January 2013 Issue | Robert Eckel, MD University of Colorado

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Welcome to *Functional Medicine Update* for January 2013. You know, I love the start of each new year. It's just amazing to think of this continuing opportunity to talk to key opinion leaders around the world as to the future of what medicine will look like as it evolves. As I look back over the last 30-plus years, it's amazing to see the distance we've traveled and to recognize that many of the things that we were talking about 20-plus years ago now seem to be common thoughts, and to be themes that people are saying, "Well, yeah, that's the way it works." I'm not saying that on *Functional Medicine Update* we've achieved 100 percent hit rate in all the things that we've discussed, but I think we've had a pretty good efficiency ratio on the things that we were led to understand through some of these key opinion leaders 30 years ago that over time now, with more and more work and evaluation, have become kind of standards of care, even standards of practice. It's a good record for us and I hope to continue it as we move through the years to come.

Certainly we are very, very excited to have as our *Functional Medicine Update* Clinician of the Month a researcher/clinician that would stand head and shoulders above the crowd as a key opinion leader in the area of vascular medicine, in the area of metabolic medicine, in the area of lipidomics. Someone who really crosses many, many boundaries and would certainly, by all definitions, be considered a translational medicine expert, and that's Dr. Robert Eckel, who has a pedigree that is quite remarkable, and a fluency in topics that relate to what we call personalized lifestyle medicine or functional medicine that puts him in that small reserved group of true global experts.

So with that in mind, let's move to our discussion with Dr. Robert Ecke

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month

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Well, here we are once again at that section of Functional Medicine Update that I look forward to with such great anticipation, and I think you do as well because it becomes the real core of the focus of each of our issues. We're very privileged this month to have a clinician/researcher that I had the pleasure of meeting for the first time personally last summer at the Kern Lipid Conference in Vail, Colorado. Dr. Robert Eckel, who is at the Department of Medicine at the University of Colorado at Denver, is quite a remarkable clinician/researcher. His breadth of expertise is beyond that which we probably can do justice in a short bio. He is obviously an MD. He is the Charles A. Boettcher Endowed Chair in Atherosclerosis, Division of Endocrinology, Metabolism, Diabetes, and Cardiology. He is a professor of physiology in biophysics, program director of the Adult General Clinical Research Center, and is very involved also in preventive cardiology and in developing new approaches towards it. His research experience includes studies in animals and humans, and spans a unique range of perspective on topics from lipidology to metabolic diseases, diabetes, metabolic syndrome, insulin signaling, and more. He is truly a cross-disciplinary (I call it translational medicine) expert, and you are going to hear from him over the next half an hour.

Dr. Eckel, it's really a privilege to introduce you to the Functional Medicine Update audience and thanks so much for being available today.

RE: Great, Jeff. Good working with you. Good meeting you this summer, and I look forward to our conversation this morning to follow.

An Update on the Relationship between Cholesterol and Cardiovascular Disease

JB: Let's start right into it. I think that you have been at the forefront, the leadership, cutting edge, so to speak, of the development of cardiology and its relationship to lipids. Could you tell us a little bit—give us kind of a clinical update—as to where are we on this whole lipid hypothesis, or lipid model, as it relates to coronary heart disease etiology and atherosclerotic etiology. It seems like we've moved beyond cholesterol and LDL, and maybe you can give us some insight as to where we are now in this whole field.

RE: I think it's important to begin with the concept that, for many years the relationship between cholesterol and cardiovascular disease was questioned because there weren't adequate ways to prove the hypothesis by lowering cholesterol , and I think we've gone beyond that stage. However, the database for cholesterol lowering is largely statin-based. We have now a substantial number of randomized clinical trials that show that patients treated with statins who are at high risk, or who have cardiovascular disease, benefit in terms of a reduction in heart attacks, and strokes, and also cardiovascular disease-related mortality. The statin story is pretty clear, and I'll just go down a bit of a tangential path for a second, in that at the University of Colorado, at my lipid clinic almost 50 percent of new patients who I see are referred for statin intolerance. So, despite the fact that statins are out there and have proven beneficial in terms of cholesterol-lowering and heart disease risk, I see the more complicated people who can't tolerate statins, mostly because of muscle symptoms and sometimes liver side effects. But the world is living longer and with a higher quality of life because of this pharmacological development.

Now keep in mind—I think just to be consistent with the program—I feel very strongly about healthy lifestyles and the importance of a healthy lifestyle in preventing cardiovascular disease. We know that diets reduced in saturated fat, particularly trans fat, are beneficial in terms of lowering LDL. We know

that an active lifestyle is probably beneficial because of blood pressure and lipid effects. Overall, healthy lifestyle really contributes to a substantial amount of risk reduction, but then the statin story I think is replete with benefits to high-risk patients.

Now I think when we venture into other lipid arenas, it's a little more confusing. Hypertriglyceridemia is a known risk factor for cardiovascular disease, and that relationship between high triglycerides and cardiovascular disease is apparently more independently related in women than it is in men. I think the reason for that is in men we see a lower level of HDL cholesterol just like we do in women who have high triglycerides, but the HDL cholesterol story is the most important aspect of triglyceride, HDL, and cardiovascular disease. With high triglycerides, the low HDL that accompanies high triglycerides in men appears to be the more important issue, and in women there is much more independence of the hypertriglyceridemia in relationship to the cardiovascular disease.

Unfortunately, Jeff, what we don't know is whether lowering triglycerides independent of lowering LDL cholesterol ensures additional benefit. We have to be careful in making conclusions about trials at this point that are inadequate or show no convincing evidence of benefit. What's really needed is the right kind of triglyceride-lowering trial where the LDL cholesterol is not further modified. Such a trial is actually being conceived right now, and will be potentially funded in the near future to test the effect of a drug when LDL in fact is fixed at a low level. We'll have to await that data to make a strong statement on triglyceride lowering in terms of the benefit for patients who are hypertriglyceridemic. And then finally, the HDL story is really an interesting one in that we know people with low HDL cholesterols have higher risk, and that's epidemiology, and epidemiology then ultimately requires mechanisms to explain that relationship, and I think what we know about HDL is it has a number of properties that look potentially beneficial, including what we call reverse cholesterol transport—in other words, downloading the macrophage that has a lot of cholesterol in it and taking it back to the liver for disposition. But HDL is also an antioxidant, it probably improves vascular reactivity. In other words, it makes the blood vessels healthier, and has anti-platelet effects. So HDL in many ways is a benefactor in terms of lipoprotein metabolism. But just like triglycerides, despite these plethoric properties of HDL—and I didn't mention anti-oxidative metabolism, anti-inflammation—we just don't have the clinical trial evidence showing that HDL-raising therapy is capable of modifying risk. Now, there's a whole new line of drugs in studies right now called the cholesterol ester transfer protein inhibitors that ultimately raise HDL substantially. We're talking sometimes about a two- to three-fold elevation in HDL. But the problem with this class of drugs right now is that they also lower LDL a lot. Now, that's not a problem for the patient if these drugs work, but it is a problem for data interpretation. Is this the HDL-raising effect of this and that property of these drugs, or in fact is it mostly the LDL-lowering effect? To summarize, Jeff, I think the story for LDL and statins is there. For other therapies and LDL, it's not quite as convincing at this point, with the inadequate trial evidence to say whether ezetimibe or Welchol or other agents we use to lower LDL are additionally beneficial. And for triglycerides and HDL cholesterol, while the relationships have been indicated epidemiologically, the benefit of therapy at this point remains uncertain. We'll leave it at that right now, and we can talk a little bit more about lipoprotein a if you want, but that's something that clearly is not evidence based, but we know it's a risk factor, and we don't know what to do about it when levels are elevated.

Statins: The Controversy between Primary and Secondary Prevention

JB: I'd like to go back and just re-explore with you this concept of statins and cardiac disease prevention.

I know there has been quite a bit of controversy back and forth as it relates to primary prevention with the statins, where there is obviously very clear benefit in the secondary prevention, but it appears to be perhaps more ambiguous with regard to primary care, particularly in women. What's the status of that discussion these days?

RE: Well, I should just reveal that I'm part of the ATP4 panel, which is currently updating our cholesterol guidelines, and that report is still not available for public report. Although it should be fairly soon, it is difficult to really make strong statements about what's going to be included in that report. But I think the evidence for primary prevention really requires patients to be at moderate or higher risk, and in that setting ultimately I think the benefit of statins is reasonably well documented. The male-female comparison, I can share minimally about that; clearly, women of younger age are less likely to show benefit than men of younger age who are at higher risk. I think honestly, Jeff, this is kind of a mistake of the Framingham 10-year risk predictor. Now, the Framingham database is a reliable database to make predictions for cardiovascular disease risk. But the problem when it is used in a 48-year-old woman or a 53-year-old woman, is that the 10-year risk is still relatively low compared to men, and so when we're looking at a 10-year risk we don't really have the database to suggest that primary prevention in women is convincingly beneficial in terms of reducing cardiovascular disease events or death from cardiovascular disease. Now as women get older, I think when we're looking at 65-to-70-year-old women where heart disease now is the major primary cause of death, then those equations may be much more predictable in identifying women who may equally be benefitted in primary prevention settings as men. I think a closing comment on this inquiry, Jeff, is the fact that if we look at coronary calcium scores, meaning looking at the coronary arteries by CT and look at the presence of calcium in the coronary arteries, when men and women get older, many people have calcium, so they do have some atherosclerotic risk. And so when we define primary prevention, we're looking at people with no symptoms or no history of events that relate to the cardiovascular system, whereas if we were going to do coronary calcium scores on everybody—which I'm not recommending—then I think we're in a position of identifying people who already have disease who don't know they have disease, and that's a somewhat different question, and at this point in time, an unclear approach clinically.

Extended Risk Factors for Cardiovascular Disease

JB: That's very helpful. Thank you. You've touched upon another area that I know has a lot of interesting controversy back and forth relating to these extended cardiovascular risk factors, things like high-sensitivity CRP (the Paul Ridker model) and how that relates to the JUPITER trial. Where are we on some of these discussions of extended risk factors, particularly maybe the high-sensitivity CRP inflammatory models?

RE: I think that Paul, in addition to other risk factors that have been examined, has nicely identified high-sensitivity CRP as a cardiovascular disease risk factor. But the consistency of that observation, though, unfortunately is not there and it's not really clear at this point in time who should have measurements of high sensitivity CRP. What's recommended in ATP3 is that people who have a 10-to-20 percent risk of an event over the next 10 years are in a position to have some of these other emerging risk factors identified and used to determine whether a decision for therapy should be seriously considered. So in settings like that, the CRP can be informative. We certainly know from Paul's JUPITER trial, which is a very, very important trial and really well-powered for outcomes in that for people who have higher CRPs, ultimately lowering their LDL cholesterol and the hs-CRP with statins was effective in reducing risk

substantially, and it was a primary prevention trial.[1] So if we're going think hs-CRP may have its importance in terms of identifying risk, it perhaps is in the patient who is a primary prevention-type patient rather than someone with existing heart disease. And an interesting point in the JUPITER trial is the fact that the benefit of lowering CRP and LDL cholesterol occurred in many people whose LDL cholesterols were quite low. So, that's an interesting open door to a trial that is very much needed, and that would be the use of an anti-inflammatory agent that modifies hs-CRP, but does not modify LDL cholesterol, and that would presumably be in people who were on statins and at high risk. Those trials, I think, are going to be started. Paul informed us last week in Boston at the Cardiometabolic Health Congress that NHLBI, the National Heart Lung Blood Institute, is instituting a trial using methotrexate. Most of us know that methotrexate has been used for a number of years now in the treatment of rheumatoid diseases, specifically rheumatoid arthritis, but also in other connective tissue diseases. Methotrexate has very few side effects when given chronically at lower dose, so that would be a trial to look at how lowering c-reactive protein without changing lipids might modify risk. And there is a company that makes an anti-IL1-beta antibody, and that is a second trial that Paul will be overseeing in terms of the benefit of an anti-inflammatory monoclonal antibody to modify inflammation in a way that could modify risk, again without changing LDL cholesterol. The hs-CRP story is an interesting one. I think the evidence for modifying CRP independently from modifying LDL cholesterol is an important task for the near future.

JB: Thank you, and I guess one other quick insight on another extended biomarker that's been discussed with some controversy that you might comment on is homocysteine. We interviewed Kilmer McCully years ago on Functional Medicine Update concerning his thoughts about homocysteine. Where does that stand these days?

RE: Homocysteine identifies patients at higher risk. I think it's well accepted epidemiologically that homocysteine is a potential prothrombotic biomarker that is related to events, but ultimately the data we have at this point in time are somewhat disappointing in that there are many B-containing vitamins, which we know can modify homocysteine levels in a favorable direction. In other words, they reduce the levels modestly to moderately. But the outcomes there have not been, actually experienced. Lowering homocysteine alone as a biomarker for cardiovascular disease has not proven to be beneficial, at least by using B vitamins. That story remains an incomplete one in terms of why homocysteine puts people at risk and therefore, lowering it does not improve that risk, so we have more work to do here, Jeff.

Insulin, the Metabolic Syndrome, and Cardiometabolic Disease

JB: So that leads us into another area where you have done quite a bit of work and published extensively, which is the connection between insulin and cardiometabolic disease, and CVD etiology. Can you give us an update as to where this discussion is emerging?

RE: Well, I think that takes us into the avenue of metabolic syndrome-related biology. What is metabolic syndrome? We often call it the elephant in the room because we kind of know metabolic syndrome in terms of what it represents and that's insulin resistance, but yet, the criteria are at best modestly supported scientifically. Ultimately, metabolic syndrome can be like feeling the elephant, depending on what part you want to feel. As we all know, it requires 3 out of 5 components. Two of them are lipids, one of them is fasting glucose, another one is blood pressure, and the final one is waist circumference. We know people who have big waists tend to have altered lipids and have altered glucose metabolism and

altered blood pressure, and that all is at least a consequence—at least most of those components—are a consequence of insulin resistance. The idea of insulin, itself, being an atherosclerotic biomarker is really validated by some studies, but not validated by others. And I think it is important for the clinician to understand, as well as the patient, that measuring insulin in the clinic is not a recommended test. Insulin levels are used in research studies to examine various aspects of insulin-related biology, but in the clinic, insulin assays are not very reliable; they are not standardized. And ultimately, the clinician is in a position to be making decisions really on other biomarkers that we have much more information about than we do about insulin. Now, an important part of this relates to the fact that in obesity, fasting insulin levels are elevated. But many people with obesity do not have substantial cardiovascular disease risk. About 80 to 90 percent of obese patients do have at least one other of the components of metabolic syndrome, but there are a few that have none, and so fasting insulin would be elevated, but not necessarily related to any other biomarkers that reflect systemic insulin resistance. And then, is Type 2 diabetes involved, where we now have fasting insulin that remains elevated. Insulin secretion, after a glucose stimulus, is not adequate. So, these people have an inability to secrete enough insulin, despite the fact that their fasting insulins are elevated. Again, I just want to caution our practicing community about not using fasting insulin as an assessment of cardiovascular disease risk or even insulin resistance. It's a poor biomarker for making strong statements. Now, the idea that insulin may be a contributing factor to atherosclerosis comes from science that relates to insulin as a mitogen. In other words, insulin can stimulate cell proliferation, and can stimulate pathways that activate many of the kinases that relate to cell growth and differentiation. That's the mitogenic effect of insulin, which is to be distinguished from the metabolic effects of insulin, which really confer effects on protein, carbohydrate, and lipid metabolism. Insulin resistance, as we describe it, as metabolic syndrome and beyond, is clinically a metabolic resistance to insulin action, not a resistance to the mitogenic effects of insulin. So, this remains a scientific dilemma that hasn't reached clinical space, and, again, insulin levels themselves are not adequately informative to make decisions. However, in the setting of metabolic syndrome, we know that effective lifestyle modifications, such as weight loss and physical activity, modify at least some of the components of metabolic syndrome and presumably work independently to modify cardiovascular disease risk.

JB: So, some individuals…in fact, there are a number of studies that have been published that looked to postprandial glucose and insulin as a better surrogate biomarker after an oral glucose tolerance test. Is that at all a stronger predictor as it relates to cardiovascular risk, when you get exigencies to our postprandial insulin and glucose?

RE: Well, Jeff, you continue to ask very challenging and difficult questions. There is a lot of debate right now whether the postprandial excursion is an independent marker from fasting glucose in terms of cardiovascular disease risk. There are studies that have been contrived and are actually implemented to try to address that issue, mostly in patients with diabetes, not in those who have impaired fasting glucose or impaired glucose tolerance. In general, the issue falls down to a very simple kind of inquiry. For any given level of hemoglobin A1c, which of course is the average blood sugar for three months, if you have an A1c of 6.5, which is right at the cut point for the diagnosis of diabetes, if you have 6.5 with basically limited variability of glucose throughout the day, versus a 6.5 which is a wide swing of glucoses post-prandially and then back to baseline, is that A1c conferring the same risk for cardiovascular disease? This is an unanswered question. In general, I think most diabetologists and people who work in the intervening Venn diagram space of diabetology and cardiovascular disease would say more glycemic excursion confers additional risk, but that has not been proven. But yet, for any given level of A1c, our goal currently is to maintain the A1c under 7 percent, which is the position of the American Diabetes

Association, the International Diabetes Federation, and also the European Association for the Study of Diabetes. Excursion is relevant, but excursion in its own right at this point is not a therapeutic decision-making variable.

The Look AHEAD Trial: Why Did the NIH Discontinue This Clinical Trial on Lifestyle Intervention in Type 2 Diabetes?

JB: Good. Thank you. You've touched, also, on this concept of lifestyle intervention, and it strikes me that we just saw the NIH suggest discontinuance of a very large clinical trial called the Look AHEAD trial that was a trial on lifestyle intervention in Type 2 diabetes to see what effect it would have—hopefully a positive effect—on reducing the incidence of cardiovascular disease. They called the trial after, I think, in its third year, now, in that they did not find any evidence of reduction in CHD risk in what they considered an aggressive lifestyle intervention.[2] Are you at all concerned about that? Are there things that we should know about that as it relates to why they didn't find this connection?

RE: Yes, Jeff, great question again. The Look AHEAD trial was designed in patients with Type 2 diabetes to look at whether weight reduction itself conferred a benefit in terms of the reduction of cardiovascular disease events and related mortality. The trial was successful in having patients lose weight. During the first year of the trial, they lost 7 to 8 percent of their body weight, and there was some recidivism. By year four of the trial, ultimately the body weight came back to about half as much weight reduction. And the control group lost a minimal amount of weight, but not very much, and there was still a highly significant difference in weight loss in the patients in the intervention versus the control group. However, if you look at risk factors for cardiovascular disease, the major one, I think, which is evidence based, was the LDL cholesterol level, and weight loss did not reduce the LDL cholesterol level any differently between the two groups. In fact, it didn't really reduce it at all. So, we know that LDL relates most to dietary composition, not so much to calories. And I think it is important to point out, Jeff, that when people are actively losing weight, their LDL falls. But after they lose the weight, unless their dietary composition has changed, they really have an LDL that comes back to baseline. Now, why didn't LooK AHEAD prove successful? I think there are a couple of reasons. These are patients with Type 2 diabetes who were deemed to have high risk for cardiovascular disease not only because they have diabetes, but because they've had diabetes for awhile. So we have a group of patients who have, if you will, more prolonged disease, and we know diabetes duration itself is a risk factor for cardiovascular disease events. Secondly, and very importantly, there is a lot of management of cardiovascular disease risk both in patients with diabetes and in those at high risk without diabetes nowadays, so that ultimately some of the benefit of weight loss may have been trumped by the fact that blood pressure was very aggressively managed and also lipids were aggressively managed. And the fact that in the control group, maybe there was more statin usage; that may have been another issue that could have conferred the benefit. Keep in mind we've not seen the final report yet. We've just been told that the trial has been stopped because of lack of benefit. And, you know, because we're reducing cardiovascular disease events substantially by other risk factor modification, I think clinical trials nowadays are very difficult to contrive that are going to have more minimal or modest effects on risk, including weight reduction. Now, to redesign such a trial I think it would be great to take patients with Type 2 diabetes who were just diagnosed and then undergo a more intensive lifestyle modification to see whether we can delay new drug treatment of Type 2 diabetes and then perhaps affect cardiovascular disease outcome. I guess I think today we're working in a space, Jeff, where aggressive management of blood pressure, lipids, in addition to glucose, is part of the clinician's mandate, and he or she is really aggressively dealing with these other

risk factors, and weight loss itself may not be so beneficial. In closing, to answer this question, Jeff, I would say that weight reduction in the impaired fasting glucose patient, or patients with impaired glucose, has really proven effective in reducing diabetes onset, which thereupon could ultimately generate some enthusiasm for reducing downstream cardiovascular disease events.

Mitochondrial Biogenesis and Cardiometabolic Disease

JB: By the way, that was a brilliant explanation. Thank you. And I think for those who have heard some of the other reports, it's going to be very helpful for them to have listened to you to kind of give a…at least on-target discussion if they are questioned about that particular study. You hit a certain concept, to me, as I'm listening to you—and I'm going back to some of your other work, as I mentioned in the introduction, the breadth of your work is quite expansive—and you've published some papers on mitochondrial biogenesis and its relationship to insulin resistance and how that tracks with Type 2 diabetes and possibly cardiometabolic disease. I'm wondering could it be possible that these approaches like Look AHEAD may have had favorable transient effects, but didn't affect some of the central cellular pathology, like effects on mitochondrial biogenesis and how that relates to oxidative phosphorylation and preservation of beta-cell function and all those things that occur with intact mitochondrial activity. Is there something here that we should be looking at, do you think?

RE: We know that mitochondrial biology is incredibly important not only for insulin action in insulin-sensitive tissues, not just muscle, adipose tissue, and liver, but critically important for glucose stimulated insulin secretion by the beta cell. I think there is no question that there is a defect in short term glucose sensing in the beta cell , but we still don't understand in detail what that defect is in glucose sensing in the beta cell; whether it is in transport, glucose metabolism, or in fact whether it relates to myocardial dysfunction. There is quite a bit of evidence that oxidative stress and ER stress is really an important mediator of the glucose-dependent defect in insulin secretion in the beta cell in Type 2 diabetes. But there is no question that in the study of weight reduction and insulin action, during active weight reduction, and ultimately immediately after weight reduction, insulin sensitivity can be improved. Long-term, that's preserved if the weight loss is maintained, but keep in mind, Look AHEAD, Jeff, was a study in which there was initially about 7 percent weight loss, but ultimately the recidivism was to 3 to 4 percent weight loss at 4 years, and I think it's difficult to have people lose weight and keep it off long term. Therefore, the benefit on insulin sensitivity is going to be probably less clearly modified favorably after the weight regain has ensued. Back to basic cellular mechanisms, I think clearly they are implicated in defects in both insulin action and insulin secretion.

JB: Yes. It just strikes me that coupling together this emerging…this cellular pathology with that of the clinical outcome in these types of studies might be very helpful to try to understand short-term transient effects versus long-term maintenance effects on bioenergetics. If this is a central mechanism, it seems like it would be really desirable to try to connect them together from the clinical side with the biochemical side. It just seems like something was missing there.

RE: Well, that's the one thing that's really fun about science as a physician. We tend to think of translational research as going from bench to bedside, and bedside to population, and ultimately then to public policy. But it's fun to think about translational research as an arrow going from right to left where observations made in epidemiological settings then give rise to mechanistic studies in humans and then back to the preclinical animal cellular/molecular level, and that's what makes science so much fun is that

every question that's addressed here deserves three more new weeks to follow, ultimately drilling down on basic mechanisms. And if we look at disease modification and cures, it comes from understanding basic mechanisms and mitochondrial biogenesis, and function really is part of that paradigm.

Adipose Tissue Physiology and Coronary Heart Disease

JB: I'd like to close with two last questions. Another area that you have been very actively involved in is this whole changing view of the what used to be considered the lowly adipose cell—the adipocyte—which we thought was just this energy storage cell that was metabolically inactive and just kind of sat there just collecting extra calories in the form of triglyceride accumulation, but now we recognize it's a pretty active part of the endocrine system through adipocytokine stimulation. Could you tell us a little bit about how you see adipose tissue physiology interrelating with the etiology of coronary heart disease?

RE: Very timely topic, Jeff. I mean, the biology of adipose tissue has really matured substantially over the last decade, and I think this began with identification at Rockefeller and Columbia that ultimately the adipose tissue contained bone marrow-derived monocytes that then could be differentiated into macrophages. I think what's occurred now is the concept of proinflammatory cytokines or adipokines being produced in adipose tissue having local effects, and some of those local effects are on insulin action itself in terms of blocking insulin sensitivity in adipose tissue and that gives rise certainly not only to defects in insulin-mediated glucose transport and metabolism, but also to increases in mycolysis. In other words, if you produce a lot of IL-1 beta or IL-6 or TNF-alpha in the adipose tissue, that drives lipolysis, which is a breakdown of adipose triglyceride stores. Those free fatty acids are released and they are systemic and cause insulin resistance in other organs such as liver and muscle. Not only that, but the released cytokines from adipose tissue sometimes do reach systemic circulation and can be measured as excessive in circulating plasma. In fact, back to an earlier discussion, the hs-CRP we see elevated in patients with insulin resistance is often derived in part from this defect in adipose tissue of an overproduction of adipose tissue proinflammatory cytokines. Jeff, where the debate is really at right now in this area of biology and potentially pathophysiology is that maybe the macrophage in adipose tissue is there to do a clean-up job, too. Adipocytes, we know, don't do turnover with time. The old thought that you're born with a certain number of adipocytes and those are maintained for the rest of your life is not true; that was a fallacy and that's been put to rest. So the idea that fat cells do turn over and ultimately apoptose and die, the macrophage may be there favorably to do a clean-up role. So there is some debate now in terms of what types of monocyte-derived macrophages are there. Are they there to be helpers, to scavenge dead adipocytes, or are they there just to be injurious and cause harm? I think there's another view, too, that perhaps ultimately, the induction of adipocytokines in insulin resistance and adipose tissue may be a way ultimately to have body weight not increase further, because if you're breaking down fat in the adipose tissue maybe you're going to prevent further weight gain; while I think that's more of an obtuse view, it still is brought into consideration.

JB: Yes, and I think it's very interesting, isn't it, as we look at Spiegelman's recent work, and others that have been looking at these base cells that sit within central fat and subcutaneous fat, that have thermogenic potential that we used to think were just kind of non-thermogenically active that can be modulated by things like exercise and maybe other lifestyle and dietary factors, that can alter then the kind of bioenergetics balance in subtle ways that might contribute to weight regulation that may be, in terms of the lifestyles that people have right now, blunting kind of the base cell conversion into these thermogenically active cells.[3] So it seems like there is a whole revolution that's occurring in fat cell

physiology right now.

RE: Yes, I think what Bruce has done in addition to other investigators, including the Stockholm Group in particular, has identified the fact that the beige cell is of a different lineage than, brown fact per se, and Bruce's work in the animal, and I think there is some evidence to support this in humans now, that brown fat itself is minimally present in adult humans. Using a series of techniques we can now pick it up using PET scanning, and the brown fat is probably of a different lineage actually it's of a skeletal muscle lineage. I think this concept over the fact that brown fat may ultimately be a way to modify body weight either by preventing obesity or treating it is maybe fraught with a bit of a problem in terms of how much energy expenditure can you really expect from the beiging of light fat? In other words, the percentage of brown fat cells within the white fat depot is typically fairly minimal to moderate, and can there be enough additional energy expenditure through that depot to really confer reductions in body weight and ultimately improved insulin action That's a really major task before us, to understand that better.

JB: Let me close—thank you, this has just been an incredibly information-dense discussion, as I would have expected from you, Bob, so thank you—but the last question is, what do you see as the trajectory of where we are going in terms of the accumulation of knowledge in this whole area pushing us towards an individualized or personalized type of lifestyle medicine intervention? I know we have had, from Framingham, a lot of public health guidance through generalized risk factors, but it is sounding more and more to me as I listen to you and also watch the evolution of the literature, that we're moving towards the era of more individualized or personalized intervention. What's your read on this possibility?

RE: I think it's a fascinating topic and I think it's in its infancy right now, Jeff. We know that certain drug adverse effects may be predicted by certain gene sequences and pathways that relate to that ligand and how it's metabolized. A most recent example of this that I find interesting is the Harvard School of Public Health Study, in both nurses and physicians, that was published in the New England Journal last week. In this study, the sequences of certain genes related to obesity predicted how children and adults would respond…actually I guess this was the adults only study (there was another study on children in the same issue)…would predict how nurses and physicians would respond to the intake of sugar-containing beverages.[4] Let's just think where we will be 20 years from now, perhaps we'll get DNA testing in our children to see if there is an obesity risk, a prevalence of genes that had modified sequences that would predict excess weight gain, and maybe we should selectively restrict sugar-containing beverages in those children and not so much in others. I think my position would be that we probably need to restrict sugar-containing beverages more in all children, but all that aside, I think we're really at the edge of now making individualized medicine or tailored medicine very possible, knowing the interaction between genes, gene modification, and response to environmental factors.

JB: Well, Dr. Eckel I want to both personally thank you on behalf of all of our listeners and those out there that are benefitting from your extraordinary work and that and your colleagues. This is really ground-breaking work and I consider it integrative translational research that takes, as you said, from bench to bedside, some very, very important concepts that are going to deliver improved health outcomes for many people. And the way you describe it is so lucid and so easily understood. It's a real skill that you have. Thank you so, so much for sharing this with us. I hope this information has some stickiness as our listeners take it in and are counseling their own patients. Thank you and keep up the great work and we hope to keep close tabs on what you are up to.

RE: Great, Jeff. Good talking to you today and I hope what we have talked about here today is beneficial to all. Thanks very much for inquiring and it's been fun being with you

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