If you are going to use high doses of folate, you want to make sure the patient is properly repleted with regard to vitamin B12. Last is the use of a complex antioxidant that contains polyphenols, bioflavonoids, vitamin E, and vitamin C. That can be secured from the diet or from supplements. This approach has been demonstrated in cardiobiology by people like Dr. John Cook at Stanford to improve endothelial function, improve blood pressure, and regulate some of the oxidative chemistry going on in the vascular wall. I am quoting from two review papers in the Lancet that follow up on a discussion of increased NO-derived production in the failing human heart.20 ,21

When NO is produced in the vasculature, part of it becomes connected to hemoglobin to form nitrosyl hemoglobin, which has some physiological importance in terms of cell signaling and cellular regulation.

There is a wonderful series of articles published in Free Radical Biology and Medicine on the physiologic, pathologic, and therapeutic implications for hemoglobin interactions with NO.22 ,23 ,24 ,25 I would encourage you to read these articles if you are interested in looking at hemoglobin/NO cooperativity.

One of the principal signaling mechanisms that has evolved in the human body over time is the S-nitrosohemoglobin signaling pathway, which is an oxygen-dependent mediator of NO delivery to vascular smooth muscle cells, thus helping to regulate vascular tone and blood flow. Central to this is the concept that the interaction between NO and hemoglobin was deficient. What happens if one has anemia or poor nitrosyl hemoglobin formation is that less time release is available for NO to regulate vascular tone, and there is more vascular injury and more risk to hypertension. This is discussed in a review that also appeared in Free Radical Biology and Medicine.

Iron Overload and Cardiovascular Disease

This raises an interesting question. When we think hemoglobin, we think iron and we think NO. What about iron overload and cardiovascular disease? Is there some kind of a balance, and what is the interconnection?

I think there is some misunderstanding about iron and CVD. There is no question that excessive levels of free iron are associated with the so-called Fenton reaction, the production of oxidants, and the alteration of redox signaling in the vasculature. In these situations, iron is either excessive relative to the binding capability, or released through tissue injury of free iron that directly participates in the Fenton catalyzed reaction of super oxide into hydroxyl radical, a very promiscuous oxidant.

In situations where the iron is bound to transferrin or within hemoglobin, there is not much risk of oxidative injury. In fact, this is discussed in a good review article, titled "Iron, oxidative stress, and disease risk," that appeared in *Nutrition Reviews*.[27] The authors talk about evidence that shows how excessive iron is found in many diseases but that it has not yet been shown to be a causative factor. Although iron can participate in oxidative reactions to generate free radicals under *in vitro* conditions, its involvement *in vivo* as a cause of progression of disease is questionable. It appears that only if iron is lost as free iron from tissue iron stores and not as bound through hemoglobin or other iron-binding proteins, that these types of reactions are catalyzed. It may be a combination of iron reserve in addition to other precipitating underlying inflammatory or traumatic issues that liberates free iron to participate in oxidative injury.

For instance, consider a hemorrhage. At the site of a hemorrhage, there is blood loss, and that blood will lose its iron as free iron, and that can engage in prooxidative chemistry. That is why minimizing blood loss and tissue blood accumulation is very important to lower the risk to oxidative injury and secondary effects from a trauma to that tissue.

Experimental studies have consistently shown that iron is a critical catalyst in generating oxygen free radicals via Fenton chemistry. Epidemiological studies conflict on the association between stored body iron markers and disease outcomes, including CHD. Stored body iron markers common in epidemiological studies, such as serum ferritin, transferrin saturation, iron, or iron-binding capacity, are actually inappropriate to investigate the harmful health effects related to iron overload. Oxygen free

radicals are produced only by free iron, but stored iron markers reflect iron bound to ferritin or transferrin, which is not able to deliver free iron, but rather is sequestered catalytically so that it cannot generate some of these oxygen free radical effects. It is generally believed that free iron rarely exists, except in iron-overload with 100{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} transferrin saturation. However, some recent studies find non-transferrin bound iron or the intracellular labile iron pool in the presence of triggers disturbing iron homeostasis. These triggers can be such things as alcohol consumption, physical trauma to tissues, ischemia, or even inflammatory mediation on those tissues that releases the intracellular labile iron pool, which can participate as a catalyst in the Fenton reaction. Research on the relationship of iron to disease outcomes should investigate these labile iron pools because they are the ones that seem to be most problematic in inducing free radical oxidative injury. These factors may explain why there have been conflicting results between serum markers of stored body iron and diseases that relate to epidemiological outcome studies.[28]

I would urge everyone not to jump on the anti-iron bandwagon too quickly. I fear that when people start worrying about iron as the cause of heart disease, they actually start producing a situation of anemia in some patients which, ironically, increases the labile iron pool by ischemic events, and increases oxidative injury rather than decreasing oxidative injury.

The story is proper hemoglobin hematocrit levels, making sure not to push a patient into anemia, and not being overly concerned about iron until there is excess dietary iron intake. For instance, some supplements in pregnancy formulas deliver 75 to 100 mg of elemental iron. That may be excessive, so we have to look at everything as a parabolic dose response curve.

Mercury and Cardioprotection

A heavy metal that deserves some consideration in a cardioprotection program is mercury. There is more and more evidence coming out looking at the atherogenic effect of excess mercury exposure. This comes through fish, as well as through other sources of mercury and its relationship to heart disease. There is a nice review of this topic in *Nutrition Reviews*,[29] looking at total body mercury exposure from fish and other dietary intakes, and amalgams, how they release their mercury content, and how this ultimately influences function.

What I have tried to emphasize in this review, following up from Dr. Guarneri's beautiful discussion about CVD prevention, is that much of the burden of chronic disease we are experiencing is modifiable, not necessarily through the use of a polypill, but a polymeal or a polydiet lifestyle approach toward modulating gene expression patterns. That is the focus of the functional medicine model which emphasizes the mechanisms of disease, rather than just their outcomes.

Thanks for being with us. We look forward to being with you in July.

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