June 2012 Issue | Mark Houston, MD, MS Director The Hypertension Institute

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Well here we are. I consider this a watershed moment in the history of *Functional Medicine Update*. I don't want to make this overly dramatic, but I have to say that a 30th anniversary—three decades of production of this educational series—to me is a pretty interesting accomplishment. This is the 30th anniversary of *Functional Medicine Update*. I've had the privilege of interviewing, over that 30 years, some of the most remarkable opinion-leading, kind of innovative thinking, new-medicine-creating individuals. And of course, we must then have selected a notable example of all of those extraordinary people for our 30th anniversary edition, and we did. Ten years ago we were very pleased to have an interview with Dr. Mark Houston. Mark set a standard of excellence during that discussion of an explanation of something that is very complicated, vascular biology and how it applies to medicine Dr. Houston has agreed to come back after this 10-year period to once again rejoin us as our as our clinician/researcher of the month 30th anniversary edition

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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In case you are not familiar with Dr. Houston, which I would find hard to believe if you are in this field—Dr. Houston is a graduate of Vanderbilt University Medical School. He's the president of the Hypertension Institute in Nashville, Tennessee. He's a practicing specialist in the area of vascular biology and cardiovascular/cardiometabolic medicine. He is very, very noteworthy. He has been voted by USA Today as one of the most influential doctors in the United States, selected as a top physician in both hypertension and hyperlipidemia in both 2008 and 2009. He was included the Consumer Research Council of America's list of America's top physicians in 2008 through 2011. I think that probably gives you the landscape of the notoriety of Dr. Houston, who is not only a clinician's clinician, but a life-long learner, a teacher, and educator, a researcher, and truly a leader in our field.
So with that, Dr. Houston, wonderful to have you once again here on our 30th anniversary, and also the 10th anniversary since we last had a chance to speak with you on Functional Medicine Update.

MH: Jeff, it's an absolute honor and delight to be with you and celebrate your 30 years. Congratulations on an incredible achievement.

JB: Well, thank you. We were both at the Institute for Functional Medicine meeting, which was the most successful meeting in the history of the Institute for Functional Medicine, with over 900 attendees at the meeting. You were a central bright light at that meeting, which was on functional medicine approaches to cardiometabolic disorders. I think there are a couple of things that we're going to talk about, one of which is your view of vascular biology related to hypertension and what it is teaching us about ways to manage this complex condition that is seen so frequently in our population in the western world, and secondly talk about hyperlipidemia's risk factors and some of the emerging new ways of looking at extended biomarkers. But as we do that, I know both of us are very fast talkers and fast thinkers, so for our listeners there may be times that they say, "Whoa, this is going pretty fast. I'm going to have to listen to this several times," so I want to give a reference to your website because it is very rich and robust site of information that people can come to later, and that's www.hypertensioninstitute.com, and we'll clearly be putting that on our information for the listeners. Also, I've had a chance to read your most recent book, What Your Doctor May Not Tell You About Heart Disease, which is just a fact-filled, news-to-to-use information guide that I would highly recommend as another source to follow up from this conversation.[1] We'll talk about those here, I'm sure, during the course of our interview, but I just wanted to make sure for people who think we're moving awfully quickly and they're not keeping up that there are these extraordinary sites and resources they can come back to.

So with that, Mark, let's move into the discussion. First of all, you have a very interesting academic background, not only in medicine, but also having graduated summa cum laude in chemistry and then later going on and getting your MS in human nutrition. Tell us a little bit about what led you into this journey and how it prepared you for the 21st century medicine.
MH: Jeff, as you pointed out, I was trained traditionally as an MD and in 1992 my father developed prostate cancer, and I went into the functional medicine literature trying to help him become healthier beyond the traditional treatments he was getting. So I learned about oncology and cancer in functional medicine initially, which was totally out of my field of expertise. We got him really back on track and he lived for another 5 or 6 years despite very bad prognostic signs, and I attribute a lot of that to the lifestyle changes we made in a functional medicine approach, so I realized if it is available in oncology it is available in cardiovascular disease. So about 1995 I really started looking into functional medicine, nutritional medicine, and totally changed my practice. Of course, as you know, when you are out there in an academic setting as an MD, there are a lot tomatoes coming out of the audience, and darts on your

board and in your back, so you have to become credible in your field, so I decided, “I’m going to go back and get a nutrition degree,” which I did from the University of Bridgeport. That really was the impetus, along with being at IFM in 2000 with you and other tremendous speakers during that setting, “The Heart on Fire,” to really catapult me into a totally different way of practice, which is what I do now, which is really an integrative cardiovascular medicine practice.

JB: You know, in those 12 years since you were a keynote speaker at the IFM Symposium, many of the things that you discussed back then have now become kind of like the “new news.” It is very fascinating to me how certain people can forecast and see the future and then they become reality to everyone else. Tell us a little bit, if you would, about what you think some of the major shifting understandings of vascular biology are and how they are getting integrated into medicine.

Inflammation, Oxidative Stress, Autoimmune Dysfunction : The Three Finite Responses

MH: Jeff, I really believe if you have a great understanding of vascular biology you can apply the concepts to every other biological system. The body is very smart, and it replicates the way it responds to injury in other systems in the same way that the blood vessel responds. One of the mantras that I continue to say—you’ve heard me say this over and over again, and you’ve been saying this for years as well—is that the blood vessel really has only three finite responses to an infinite number of insults: inflammation, oxidative stress, and autoimmune responses. So if you throw the millions of insults that we’re faced with every day on top of our genetics and our epigenetics, and you look at a systems biology approach to the person, vascular biology becomes the root of really understanding of how to apply those concepts to neurodegenerative disease, to gut health, and to anything else within the functional medicine matrix that you want to look at. We’re doing a sort of different approach now. We take the finite responses and look at those to do markers, and then backtrack and say, “Okay, we’re inflamed. Why are we inflamed? Let’s go back and find those insults that caused the inflammation.” As opposed to going the other way, which is what we’ve been doing for years in traditional medicine.

JB: To me, that’s very interesting from a historical perspective, going back to, Rudolf Virchow back in the 19th century, who is arguably considered the father of modern pathology, and who had a pretty interesting debate going about the etiology of what we call cardiovascular disease today. He was talking about the injury theory, and about the fact that the atheroma looks like a wound. Although he was clearly a genius and made so many contributions to the pathology, his views weren’t widely held. And then, of course, at the turn of the 20th century, the Anichkov concept of the lipid hypothesis kind of overrode the Virchow injury model. But it looks like we’re coming back to revisit this injury/insult model related to vascular biology and pathogenesis of atherosclerosis, and it seems to tie so closely to that marker tissue or marker cell type called the vascular endothelium, which was neglected for so long as just this one-cell-thick lining of the vessels. Maybe you can tell us a little bit about how you see that emerging understanding applying to both the origin of and treatment of vascular disease.

Endothelial Dysfunction (ED) as a Marker for Predicting Vascular Problems

MH: I think one of the major breakthroughs, Jeff, in cardiovascular medicine is this: When the blood vessel responds to one of these insults or one of these injuries, it is doing what it is supposed to do. It is an acute response that is the correct response. It is basically applying a defense mechanism against an invader. Now, when we do that acutely everything is fine. You take care of the problem, whether it is a microbe, or it’s a toxin, or it has oxidized the LDL cholesterol, or whatever. But when you continue to respond to that insult you continuing to insult the endothelium, and then it becomes what I call the innocent bystander of a chronic, dysregulated response, and it’s the same three responses: inflammation, oxidative stress, and immune dysfunction. Over time, the body’s normal response to injury becomes

actually a dysfunctional problem, and later, as we progress, becomes a disease and we can put a name on it. But in that intervening period, which can be decades before we can actually define the disease, you will have endothelial dysfunction (ED), which becomes the best marker for predicting stroke, heart attack, coronary heart disease, congestive heart failure, renal disease, and a lot of other vascular problems. So the new movement in cardiovascular medicine is to be able to identify the insults, to identify ED with non-invasive basic testing, and start prevention and aggressive treatment before the patient develops a known disease related to cardiovascular illness.

JB: That's extraordinarily powerful information. I hope everyone who is listening got the "a-ha" there. That, to me, is really setting a tone for a whole different view of both the etiology end and the potential prevention and treatment of vascular disease. Let's move to a level of kind of clinical granularity here for a second, and that is: How do you measure vascular endothelial function? Are there ways that one can do that in the clinic?

EndoPAT: A Non-Invasive Test to Identify Endothelial Dysfunction

MH: Absolutely, and this brings up the second concept which I really want to talk about, and that is what I call the vascular risk factor disconnect. What I mean by that is you may have 400 risk factors out there, but not everyone responds the same way for obvious reasons (genetics, epigenetics, and so forth). But just because you have a risk factor doesn't necessarily mean you get vascular disease or ED. And the reverse is true: Just because you don't identify a risk factor doesn't mean you won't get ED. So the vascular insult hypothesis has to be what's called vascular translational medicine. What we are doing now is we look at people and we do these wonderful scores—Framingham score, INDANA score (INdividual Data ANalysis of Antihypertensive Intervention Trials), PROCAM Score (Munster Heart Study)—and we give them to people: "Okay, your score is 15. That puts you at a moderate risk for coronary heart disease." The problem is that's a number that doesn't necessarily translate into a functional or a structural problem in the blood vessel. So what we're doing now at the Institute, which is I think is where cardiovascular medicine is moving, is we now have non-invasive tests which actually will identify ED very early. One of the best ones is called EndoPAT. It's a commercially available product. It takes a probe on your finger, a blood pressure cuff, and in about 15 minutes you have one of the most accurate assessments of ED presently available. There are other tests out there, but this one, in my feeling, is probably the single best one right now, and the correlations with outcomes for CV disease are better than anything we have. They trump any sort of risk scoring we have available, and actually trump looking at risk factors by themselves. So this is the key to translational vascular medicine, I think.

JB: I'm really excited to hear of your support of EndoPAT. We, in our research setting in Gig Harbor, have been working with EndoPAT over the last eight months now, in several hundred patients that have come through the clinic. Our clinical view of the procedure (it's non-invasive) is very similar to what you're saying and we're very excited about it. It seems to be a very sensitive indicator because you can demonstrate in a month or so positive changes in the EndoPAT valuation, so it's a way of not only assessing but also a way of following the response to therapy. Has that been your experience?

MH: It is, Jeff, and the other thing that is really interesting--and I didn't realize this until I started doing it—we've done probably about 1500 EndoPATs in the last couple of years, so our data is very good now, and there's a couple of things I want to say that will help, I think, our audience understand how valuable this tool is. First of all, when you do the EndoPAT in someone who looks like they are very healthy and they have no risk factors but their EndoPAT shows that it's abnormal, what it does is it takes you to a whole different direction of looking at tests, and diagnoses, and treatment: What am I missing, here? Something's not right. So you are going to go and do a better search for a missing risk factor, or a missing mediator. I can't tell you how many times I've found something just because the ED was

abnormal on the test despite the fact that the risk factors were totally normal. And then at the other end of the spectrum is someone who comes in, they are about a year out from a coronary bypass graft, they have horrible vascular disease, but you've done everything in your power to improve their endothelial function with nutrients, lifestyle changes, weight loss, medications, etc., and guess what? Their EndoPAT is normal. Now, what that says to me is that even though you have bad vascular disease you can stabilize it and even reverse it if you know what you're doing and have the appropriate test to monitor and track it.

JB: You said something just in passing there that I wanted to pick up on as a sidebar. You used the term, or the abbreviation for, endothelial dysfunction (ED). That also obviously is an abbreviation that is used in the parlance in the common language for erectile dysfunction, and there is some data suggesting that ED correlates with erectile dysfunction. Have you clinically observed any of those things in your practice?

MH: That's absolutely correct, Jeff: ED equals ED. One of the key questions to male patients when they come in your office is you ask him about erectile dysfunction, and if they have it, you're almost guaranteed they are going have endothelial dysfunction as well.

JB: I think that's a very interesting part of your systems biology discussion, that things are connected together in these networks and these webs. I don't want to bear too much on the erectile dysfunction connection, but I think mechanistically if we think about how sildenafil (Viagra) works, it works by modulating cyclic GMP activity and how that relates, then, to the release of various mediators or molecules that regulate vascular tone, and one that comes up in mind as it relates to endothelial function in general is nitric oxide and endothelial nitric oxide synthase (eNOS). There must be a connection here somewhere. Can you help us understand that?

Nitric Oxide is the Key to Understanding Endothelial Dysfunction and Vascular Health

MH: Absolutely. As you know, the nitric oxide story was one of the reasons for winning the Nobel Prize. Nitric oxide (NO) is really the key to understanding endothelial function and vascular health. It has numerous functions. It's not just a vasodilator, but it's an anti-inflammatory, an anti-atherosclerotic, it reduces cell adhesion molecules, it reduces growth hypertrophy, oxidative stress, and even autoimmune dysfunction. So if you have a normal nitric oxide level (or bioavailability, I should say—that's a much better term), if your NO bioavailability is good then that's a good signal that you're going to have good endothelial function. There are so many things that decrease nitric oxide in your system. A lot of these insults we talked about have direct effects on reducing nitric oxide bioavailability. And there are indirect ways of measuring nitric oxide. There is not any great way to measure it directly, but one of the things we use clinically is asymmetric dimethylarginine (or ADMA). If that is high it is considered an inhibitor for eNOS, which is the enzyme that forms nitric oxide, so that's a great way to get a handle on whether someone might have low NO bioavailability in a study of ED.

JB: I think, again, there are so many levels in this discussion that we could take it, but let me just go one level more down. We won't go too far down, here, to lose everybody. This ADMA story is also a very interesting story because it has something obviously to do with methylation. The ADMA is an arginine that has been methylated and it is part of the catabolism of protein in arginine-containing proteins. As it builds up as a consequence of, say, insulin resistance, which then inhibits the enzyme that is used to clear or detoxify ADMA, then what happens is you start, as you said, interfering with eNOS activity and vascular compliance. So here is another example, I think, of the web, where insulin resistance/hyperinsulinemia is tied to a metabolic distortion which then has a downstream effect on vascular endothelial function. Am I saying this correctly?

MH: Absolutely, you're right on track. There are so many co-factors in the activity of the eNOS enzyme

that have tremendous therapeutic effects that we can do clinically to up regulate the eNOS enzyme and therefore increase the conversion of arginine to nitric oxide and citrulline.

JB: So I know one of those interesting co-factors is tetrahydrobiopterin, which has a precursor—it has a number of precursors, but one of those precursors is 5-methyltetrahydrofolate, a derivative of folic acid, which then seems to tie back to people with methylenetetrahydrofolate reductase (MTHFR) polymorphisms that are slow methylators of folic acid may be more at risk. Is there a place for genotyping MTHFR in looking at relative risk?

MTHFR Should be a Routine Test

MH: I think that should probably be a fairly routine test now because it is so easily available and inexpensive because the methylation story, not just through detoxification and vascular biology but a lot of other things which everyone's aware of, is extremely important. And certainly you can give activated folic acid. You can also give tetrahydrobiopterin orally as well. It may be a bit more expensive, but the idea is to try to identify factors that are affecting the production of NO and then backtrack. I tell all of my students: "If I ever ask you a question and you don't know the answer, if you come back with the following answer you are always going to be correct, which is 'What could be messing up the eNOS enzyme?'" And you say: "Oh, it could be inflammation, oxidative stress, or autoimmune dysfunction." Everything ties back to those three basics when you start looking at enzyme function and also production of a lot of different compounds.

JB: A number of years ago we were very fortunate to have a discussion on Functional Medicine Update with Lou Ignarro, who is one of the three people who received the Nobel Prize in medicine/physiology for the discovery of the NO connection in physiology. Lou made the comment that this NO pathway that is consistent with what you've just said about inflammation, oxidative stress, and autoimmunity is very dependent on redox potential within the cellular milieu and therefore specific types of antioxidants or complex networks of antioxidants may be very helpful in restoring eNOS activity and NO production in the vascular endothelium. I think that's kind of a recapitulation of what you've already stated, but have you had some clinical experience and benefit to patients who get kind of complex cocktails of antioxidants in improving their NO production?

MH: Absolutely. One of the things we've looked at, and you probably do the same thing with your EndoPAT, is we'll take a patient and we'll do a baseline EndoPAT, and then we'll do something: either give them a donut, or we'll give them some antioxidants, and then we recheck their EndoPAT a few hours later and see what happens. And it is amazing. You probably remember the old McDonald's study, where they gave a McDonald's hamburger with one group, and a McDonald's hamburger with vitamin C and E and some other things, and showed that endothelial dysfunction was blunted when you took some antioxidants despite the fact you were doing the hamburger.[2] Well, we've done the same thing in showing that you give what I call a bad food or a good food, or a bad food with some antioxidants, and do the same thing and blunt. We're trying to go through systematically and identify which antioxidants or which foods are most likely to blunt that ED. One of the things that I have learned—I say this kind of jokingly—is if you are going to go out and have a Krispy Kreme donut and a cup of coffee, have a little broccoli and red wine with it at the same time.

JB: That's an interesting combination. There's a new cookbook.

Atherosclerosis is a Post-Prandial Disease

MH: But the point I'm making is atherosclerosis and ED is a post-prandial disease with endotoxemia, bacterial microbes, and other nutritional toxins that get through leaky guts, and that sets up an

inflammatory response in your arteries, along with the other two things that are the finite response. And if you can mediate some of that receptor inflammatory response with different types of nutrients and antioxidants, you can blunt even a very bad diet and a very leaky gut through some preventative techniques.

JB: Well now you've crossed over into a very interesting area that I was going to hold for later, but this is a great segue into it,that is this connection between gut function and vascular function, which might appear to be very distant in the minds of some. That connection is not so distant at all if you look at the more contemporary literature you're describing. We were just involved, actually, in a collaborative study with Patrice Cani and Nathalie Delzenne from Louvain Catholic University Medical Center in Belgium. Arguably their lab is one of the world's experts in endotoxemia and this so-called leaky gut area. They just published a wonderful study that is a result of looking at, in a mouse model, the effect on vascular function in that animal who is fed a high-fat diet and then given specific types of phytochemicals to see if, on the same diet intervention, they can neutralize the adverse effect on dysinsulinism, hyperglycemia, and dyslipidemia.[3] Interestingly enough, they were able to demonstrate that there are a number of phytochemicals, including modified hop extracts, that are very useful in kind of neutralizing adverse effect, in this animal model, of a high fat diet on vascular function and insulin resistance. I think the gut connection—and this term "leaky gut" that we started using in functional medicine 20 years ago, which at the time was considered kind of antithetical to good language, has now started to rise up in prominence. Give us your thought about the trajectory in this whole field.

MH: Yes. You know, as a preventive cardiology person, I tell everyone that if you do not clean up your gut, you will not clean up your cardiovascular system. It's that simple. And that's because the relationship between the brain, the heart, and the gut are really absolutely key for neurodegenerative disease as well as all the things related to gut health and cardiovascular ED. One of the things you mentioned, Jeff, which I think is fascinating, and this is a new factoid—here's a new concept for our listening audience: 75 to 80% of the people who walk into your office with dyslipidemia, the cause for it is nutritional and microbial endotoxemia.

JB: Wow. That's a very powerful statement of the new medicine. Wow.

Most of the Time Dyslipidemia is an Environmental Issue

MH: And I couldn't have said that about three or four years ago, but I've really researched it and looked into it now and I feel pretty comfortable that I could back all this up with a lot of data. The concept is this: there is only about probably 20% of the population that really has a genetic dyslipidemia. For most of us it is clearly environmental, and the two environmental causes are intestinal absorption of what I call inflammatory nutrients or dyslipidemic nutrients, and the endotoxemic microbes. So now we've tied together infectious vascular disease and bad micronutrient vascular disease, and these two have exactly the same pathogenesis. The blood vessel doesn't care which of those two is coming in as its insult. The pattern recognition receptors, the Toll-like receptors, the Nucleotide Oligomerization Domain (NOD) receptors, the caveolae, the whatever you've got sitting on your endothelium as a receptor to transmit signals into the cell from its inflammatory signals or whatever, the endothelium is going to respond the same way. So if you realize that dyslipidemia is most of the time an environmental issue, then instead of saying, "Okay, I'm just going to treat your lipids," instead say, "Let's track back why you have dyslipidemia, fix that problem, and guess what? Then your lipids will be normal and you don't have to take anything for your lipids, specifically not a statin."

JB: This is so fun, this conversation. I'm looking at this paper that just appeared in the March 2012 issue of PLoS One titled "Tetrahydro Iso-alpha Acids from Hops Improve Glucose Homeostasis, Hyperlipidemia, and Reduce Body Weight Gain and Metabolic Endotoxemia in High Fat Fed Mice." [4] I

think it relates directly, in a controlled study, to what you're speaking to. Recent evidence suggests that many different phytochemicals impact adipocyte metabolism and glucose tolerance in obese and diabetic animals. In this study they found that administration of this phytochemical, tetrahydro iso-alpha acid, to high fat fed, obese and diabetic mice for eight weeks reduced body weight gain, the development of fat mass, glucose intolerance, fasted hyperinsulinemia, and normalized insulin sensitivity, and reduced hyperlipidemia. This was associated with reduced portal plasma lipopolysaccharide (LPS) levels, meaning the actual leaky gut component that leads to bacterial endotoxemia was reduced in the blood—kind of like chronic sepsis, basically. It reduced gut permeability and led to higher intestinal tight junction proteins Zonula occludens-1 and occludin. It also increased the cytokine granulocyte colony-stimulating factor, and reduced the proinflammatory cytokines, and increased the anti-inflammatory cytokine interleukin-10, showing—according to these researchers—a novel mechanism that allows us to decipher the connection of the gut to insulin resistance, obesity, and vascular dysfunction. So this sounds to me like it's an emerging, extraordinary new chapter in our lexicon of etiology of vascular disease.

MH: That's fascinating, and it's consistent with we're seeing and what I've read. If you want to make this really simple for people now, you can say that hypertension is an inflammatory, autoimmune, oxidative stress disease, and so are cardiovascular disease, and coronary heart disease, and congestive heart failure. If we can start to block those three responses, we're going to have a good chance in reducing all of those outcomes. There are so many phytochemicals out there that we know about now that block the toll-like receptors and have a lot of anti-inflammatory effects. They are more of a shotgun approach as opposed to our typical pistol approach that we take with pharmacology.

The Cholesterol Conundrum and Statins

JB: So you mentioned something else previously that I want to come back to pick up because it's a big one. It's on everybody's mind. It's the dominant theme in the whole kind of dogma as it relates to the etiology of coronary heart disease, and that's the cholesterol conundrum and how that relates to statins, and what the story is that's emerging. Tell us a little bit about the JUPITER trial, because it appears the JUPITER trial with Dr. Ridker changed some of the conceptions and maybe also how we're looking at statins.

MH: Basically, as you know, Jeff, statins were developed primarily to reduce LDL cholesterol. In the process of defining how they really worked we realized that they have other pathways, some of which are beneficial and some of which are very detrimental. One of the pleiotropic facts is that they reduce inflammation. And so the JUPITER trial was a hypothesis: Let's give a statin and see if we can see which of these two markers is more important--is it the LDL, is it the inflammation, or is it both? The bottom line was if you lowered the C-reactive protein (CRP), you still had an independent reduction in cardiovascular risk regardless of what you did to the LDL. Then you say, "LDL is important." Well, yes, it's important, but it's way beyond LDL levels now. It's the size of the LDL. It's the particle number. It's whether it's modified. And then there are another 38 different mechanisms that we talked about during the symposium that really change your whole approach to dyslipidemia now. The bottom line here is that inflammation is sort of evidence by CRP, and JUPITER was your typical double-blind, placebo-controlled trial that said: "Inflammation is really important in cardiovascular disease so we need to start looking at it." That's something that we didn't already recognize, but now it's got validity at least through the JUPITER trial related to statins.

JB: I know in your book What Your Doctor May Not Tell You About Heart Disease you have a very—I think—lucid and understandable explanation of this whole cholesterol concept: where it developed, how it became a dominant theme, some of its strengths and limitations, and how not to get high centered by it when you are looking at true overall relative risk. I want to compliment you because I think that is a very

complex area with a lot of—I guess you call it—legs on it, and I think you've done a really good job of simplifying it and making it understandable, and also in a status that it can be used clinically. I think the information is there to use. I want to compliment the way you've handled that difficult topic.

MH: Thank you, Jeff. One of the things I do want to say that maybe will help people understand this connection a bit better is this. Your native LDL for the most part is not an atherogenic molecule. It's part of your normal body's production so it's not recognized as foreign. It is only when it becomes modified, and that modification can be oxidation, acetylation, glycation, or a combination of the above. When that happens, the body recognizes it as a neo-antigen; it is now a foreign particle. So then it mounts the response that it's supposed to, which is to get rid of the oxidized modified LDL. And we all know the downstream responses after that, with macrophages, and foam cells, and cytokines and all that. The idea is not just to lower LDL burden, but also to prevent its modification, and prevent some of those other steps that go from the time it becomes modified to the time it goes all the way through the endothelium and becomes a foam cell in the plaque and then it ruptures and you have, of course, myocardial infarction.

Apolipoprotein A1 and the HDL Particle

JB: That is a beautiful segue into another chapter in this very multi-chaptered book on vascular biology and vascular disease, and that has to do with the particle in the blood, or the apolipoprotein that's associated with cholesterol efflux and transport of some of these modified cholesterol forms out of the body so they don't sit in residence and create havoc. I'm speaking about Apolipoprotein A1 (ApoA1) and its interrelationship with one of the most complex…I don't think it is one of, I think it is the most complex lipid particle, which is the HDL that has over 40 proteins in its composition, and HDL associated with cholesterol efflux and how that relates to the functional HDL, and of course how that relates to the niacin story. Can you tell us a little bit about your position on HDL, niacin, and its function?

MH: Yes. Let me give you a clinical study that will totally change your thinking about HDL. We have found, through the IDEAL trial and several others, that if you're HDL is around 85 milligram percent, it is most likely to be dysfunctional, and offers no cardiovascular protection.[5] So, in traditional office practices now, where people measure only your standard lipid profile, and they say to you, "Oh your HDL/LDL ratio is fine. You don't have anything to worry about," particularly if they have a high HDL they are getting the wrong message. Starting around 70 milligram percent, as HDL starts to go up there is a higher and higher chance it's dysfunctional HDL because it is inflamed, and all these proteins are disorganized. They just don't work. So HDL and ApoA1 don't do reverse cholesterol transport among about 20 or 30 other things that HDL is supposed to do to prevent atherosclerosis. But if you take all the risk factors and risk markers out there that we have available, reverse cholesterol transport is one of the greatest predictors of cardiovascular disease. And one of the best ways to indirectly look at reverse cholesterol transport right is through myeloperoxidase (MPO). We don't have good clinical assays yet, but that one is available because it tells you you're inflamed, and MPO basically makes ApoA1 become dysfunctional.

JB: I understand there are a number of clinical laboratories that are now providing MPO serological analysis, so it can be actually measured by the clinician.

MH: Yes, it can. Absolutely. And I would highly recommend it in people who have these sort of high-end HDLs, because you'll find that if you do MPO, the MPO is high. You get a very false sense of security in people who have high HDLs if you don't check their MPO levels and realize that they're really at high risk because their HDL is not functioning correctly.

JB: Is there any clinical correlation that you've seen between elevation of MPO and phospholipase A2 serology (a positive PLAC test)?

MH: They do. They run in very high correlation because they are both very good oxidative stress

markers, and they are also very good markers for plaque rupture. If you have a plaque that has a very thin fibrous cap and a lot of inflammatory mediators within the plaque that are trying to eat through that cap and erode into the artery, then you're going to have a high risk for a thrombus and a myocardial infarction. Both of those are good markers predicting that risk.

The Niacin Controversy

JB: So let me come back to the niacin question because this has been a big recent controversy given the study that was published two years ago in the New England Journal of Medicine suggesting an increased relative incidence of vascular disease on niacin-supplemented patients.[6] What's your opinion on that in comparison to the other literature that exists on niacin?

MH: That was one of the studies I took apart and dissected and read through, and I'm satisfied, Jeff, it was a terribly designed study—bad methodology, asked the wrong question. There were a lot of issues, but I think that study stands out as contrary to all the other great clinical data on niacin, and it has not dissuaded me in one way or another to not use niacin. I still use a lot of it. Niacin is one of the best agents we have to not only increase the size of HDL to a 2B, but also increase the HDL particle number, to improve its functionality, and then it has other great effects that are independent of HDL and other lipid parameters and other vascular markers. So the HDL story, the niacin story, I think got miscommunicated with that study, and if you really look at it and you're honest with yourself you would say that study is probably a fairly bad study.

JB: Let me loop back now to the previous discussion we were having concerning statins. At one time—not too long ago—there was a very strong advocacy that children should be started on statins if they have any degree of dyslipidemia. In England, statins were put over-the-counter for more regular consumer use. There is this trend to think that statins are benign, safe--the safest drugs that have ever been developed--and that everybody who has a problem should be on statins. But yet, then we see this most recent meta-analysis study on the prevalence of type 2 diabetes in postmenopausal women who are on statins showing increase in the incidence of diabetes in women taking statins versus age-matched cohort of women not taking statins postmenopausally.[7] Where do you weigh in on this very, very controversial area?

MH: It is very controversial. The key issue is the risk/benefit story. There are clearly patients who are going to have benefit from taking statins, and that's primarily in your secondary prevention patients who have already had an MI, or who have significant CHD. But on the other hand, it has started to come out that for primary prevention in anyone, whether it is a child or adult, it gets very questionable then, and the benefits really don't outweigh the risk. To me, the real risk of a statin is it is a mitochondrial toxin. If you look at studies, most of the things that happen related to statins are related to the slow destruction of your mitochondria in your skeletal muscle and other areas. And I think actually the diabetic issue is partly related to mitochondrial dysfunction and loss of lean muscle mass. But all the nutrient deficiencies, as well, contribute: CoQ10, carnitine, vitamin E, omega-3 fatty acids, selenium, the protein pathway, thyroid dysfunction, anemia, the list goes on, and on, and on with the statins. I'm beginning not to use nearly as many statins as I used to in the past. I'm very, very selective about who I give them to. I usually don't go to higher doses. I'll do interrupted therapy. I'll monitor things carefully. If I start seeing any problems—and I do a lot of tests to monitor--then I go to alternative therapy, and we've actually published now, Jeff, several articles that show that by using some very powerful nutraceuticals I can get exactly the same LDL reduction, same reduction of CRP, that you can get using some of the statins on the market, and I'm talking about 50% decreases in LDL cholesterol with nutraceuticals.[8],[9]

JB: That's very, very exciting. Talk about really giving a broad spectrum of options to the clinician.

Lastly, I know this is a big topic and I'm asking something that is impossible to answer in a short summary, but I guess I'm going to challenge you a little bit and say maybe you can give us a top line, and that has to do with hypertension and the way we're approaching it, knowing that the guidelines for hypertension have been established to be lower now in terms of systolic and diastolic pressures. More and more people—a percentage of the population—are diagnosed as being either pre-hypertensive or hypertensive. The treatments of choice are drugs that were really designed, initially, to manage more overt hypertension, so one questions the risk/reward sometimes, or the risk/benefit in treating marginal hypertension with things like beta-blockers, diuretics, calcium channel blockers; maybe not so much with ACE inhibitors or angiotensin receptor blockers (ARB). It seems to me this concept that came out of the Dietary Approaches to Stop Hypertension (DASH) report, that before you get into pharmacotherapy you ought to do a lifestyle medicine intervention, is prudent in this area.[10] You are one of the world's experts in hypertension management. Can you give us your opinion, which probably is the most educated opinion I could ask for?

Disconnect Between Blood Pressure and Vascular Pathology

MH: Here's what I'm doing right now, Jeff, and I think I've got pretty good data to back up what I'm going to say. There is a disconnect between blood pressure, and vascular pathology, and ED. It's the same concept that I mentioned earlier with translational vascular medicine. What I mean by that is if someone has an elevated blood pressure, let's say of 140 over 90, and you were to put them on a diuretic or beta blocker and you dropped them to 120 over 80, at the end of two years, would you get the same results on endothelial function, vascular smooth muscle hypertrophy, structural and functional changes if you had done either nutritional therapy or picked a different drug, like an ACE inhibitor or an ARB? We have clear data now both in surrogate studies looking at actual gluteal muscle biopsies from Ernesto Schiffrin in Canada, we have outcome studies with the ACCOMPLISH trial and the BPLA study out of Scandinavia.[11], [12], [13] The bottom line is this: lowering the blood pressure is not necessarily going to reduce target organ damage because how you get there is as important as getting there. So diuretics and beta blockers in general—and there's a few exceptions within those classes—are inferior drugs to reduce all the things we're trying to do with cardiovascular outcomes compared to lifestyle, nutritional changes, nutraceuticals, and specific pharmacologic agents, like dihydropyridine calcium blockers, ACE inhibitors, and ARBs.

JB: That was an unbelievable concise and fantastic summary of a huge body of work. Thank you very much. Obviously you've been asked that question before. That was remarkable.

MH: Thank you.

JB: In the close—and, again, we so appreciate you giving us this amount of time on our celebratory 30th anniversary edition—I'd like to use your forecasting and your clairvoyance to look out at the horizon for a moment, knowing that there is some risk for any of us to try to be predictors of the future. From your position, which is a pretty lofty position, where do you see medicine going, say over the next 10 to 20 years?

MH: I think we're on a precipice of a revolution, not only in cardiovascular medicine but in medicine in general. We're one of the best countries in the world if it comes to an acute problem. That's where I want to be if I have a heart attack. But we're one of the worst countries in the world when it comes to prevention. So we're not doing things correctly and it's time that we looked at what we're doing and started to change it. I see us moving into a systems biology approach to medicine, looking at all the interconnections in a functional medicine way, trying to get to the basic reason why people have symptoms, trying to get away from the concept of let's just label somebody with the disease and think we've done a great job. Robert Rountree, MD—I love this—he says, "If you come into my office and you

don’t have all the criteria for multiple sclerosis, I’m not going to give you a jersey for my team so you can’t play ball with me.” The idea is, in traditional medicine, we have an ICD-9 code, we give a diagnosis, and we’re good, we just pop a drug. That’s not the way we’re heading. We’ve got to start looking at the patient in a much more complex systems biology approach with the nutrigenomics, metabolomics, and all of the things you know so well and teach so well before we’re really going to be able to really have an impact on disease management worldwide.

JB: Well, Dr. Houston, as advertised, you are the perfect guest for our 30th anniversary. I think not only did you give the news-to-use down at the level of stuff on the street for clinical outcome improvement, but you’ve given us the vision as to where we are heading in a way that I think is an aspiration that is realizable through continued commitment to the evolution of medicine. It’s really a privilege to share this field with you. When we first met back in 2000 I was immediately impressed, as people are when they meet you. I think your authenticity and your commitment to excellence really is a watchword for where this field is going and how it’s going to pull itself up and be a catalyst for the transformation of medicine as a whole. I want to thank you as a leader, I want to thank you also as a guide, and as a colleague, and as a friend. I think this has been really a wonderful run this last 12 years, and I think the next 10 years are going to be very robust in seeing medicine mature. Thank you so much.

MH: Jeff, I want to thank you for allowing me to be on your 30th anniversary. It’s really an honor to do this for you. As you know, I’ve respected you for years and we’ve become great friends over the years. I always learn so much when we have conversations. It’s like you set off all the neurons in my brain and synapses start flying. When we start talking, we go into a different arena of biochemistry and medical technology. Thanks again for your expertise and all the work you’ve done, and congratulations again on this wonderful achievement of 30 years of FMU.

JB: Thank you, and once again I want to remind the listeners because we’ve spoken fast across a wide platform of different conversations here. For following up in more detail, Dr. Houston’s website is www.hypertensioninstitute.com, and of course, his recent book is a wonderful treasure trove of good news-to-use: What Your Doctor May Not Tell You About Heart Disease. Mark, once again, best to you and I look forward to many more years of collaboration.

MH: I do too, Jeff. Thanks so much.

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