July 2007 Issue | Roger Newton, PhD Former Senior VP and Director

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Welcome to *Functional Medicine Update* for July 2007. We are in store for an exciting time together on this edition. We are fortunate to have with us one of the world's leaders in the fields of cholesterologenesis and atherogenesis. He is going to open some new doors for us in understanding the prevention and management of atherosclerotic disease. Before we hear from him, I want to set the stage by talking about the concept of atherogenesis (or the origin of atherosclerosis) from a lifestyle, gene, and nutritional perspective.

Before I get started I'd like to say a couple of quick things about two new educational products we put together. The first is a compiled and edited collection on autism. Over the last couple of years, I have had the good fortune to interview some world leaders in the study of autistic spectrum disease etiology. We excerpted four interviews and compiled them with my comments to provide an overview of what is going on in this field. You can get more information by checking our website, www.jeffreybland.com , or you can call the Synthesis office on our toll-free number.

The second audio course we have is a seminar on insulin resistance. It is called *Beyond Metabolic Syndrome* . I think you'll find this seminar helpful and useful from a clinical perspective if you are interested in understanding how to better recognize and manage insulin resistance/metabolic syndrome beyond just the pre-diabetes conditions, that is, into cardiovascular disease, dementia, relationships to autoimmune disease, and how that inter-relates to inflammatory conditions.

Again, there are two new educational products available from Synthesis. The first is our autism collection, which is on four CDs, and the second is the *Beyond Metabolic Syndrome*seminar, which is on six CDs. Both products are available through Synthesis by either contacting the jeffreybland.com webpage or contacting our toll-free number. By the way, seminar courses like *Beyond Metabolic Syndrome* not only include the audio, but also the visuals (the Powerpoint slides) that I discuss throughout the course of the seminar.

Now let's move to the main topic of this issue of *Functional Medicine Update:* functional cardiology. If we were to sub-categorize it even more, we might call it functional HDL and LDL physiology.

Obviously most of us have some familiarity with the use of lipid measurements in assessing relative risk to cardiovascular disease, the total cholesterol (LDL cholesterol and HDL cholesterol) analysis. An understanding of these dynamics at a level that gives us a new insight into the personality of lipids and how they relate to atherogenesis and vascular health is emerging, and it is that focus that I want to take you through in this issue of *Functional Medicine Update*. There is going to be some language that is probably new to you, but there is also going to be some news to use: how we might use things like the

apoB-to-apoA-1 ratio as an assessment tool for evaluating cardiac risk; how we might use the subfractions of HDL; and how we might look at dense versus buoyant LDL particles in terms of atherogenicity. This will be an update on what I call functional cardiology through the lens of lipoproteins and apolipoproteins.

In order to do justice to this, let me take us back to the 19th century. I want to speak about the father of modern pathology, Rudolph Virchow. As you probably know, he was the person who was credited with starting our categorization of pathology into a discipline in medicine. He published his masterpiece, *Cellular Pathology as Based upon Physiological and Pathological Histology*, back in the late 19th century. He wrote that the cell is the ultimate irreducible form of every living element. Dr. Virchow was (in some senses) the father of cellular biology and cellular pathology, as well as the father of overall organ pathology.

The reason I think this is an interesting part of the story and relevant to this issue of *Functional Medicine Update* is that when Dr. Virchow was looking at atherosclerotic disease back at the end of the 19th century (which was very uncommon at that time), he did gross pathology, looking at the coronary arteries of patients who had heart disease. He visualized the arteries as being injured. It looked like there was a wound and that the wound had tried to heal, forming what we now call a plaque, but then looked like a scab. And so he came to the concept that atherosclerosis was really an inflammatory condition, like a wound on the inside of the artery wall.

In the early 20th century, a Russian physiologist by the name of Anichkov had a slightly different view of the origin of atherosclerosis. He was able to take white rabbits and feed them high-cholesterol and high-fat diets and induce, then, this plaque on the arteries that was associated with atherosclerosis. And so the cholesterol hypothesis was born out of the Anichkov work, and the injury and inflammatory model was born out of the observations of Virchow. From those two emerged the dominant intellectual lineage in terms of the origin, treatment, and prevention of vascular disease. The emphasis was more focused on the cholesterol hypothesis than on the inflammation hypothesis of Virchow's. Cholesterol seemed to be the *sine qua non* for the etiology of atherosclerosis.

But then later, in the 1960s and 1970s, a pathologist at the University of Washington School of Medicine, Earl Benditt, talked about the monoclonal theory of the origin of atherosclerosis. Dr. Benditt proposed that if you looked at atherosclerotic lesions, they were monoclonal in origin, as if they had been induced by a single cell undergoing injury and then developing a clonal response as a dedifferentiated cell. He felt that this clonal response was a consequence of an injury to that cell, a mutagenic injury. It was not a cancer as such, but it was more like a benign tumor that we call the atheroma, which then caused alterations in vascular flow and activated the immune system, which ultimately led to infiltration of cholesterol and calcium and stage 3 atherosclerotic lesions. Dr. Benditt, along with his research group, published a number of papers about the monoclonal theory of hyperplasia. The theory was reminiscent (in part) of the Virchow model of inflammation and injury as the origin of atherosclerosis.

In the years since, there have been tremendous advances in the basic understanding of atherogenesis, as well as new perspectives that open up the possibility of new therapeutic strategies. There was a wonderful series of review papers that published in *Nature Medicine*in 2002. This series included a discussion of the vascular smooth muscle cell (VSMC) contributing to vessel wall inflammation and lipoprotein retention and that atherogenesis was, in part, an inflammatory condition at the artery wall. Virchow and his injury

model, and even Benditt and his monoclonal hyperplasia model, were not too far off from the role of the vascular smooth muscle cell alteration in atherosclerosis.[1,2,3,4,5]

When the vascular smooth muscle cell undergoes a proliferative response as a consequence of an inflammatory message, it leads to the development of all sorts of alterations in the vascular wall in terms of its physiology and function. This can lead to things like restenosis after stents are placed, or bypass graft occlusion, or transplant vascularopathy, which are all secondary conditions of atherosclerotic risk associated with increased inflammatory burden. This inflammatory marker became an important new component of the presumed etiology of atherosclerotic disease somewhere in the later 1970s, the 80s, and the 90s.

The macrophage converts itself into the foam cell. Once it infiltrates the artery wall, it undergoes a personality change with regard to its gene expression. It becomes, then, a cell type that is incorporated within the artery wall that engulfs a lipid. It engorges itself. It has a different physiological dynamic. The artery wall shifts into an oxidative chemistry. You get LDL oxidation and you start, then, getting this free radical oxidative process of inflammation and injury.

This process implies that there is an innate immune component related to atherogenesis. As a result, there may not be a complete independent separation between atherosclerotic disease and autoimmune disease. Data have been published (that we have described in previous issues of *Functional Medicine Update*) that have correlated increased incidence of cardiovascular disease in patients with systemic inflammatory autoimmune disease, like systemic lupus erythematosus or rheumatoid arthritis. What is emerging is that these diseases are connected by mechanism; they are not connected by diagnosis. And inflammation plays a role as it pertains to altered vascular wall dynamics.

What induces systemic inflammation? Is it just chronic infection? We know certain organisms-*H. pylori* and various pneumococcal organisms-have been identified as potential risk factors for cardiovascular disease. Are we then looking at atherosclerosis as an infectious disease? The answer may be, in some cases, yes. Could it be nanoparticles, like viroid particles, or cell-well-deficient forms of bacteria that induce immunological changes? And the answer might be yes to that. Could it be other factors of ischemia that induce inflammation and altered arterial wall dynamics? And the answer is yes. In other words, the etiology that could trigger inflammatory response and altered immunological function at the artery wall is multifactorial.

A whole cascade of events leads to the plaque, which can be stable or unstable. An unstable plaque cap raises relative risk to a sudden coronary event. When that fibrous cap breaks off, we get all sorts of platelet activation and thrombus formation, and now we have a life-threatening coronary event.

So, it is a very complex process with many players and many environmental inputs. Genes underlie risk at a certain level, but layered onto genes are all these other environmental factors that modulate and help synchronize these complex processes that pertain to immune defense, vascular smooth muscle cell function, intimal function, and endothelial cell function. It is becoming more and more recognized that this one-cell-thick lining that lines the outside surface of the artery wall (the endothelium) plays a very important role in communicating to the interior of the wall (the intima and the vascular smooth muscle cells) what is going on in the outside world. That translated message of altered endothelial function can produce altered arterial function.

We now see this mechanism as much more complex than previously recognized. Therefore, looking only at lipids in a snapshot through a blood chemistry, like a cholesterol or an LDL or an HDL, is only (at best) kind of a shadow on the wall of the cave (to use Plato's analogy). It is not really looking at the dynamic process that is occurring within the artery itself. We do know, however, as this story started to emerge, that it has implicated many lifestyle and dietary factors that can influence this synchrony and dance of the dynamic process that we associate with atherogenesis.

Looking at stabilization of atherosclerotic plaque, there are a number of papers that have been published recently that demonstrate that diets that are higher in omega-3 fatty acids (the EPA-DHA) help to stabilize atherosclerotic plaque (the fibrous plaque), while saturated long-chain fatty acids destabilize plaque and increase relative risk to a thrombotic event. I am quoting from one of many papers that appeared-in this case in *The Lancet* -titled , "Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial."[6] This was a randomized controlled trial intervening with very high dose fish oils providing very high levels of EPA and DHA, in this case 16-20 grams per day of EPA-DHA, and showing stabilization of plaque.

In other secondary prevention trials that have been published, the doses used are much lower-much more practical-in ranges of about 1.8 grams of combination EPA-DHA each day. That would be a dose that would be certainly achievable either by supplementation or by eating more coldwater fish. So we are starting to see that diet can modulate not only the initial lesion that is associated with atherogenesis, but also stability of the plaque once it has formed.

Certainly, hypercholesterolemia is part of the story. We don't want to throw the baby out with the bathwater. When we take our snapshot of lipids in the blood chemistry and we see elevated cholesterol (elevated LDL cholesterol) and a reduced HDL-C, those are risk factors that the Framingham and Lipid Research Center studies, as well as other intervention trials have demonstrated to be surrogate markers for risk to vascular disease. So hypercholesterolemia is a risk. But then we actually have to ask the question, how does high cholesterol connect with the dynamic process that we associate with atherogenesis? And how does that then relate to diet and lifestyle factors that can modulate cholesterol and lipids in such a way as to stabilize arterial wall physiology?

Cholesterol, in and of itself, be it either high or low, is not the be all and end all in determining exactly what is going on at the arterial wall relative to atherosclerosis. It is only a marker. In a wonderful article by Daniel Steinberg (from the University of California, San Diego and credited with the discovery of LDL oxidation) he talked about how high cholesterol is associated with inflammation as "partners in crime" in the atherogenic process.[7] This appeared in the *Nature Medicine* series. Dr. Steinberg talked about the fact that the historical perspective going back to Rudolph Virchow and the origin of atherosclerosis allows us to reflect on the hypothesis that injury caused by inflammation may ultimately result in plaque formation and, therefore, high cholesterol may be an associative factor with this process, but in and of itself, it is not the whole explanation for the origin of atherosclerosis. We need to then look at the processes that relate to cholesterol oxidation and lipid dynamics (moving in and out of the artery wall), including triglycerides as well as cholesterol, and the packaging of lipids into the various lipoproteins-lipoproteins that constitute LDL, HDL, VLDL, and the different forms within each of those because there are sub-fractions, as we now recognize, within each of those lipoproteins that are constituted by various percentages of different apolipoproteins.

So we recognize there are many variables and many different messenger molecules that contribute to these concepts of vascular reactivity. Some of those relate to these lipid transport molecules that we call apolipoproteins. Let me just take a moment to give a quick summary about apolipoproteins.

Apolipoproteins have names like A, B, C, D, and E. Apolipoproteins are synthesized principally in the liver after messages come to the liver cells. These are proteins, obviously, which have the principal responsibility for binding certain families of lipids and aggregating themselves into certain particles that then travel in the vascular fluid, allowing transport of lipids in a water matrix.

We can think of an apolipoprotein in a very simple way: as a detergent. It basically solublizes fats so they can be transported in the blood, which is principally water. That's a little bit overly simplistic, however, because these apolipoproteins like A, B, or E are not nonspecific detergents; they are very specific in the way they accumulate certain fats and how they assemble themselves with other proteins and other constituents (other active enzymes) to then transport that fat to specific receptor sites on the surface of the arterial wall. So they are not just kind of general and nonspecific; they have a very unique personality and therefore a lot of what we might consider the personality of atherogenesis is tied together with the personality of the apolipoproteins-how they are synthesized, and how they are transported, and how they are delivered to the cell at the surface of the arterial wall.

I want to emphasize this for the following reason. When apolipoproteins, are synthesized in the liver, their synthesis is dependent upon messages that the liver cell receives. These messages are hormonal messages and neurological messages that upregulate gene expression of specific apolipoproteins. If you ask, how can stress influence atherosclerosis? How can toxic exposure influence atherosclerosis? How can dysinsulinism influence atherosclerosis? You would, in part, have to know how each of those factors is translated in the liver cell to lead to the modification of apolipoproteins, and then what does each specific apolipoprotein influence in that individual? If a high stress situation in a person results in his or her liver cell getting the message to make more apolipoprotein B, then what that will do is transport lipids in a certain way to deliver more cholesterol to the arterial wall and engage in more potential oxidized LDL, so now what we get is the potential atherogenic risk, i.e. stress connects to heart disease risk through this complex cascade of events that is related to altered cellular signaling.

You'll notice I'm setting up a very different view of atherogenesis. It is not that we've just got these fats floating around in the blood and they bump into the artery wall and they cause injury or they stick to the artery wall like sticky fat molecules and they produce atherogenesis. This is a simple-minded model that really is not functionally correct based upon what we are now understanding as the origin of atherosclerosis. It is a complex inter-relationship between genes, environment, and the function that they translate through via these messenger molecules that is involved with either influx or efflux of lipids (meaning influx, delivering it at the site so it goes into the cell, or efflux, pulling it out of the cell and taking it back to the liver where it can be processed and ultimately excreted in the bile as bile salts).

When we start looking at the effect that various messages have on the synthesis of apolipoproteins in the liver, one of the messages that comes up very strongly and modifies apolipoprotein synthesis is insulin. When we get very high levels of insulin, like in hyperinsulinemia, it alters the synthesis of apolipoproteins-it actually increases apolipoprotein B-and that then changes vascular reactivity. It can alter cardiovascular function in a person who has metabolic syndrome or type 2 diabetes. Ultimately this cardiovascular risk is a consequence of the connection between a signaling molecule (insulin) and an

apolipoprotein. I'm now quoting from one of many papers in this area. This came from the *American Journal of Clinical Nutrition* in 2007 that looked at the postprandial effects of increased dietary fish oils (omega-3 polyunsaturated fatty acids) and found lowered apo B-containing lipoproteins and vascular reactivity, and improved insulin stability. These changes result in lower cardiovascular risk.[8]

What I am saying is that this story needs a lot more exposition than just saying, "Let's take a snapshot in the blood of the cholesterol and LDL levels and from that we know everything we need to know about a patient's risk." I still hear some people say cholesterol is the whole story. And then I hear other people say cholesterol is not the story at all because there are people with high cholesterol who never get heart disease, and there are people with low cholesterol who do get it, so what value is cholesterol?

My position is that cholesterol is somewhere in between. Cholesterol is part of the story, but only part. It is like a snapshot or a surrogate view into a much more dynamic process that we need to take into account. If you have a high cholesterol (a low HDL and an elevated LDL), you want to take account as to why that is present as your snapshot in your blood chemistry. What are the dynamic processes that may contribute to that? Is it hyperinsulinemia? Is it related to allergy? Infection? Is it related to a toxic exposure? Many variables might influence changes in your lipid dynamics.

I want to emphasize that these things are not in isolation. They are all part of the functional web of physiology, which helps us to better understand the body/mind connection and associate it with cardiovascular disease. It helps us to understand how the neuroendocrineimmune system can be connected to the vascular system, and how the heart is an organ of immune and neurologic function as well as a mechanical pump. All of these things are interconnected.

I have mentioned that insulin plays a role in this process and high levels of insulin (as seen in hyperinsulinemia and insulin resistance) can be associated with altered apolipoproteins generally associated with a lowered level of apolipoprotein A-1, which is a principal lipoprotein in HDL, and increase in apolipoprotein B, which is an apolipoprotein associated with LDL. And so you might say, how does that actually work? What is the relative role that insulin plays in vascular injury? It is not only related to the apolipoproteins. It is also related to the fact that insulin influences other enzymes and proteins that are within the vascular

One of those is dimethylaminohydrolase, an enzyme that is involved with the metabolism of asymmetrical dimethylarginine. Asymmetrical dimethylarginine is formed when certain proteins (proteins that are high in arginine) in our body get tagged for breakdown by being methylated at the arginine residues in these proteins to form these asymmetrical dimethylarginine components. When the protein is broken down for reassembly, it releases what is called ADMA, which is asymmetrical dimethylarginine. Asymmetrical dimethylarginine has to be metabolized or detoxified by dimethylaminohydrolase, which is an enzyme that is inhibited by high levels of insulin. In cases of hyperinsulinemia with metabolic syndrome, ADMA levels generally tend to rise. ADMA, in turn, is an inhibitor of endothelial nitric oxide synthase, and therefore it lowers nitric oxide production at the endothelium. It alters, then, the eNOS activity such that it now produces more peroxynitrite. This is a very caustic oxidizing chemical, and so now the endothelium is shifted into an oxidative chemistry with the formation of peroxynitrite, and that's another contributor to atherogenesis. Again, I want you to recognize the web of interacting variables. We are not just on one path to enlightenment.

The disruption of dimethylarginine metabolism impairs vascular homeostasis and that has really been seen now in multiple studies published over the last several years. One, which I cite, is from *Nature Medicine* in 2007 and talks about the fact that asymmetrical dimethylarginine (which is produced endogenously) accumulates in various disease states, including renal failure, diabetes, and pulmonary hypertension if it cannot be broken down properly by the enzyme that detoxifies it.[9] Its concentration in the plasma is strongly predictive for premature cardiovascular disease and death, and therefore it also relates to lowered nitric oxide signaling in the endothelium and the vascular bed. That lowers vasoreactivity and produces higher vascular tone, which is associated with hypertension. So we see all sorts of things happening that are not so good related to the atherogenic process. One is when insulin blocks the dimethylaminohydrolase enzyme that is involved with the detoxification of the asymmetrical dimethylarginine.

I think that we are seeing some very interesting multifactorial inputs into atherogenesis. The nice thing about this story is that each one of these is a factor that is modifiable by proper diet and lifestyle intervention. If we control insulin sensitivity, we control lipogenesis. Then we are going to improve dimethylarginine metabolism; we are going to improve nitric oxide output at the endothelium; we are going to improve redox potential in the artery wall by lowering oxidative stress; and we are going to help normalize some of the immune activation that is associated with inflammation. Asymmetrical dimethylarginine independently predicts total and cardiovascular mortality in individuals with angiographic coronary artery disease even in the absence of elevated serum cholesterol levels, so it is a cholesterol-independent risk factor to cardiovascular disease. I'm now quoting from a recent paper published in *Clinical Chemistry*in 2007.[10]

How can you lower ADMA levels? First of all, improve insulin signaling. And second of all, therapeutic doses of oral arginine (L-arginine) have been used to improve the reduction of asymmetrical dimethylarginine (generally 6 to 9 grams per day or higher is used to lower ADMA levels in a person who may be at risk due to the accumulation of this arginine metabolite). So you'll notice again there is another interesting role that diet plays because vegetable proteins are generally higher in arginine. I'm thinking of soy protein or pea proteins: high arginine, lower in lysine, as contrasted to animal proteins that are generally higher in lysine and lower in arginine.

In looking at diets that contain higher vegetable proteins, what do we see epidemiologically? We see generally lowered incidence of cardiovascular disease. Most people say that is because you are getting lower amounts of animal fat when you eat more vegetable protein, and that is part of the story. Remember, we don't eat one molecule at a time in our diet. Our diets have a specific signature that is related to the foods that we consume. That dietary signature sets up a different panel of genes that are turned on and turned off to express different functions, so it is not like pharmacology (one drug at a time). We have actually set up a pattern-a symphonic orchestration of our gene expression-that occurs in these polygenetic conditions that relate to vascular disease. By eating a diet that is high in animal protein and higher in animal fat, it sets up a different gene response profile of increased inflammatory response, decreased insulin sensitivity potentially, increased ADMA levels, decreased nitric oxide output from the endothelium, increased oxidative stress, and so forth.

You'll notice we are talking about a complex mechanism of which cholesterol is maybe only the tip of the iceberg. We know as this process occurs (as Virchow predicted over a hundred years ago) that this will induce these inflammatory responses with a change in the immune response. And so we often use the

surrogate marker, high-sensitivity CRP (or C-reactive protein) to evaluate relative risk to cardiovascular disease associated with inflammation. And many clinical trials have been published. We have discussed a number of these in previous issues of *Functional Medicine Update* in which we have talked about values of hsCRP above 2 milligram per Liter being associated with increasing risk to coronary events. We would generally like hsCRP to be less than 1, but you get above 2 and you get into increasing relative risk.

And now you're going to say that patients who have autoimmune disease or inflammatory disease often have hsCRPs above 2; they might be 10 or 15 or 20. The answer is yes; that is another risk factor for vascular disease. Not in the moment of inflammation, but it is over time. If a person has the flu, his or her hsCRP may go up transiently, but it may only be elevated for a month. But if it is elevated for a year, or five, or ten, now the state of function of that individual is an inflammatory state with immunological imbalance and now they have a relative risk to these processes that we are talking about pertaining to oxidative stress, vascular smooth muscle cell change in the artery wall, and proliferative responses that lead to atherosclerosis. I am quoting from another interesting article about C-reactive protein and atherosclerotic risk that appeared in *Clinical Chemistry* in 2007.[11]

What do we know that can activate oxidative stress and can induce free radical pathology? One of the families of substances that do that is the transition metals. The transition metals include iron (probably the most common in our bodies; at the highest prevalence). Iron can exist in multiple oxidation states: ferrous iron (Fe+2) and ferric iron (Fe+3) are the common oxidation states. There is an Iron-Heart Hypothesis, which was actually put forth first by Sullivan in 1981, that suggests that increased body iron stores are a risk factor for coronary artery disease and thus iron depletion through phlebotomy could lower relative risk. This hypothesis was based on the markedly lower incidence of coronary heart disease in premenopausal women, who lose iron through menstruation, compared with men (and also with postmenopausal women), and seemed intuitively appealing. However, as this has been tested more over the last 25 years, the hypothesis doesn't seem to bear out very strongly.

Support for the Iron-Heart Hypothesis in humans has focused on epidemiological associations. Serum ferritin -- the iron storage protein for which levels are elevated with iron overload and proportionally reduced with iron depletion -- is considered the best biomarker for long-term iron stores. Recently Salonen conducted the first prospective cohort trial to suggest a positive association between serum ferritin concentration and the risk of coronary heart disease in a Finnish population.[12] After adjustment for established risk factors, this small study showed a more than two-fold increased risk of acute myocardial infarction among men having serum ferritin levels of 200 ng/mL or greater compared to those having lower serum ferritin. However, these promising results have not been confirmed in a number of subsequent studies that have been published the last couple of years.

There are actually polymorphisms or gene alterations that might be more susceptible to this iron story than the wild-type gene, so it is a more complicated situation than we originally thought. In a recent paper in the *Journal of the American Medical Association*, outcomes from a multicenter randomized controlled single-blinded trial on the effects of iron reduction through phlebotomy were reported.[13] This trial was conducted from May 1999 through April 2005 at the VA and enrolled 1277 patients with symptomatic peripheral artery disease. Nearly all the patients were men. More than 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} were white. Their mean average age was 67 years. And during a mean follow-up period of approximately 4 1/2 years, there

were no significant effects on either primary (meaning all-cause mortality) or secondary (death plus nonfatal myocardial infarction or stroke endpoints). Reduction of iron stores had no effect on the incidence of myocardial infarction or stroke. However, in a post hoc subgroup analysis, a significant interaction between treatment and age was found. Younger patients (43-61) randomly assigned to undergo iron reduction did have a significant decrease in primary as well as secondary endpoints, but these benefits were not significant in older patients.

This kind of still leaves the iron hypothesis out there as having potential, but it raises the question, are there subtypes of individuals that are more susceptible than others? Is iron itself, without looking at its physiology in the individual, the culprit and at what age would you intervene to lower iron stores to lower cardiovascular outcome? I think, again, what seems to emerge from this is people with inflammatory situations onboard have a higher implication of iron-induced free radical pathology. Again, we should probably look at this in a multifactorial situation. Lowering inflammatory risk and lowering insulin resistance makes the iron story less a concern, so, again, I think it is weighting these factors in terms of our general understanding.

With all of that as context, it leads us into the question of apolipoproteins and lipoprotein physiology and how we can regulate friendly lipoproteins to reduce atherogenic risk and reduce the unfriendly lipoproteins to accomplish the same goal. Of course, there is no better way to do that discussion than to recruit a world expert who is probably one of the few people who knows more about this topic than anyone else. A person who can tell us a little bit about why the recent CETP trials were not positive. In fact, Pfizer had to pull their drug, Torcetrapib, off of the potential approval cycle because of increase in the relative risk of cardiovascular incidence in people who had their HDLs increased by this medication, this CETP inhibitor, Torcetrapib. By the way, this was discussed in an article published the *new England Journal of Medicine* in 2007.[14]

So, we are going to go to the source and learn more about how one modulates these lipoproteins in such a way as to reduce relative risk to these complex atherogenic processes.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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I think all of you who have been long-standing listeners to Functional Medicine Update or supporters of the written transcript know how much I look forward to our clinician or researcher of the month part of each month's sequence because of the "new" news and the opportunity to learn from world leaders. We are not going to be disappointed this month. We have with us a very remarkable person who is going to talk with us about something we all need to know more about: the lipoprotein story and its connection to inflammation, vascular disorders, and now what is even emerging to be type 2 diabetes and metabolic syndrome. I'm speaking about Dr. Roger Newton. I've had the privilege of getting to know Roger over the last several years. He is quite a remarkable researcher in what you might consider the drug development area, but that would be a very myopic definition of the breadth of information and his contributions to the

field.

Just quickly-to give you a little thumbnail vignette of his background-he started off with a PhD in nutrition from the University of California at Davis, which is a very well-respected institution in the nutrition area. That followed from a Master's in science and nutritional biochemistry from the University of Connecticut and a Bachelor's in biology from Lafayette College. After that he went on and did a postdoc with Dan Steinberg. All of you are probably well aware of the name-having won acclaim for his work in the discovery of the oxidation of LDL at the University of California at San Diego. It was there that Roger really started to develop his interest and expertise in lipid management and in the area of regulators of cholesterol biosynthesis and I'm speaking specifically of the statin family of medications. It is interesting, however, that in the more than 60 publications that Roger has in the science literature, his first publication that I could find listed in the Library of Medicine is titled, "The Effect of Diet on Fatty Acids in the Lipoprotein Cholesterol Esters of Type 2A in Normal Individuals."15 This appeared in 1975 in the journal, Lipids. It shows how his lineage-his academic lineage-really started in nutrition and wove its way, then, into pharmacological agents to modify cholesterol.

He has been given the credit (and I think rightfully so) as a co-discoverer and product champion for what we all recognize as the most prescribed cholesterol-reducing drug in the world, which is atorvastatin, or Lipitor. He worked with the inventor of Lipitor, Bruce Roth, to really bring this product into the full amplified clinical support, and there are more clinical trials on it now than any other cholesterol-lowering agent. The mechanisms of action and all the various subtleties that underlie the support of that medication really came out of the work that was pioneered and championed by Roger.

He has been the past chairman of the Great Lakes Venture Quest and a member of the Michigan Life Sciences Quarter (a steering committee). He has had numerous responsibilities: adjunct professor and professor at the University of Michigan in the area of biologics and the nature of life sciences, Department of Pharmacology at the University of Michigan. I would say that he represents, as a co-founder of the company Esperion Therapeutics, a visionary who has spanned many, many different academic disciplines. It is sometimes hard to do this because we are likely to be pigeon-holed (by our colleagues) and defined in myopic ways so that they can get a tidy little definition of who we are and what we do. Roger has really forced back that definition. He has spanned wide ranges of explorations in science and discovery. He is also known as a tremendous leader and motivator and champion of high-quality work. The people who have worked with him revere him for his leadership ability and his ability to steer clear direction in sometimes murky waters.

It is a great pleasure to have the co-founder and former president/CEO of Esperion Therapeutics here. Actually, he is also quite an entrepreneur, having been successful with his colleagues to sell his business (in February of 2004) for over a billion dollars to Pfizer and then work with Pfizer Chemical.

Roger, thanks for being part of our Functional Medicine Update 25-year history.

RN: Jeff, it's a pleasure to be here and thank you for the opportunity to talk about lipoproteins and atherosclerosis, something I am very happy to talk about.

JB: For a lot of our listeners, it might be interesting for them to get a thumbnail sketch from you as to how your interesting journey in life took you from a PhD in nutrition and working on effect of diet on

fatty acids up to and through Esperion to today.

RN: Sure, I'd be happy to, Jeff. The light went off in my head about what to do in my career back when I was at the University of Connecticut. It was one night, working in the lab, and I'd been reading a book about atherosclerosis. Interestingly, a person by the name of Charlie Day had edited it, and there were both nutritional as well as pharmacologic intervention studies that were presented in that book. It came to light that wouldn't it be interesting if I could find a way to intervene and treat the disorders that lead to atherosclerosis, which obviously included hyperlipidemia/dyslipidemias. I then went on and did my PhD (after getting my Master's at the University of Connecticut) at the University of California at Davis, where I initially worked in metabolism with Dick Freedland and understood intermediary metabolism and the importance of lipogenesis, fatty acid synthesis, and cholesterolgenesis in liver cells.

I took a pharmacology course (interestingly, pass/fail). I did pass it, and that's the only pharmacology course I ever took during my academic career. But that opened up a whole door of the combination of pursuing nutritional and pharmacologic intervention and the interplay that metabolism has in lipoproteins, cholesterol synthesis, and its role in the production of lipoproteins and the degradation and its regulation. And then going on and working in Dan Steinberg's group.

I then began to work on another metabolic inhibitor, which was discovered by Akira Endo at Sankyo (the first statin, which never made it to the marketplace, Compactin). Using liver cells as a means of being able to evaluate the interplay of cholesterol coming in from a lipoprotein source versus that which is synthesized and the impact that has on lipoprotein synthesis as well as degradation, I began to understand a little bit more about the importance of de novo fatty acid synthesis through using Compactin as a metabolic inhibitor.

That then led to finishing my postdoc after 2 1/2 years and looking at industry and academia as a potential career, and I basically read this letter on a wall that said, "Interested in working in lipoprotein metabolism at Warner-Lambert/Parke-Davis in Ann Arbor, Michigan?" I went out and interviewed, and they wanted to start up a statin program different from that that Akira Endo had done, which was looking at fermentation beers and isolating metabolites that would inhibit cholesterol synthesis. We began a medicinal chemistry approach. And so, with that, I came into a group of about five people, and basically (to make a long story short) I chaired the atherosclerosis group for 12 years.

We had 11 lead compounds. Interestingly, Lipitor was the fifth lead compound in our HMG-CoA-reductase inhibitor program, so we learned a lot from those first four failures. Over about a six- or seven-year period we improved dramatically on our capabilities of making a chiral synthesis of the active inhibitor, which later because CI-981, that also became known as atorvastatin, calcium, and Lipitor.

I then decided that that part of my career (working on cholesterol synthesis and LDL and reducing LDL) was over and was approached to start a biotech company called Esperion. Here we were going to be using (interestingly) a recombinant form of the major protein in HDL, apoA-1, and this variant was apo A-I Milano, which had been discovered in 1979 by Drs. Sirtori and Franceschini. And there was only a single amino acid substitution of a cysteine for an arginine at amino acid 173, and interestingly, that changed everything because it changed the efficiency of the capability of the A-1 as a monomer or a dimer to remove cholesterol from cells. Hopefully, what we wanted to prove by making synthestic HDL, to actually promote removal of cholesterol from arteries and cause regression of plaque. So I started that

company in 1998, and as you said in my introduction, we then became part of Pfizer in February of 2004.

So that's kind of the long, fast way to where I am today. Interestingly enough, I'm no longer a Pfizer colleague because they closed the facilities in Michigan as part of a restructuring process. I'm looking to do new and novel things down the road. So, that's the story.

JB: Well it's an incredible story and obviously that's just really the superficial topline, but I think it gives all of us (the listeners) an opportunity to see the depth of your background. Let's go back, if we can, to this apolipoprotein story and the discovery of Milano protein and how that relates to genetics, and what is HDL-why do we call that the "good" cholesterol and why do we call LDL the "bad" cholesterol? There's probably no one who can tell that story better than you. Can you take us down that road a little bit?

LDL and HDL Physiology

RN: Sure, I'd be happy to. The original evaluation of LDL cholesterol and HDL cholesterol being respectively "bad" and "good" came from epidemiological studies years ago. These studies basically showed that in individuals who had risk for heart disease (and mostly through primary prevention and dietary means), that those folks who had higher HDL cholesterol seemed to be protected (most of the time), and those who had high LDL weren't. And so this ying-yang of LDL bringing cholesterol to the periphery and laying down that cholesterol to cause the nasty plaques that caused increased heart attacks (particularly when they are unstable plaques and they rupture), that link and the antagonism of HDL trying to remove that cholesterol and other lipids from the plaque, this is where the story became much clearer from a functional point of view. In our own way, we do clinical chemistry: we take a static measurement of a dynamic process. Obviously sometimes you want to have a fasted level to have any possible involvement of VLDL due to dietary fat and chiral microns. You want to take a fasted sample to get the LDL/HDL cholesterol. That then tells you (perhaps) whether somebody is at risk. It also tells you whether your diet is having an effect of reducing the LDL and perhaps raising the HDL or whether your pharmacologic intervention is going to have that effect.

But really, that doesn't tell you about the real metabolism and physiology because as I mentioned earlier, it is a static measurement of a dynamic process. So what has happened in the field is that through a great deal and a great number of researchers doing seminal studies on understanding the interplay of cholesterol and between LDL and HDL. We now understand much better that a lot of the LDL comes from VLDL as a breakdown product. There are some people who will directly synthesize an LDL-type particle, but most of the time it comes from the degradation (and remodeling, if you will) of the VLDL particle as it loses its triglyceride due to lipoprotein lipase acting on it, and other lipases like hepatic lipase, for example. This, then, forms a lower density particle that has a larger amount of cholesterol and basically has one apoprotein called apo B. This makes LDL either the buoyant form, which is larger and has more triglyceride, or the small, dense form, which has more cholesterol ester. Really, it is a way in which we can look at the subfractions and determine whether an individual has a greater or lesser risk. The more small dense particles of LDL, the greater the possibility of having atherosclerosis and also the higher potential for the apo B to be oxidized.

HDL is a very complicated series of particles because there can be an interplay of exchange and transfer of lipid and protein. There are about 17 different proteins on the HDL particle. Those that are related to apo-A (there is apoA-1, A-2, A-4). A-1 is really the one we were thinking of as a possible therapeutic opportunity with respect to A-1 Milano because we knew that in animals that had a transgenic human A-1

put into their HDL physiology, they would have a rapid effect of regressing atherosclerosis. Therefore, as a result of that, we thought, perhaps this variant form, which has a disulfide amino acid (namely, cysteine) substituted for an arginine, you may have a greater capability if it is in a dimer form with itself. And, indeed, Franceschini and Sirtori and their colleagues have done extensive and very eloquent research in evaluating how the A-1 Milano, as a potential therapeutic, actually regresses plaques in animal models. Also P.K. Shaw at Cedars Sinai in Los Angeles has been very active in looking at this under a variety of conditions, both as chronic effusions as well as doing transgenic animal studies to compare it to apo A-1 (the wild type), and showing it to be about twice as effective at reducing the amount of cholesterol in the plaques of animals such as rabbits, and also showing a significant increase in regression.

The other part about HDL is it has not just A-1, but it has antioxidant enzymes such as myeloperoxidise and enzymes that affect platelet aggregation. These enzymes and proteins have effects of beneficially reducing inflammation and oxidative stress within the body, as well as (in the case of apo A-1 Milano) affecting hypertrophy and hyperplasia after injury, having effects of reducing inflammation, particularly at the endothelial level of the artery. HDL is not just having an effect of being the good cholesterol; it is also having an effect of reducing inflammation in a significant way.

So these are very, very different siblings (if you will) in the same family. They are all lipoproteins, but they have very different actions and very different metabolism and physiology, both in a normal state as well as in a dysfunctional state.

JB: That was the most remarkable summary of very complex clinical chemistry. I applaud that. Obviously you've done that a few hundred times. That was beautifully done.

RN: Thank you.

JB: You raised a very interesting point that I want to come back to for our listeners. I think you just provided an explanation that most of us need to reinforce in our understanding related to the connection between insulin resistance and cardiovascular disease as it pertains to these apolipoprotein dynamics. Let me just set the context of this.

Most of our docs who are listening to this are familiar with, and probably use the surrogate marker for insulin resistance -- the fasting triglyceride-to-HDL ratio. They would say that, as that ratio gets above 4, the higher it is, the more relative risk and prevalence of metabolic syndrome or insulin resistance. They may not understand that what they are doing (that you have just described) through the use of this ratio is to indirectly be looking at (at least the shadow of) the apo B to apo A-1 dynamics and how that then relates to lipid efflux and influx at the arterial wall. Could you help us maybe to make that connection just so people can kind of lock that down between the cardiometabolic risk of insulin resistance and how that relates to these apo B and apo A-1 dynamics?

Reverse Cholesterol Transport

RN: Yes, I'd be happy to Jeff. The point you make is a very valid one: there is an integral link between your triglyceride levels and your HDL cholesterol from a metabolic point of view. What happens in those individuals who are hyperglycemic and don't have very good glucose regulation, whether it is in diabetes or a pre-diabetic state or obese state in metabolic syndrome is that the amount of triglyceride that is present in the HDL particle is quite high relative to a normal HDL composition. Normally cholesterol

esters in triglycerides are found in the HDL particles as they are metabolized from the discoidal particles that are produced by the liver and intestine everyday. These discoidal particles are basically lipid-poor discoidal particles that contain phospholipids and apo A-1. They then are remodeled (if you will) and pick up more protein in the plasma compartment, as well as pick up more cholesterol ester and triglyceride through different transfer proteins and exchange proteins such as cholesterol ester transfer protein, which basically transfers cholesterol ester to LDL, and triglyceride comes into HDL. The issue that you have with folks who have too high a triglyceride, particularly if their A-1 particle number is static, is that you have too much triglyceride in the core of the HDL. Therefore, the capability of the A-1 particle to remove cholesterol is highly limited. So this process -- called cholesterol efflux, and the most important (I think) metabolic pathway by which HDL functions in cholesterol metabolism -- this reverse cholesterol transport, can't take place in an efficient manner. Therefore, if you are able to put yourself into glycemic control through a variety of means, both from a nutritional point of view as well as a pharmacological point of view, you can reduce the amount of triglyceride in the HDL particles, and you can also change the composition of the particles such that they have the capability of removing more cholesterol from the arterial wall. This ratio of triglyceride-to-HDL is obviously an arbitrary measure that doesn't tell you about the functionality of the particles. I think the point I really want get across to the listeners is that we really need to better understand the functionality of the particles that we are working with. How to do that is hopefully something that we will be able to do in a micro method down the road, which could be looked at as an additional "peeling away of the philo dough," if you will, to better understand how this individual's physiology or abnormal physiology for the metabolism of HDL can be more insightful into which problem they have and how to treat it: whether it is the carbohydrate side that is influencing the lipid side in a negative way; or whether it is the lipid side that is affecting the carbohydrate side. Certainly measuring triglyceride-to-HDL gives you some insight, but it is only giving you (I think) a high level (a 30,000-foot level) of what is actually going on in an individual's metabolism.

JB: Once again I want to applaud you for the opening statement you made, which I think is kind of an "aha" for all of us, and that is this these lipid measurements that we are commonly using in our clinical chemistry (the LDL, HDL, triglycerides) are these static measurements of this dynamic process. I think that gets us back to the whole functional medicine model where we are looking at the dynamic physiology. We call it the web (or however we want to define that). It is kind of your biological systems approach-looking at how things interact rather than just freeze frame, which is often what we do in medicine: to look at that moment in time that is associated with a pathology. I think that to think of these as dynamic processes where things are moving in and out of cells is a very different view than the one in which probably most of us were trained.

Let me, if I could, go back to your HDL composition because I think it is a really important point. We often hear clinically about the different kinds of HDL. We have heard that certain HDLs have different atherogenicities or anti-atherogenicities, and that alcohol consumption raises certain HDLs, and exercise raises other HDLs. Could you help us to understand a little bit more about that? The different types of HDL?

The Different Types of HDL

RN: Yes. These are, again, ways (like I mentioned earlier with LDL) to try and better understand the particle number (the apo B relative to particle number) as well as the different composition of the particles to try to associate or better understand what the relative risks would be.

It is well known that the cholesterol carrying capacity of the pre-beta HDL particles is substantial. It is

more than any other HDL particle. It is the alpha particle, if you will, of HDL as it picks up more cholesterol and picks up A-1 phospholipid. And those that are phospholipid-rich HDL particles have a greater capacity for removing cholesterol. So these smaller particles are really like the tortoise versus the hare, if you will, where they are very rapidly removing cholesterol, taking it back to the liver, and then cycling back and forth to pull more cholesterol out of cells and hopefully out of the arteries. As these particles get larger-when you get from the pre-beta (the alpha particle) to the HDL 3, HDL 2, and HDL 1-they become more like the tortoise (so to speak) with respect to the capability of carrying cholesterol, the flux that these particles can go through and remove cholesterol, and they get a bit sluggish. I guess the word sluggish is probably the best way to say it. They get sluggish at removing cholesterol and promoting this process called reverse cholesterol transport.

So there are associations that clinicians have made at the relative ratio of the HDL to the HDL 3 ratios and what that means, whether it is by diet or whether it is by pharmacologic intervention. And people have tried to associate a very clear line of, "Oh, the risk would increase if you have a higher ratio of HDL 2 to HDL 3." Again, I think it depends upon the patient population. It depends on the predisposition of that patient based on the etiology of their hyperlipidemia as to whether it relates to risk-whether they are a diabetic, whether they are obese, whether they are abusing alcohol in a way that could affect the particle number and the composition. My personal point of view is that the more you understand about the apo A-1, and the more you understand of the A-1 ratio and the phospholipid composition, the more you'll understand the efflux capabilities of those particles. Interestingly, as a segue into the whole idea of inflammation and oxidative stress, Jay Heinecke and Stan Hazen have looked at A-1 from the potential of it being oxidized by an enzyme that is very elevated in oxidative stress called myeloperoxidase. This enzyme has the capability of producing hypochlorous acid. Hypochlorous acid is bleach, basically, and it can cause pretty negative consequences on the capability of the A-1 particle to cause efflux in cells as well as hopefully in arteries. The tyrosine residues of A-1 can be chlorinated as a result of this chemical process that occurs, and it can also be nitrosylated. What we know is the tyrosine residues in apo A-1 are very, very important for the efflux capacity. If you just measure HDL cholesterol you get one indices. If you measure the amount of apoA-1, you get other indices. But unless you evaluate the functionality of those A-1-rich particles, you won't understand whether you are having oxidation of those proteins.

You may think that because someone has high apo A-1 that that person is going to be protected. Well, you really don't know for sure unless you evaluate his capability for cholesterol efflux in cells. That is the issue that I think happened to some extent with the CETP inhibitors, where there was this belief that increasing HDL cholesterol, in any way, would then lead to a mechanism that would be protective of the artery wall and perhaps even cause regression of the size of the artery and the atherosclerotic plaque, itself. That was not the case in recent studies that used a combination of Lipitor plus a CETP inhibitor called Torcetrapib. But, it remains to be seen why that happened. Just like the situation with Compactin, which was at the first representative compound from the statin class, parous patches were found in the intestine. The results with the CEPT inhibitor, Torcetrapib, don't necessarily mean that all of this class of new drugs will be negative. There are other companies moving forward in this area. We all learn from the knowledge that we have and the research that we do to potentially make better statins or make better CETP inhibitors, so it doesn't mean that the whole mechanism is... let's put it this way, will cause the end of CEPT inhibitors altogether. I think we need to learn more. And so as we uncover this information and better understand the metabolism of HDL and about these particles that the CEPT inhibitors cause to become prevalent in the blood, namely these large HDL particles, we will have a better understanding of what we want to do and what we don't want to do. Because it may be an adverse particle that you are

producing, in spite of the fact that you measure a high level of HDL cholesterol.

JB: I've heard you use the term, "starved" HDL. I think that is a very interesting term because it gets us to think visually. It is actually the nourishment of your body that determines your function, so a starved HDL is an interesting concept.

You are dropping in so many pearls right in a row here that it is hard to pick them all up. One in the lineage of the pearls that you have dropped is this relationship between myeloperoxidase and oxidized apo A-1 and the chlorination of tyrosine residues. We learned (most of us) in our immune courses back in pre-med or med school that myeloperoxidase was part of the microcidal killing reaction that white blood cells have as they try to engulf (in the innate immune system) foreign invading viruses or bacteria and kill them by bleaching them to death. It is like chemical warfare. So now you have introduced the idea that the HDL can actually have myeloperoxidase activation. This sounds like there is an immune connection -- like atherosclerosis might have an autoimmune component -- emerging as part of the etiology.

RN: That is correct. There are actually small biotech companies right now looking at the potential of autoimmunue and immunity to atherosclerosis depending upon what effect some of these oxidative processes have on altering the primary structure of some of these very important proteins that contribute either in a positive or negative way to atherosclerosis. It is being looked at, particularly around HDL, in a pretty aggressive way. I think that, in the last three or four years, there have been two or three companies that have begun to pursue this and have venture capital in order to aggressively look at this opportunity.

My thoughts are that atherosclerosis has a multifactorial etiology. Unless you have a way of being able to actually understand the immune component of atherosclerosis and what the inflammatory component or oxidative stress may have to contribute to this, and whether it is an effect on apoA-1 or whether it is an effect on a phospholipid or an epoxy fatty acid, or too much oxidation of cholesterol itself that might cause this kind of response. We have to understand much better the pathways in which this type of response would occur before we can really pursue which patients might be susceptible to this problem, and then, of course, how to treat them.

JB: So now I would like to give you the luxury, if you are comfortable, to kind of-with all the years of experience and wisdom you have accrued in this field-be speculating and theorizing with me. We know that there are certain cultures that have low levels of atherosclerotic disease and in age-adjusted studies we recognize that they have certain diet and lifestyles, and we even know they have certain genes. But often when they travel from their homeland and eating their traditional diets and move to the Western world and consume the diets of our fast food nation the genes don't protect them. They end up with high levels of atherosclerotic disease. It would suggest that there might be something in the message that triggers all these lipoprotein dynamics and this -what you have indicated-is an extraordinarily complex process of things moving in different directions. In fact, even the apolipoproteins themselves, which we might have thought of as kind of benign carriers of lipid, are really active molecules that are regulated by hormones and they are playing a role in receptor sites as well. It's this dance of many, many different parties that are inter-related with the information that they are getting from their diets. Do you feel (from all of this) that we are starting to emerge a molecular understanding of the role that diet plays in the modulation of atherosclerotic disease?

RN: Absolutely. I think that as we better understand the importance of biochemical individuality and the

interplay of the environment, nutrients, lifestyle on various genes and their expression we will have a better way of changing the paradigm of how we treat people. The approach that people have taken is to look at those who are at high risk and treat them chronically with pharmacologic agents and to try and institute lifestyle and nutrition or diet therapy as a means of potentially improving their lifestyle and situation of how they live as a means of reducing their potential risk. This is not easy to do in the world in which we live, and particularly the Western civilization because we have all these temptations that the food industry has provided that are basically unhealthy and that actually have a negative effect on regulating the positive genes that we want to have a significant effect on.

If we look at how we treat disease, we are going to have to look at the situation and say, "What are we going to do to change the chronic disease treatment paradigm?" As we better understand the interplay of nutrients and the really subtle changes of nutrients on nuclear receptors and transcription factors and gene expression, and particularly genes that are related (my focus would be) to lipogenesis. We may have, then, a better way in which we can treat people, and not just from a dietary point of view, but also from a pharmacologic point of view. I think that the wall of demarcation between nutraceuticals, medical foods, pharmacopeia (if you will), and the separation that exists within the industries-I think that is going to change significantly because personally I don't think the existing healthcare paradigm is sustainable. There is going to have to be some major efforts made by the food industry to create more nutritional foods and foods that will benefit society as opposed to snack foods that won't. And I think it is also imperative on the part of the pharmaceutical industry to begin to look at not providing…let's put it this way, compounds and molecules from medicinal chemistry that are foreign to the body, but also look at natural products and their potential role, and particularly the fact that if we have been eating them for generations we don't have an issue with respect to toxicity.

I believe that the melting pot will be a combined nutritional-medical food-pharmacological intervention that will be harmonious. It will be an integrated process as opposed to one where what drives the business sector and the economy of pharmaceutical companies and nutraceutical companies, which are all very independent. I think that there is going to be much more of a harmonious integration. It has already started with the pharmaceutical companies and the device companies. That started about five years ago. They are having meetings now where they are talking to each other and they are realizing there is a lot more overlap and a lot more commonality to what they do.

I hope this then translates into a better definition of acute and subacute medicine and how we treat people who already have a disease, and making improvements in how we treat people who are at risk or people who have chronic disease. Let's face it, the quality of life that we want to have in our later years and how long we live is extremely important to people like me who are part of the baby boomers. I don't want to live to 85, but by the time I am 75 years old have to deal with what would be 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of my prescription bill during that particular time and not really have a high quality of life. There needs to be, I think, a dissecting of what we are doing in the healthcare system to make it cost effective and to also make it worthwhile for all of us to follow a certain way of how we live, the environment that we live in, the nutrition that we have, and, if we need medications, not take seven medications, but take only the ones that really need.

JB: That's an incredible model and it is certainly very consistent with this whole functional medicine story that we have been evolving over the last 25 years. I am reminded of the story that you started off with

about the Milano protein. I can just visualize this family in Milan that happened to have the luck of the draw in their genes that they had this cysteine substituted for the tyrosine that made their HDL apo A-1 less able to be oxidized and so they were kind of protected a little bit against the abuses that maybe other people would be susceptible to. It is not just that our genes can put us at risk, they can also protect us, and so what we are really talking about is the majority of our wild type genes, which is the majority of the population-what is the right nutritional information that washes over those genes to give rise to lowered oxidative stress, lowered immune upregulation, improved lipid dynamics, improved cholesterol efflux and influx balance effects, and how does insulin play a role-this whole symphonic orchestration of our metabolism.

That's obviously not what medicine has been focused on the last 30 or 40 years. It has been focused on dealing with each part of the system that is broken individually, compartmentally, in a silo way, so that each specialist of medicine has his or her own list of pharmacological agents that treat the body in isolation from other parts. That's just not-as you have described the story-the way the body works. I think we are witnessing, based on what you've told us-the emergence of a new medicine.

RN: I should hope so, Jeff, because I think the whole approach…let's put it this way, the institution of molecular biology and then the genomics that followed and the better understanding, if you will, of the blueprint of life, to some extent fit right in to the reductionist mindset of many basic scientists, clinician scientists, and really looked at the idea that you could control the biological systems if you understand the genes. Not including what I would think is the most important and that is the environment and all these signals that come in from our day-to day existence as well as the food that we eat.

I think we have to change that. We have to change that myopic kind of view to a much more integrated metabolic approach where people understand to a greater extent-and as the individual biochemistry comes forward and we are able to evaluate this in a really meaningful way-people can better then judge what they should or should not do with their bodies, as well as realize that being on 4 or 5 or 6 medications where there are drug-drug interactions that occur and where there is this polypharmacy paradigm, that's not going to lead to optimum health.

I think understanding how each individual person can reach that potential is hopefully what will happen down the road with a multidisciplinary approach to health and to treating chronic disease. I think the years of thinking that genomics is going to lead to a plethora of new pharmacologic agents…I think a lot of people have realized that that has not happened over the last 5 to 10 years, nor do I think it will happen. It is going to take a lot more understanding to really get to that point where you can then intervene. If you really look at it,
2{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of human disease actually is monogenic with respect to those diseases that really affect people in a negative way. The remainder are polygenic-or multiple genes interacting-as well as the involvement of the environment. To say that we can actually treat people by doing a single-gene therapy-that can only occur in a minor number of people in the population. And we have to be very careful that we know what their genetic predisposition is before we do that. Really what I think we need to do is look at a more integrated approach to medical treatment where you have people with different expertise contributing to the overall well-being of somebody's lifestyle and health, as opposed to just being myopic and think that you can treat one specific receptor or one specific enzyme or one particular event in the nucleus. In the biological hierarchy, this particular target that you have is going to have a multitude of effects in improving the

whole metabolic picture and the overall well being of that individual. I think those days are waning, let's put it that way.

JB: Personally, I want to thank you on behalf of all of our listeners for the years of contribution you have made. You have been a pioneer and a true seeker for a long time and it is starting to show the results of your efforts and many like you to create this new horizon for medicine to evolve to. I just want to personally thank you for the diligence that you have brought to the field and for your vision. I think if we could collect enough people like you together we would transform our medicine to become truly a healthcare system and not just a disease care system. Thanks a million and we'll look forward to traveling down this road in your journey with you, Roger.

RN: Jeff, thank you very much for the opportunity.

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