

February 2003 Issue | Richard Delany, MD Medical Specialty Group

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Welcome to *Functional Medicine Update* for February 2003. We are focusing our attention on functional cardiology as a prelude to the 10th International Symposium on Functional Medicine, to be held at the Westin La Paloma Resort in Tucson, Arizona, May 21-25, 2003. We have had principal investigators in cardiology as our *FMU* guests, at both the research and clinical levels. Those guests have included Dr. Louis Ignarro, 1998 Nobel Prize winner in Medicine and Physiology; Dr. John Cooke from Stanford; Dr. Mark Houston from Vanderbilt University Medical Center; and this month's Clinician of the Month, Dr. Richard Delany.

Cardiovascular disease remains the single highest cause of mortality in the United States. When an individual experiences a sudden coronary event, he or she is robbed of many productive years of life. Many such individuals do not get a second chance. The first coronary event is often the last event of their lives. Many who are fortunate enough to survive experience some limitation in their functional ability for the rest of their lives. Clearly, this major health problem looms as significant as ever.

Cardiovascular Disease and Gender Cardiovascular disease has increased in visibility as a consequence of the discovery that women on hormone replacement therapy (HRT) continue to be at risk. In fact, as the HERS Trial revealed, equine estrogens plus synthetic progestins may slightly increase the relative risk of vascular events in some women.

Cardiovascular disease is revealing itself to be a non-gender-specific condition. It is not only the major cause of mortality but it also makes a significant contribution to morbidity.

Statin Drugs

Cardiovascular disease has fueled the development of an extraordinarily successful new component of the pharmacology industry. I refer to lipid-lowering drugs, particularly those born out of the statin family of drugs, as well as the fibrates. These fungal metabolites called monocolins, which were discovered in Japan, have influence on lowering LDL cholesterol. They also have far greater effects on cellular physiology and pathophysiology than simply blocking an enzyme called hydroxymethylglutaryl coenzyme A reductase (HMG CoA), which is the rate-limiting step in cholesterol biosynthesis.

Researchers are now finding the statin drugs influence a number of other functions related to vascular outcome. We will be speaking more about that over the course of this month's *FMU*.

A review of functional cardiology reinforces the view most of us have long held, that the cardiovascular

system is connected to the legs, arms, and trunk of the body. Therefore, what we do in terms of activity plays a role in our cardiovascular function. It is the old “use-it-or-lose-it” adage.

Manson et al. last year published an insightful paper in the *New England Journal of Medicine*, titled “Walking Compared with Vigorous Exercise for the Prevention of Cardiovascular Events in Women.”^{1,2} This paper reinforced some things we already knew, but it also provided compelling new research support. Investigators in this study used questionnaires to measure recreational physical activity levels in 73,743 postmenopausal women in the Women’s Health Initiative Observational Study. The study excluded women who had coronary heart disease or other selected medical conditions. The researchers were looking at individuals who were presumably healthy.

Measuring Metabolic Equivalent Hours (METs)

Participants were followed for an average of three years, during which 1551 participants had cardiovascular events. The subjects were divided into quintiles of physical activity according to their weekly energy expenditure in what are called metabolic equivalent hours (METs). Exercise evaluations reflect MET capability. One MET equals a level of oxygen consumption of 3.5 ml per kg of body weight per minute, as defined by exercise physiologists. This approximates the average energy expenditure during rest. One MET is about the amount of oxygen a person would be consuming at rest.

Let’s look at the energy expenditure of walking three miles per hour. Those of you who use pedometers would agree that is a vigorous walking rate on level ground. It is equivalent to about 3.3 METs, or 3.3 times the resting energy expenditure compared to sitting and thinking about walking. You might think that if you walk three times as long, you would get the same benefit, but that is not how it works. Raising the activity of your vascular system has a neuroendocrine cardiovascular impact that has positive benefit in maintaining health of the vasculature.

Exercise and Cardiovascular Events

In the Women’s Health Initiative Observational Study, the women in the highest quintile of physical activity had 23.4 MET hours per week, which is roughly equivalent to walking three miles per hour for an hour each day. These women were compared to all other subjects with lower levels of activity. After adjustments for possible confounding factors, the researchers found that as women became progressively more active, they had progressively fewer cardiovascular events. The women at the highest level of activity (three miles per day, seven days a week) had about 28 percent fewer cardiovascular events than those at the lowest level. According to the unadjusted data from this trial, women who spent a total of between 45 minutes and 7 hours each week exercising had between 3.6 and 7.8 fewer cardiovascular events for every 1000 participants during the three years of the study. A 3.6 reduction in a life-threatening condition is quite good. That was the reduction in cardiovascular events achieved by the modest walking group, the group that walked only 45 minutes per week.

More Exercise, More Risk Reduction

Many people complain they don’t have time for such activity, but we are only talking about 10 minutes per day. Perhaps it is poor use of one’s time if one cannot find time for 10 minutes per day of exercise.

Even at the low levels of activity in the study (45 minutes per week), there was a significant advantage. At the high level (seven hours per week, or one hour per day), participants experienced 7.8 fewer cardiovascular events per 1000 participants.

Exercise Compared to Statin Drugs

How do those results compare to drug therapy? The reduction in cardiovascular events that was observed in this study compares to the result when healthy women were treated with lipid-lowering agents over five years, which is a reduction by four for every 1000 women. That means modest exercise is equivalent to the results one would achieve with statins. Statins involve some potential untoward side effects (neuromuscular or hepatotoxic). I know of very few people who experience toxic side effects from walking 45 minutes a week, or even seven hours a week.

This study indicates it is not necessary to participate in extraordinarily vigorous exercise to achieve marked benefit for the cardiovascular system. As our society evolves, it sometimes appears that our major evolutionary objective is to exercise less and less. The more we sit around and allow ourselves to be transported by mechanical means, the better off we suppose we are. In fact, according to the *New England Journal of Medicine*, the U.S. Postal Service is currently evaluating a human transporter, a self-balancing personal transportation device that will permit letter carriers to make their appointed rounds without walking. If the U.S. Postal Service adopts that device, very few occupations will continue to involve any kind of activity. We are becoming a more and more sedentary population, and cardiology is becoming a more and more important subspecialty in medicine.

Another part of the evolution of understanding functional cardiology is the role of insulin resistance and hyperinsulinemia as a cholesterol-independent risk factor to cardiovascular disease. We increasingly recognize that type 2 diabetes, syndrome X, and the precursor condition—hyperinsulinemia or insulin resistance—track against the relative risk to cardiovascular disease. This connection was described in an article in the *Lancet*, titled “Diet and Risk of Coronary Heart Disease and Type 2 Diabetes.”³

The author of this paper discussed the epidemiology of cardiovascular disease and showed that populations whose diet is high in simple sugars, saturated fats, and alcohol have a much higher incidence of both diabetes and cardiovascular disease. These two disorders do not correspond exactly with one another, however. This diet contributes to the etiology of diabetes in a slightly different way from its contribution to heart disease, in a traditional sense of heart disease coming from cholesterol elevations.

The Role of Diet and Lifestyle in Insulin Resistance and Hyperinsulinemia

Diet and lifestyle play significant roles in modulating relative risk to cardiovascular disease associated with insulin resistance and hyperinsulinemia. We have discussed this role in previous issues of *FMU*. We pointed out that the first step that should be taken with a patient who has insulin resistance or hypercholesterolemia, before we intervene with insulin-stabilizing or glucose-normalizing drugs, is to introduce lifestyle therapy. (An exception, of course, would be a patient in a fulminating state of diabetes.) In the precursor marker stages of diabetes, such as syndrome X or insulin resistance, intervening with diet and lifestyle may be preferable.

The recent National Institutes of Health guidelines, the Therapeutic Lifestyle Choices Program (TLC), advocated intervention first with diet and lifestyle before intervening with a medication. This important component is often overlooked in the traditional practice of medicine, because it is assumed that the patient won't change his lifestyle, so he is never given the option to make that choice. Most doctors' first resort is to the prescription pad, and from then on the patient is recruited into a pharmacological management program.

It may turn out that some patients, if given the option, would choose not to make therapeutic lifestyle changes and would opt for the prescription pad. But there may be others whose first preference would be to retain a locus of control and choose to manage their own lives. Rather than have their condition managed by something out of a bottle, they would prefer to be counseled in regard to controlling both sugar and blood lipids through diet and lifestyle

One of the principal features, from a physiology perspective, that seems to contribute to the insulin resistance/ hyperinsulinemia, decreased HDL, increased triglyceride profile associated with cardiovascular risk, is central adiposity, or the accumulation of visceral adipose tissue (VAT). Many people who do not necessarily look “fat” may actually have a problem with VAT rather than fat. VAT accumulates in the inter-abdominal region, around the organs. It appears to have the greatest correlation with relative risk to vascular disorders and diabetes, and it is associated with increased waist-to-hip ratio if you are doing physiognomy and anthropometric measurements.

The concept that allows patients to retain locus of control is the Albert Bandura approach. Bandura, a professor at Stanford University and a social theorist, is author of the book, *Self-Efficacy: The Exercise of Control*.⁴

Using this approach, the clinician would introduce the concept that the individual patient has the ability to create a different shape by making diet and lifestyle changes. The physiological impact of increased visceral adipose tissue is that this tissue has the differentiation of pre-adipocytes into mature fat cell components. These components then elaborate from their genes the specific messenger molecules that create a different physiology.

The Active Role of Adipocytes

Fat is not benign, at-rest, tissue, as we have traditionally thought it was. It is not just the stored result of all those abusive meals we may have consumed. That concept of body fat is changing. We now recognize that fat cells, adipocytes, are metabolically active and elaborate their own messenger molecules. These messenger molecules include a family of proinflammatory cytokines, like tumor necrosis factor- α and interleukin-2 and -6. Therefore, the visceral adipose tissue in our bodies may be releasing into systemic circulation, or into adjacent regions, messenger molecules that change physiology and function of cells, tissues, and organs. We end up with a biological response that shifts the body into a state of alarm or inflammation.

Scientists have recently found that adipocytes can also elaborate angiotensinogen and can influence blood pressure and electrolyte regulation in the body.⁵ This is a fascinating new chapter in the emerging story that body fat secretes its own messenger molecules and creates a different systemic physiology.

Angiotensin

Recent findings indicate there is a mechanism by which transient or chronic overexpression of angiotensinogen in adipose tissue favors the synthesis of lipids and the accumulation of triglyceride in the adipocyte. This process sets up a vicious cycle. It stimulates production of angiotensinogen and accumulates more light lipids in the fat, and the cycle continues.

Once it starts, the problem is self-replicating. You may frequently have observed patients who never had weight problems until a particular point in their lives. Then it seemed that just thinking about food

resulted in weight gain, and nothing could reverse it. That's a changed state of physiology.

Homeostasis of Dysfunction

We often think of homeostasis as the regulation of physiological function around health, like good glucose, good oxygen, CO₂ levels, good electrolyte balance, and good redox potential. We can actually be in a homeostasis of dysfunction, however, in which there is a balanced equilibrium of inflammatory mediators or other molecules of alarm that are creating a long-term, chronic problem.

That state was often associated with the accumulation of visceral adipose tissue. VAT is interrelated with hyperinsulinemia/insulin resistance, inflammation, and coronary heart disease. It is involved with the recruitment of monocytes that start to become foam cells, and all the things that are associated with atherogenesis, as well as increased blood pressure, decreased HDL, and increased triglycerides. When we look at functional cardiology, we are looking at the heart and vascular system in the context of the whole body, interconnected with all of the other tissues and organs

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Another component of this relationship is the folate cycle and the interrelationship of inflammatory mediators to increased homocysteine levels. There seems to be a clinical correlation between elevated homocysteine and elevated inflammatory mediators and between homocysteine and homocysteine thiolactone. These elements all seem to be related to the triggering of inflammation signals. Patients with elevated homocysteine often also have elevated high sensitivity C-reactive protein (CRP) in their blood, suggesting a relationship between the two.

The metabolic state that results in elevated homocysteine is tied to some type of insufficiency in the folate cycle. Therefore, we have often jumped to conclude this must mean that a particular patient has a folic acid insufficiency. The first-line treatment choice for hyperhomocysteinemia would be elevated intake of folic acid at 400 mg, 1000 mg, even up to as high as 5000 mg, or its vitamer called 5-methyltetrahydrofolate. This is the methylated derivative of folic acid that has already been processed through the methylenetetrahydrofolate reductase pathway. Considerable genetic polymorphism exists in this pathway, which may involve a slow methylating step. By giving 5-methyltetrahydrofolate as a supplement, you may bypass that particular blocking step in the folate cycle. High doses of folic acid or 5-methyltetrahydrofolate have resulted in reduced homocysteine levels in many patients.

On the other hand, some patients seem to be refractory to folic acid supplementation alone, and their homocysteine levels remain elevated with this supplementation. This was the topic of a recent *Lancet* paper titled "Effect of Supplementation with Folic-Acid on Relation between Plasma Homocysteine, Folate, and Vitamin B12."² Here the story becomes more important clinically.

In another *Lancet* paper last year, Quinlivan et al. reported that both folic acid and vitamin B12 are

important in reducing the risk of vascular disease, and that as one supplemented with higher doses of folic acid, the need for vitamin B12 became more important.⁸ Therefore, you could have fulfilled the need for folic acid only to have B12 insufficiency exert a limiting effect on homocysteine reduction. In this recent *Lancet* paper, the authors say to make sure you are giving B12 because you may not be getting the kind of benefit in homocysteine reduction by giving folate alone. The B12 may have to be given at fairly large doses, depending upon the genetic polymorphisms of that individual and how he or she handles vitamin B12

The authors of a recent paper in *Clinical Chemistry* talked about some of the genetic polymorphisms found surrounding vitamin B12 metabolism. The more individuals examine this issue, the more they find different types of SNPs that relate to vitamin B12 metabolic uniqueness, such as polymorphisms in what is called the transcobalamin gene that relates to vitamin B12 metabolism⁹.

In this paper, the investigators reported that, of the individuals in the highest quartile of vitamin B12 distribution (blood levels greater than 299 pmol/L), those with the unique nucleotide polymorphism of the transcobalamin gene called the 259PP polymorphism (the homozygous form) had a much lower total homocysteine than those without this polymorphism, indicating that these individuals may be more likely to respond to B12 by lowering homocysteine. These individuals may, thus benefit more from supplemental B12.

Individualizing Folic Acid and B-Vitamin Supplementation

Other SNPs of this particular transcobalamin gene were less efficient in utilizing vitamin B12. At the same level of vitamin B12 intake, they would have higher levels of homocysteine. Again, this shows there is genetic variation in homocysteine related both to folic acid and vitamin B12. This study indicates there is a genetic variation both in how vitamin B12 is metabolized, stored, transported, and utilized in methylation reactions, as well as genetic variation in how folic acid is metabolized. One could, therefore, see a potential for adjusting doses of these individual vitamins in order to create the right outcome in that patient based on his own genotype.

This same argument applies to vitamins B6 and B2. They also play roles in the folate cycle, along with the methylating cofactor betaine, or trimethylglycine. All these substances work together to regulate the management of methyl groups in the folate cycle to reduce the level of homocysteine.

A recent paper in *Clinical Chemistry* revisits the question of expensive urine. If you supplement with vitamins and your urine suddenly turns a bright yellow color, many individuals suggest you are wasting those vitamins because they are passing right on through the body and spilling out in the urine.

What's wrong with that model? It assumes that as the vitamin passes through the body, it does nothing along the way, that it is eliminated directly without any kind of molecular exchange or events at the cell physiology level. If that were true, we could also say that drinking water is a waste of time because it just gets urinated away. As a vitamin passes through the body, it does something along the way. In the same way, we ultimately get rid of the food we consume, but it has done something on the way through the body.

Riboflavin, FMN, and FAD

Another article in *Clinical Chemistry* is titled "Riboflavin, Flavin Mononucleotide, and Flavin Adenine

Dinucleotide in Human Plasma and Erythrocytes at Baseline and after Low-Dose Riboflavin Supplementation.”¹⁰ Riboflavin, or vitamin B2, is a precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These compounds serve as cofactors for many reduction/oxidation biochemical reactions related to energy production or energy management in the body. We would consider them energy-stimulating or -supporting nutrients, and their relationship to the folate cycle is very important.

FMN and FAD are involved in the metabolism of folate, vitamin B12, vitamin B6, and other vitamins. This probably explains why plasma riboflavin is a determinant of plasma homocysteine, which is associated with risk to cardiovascular disease, neurological disease, and inflammatory disorders.

Challenging the Expensive Urine Model

Pregnancy complications such as neural tube defects, spina bifida, and cognitive impairment related to dementia are all associated with riboflavin sufficiency. Considering all of its important roles, riboflavin appears to be a very important nutrient.

According to the expensive urine model, however, those who eat a well-balanced diet of variety and moderation containing RDA levels of riboflavin need not worry. They must be producing, in their plasma and in their cells, adequate levels of the enzymes that convert the riboflavin into its respective cofactors, FMN and FAD. Therefore, additional supplementation of that nutrient would only cause expensive urine because we are already near or at saturation of those enzymes related to that function.

The Stimulation Test

Subjects in the study described in *Clinical Chemistry*, who were apparently healthy individuals with a mean age of 69 years, participated in what is called the stimulation test. Investigators removed red blood cells from the subjects and stimulated them with additional riboflavin in the test tube. (Red blood cells provide a good measure of intracellular FMN, FAD, and riboflavin levels.) They found an activation of the effectiveness of that cell function that depended on riboflavin. The degree of activation indicates how deficient the cell is or how far it is from saturation of that vitamin. The more activation you get when you add the vitamin to the test tube, the further away it is from saturation.

What did they find in these apparently healthy individuals? An activation number above 1.2 reflects a marginal vitamin insufficiency. The average of these people was 1.18; the range was from 1.07 to 1.29, and almost half of the subjects had values of 1.2 or greater. Based on a fairly conservative intracellular measurement of functional vitamin utilization, this means that people who were presumed to be healthy at the age of 69 had a functional vitamin insufficiency.

Effects of Riboflavin Supplementation

These individuals were then supplemented with riboflavin, i.e., they created expensive urine. The investigators once again studied their red cell levels of FMN and FAD and their activation levels. As we might expect, their activation levels went down, meaning they were closer to saturation. The levels of erythrocyte FAD and, in particular FMN, went up considerably higher than the elevations in the plasma of FMN, FAD, or riboflavin.

If we only used plasma analysis to determine blood vitamin sufficiency, it seems we would be led to misunderstand the relative status of those vitamin levels in tissues and cells. By increasingly

supplementing with those vitamins, we drive them into the coenzyme form that can function within the cells. This is independent of polymorphisms. I haven't even mentioned the additional complicating factor of people who have specific polymorphisms related to difficulty in metabolism of these nutrients.

Individualizing Supplementation to Support Methylation

When you are dealing with a cardiovascular risk pertaining to the folate cycle, make sure you personalize your vitamin recipe with regard to riboflavin, pyridoxine, vitamin B2, vitamin B6, folic acid, and 5-methyltetrahydrofolate or 5-formyltetrahydrofolate, vitamin B12, and betaine or trimethylglycine. All of these nutrients play roles in covering the range of polymorphisms and individual needs. One size does not fit all.

What we are dealing with here is methylation. Methylation is related to cardiovascular disease, neural tube development, insulin management, inflammation management, neurodegenerative disease, and also cancer. All of those disorders are related to the methylation pathway. If you want to follow up on this topic, I urge you to look at a series of papers that emerged from a symposium on diet, DNA methylation, and health. They appeared in the *Journal of Nutrition*. [11.12.13.14.15.16](#)

Gene/Nutrient Interactions and DNA Methylation

These papers discuss gene/nutrient interactions and DNA methylation. They explain the important role methylation can play as an epigenetic variable that controls cell differentiation and cell cycling. Our genome may carry information that can only be properly expressed by methylation. Folic acid insufficiency has an adverse effect on DNA stability. DNA methylation-related processes are involved with atherosclerosis, diabetes, cancer, and neurodegeneration. All of these topics are discussed in these papers. Last month we also discussed S-adenosylmethionine (SAM) and its relationship to folic acid. This is a very powerful emerging story.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: Continuing with our theme of functional cardiology, we are pleased to have as this month's Clinician of the Month Dr. Richard Delany, a board-certified internist and cardiologist who has been in practice in the Boston, Massachusetts, area for about 23 years. His practice is focused on personalized functional cardiology. Dr. Delany is a leader in his field, having organized an Independent Physicians Association. He is familiar with all the eccentricities of the managed care system and how to deliver quality care within the constructs of the present financial medical establishment. He has been a leader and an innovator, always pushing the envelope of new knowledge and information, which includes his commitment to attend a science and nutrition course at the Harvard School of Public Health in the late

1990s. We are pleased to have Dr. Delany as our guest this month.

Evolution of Dr. Delany's Career

Rich, I'd like to start off by asking how your evolution through your academic medical training and the development of your practice helped you arrive at this point in your career?

RD: Thank you for inviting me to be your guest today. My evolution as a physician is ongoing; it never stops. In recent years my approach to medicine has become more and more personalized, down to the individual level. Attending your lectures on functional medicine over the past 10 years taught me to think about each patient, link his or her illnesses, and look at each patient as an individual.

The focus in cardiology has always been a single cholesterol measurement, but the risks are much more global than that. There are many other individual risks that affect a person, and my treatment over the last few years has been with a global, personalized approach to the risk factors.

A Personalized Approach

After taking a history, doing a physical exam, and getting the results of various blood tests, I tabulate to find out what that patient's individual risks are that we can identify now, because there are going to be new ones coming along. Then, in a very methodical way, I try to correct those abnormalities, starting with diet and exercise and appropriate pharmaceutical medications, always trying to think about what the patient's response is, if the individual can afford it, and whether his or her health plan allows it to happen.

I collect each patient's uniqueness in a methodical way. I think the future is with genome analysis, and proteomics is going to provide even further definition of those who are at risk and how we can modify what they need to do in their lives to prevent atherosclerosis.

Assessment Tools

JB: Most doctors use a triad approach—assessment, diagnosis, and treatment. When a patient comes to you, how do you use the presently available noninvasive, invasive, chemistry, and genomic assessment tools? Have you constructed a panel of tests that allows you to assess aspects of personalized risk?

RD: People always ask me that. What tests do I order on patients? Do I have a panel? Yes, I do. I have a basic panel, and then it spreads it out depending upon the patient's individuality. The first thing I do is to take a family history; that is so significant. That's not any test you do; you just sit down and think about the patient and his or her family. That begins defining how risky the patient is.

Then I do an examination. I look for cutaneous evidence about the sclerosis; I look at blood pressure; I look for funduscopic changes in the eyes, like every traditional doctor does, to get a sense of whether this patient is healthy, very unhealthy, or in between. Where is he in his cycle of life down this path of atherosclerosis if he's atherosclerotically prone?

Blood Tests

The blood tests I do include a standard lipid panel and then a specialized lipid panel. I try to break the patient's LDL molecule into subfractions, the HDL into subfractions, and the triglyceride into subfractions. That involves sending the test to a lab that does that type of subfraction analysis. For patients who have clear risk of atherosclerosis based on a family history or who have already had the disease, I find the specialized analysis of the subfractions very helpful. It guides me, not only in terms of how to raise HDL cholesterol, but how to raise the good fraction of the HDL, not only lowering the LDL, but lowering the small dense LDL.

What part of the triglyceride is abnormal? Is it the risky one that is elevated, or is it the non-risky one? I try to individualize my assessment in that patient to bring it down.

Specific Panels

First of all, I order a lipid panel, and then sometimes a lipid panel that's more specific. The next test I run is a homocysteine, LpA, a fasting blood sugar, a serum insulin level if I think the patient has insulin resistance, and a CRP. I think we're going to move into some of these atherosclerotic-prone genome analyses, especially when we find the single nucleotide polymorphism, the SNP. We will need to know if that information is going to change what we do in the patient. It is going to allow us to tell the patient that he or she really needs to go on a low-fat diet, that the patient really needs to exercise and enhance his or her compliance. We're going to find that out in the next few years as they begin running these tests.

Up until recently, the tests for a procoagulant patient, someone who tends to clot more, would allow us to check to see if he or she had too many platelets or if the patient had protein C or protein S deficiency. Now, with these genome tests, we are going to begin separating out those patients who have individual protein polymorphisms. That's my basic initial panel.

Assessing Syndrome X

JB: Let me pick up a couple of components in a little more detail. According to Dr. Gerald Reaven, the father of syndrome X, the hyperinsulinemic predecessor to type 2 diabetes, one of the hallmarks of syndrome X is elevated dense LDLs. Do you use lipoprotein fractionation of LDL as a marker that ties to insulin resistance/hyperinsulinemia?

RD: Yes I do. When I receive the profile on my patients, it's subfractioned into the dense and non-dense LDLs. I find an order of treatment; I determine what I'm going to treat first. The most important thing is to get the LDL cholesterol level down. Once that is down, sometimes it normalizes and sometimes it stays in the dense fraction. Usually, the person who has that mixed insulin resistance pattern that Dr. Reaven talks about has a depressed HDL triglyceride. If you focus treatment on normalizing the triglycerides and getting the HDL up by exercise, diet, and possibly the addition of combined treatments to treat the hyperlipidemia, the dense HDL takes care of itself.

That's like a red flag, and I know I need to be aggressive about it. It tells me that I'm probably going to have to use two medications; some traditional statin or a fibrate to lower the LDL if diet doesn't work, and the addition of something like niacin to boost up their HDL and lower their triglyceride.

When you do that combined approach of treating the hyperlipidemia, the dense LDL normalizes itself. I look at it and know that when I treat everything else, that's going to normalize, and it usually does. The key is that all those patients have truncal obesity. They all have highfasting serum insulin levels. None of them exercise. They all skip breakfast or they eat a lot of carbohydrate at breakfast. I spend a lot of my time looking them in the eye and asking them to please modify their diet and do the exercise as we go ahead and correct the rest of the risk factors.

Measuring C-Reactive Protein

JB: Another analyte that's very much in the news right now is C-reactive protein (CRP) as an inflammatory marker. According to Dr. Ridker at Harvard, we ought to be measuring high-sensitivity CRP, because normal CRP measurement is not sensitive enough to pick up the differentiation. Others maintain there is no justification for CRP testing; it is overutilization and doesn't provide enough

additional diagnostic value. What's your opinion? Is there justification for measuring high-sensitivity CRP?

RD: Good question. I think it's so sad when some blue ribbon panel says a test is not cost-effective or justified. We need to treat people as individuals, and there's no doubt in my mind that high-sensitive CRP is justified. I was always taught that if you do a test and the result of the test changes what you do, then you should do the test. That doesn't mean you do a test for which one out of a million people has an abnormality, however.

In a recent article in the New England Journal of Medicine, published in November, Dr. Paul Ridker discusses CRP as an independent risk factor. He points out that when a group of women modified their CRP it was more predictive than LDL. That brings to bear the independent risk factor nature of CRP.¹⁷ That article pointed out that LDL was a risk factor and CRP was a risk factor, and synergistically that added to a person's risk.

The Inflammatory Element of Atherosclerosis

When I was in training to be a cardiologist, we talked about lipids and then we talked about clotting. We devised all sorts of methods to stop the thrombotic element of atherosclerosis by aspirin and giving people thrombolytic therapy and lowering lipids by diet and medications. Now this inflammatory element of atherosclerosis has been identified and it's very key.

In answer to your question, I think it is important. I routinely do it. When I have a patient who has atherosclerosis or who is at high risk of it, I first treat his or her LDL, HDL, and triglycerides. If I have done that adequately and the patient still has an elevated CRP, I look around the body to make sure there's no secondary inflammatory process that invalidates the interpretation of that test. If the person has chronic arthritis of his right knee, that mitigates the interpretation again. You can't really interpret it.

Lowering CRP

In the absence of any obvious inflammatory process, I conclude that the patient is upregulated. I don't do an interleukin-6 value, but if I did, it would be elevated. I then try to add in something that would lower the CRP. The question is, what do you do then? Medications that can lower CRP are statins, aspirin, very high dose vitamin E, getting rid of the visceral obesity. That is the key because I'm not sure we know exactly where the CRP comes from. It comes from interleukin-6, but it's probably produced by the fat cells that you see on a CT scan of someone's abdomen.

Again, we're back to that old metabolic profile that Dr. Reaven talks about. If we can get the person to lose weight and they lose the weight in the trunk area, it reduces insulin resistance, improves HDL, lowers triglycerides, makes the small dense particles become large, and lowers the CRP. I think measuring CRP is important. Once you see it again elevated, it tells you to focus on that patient. Get him to lose weight, give him aspirin. If he's not on a statin and that's what you need to do to bring it down, we probably should bring it down.

Homocysteine Testing

JB: You discussed another area that I know is considered controversial, and that is homocysteine and whether testing for it is cost-effective. If it is, at what levels do we start to have risk; is it 11 or 12 nanograms per ml, or it is 8? What's your opinion on the homocysteine connection?

RD: This is interesting. About 12 or 13 years ago the Lancet contained a simple article on homocysteine,

and a group of doctors in England who were giving patients a supplement of vitamin E, B6, and folic acid. They simply reduced homocysteine. This was well before homocysteine as a risk factor was common news. Since then, I've been treating homocysteine for over 12 years with some form of a compound that has that mixture.

If you go into the literature, you'll read that homocysteine thiolactone is clearly irritating to the endothelium. We know it's a risk factor. Interestingly, Time magazine, which certainly more people read than they do our medical journals, contains a summary of homocysteine. The article said it really doesn't help that much. It only reduces your risk (as I recall the article's stating) about 12 percent. Well, 12 percent is a lot. We now give statins, production of which is a billion dollar industry, to lower LDL cholesterol. Statin drugs reduce the risk of heart disease between 24 and 30 percent; that's the maximum. If you raise the HDL, you can get another 30 to 40 percent decrease in risk.

Reducing Risk by Lowering Homocysteine

We're left with people who have an elevated homocysteine, and each of those individuals is probably at a higher risk. If I can lower that person's risk another 12 to 15 percent by giving him or her a pill that costs about 6 cents a day, it's just intuitive to synergistically treat that patient's risk factors. In summary, I check homocysteine all the time. I make sure the patients don't have B12 deficiencies, so I check their B12 level. I also check methylmalonic acid level, because I find that a serum B12 level is not a good excluder of B12 deficiency. If the methylmalonic acid level is elevated, I look for and treat B12 deficiency.

Once I correct that, then I treat them with folic acid, in increasing doses, in combination with oral B6 and B12. If that doesn't work, I move on to the methyltetrahydrofolate acid that you've talked about so much, Jeff. That has also been helpful. In summary, in my experience, when I give somebody a combination of B6, B12, and folic acid, I have about 85 percent response in my patients.

The objective is to get the homocysteine down to less than 8. Each year the recommended level keeps coming down, but the most recent recommendation is less than 8. If that fails, I add in methyltetrahydrofolate acid. I find another 50 to 60 percent of the remaining people drop their homocysteine into the normal range. People who still don't respond are patients who have chronic renal failure and then a few others we are probably going to ferret out in the next few years. I also think it's important that when you give someone methyltetrahydrofolate acid, you also give him or her folic acid so you don't just isolate one part of that pathway.

Medicine for the Average Patient

JB: Your point about homocysteine's ability to reduce risk an average of only about 12 percent brings up another important part of this story. The concept of medicine for the average patient, within two standard deviations of the mean, versus medicine for the real person may be one of the biggest challenges in medicine. It may explain why certain things have not worked and why certain things have been excluded in therapy because they didn't work in the average.

RD: Jeff, the point you just made is so important. We treat people by the mean. I have a slide when I give lectures, of response to a therapy. I have the arrows going up the graph, straight across, neutral, and then down. The next slide has a mean showing slightly positive change. I ask people in the audience how they would like to be this person, and I point to people for whom the arrow went down, and then the person over here who went way up.

Everybody is an individual. An example of this phenomenon is in the HERS Trial with estrogen. They showed that when patients who had atherosclerosis were put on PremPro, the nonbiologically identical estrogen and progestin, that they increased their risk of heart disease for the first 15 months and then over time, got no net benefit. If you look at the subclassifications, those women who had an elevated LpA, markedly improved. In other words, you have to look at subgroups.

Medicine for the Individual

I agree with you completely. If you took groups of people who have a slightly elevated homocysteine and you treated all of them, you get a 15 percent improvement in this group of people. If, on the other hand, you looked at the individual person, the results might be entirely different. An example is the person who comes to my office following a heart attack. His lipids are normal, his blood pressure is normal, and yet his brother had a heart attack and his sister had a heart attack. The only abnormality was homocysteine. For that patient the improvement has got to be more than 15 percent.

That's why I think the approach must be on an individual basis. Find out what characteristics that patient has, what his lipids are, whether he has insulin resistance, if he is obese, and what his homocysteine level is. Then you treat. And you see that evidence-based medicine shows only a 12 percent decrease. Well, if 12 percent adds to that benefit, it's just great. Synergism in a single individual is the way to go.

Genomic Analysis and the Future of Medicine

JB: You also talked about genomic analysis and what that might mean in the future for pinpointing some of these personalized relative susceptibility factors. You asked if genomic analysis will change the way we practice medicine. What's your feeling about that?

RD: To give you an example, in the December 11, 2002 issue of JAMA (Volume 288[2813]) there was a brief mention of a recently published study in the Journal of the National Cancer Institute¹⁸ that pointed out that the presence in certain patients of H. pylori together with predisposing SNPs involving the interleukin 1 receptor antagonist and interleukin 1B were associated with a markedly increased risk of stomach cancer—up to 90 times greater risk! Thus, if you happen to have H. pylori (the environmental stress) and the predisposing SNPs, then your risk is much higher. Tailoring therapy specifically to eradicate H. pylori and to carefully monitor these patients, is an example of bringing medicine down to the individual, i.e., personalized preventive medicine.

I think that it's also going to happen with the genomic analysis of patients who are at risk to atherosclerosis. I expect we will find individual abnormalities of a host of biologically plausible links to atherosclerosis, such as abnormalities of lipoprotein lipase or SNPs, that relate to the individual handling of HDL. This beneficial lipoprotein has great promise in reducing the risk of atherosclerosis if we can learn what environmental elements in the individual can enhance or worsen HDL's function. Then we're going to devise ways that the individual person can live a lifestyle, or consume a dietary nutrient that will modify his/her risk by modifying the function of HDL. Lastly we will find some medication that will modify the risk. The key concept is to bring treatment down to the individual level based on a knowledge of his/her genetic predisposition and a knowledge of the environmental influences and/or medications that can promote a desired biological effect.

This is the way I feel that genomic analysis will be used by clinicians for their individual patients. I am just beginning to perform gene testing on my cardiac patients and will have more first-hand experience in the practical application of these principles in the individual patient over the next year.

Statin Drugs

JB: Statin drugs have created a revolution in cardiology. We now have, in a sense, a preventive pharmacology with the statins being used to lower LDL cholesterol. Recent evidence indicates the role of statins is more than just as an HMG CoA reductase inhibitor. They actually can do things like recruit macrophages to the edges of atherosclerotic plaque leading to healing, and they may have a variety of other influences on cell recognition and gene expression. As a cardiologist, what's your view of the evolving statin story?

RD: I think we are just touching the tip of the iceberg of how the statins reduce risk. Traditional thought was that they work by lowering LDL cholesterol inside the cell, which makes more receptors by competitive inhibition of the enzyme, increasing the likelihood of a cell's making more receptors so it can pull more cholesterol out of the bloodstream and therefore reduce risk.

We also know there's another pathway off that through G protein isoprenylation and that's probably how it becomes antiinflammatory. It blocks that side pathway that comes off if you looked at the pathway before it gets down to cholesterol. And that same pathway is the way those biphosphonates work to stop osteoclasts from chewing up bone.

Statins and Risk Reduction

Fosamax™ works in the same pathway, blocking an enzyme right off that pathway, but specific for the bone. That's why some statins that can get into the bone also reduce osteoporosis. They also reduce Alzheimer's disease by some other mechanism yet to be determined, but it's probably antiinflammatory because we know that nonsteroidals also reduce risk of Alzheimer's disease or the progression of it.

I think we're beginning to find, when we give someone a statin, that besides lowering LDL cholesterol, it does something to macrophage function. It does something to the inflammatory aspect of this disease for which our only surrogate marker now is CRP. It's quiet. It's happening in the body quietly, so we give the person a drug that goes into this body that's clinically quiet and yet inflamed, and it dampens it. It dampens it at the brain and prevents or delays Alzheimer's; it dampens at the bone and prevents osteoporosis; it dampens at the vascular level and prevents activation of unstable plaques. It does so by mechanisms we still have not defined, probably the macrophages, probably the G protein isoprenylations so they can't create some inflammatory cytokines.

Individualizing Therapy with Statins

It's very exciting. It's difficult, though. When doctors are taught to look at just LDL cholesterol, and the LDL comes down to where they want it, since it's a different pathway, it's not dose-related. When you look at the studies, CRP reduction is not dose-related, so you have to do something difficult. You have to individualize it. You have to determine what the CRP is.

It is interesting when we see a patient as a total. It always excites me to see someone who has a risk for Alzheimer's disease, has a risk for osteoporosis or already has it, has atherosclerosis, and has elevated CRP. That is a person who should have a drug that hits all forms of those pathways. That would be an appropriate use of statins.

Application of Functional Medicine

JB: It is interesting to hear you talk about cell biology, cellular mechanisms, and applied biochemistry. It warms the heart of a functional medicine advocate to hear this strategy and the logic that goes into the

way you construct these personalized therapies. This is the kind of medicine that as a student you thought you were ultimately going to practice.

RD: I attended your Applying Functional Medicine in Clinical Practice course in Gig Harbor a couple of years ago. I learned about the concept of thinking about a patient and linking it to all his or her bodily processes, trying to understand that individual person at that point in time. I learned the importance of understanding the history that came before and using it to prevent a pathogenic history in the future.

That's what functional medicine is. It's thinking and linking and using alternative medicines, diet, pathophysiology, appropriate pharmacological agents. If you can kill two or three illnesses with one stone, all the more power to you, but you have to understand and think about these things.

Thinking and Linking

JB: I think you just created a sound byte we will have to capture and attribute to you. "Functional medicine is thinking and linking." I like that. It's a very interesting concept.

RD: As opposed to naming and blaming?

Red Rice Yeast for Cholesterol Management

JB: Well said. I recently had a discussion with Dr. David Heber at UCLA. He is doing some work on red rice yeast monocolins, which is a mixture of statin-like molecules. Statins were originally natural products. They isolated one of the monocolins that came to be known as lovastatin. Dr. Heber has been studying this mixture of the monocolins and finds that, as a mixture, they have lower hepatotoxicity than when you use a single molecule as a drug. Have you had any experience in looking at some of the natural products for cholesterol management?

RD: I have done a few gene analyses, and included in the recommendations from the panel was rice yeast. I started looking that up, and I put myself on red rice yeast about two weeks ago to lower the LDL naturally. I haven't had much experience with it yet, but I think it's biologically plausible. It's probably very safe for the liver, and so I think that plays a role. The question I would want someone to answer in the future is what does it do to the subfractions of LDL, HDL, and triglyceride, and what does it do to CRP, the inflammatory surrogate marker?

In addition to lowering LDL naturally, I want to know what it does to the subfractions. I want to know what it does to the inflammatory element like the statins, because then I'll know where to put that into the decision tree analysis and treatment that I use for an individual patient.

Nutritional Support Products

JB: We will be sure to ask Dr. Heber those questions. He has been actively exploring this over the last several years. As a final question, I know you use a variety of tools based upon what you feel is best for the patient, from pharmacology to nutrition and lifestyle intervention and even nutritional pharmacology. Do you have a list of nutritional substances that you find most effective in the patients you've been treating? If a doctor new to this field asked you what's on the short list of things that really prove to be useful as adjunctive nutritional support products, what would you tell him or her?

RD: In terms of nutritional products, I try to have my patients take a soy protein shake in the morning and in the afternoon to try to get rid of the high glycemic carbohydrates and give them a healthy form of protein. I have them take a synergistic antioxidant, notwithstanding all the studies that show that if you give someone with well-established coronary disease vitamin E for four years, it doesn't do anything. Again, it's looking at the wrong patient at the wrong time in their natural history.

Looking at vitamin E alone, you need a synergistic antioxidant, so I give my patients a combination of mixed tocopherols, coenzyme Q10, lipoic acid, vitamin C, and tocotrienols, which is that subclass of vitamin E. It also works in a post-translational way to lower HMG CoA reductase inhibitors.

I have patients who can't take any statins on high-dose tocotrienols, trying to get γ -tocotrienol, which lowers LDL in a post-translational way, blocking the effect of that enzyme. To answer your question, in terms of antioxidants, I use a synergistic antioxidant. I always use folic acid now because it not only helps lower homocysteine, but it helps DNA methylation that patients need to prevent cancer and all the other ravages of age and free radicals. I try to focus on their diet and get rid of that truncal obesity and insulin resistance.

Simplifying the Complex

JB: That's an extraordinary summary of a vast amount of information, and something a person could put down on a note card and paste up in their exam room and practice with their patients. Thank you very much for taking the complex, rapidly evolving field of cardiology and distilling it down so we can all understand and take away some very practical and useable information.

RD: Thank you, Jeff.

I would like to add some comments to Dr. Delaney's eloquent discussion of personalized functional cardiology. Beginning with the current issue, we will be adding a new section to each issue of *FMU*. That section, which will be titled "From the Lab to the Clinic," will provide how-to information for clinicians who want to apply the concepts that are presented.

Agents that increase inflammatory mediators, the inflammatory cytokines, are those elements of our environment that initiate chronic inflammatory response. We think of chronic infection, for instance, in terms of the relationship of *H. pylori* to cardiovascular disease, or *Pneumocystis carinii* and its relationship to chronic inflammatory mediation. Another is allergy and the relationship of allergens to alteration of the ratios and balance between the thymus dependent-1 (Th-1) and thymus dependent-2 (Th-2) cytokines. We generally think of allergy as shifting the balance toward the Th-2-dependent cytokines and increasing inflammatory load based upon an imbalance between Th-1 and Th-2.

Perilla frutescens and Th-1/Th-2 Imbalance

For several years I have been following Japanese literature that has discussed the development of a food concentrate that can be used to assist in Th-2 imbalance situations, the allergic profile, the IgE-mediated profile, either the pulmonary allergen or the food-related gastrointestinal allergen. This concentrate is a mixture of flavonoids derived from the concentrate of *Perilla frutescens*. This interesting fruit has berries that contain a rich array of flavonoid-like molecules unique to this particular fruit.

The perilla seed, when concentrated, has very high levels of luteolin and other unique flavonoids, which have been found to be IgE modulators. They influence IgE modulation in such a way as to lower allergy potential. They help stabilize mast cells; they help prevent degranulation; they help prevent the release of the Th-2 proinflammatory cytokines; and they help restore balance of Th-1 and Th-2 function.

Perilla Seed Concentrate and Liver Inflammation

A number of papers have described the effects of *Perilla frutescens* concentrates in cell culture systems, in animal models, and in human trials. In one such paper, researchers examined a major polyphenolic

component of perilla for its ability to reduce lipopolysaccharide (LPS)-induced liver inflammation. Supplementation with this substance had some profound stabilizing effects in an animal model.¹⁹

In clinical trials the level of standardized perilla seed concentrate used to manage allergic-type IgE-mediated disorders is in the range of 100-200 mg per day. This level proved to be a great help in stabilizing mast cells against degranulation. It is interesting to note that it has an effect at a lower level than chromolyn sodium, which is also a mast cell-stabilizing substance that helps to block IgE-mediated effects. The perilla concentrate, in doses of 100-200 mg, may be a clinically useful product for those individuals who have inflammatory shifts as a consequence of allergic potential.

Estrogen and Catechol Ortho-Quinones

One other area that we know increases inflammatory potential is the production of the so-called 4-hydroxyestrogens. We have talked at length in previous issues of *FMU* about the “flame-dancing estrogens.” Those are the estrogens of the hydroxylation pattern of the 4-position on the estradiol or estrogen molecule, the carbon No. 4 of the A ring of the estrogen, which produces catechol estrogen that then undergoes auto-oxidation to produce a quinone estrogen.

This quinone estrogen can chemically react very rapidly with DNA in the adjacent tissue, causing chromosomal injury and becoming potentially carcinogenic. This approach talks about the role of a metabolite of estrogen as an endogenous toxic molecule, and how that interrelates with proinflammatory potential of estrogen and carcinogenic implications of estrogen.

Auto-Oxidation

These are called the catechol ortho-quinones of estrogen. Estrogens are not the only molecules that undergo auto-oxidation to form quinones. The catecholamines do this as well, and that may be why increased catecholamine in a specific tissue with increased oxidation can be associated with neurodegeneration. I am talking about Parkinson’s disease.

I have connected what appear to be dissimilar facts, one of estrogen and breast cancer, and the other of dopamine and Parkinson’s disease into a singular model related to auto-oxidation to form these quinone molecules, these catechol ortho-quinones. High production of dopamine oxidation products or high production of 4-hydroxyestrogens can interrelate to these risk factors.

Redox Potential

An interesting discussion of catechol ortho-quinones was published in *Carcinogenesis*.²⁰ It indicates that redox potential in the cells, i.e. the brain or the breast, may be important in protecting against the formation of quinones that can cause injury. Redox potential means specific antioxidants like lipoic acid, green tea catechins like epigallocatechin gallate compounds (EGCG), and limonene from citrus. All of these substances have important roles as food-derived, redox potential agents that help protect against the formation of these quinone-like molecules. If you are producing an excessive level of these oxidation products, you are at risk to DNA injury and inflammatory insult.

In the case of estrogen in animal studies, one study found that the 4-hydroxylation pattern is generally a low-activity pathway.²¹ There is not much 4-hydroxylation. But in some cases there may be upregulation due to exposure to various potentiating agents like dioxins or other petrochemical hydrocarbons. When the body’s detoxification machinery has been upregulated by certain of the P450 cytochromes,

production of 4-hydroxyestrogens is increased. Therefore, as we look at protecting a woman against her own estrogens, we would want to achieve balance by increasing the production of the 2-hydroxyestrogens and their methylation to form the 2-methoxyestrogens, and reducing the production of the 4-hydroxy compounds.

Managing Estrogen Risk

Research has shown that diindolylmethane (DIM) and indole-3-carbinol (I3C) help potentiate the production of the favorable 2-hydroxyestr

If a woman is at risk to her own estrogens, she needs to get higher levels of the B complex vitamins, consistent with what we discussed on side I of this month's issue of *FMU*. She needs to lower her exposure to the toxic substances that are upregulating the production of quinone estrogens, and she needs to increase her cruciferous vegetable intake to two or three portions a day (150-200/day equivalent of I3C).

We have talked about the web that Dr. Delany described, the connection of various functions that make cardiology a functional cardiology.

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

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