

March 2008 Issue | Valori Treloar, MD Integrative Dermatology

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Welcome to *Functional Medicine Update* for March 2008. I have a real treat in store for you this month in that we are going to have the opportunity to speak about the dermatological implications of functional medicine with an expert functional medicine practitioner, Dr. Valori Treloar, who is a board-certified dermatologist and a functional medicine practitioner. Dr. Treloar will talk about the relationships of functional matrix-related assessment for dermatological conditions. I think you are going to find this fascinating because we know the skin is important in an overall assessment of physiological health status. Certainly in nutrition we learn, early on, how to use the skin for assessing certain things: petechia formation with hemorrhagic problems, chilosis (looking at the nose as an indication for B vitamin sufficiency), or looking at skin lesions that have to do with dermatitis (such as gluten sensitivity). The skin is a valuable tool for doing kind of a systemic run-through of factors of the immune system and nutritional status. You are going to hear much more about that as this evolves beautifully with Dr. Treloar and her concepts.

Before we get to the interview, however, let me talk once again about how signals are established in the body that ultimately weave themselves into physiologic function. I think we recognize that we often use, in medicine, surrogate markers for evaluating what we consider the flame or the fire that is going on at the physiologic level. We look at the smoke (which is my analogy for the surrogate markers), and define what the flame looks like (i.e. the pathology). There are many, many different markers that we use in medicine for evaluation to at least gain some insight into what is going on. Some of these markers, such as lipid functions and lipid analyses, become early-warning assessment tools for cardiovascular disease risk and other functional problems related to alterations in the web of physiology.

Let me focus on lipoproteins for now. The understanding of lipoproteins has been a major breakthrough in functional cardiology, and it now turns out that it relates to many other endocrine, inflammatory, and immunological factors. Other than just being owned by cardiology, itself, we now see lipoproteins as surrogate markers for many different distortions in physiologic function.

Let's talk about the HDL/LDL/VLDL/IDL-type of nomenclature, which has to do with density of various lipoproteins. When they were first identified by ultracentrifugation, you could see various bands that were related to certain densities of material. We know that fats don't dissolve in blood well because fats and water don't dissolve. Fats have to be transported in the body by detergent-like molecules that we call apolipoproteins, and these apolipoproteins have names like A, B, C, D, and E. These apolipoproteins are synthesized in the liver, generally, by signals that occur from outside the body and inside the body that stimulate upregulation of the genes that express the formation of these proteins (or at least the messenger

RNA that later become these proteins, which then encode the names of apo A, B, C, D, and E). There are subcategories under each one of those big families of apolipoproteins.

Each one of those apolipoproteins, when synthesized in the liver, transports different lipids. This could be different distributions of long-chain, medium-chain, and short-chain fatty acids, triglyceride remnants, or particles and other fat soluble molecules. These are all bound together in lipoprotein particles that have different densities, therefore they are given names such as IDL, HDL, or VLDL.

Over the years, what we have found is that certain of these particles are associated with increasing risk to disease, and others appear to be associated with decreasing risk to disease. These associations are why the "good cholesterol/bad cholesterol" nomenclature emerged. LDL is the low-density lipoprotein associated with particles that appear to have greater atherogenicity (or at least be associated with the atherogenic process). Those lipoproteins associated with HDL appear to be antiatherogenic and are involved with cholesterol efflux (meaning cholesterol moving out of the artery wall).

We had a wonderful discussion of the different associations in a past *Functional Medicine Update* clinician/researcher of the month interview with Dr. Roger Newton. Dr. Newton told us a great deal about the HDL particle. We have started to see an increasing focus on HDL lipoproteins and their association with a reduction of cardiovascular risk. These particles (be it HDL, LDL, or VDL) don't just occur spontaneously in the blood. They are synthesized in the liver as a result of signals that can be endocrine-, immune-, or inflammatory-related. These particles reflect a state of function of the whole body.

Changes in Physiological Function Can Lead to Changes in Lipoproteins

As a person's state of physiological function changes, their lipoproteins can change. With women who undergo the menopause, it is a rule of reasonableness that often their blood lipids change (their cholesterol goes up). This change in cholesterol is not because a woman started eating a higher cholesterol and fat diet, but because the synthesis of her apolipoproteins changed upon reduction of ovarian estrogen secretion and altered androgen/estrogen levels, which then triggers the liver to manufacture different apolipoproteins and transports lipids like cholesterol in different ways out of the liver into the systemic circulation.

To put a woman solely on a fat-restricted diet will not be effective. To modify her atherogenic dyslipidemia, it is necessary to regulate the signals that associate themselves with the proper construction of these transport molecules, as well as cholesterol biosynthesis and triglyceride biosynthesis. This is an issue that is much more complex than just fat restriction; we are talking about endocrine-related signaling that regulates the production of these lipoproteins that take fats out of the liver into the blood.

We know that stress hormones also affect the production of apolipoproteins. You often see people under stress have differing lipoprotein levels in their blood and different serum lipids. You can have a person who has experienced a high immediate stress and his or her triglycerides might go up even though a high-fat meal was not eaten. My recollection is that this was shown in a study in the early 70s with Le Mans race car drivers. As I recall, during the course of the 24-hour race, the drivers' serum triglyceride levels went up even though they weren't eating and it took several weeks after the race for them to come back down into normal range because they were actually under stress hormone modulation, producing different transport molecules to bring lipids out of the liver into the blood. You might say, why does the body do

that? There could be some evolutionary benefit (to try to feed cells with energy in response to stress). In this case, the energy is the lipid--these fat molecules like triglycerides that can, in fact, be used as a source of metabolic fuel.

When we are examining these markers in the blood that we call lipoproteins, we are examining very complex factors related to an endocrine, immune, and/or inflammatory, environmental response. Even xenobiotic exposures can alter serum lipid levels and can induce hepatic changes in lipid biosynthesis. With regard to the HDL particle, an understanding of the metabolism and biological actions of HDL is really starting to emerge very beautifully. Roger Newton published a wonderful paper in *Atherosclerosis Supplements* back in 2002 related to HDL therapy for acute treatment of atherosclerosis and the understanding of the metabolism and biological actions of HDL that I think helped point us in the right direction as to how important this lipoprotein is in signaling antioxidation and proper lipid transport.¹

HDL is the Most Sophisticated Lipoprotein Particle

From the work of Jay Heinecke and his colleagues at the University of Washington School of Medicine, we know that the HDL particle is the most sophisticated of the lipoprotein particles in that it contains some 42 different proteins, and these proteins are involved with lipid metabolism.^{2,3} Some of these proteins are protein ACE inhibitors, some are acute-phase response proteins, and others have complement regulation. They all, then, have a functional component.

HDL is more than just a particle that transports fat and helps keep cholesterol and triglycerides from building up in the artery wall. It has a very dramatic influence on signaling processes by docking to receptor sites for the HDL on the surface of cells and signaling through the composition of these protein-specific types of activity. Within the HDL lipoprotein you have apo E, for instance. You can have apo E-2, 3, or 4, and we know that depending upon the genetics of the apo E configuration you might have differing relative risk. Apo E-4 double alleles we associate with increasing risk to cardiovascular disease and Alzheimer's dementia, whereas apo-2,3 variations are lower risk categories. People who have the conferred benefit a double apo E-2 haplotype are those who seem to have longevity genes. This is because the apo E has an effect on cellular antioxidation, so an HDL particle is actually seen as an antioxidant particle in some instances. It also has enzymes like myeloperoxidase within the composition of the HDL particle and that has its effects, then, on serving as part of the body's immune defense system and part of the redox pathway of the body.

What I am trying to get you to understand is that these lipoproteins are more than just transport for fat. They have functional characteristics that are regulating--at peripheral cellular sites--many different functions that influence gene expression patterns in those cells. And based on the composition of the apolipoproteins (which is, in fact, related to the stimulation of gene expression for their synthesis through the endocrine, nervous, and immune systems), you can alter not just the transport of fat from the liver to the blood, but also the effect that those apolipoproteins have on peripheral cellular sites serving as functional characteristics.

This is a genes-and-environment situation. If you are conferred with the genetic luck of the draw and you get the Milano protein apo A-1 configuration, you have a very low HDL, but you have a very low incidence of cardiovascular disease because these Milano A protein mutations confer a reduced risk of oxidative injury and inflammatory-induced atherogenesis. Apo A-1 is part of the HDL particle that helps to pull lipids out of the artery wall, so you want your apo A-1 levels to be high, and you want your

apolipoprotein B levels to be low because apolipoprotein B is the principle apolipoprotein associated with LDL atherogenic particles and the delivery of fat into the artery wall (cholesterol and triglyceride). You want your apo B to be low and your A-1 high, which leads us to recognize that the apo B-to-A-1 ratio is a very important risk factor determinant for atherogenicity and cardiometabolic syndrome. You can have the laboratory measure apo B to A-1. If that number-that quotient-is greater than 0.6 to 1 when apo B is divided by A-1 levels, then it is associated with increasing relative risk. When you get up to 0.8, relative risk to cardiovascular disease is almost double. You want your apo B to A-1 ratio to be below 0.6 to 1. Diet and lifestyle intervention plays a very big role in lowering the apo B to A-1 ratio. In fact, Dr. Katherine Esposito, in a recent issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, describes her work on optimal treatments for metabolic syndrome and cardiometabolic syndrome and she points out that the Mediterranean Diet has a very desirable influence on altering the apo B to A-1 ratio (lowering the apo B to A-1 ratio).⁴ It also increases the activity of paraoxonase (PON1, as it is abbreviated), which is an antioxidant enzyme within the HDL particle. Through intervention with Mediterranean Diet, you get increased antioxidant activity, which lowers the apo B and increases the apo A-1 component, and you get reduction of myeloperoxidase-induced oxidation, another positive benefit.

What is my takeaway? My takeaway is that diet (as altered cellular signaling) has a much more profound influence than just delivering lipid, protein, or carbohydrate. In a complex diet like the Mediterranean Diet that is rich in fruits, nuts, berries, and vegetables that have differing phytochemical compositions that influence gene expression, the information molecules influence intercellular signal transduction in such a way as to induce or encourage proper lipoprotein composition to transport the right fats to the right place, and also serve functionally as antioxidants and cellular restorative agents.

I hope this gives you a different perspective about the physiologic function of apolipoproteins than that which you might have had in the past (where you just thought of them as lipid transport agents). The apolipoproteins have become important markers and managers of cardiovascular risk. This was actually described in a *Quarterly Journal of Medicine* paper back in 2006.⁵

The ratio of apolipoprotein B to apolipoprotein A-1 has become not only an important risk factor for cardiometabolic syndrome, but also an important therapeutic target for how diet, lifestyle, and exercise can improve outcome in patients who have dyslipidemia. I am now quoting from the *Journal of Internal Medicine* 2006.⁶ In metabolic syndrome, the ratio of apolipoprotein B to apolipoprotein A-1 becomes a very important risk factor identifier for cardiometabolic risk. This is some wonderful work by Dr. Walldius and his colleagues in which this ratio of less than 0.6 to 1 of apo B to A-1 is a desirable target for intervention and can be used for following the success of therapy as we try to lower apo B and increase apo A-1 as indicators of cardiometabolic risk associated with intervention.⁷ This is one kind of surrogate marker/risk factor/analyte that you can use when you are establishing your intervention program and you want to follow it in the patient to determine how they are proceeding..

What other analyte has emerged to be very valuable for assessing relative risk of cardiometabolic syndrome and insulin dysregulation? The one that I have seen with increasing frequency in publications in top-flight journals is lipoprotein-associated phospholipase A2 (sometimes this is called the PLAC test). This is a measurement (indirectly) of atherogenic inflammatory lesions. I am now quoting from a paper in *Circulation* from 2005 looking at the Rotterdam Heart Study and examining the value of measuring lipoprotein-associated phospholipase A2 activity and finding that it was very strongly associated with risk of coronary heart disease and ischemic stroke.⁸ The study clearly demonstrated that elevated levels of Lp-

PLA2 activity was an independent predictor of coronary heart disease and ischemic stroke in the general population, and might be a very good extended risk factor for vascular disease, particularly for those individuals with inflammatory underlying etiology because it is measuring inflammatory markers associated with arterial plaque.

This is just one of many papers that have identified PLA2 as being a very important independent risk factor. Another paper that you might be familiar with comes from the West Scotland Coronary Prevention Study Group work published in the *New England Journal of Medicine*.⁹ This group found that lipoprotein-associated phospholipase A2 was an independent predictor of coronary heart disease beyond that of just cholesterol HDL or LDL itself, again because it provides a strong risk factor assessment for inflammatory arterial endothelial dysfunction.

Comparison to hs-CRP

How does this compare to hs-CRP, the Dr. Robert Ridker-extended risk factor for inflammatory connections to atherosclerosis? I think the PLAC test, or the PLA2 test, along with the apo B to A-1 ratio, the atherogenic particle number, and hs-CRP frames a new, extended panel for cardiovascular risk factors that evaluates cholesterol dynamics, lipoprotein physiology, and inflammation simultaneously and can give us a much better trajectory towards cardiovascular function that is modified by hyperinsulinemia. I would say that the lipoprotein-associated phospholipase A2 should be added together with hs-CRP, and the apo B to apo A-1 ratio analysis. I think we can say-in fact, I am actually quoting from a paper in the *Journal of Endocrinology and Metabolism*-that lipoprotein lipase A2 has benefits beyond that of the other traditional risk factors for picking up people who have this underlying inflammatory component.¹⁰

I am often asked a question: How do you evaluate, more specifically, inflammatory potential associated with atherogenic risk and ischemic stroke risk? I would suggest the lipoprotein phospholipase A2 in plasma as a useful tool for evaluating high risk. More and more papers are being published on this important area. A paper in a 2006 issue of the *Arteriosclerosis, Thrombosis, and Vascular Biology* journal again showed that this marker predicts future cardiovascular risk in patients.¹¹ I think we can say that we are witnessing the emergence of a profound new extended risk factor that allows better assessment of vascular inflammatory potential.

How does this all translate clinically? What we are really saying is that when we analyze a patient's plasma or serum for various analytes, and we look at markers such as cholesterol (LDL cholesterol, HDL cholesterol, or triglycerides), that we are really measuring a functional status of how those lipids are being transported around the body--out of various sites where they are biosynthesized, to delivery into other cells at a distance (or tissues at a distance like the artery wall)--and that this transport occurs on the backbone of molecules that have the personality and responsibility for making fat soluble in the blood, which is water, and are called apolipoproteins. This synthesis of the various apolipoproteins (these transport molecules) is reflective of the overall function of individuals, both how their genes make these apolipoproteins (that means their genetic history) and how the stimulation of the genes by environmental signals trigger the genes to produce these transport molecules. Again, it is genes and environment.

If a family has a familial hypercholesterolemia, they have the genes that both synthesized cholesterol (or triglycerides) at higher levels, and they may also have genes that increase the production of these transport apolipoproteins. That is a genetic situation. Beyond that, then, are the environmental factors that influence the synthesis of these transport agents and the lipids. For most people who have elevated blood

cholesterol and triglyceride levels, it is not the specific genes that control this (like "hard-wired"), it is the environmental factors that modulate gene expression that induce, then, the hyperlipidemias.

What are the environmental factors? What is modifiable? How do we think, functionally, of a systems biology approach towards this? We look at things that increase inflammatory potential, things that increase immunological dysregulation-this could be allergies, toxins, infectious agents, microbiological agents-that induce altered immune function, and then lastly, obviously, we would look at things like environmental agents (toxic chemicals that might alter various redox processes within the liver that cause alterations in the syntheses of these apolipoproteins and then transport lipids differently to arterial cell walls.

If we put all of this together, I think we recognize that it is not simple and we cannot just say, "Oh, the number is high. Let's just deliver an agent to lower that number." What we should really be doing is looking at the environment (the context of that patient). We should be looking at the signals they are receiving at the genetic level that are modulating lipoprotein synthesis and lipid synthesis and creating what we see as elevations or reductions in certain lipoproteins.

Insulin is one of those surrogate markers, or signaling molecules, that influences the synthesis of these lipoproteins. If you have hyperinsulinemia (meaning a higher circulating level of insulin than normally required to cause uptake of glucose and glucose transport), one of the effects is activity of gene expression that regulates and alters your apolipoprotein levels. We have said metabolic syndrome/hyperinsulinemia is associated with altered levels of apo B to A-1 (increasing apo B, decreasing apolipoprotein A-1). That becomes a marker that can be used as a tool for evaluating related insulin signaling function.

Is this analysis something that every person should routinely have done? It is an expensive analyte; if you don't have to do it, why should you do it? Why should you put apo B and A-1 in your panel? I would say that for general, garden-variety assessment, it is probably not cost-effective to include the apo B to A-1 ratio. But for patients who have evidence of insulin resistance, with an elevated triglyceride/low HDL, then I think that inclusion of the apo B to A-1 ratio is valuable because it tracks so closely with relative risk to cardiometabolic dysfunction. As you probably know, cardiac disease associated with insulin resistance is one of the major risk factors, so I think the apo B to A-1 ratio becomes effective and important there

The companion to this is what we call the atherogenic particle size and particle number. There are a number of laboratories that do this now as another cardiovascular risk factor determinant, when you look at both the atherogenic-dense particles and their size and number. This could be done by NMR or by other technologies whereby you get a particle number and atherogenic index. That can be coupled together with your apo B to A-1 ratio to better define relative physiological function that can be seen later as associated with focal inflammation of the artery wall (so you get a higher calcium score, and you get higher atherogenic risk).

We are going back in time, aren't we, looking at an earlier progression of signs before we get to acute pathology and a defined disease state. We are looking at ways to intervene and track successful intervention early. By going earlier, it requires less hard-hitting intervention. This implies that we would get more benefit if we were (early on) doing diet and lifestyle intervention. Early warning, milder

intervention, improved function. That's the strategy as opposed to waiting much later in the sequence of events where pathology starts to develop—we get an atheromatous plaque, it is fibrous, it's got a fibrous cap on it, and now we have a whole different thing about stable versus unstable plaque, which is a different concern than if we were to catch this earlier and have a much less aggressive need for intervention (meaning stenting or bypass or more aggressive pharmacotherapy).

I think the use of such things as the apo B to A-1 ratio, the lipid particle size and number, things like hs-CRP and the PLA2 (or PLAC) test become all very important parts of our understanding of defining relative risk and then tracking a patient on intervention to see how these parameters improve over time. "Over time" means 6 to 12 weeks; generally that is how long it takes, by diet and lifestyle intervention, to start seeing demonstrable improvements in these analytes. So a 6 to 12 week intervention using a Mediterranean-style diet, regular exercise program, stress management, and obviously smoking cessation. Now we start to provide alternatives: phytochemical-rich diets that modulate these intercellular signaling processes that are associated with inflammation and oxidative free-radical pathology. This all becomes the standard for a functional medicine early warning intervention.

I hope I have put this into some context for you. Often we are confronted in this field with the question: What tests are cost effective? Obviously if we were to put the whole kitchen sink behind analysis, the bill for evaluation could run in the tens of thousands of dollars, so you have to ask what are the most cost-effective, evaluative tools for a functional assessment and how do you layer these on. You want to start with the least expensive profile, and then as additional questions become more of concern, you start adding more tests to get more specificity. My suggestion is to start with a standard lipid profile, do an anthropometric evaluation of waist-to-hip ratio, look at the traditional metabolic syndrome risk factors -- blood pressure, elevated triglyceride/HDL ratio -- and look at elevated uric acid levels in the blood. If all of these things demonstrate a trajectory towards metabolic syndrome (triglyceride/HDL ratio is above 4 to 1, you have marginally elevated triglyceride levels, you've got GGTP levels that are in the upper level of normal [that is gamma glutamyl transpeptidase levels], you've got some marginal elevation of ALT or AST suggesting nonalcoholic fatty liver disorder, you've got increased central adiposity, and increased marginal systolic and diastolic blood pressure increases), now you say, "Well this patient really has all of these risk factors for metabolic syndrome. I want to track the success of intervention by utilizing something that is sensitive to the major concern, which is cardiac risk." So now you might, then, layer on the apo B to A-1 ratio test and also the atherogenic dyslipidemia-type of inflammatory test using plaques, and the carotid IMT test, and the peripheral vasal occlusion test that I have talked about (the use of brachial artery occlusive test). All of these become, then, different layers of functional assessment that one can employ to both design personalized intervention and to follow the success of therapy.

When we put this all together, it obviously, then, suggests that there is a systemic influence from hyperinsulinemia and dyslipidemia; it is not just a localized effect on the vasculature. The systemic effect is because these signaling molecules, like insulin, affect gene expression in multiple tissue types, not just solely on that related to diabetes or cardiovascular disease. That is why looking at a whole-body assessment and taking the functional medicine assessment (which is antecedents, triggers, and mediators resulting in signs and symptoms) becomes a different strategy for patient work-up than just looking for the differential diagnosis. We want to start by looking at a variety of different signs and symptoms from a detailed personal health history, a good physical examination, a good family history, so that we start piecing together this puzzle of antecedents, triggers, and mediators resulting in the signs and the symptoms the patient presents with.

The signs and the symptoms are related to the multi-organ types of observationals that come from a very good physical and history. It comes back to not relying on laboratory, but relying on the art of being a good observer-of using the brain as a device to develop patterns. Our brain is more capable of doing that than the best of supercomputers. We are taking in multiple data, collecting it, analyzing it, processing it through our skilled observer status, and then coming from that to an understanding of where that patient appears to lie on this trajectory of risk associated with things like dysfunctional insulin signaling or hyperinsulinemia. That is why this interview that we are going to move to next is so important.

Because a web of interconnectedness becomes our basis for doing a physical and health history and assessment, it takes us into areas that are outside our normal disciplinary myopia. Organs aren't just cut off at the boundaries of that organ; they are interconnected through signaling molecules to all other organs. This is why our discussion with our clinician of the month, Dr. Valori Treloar, is so important. As a dermatologist, her lens that she sees the world through has to do with the skin (its integrity and function). The skin is going to be influenced very heavily by the same signaling molecules that affect other organs of the body: the inflammatory mediators like TNF alpha, IL-6, interferon gamma. These influence replication and inflammation processes that pop up on the cutaneous portion of our body and may be reflective of what is going on systemically. Insulin and hyperlipidemias all relate, as you know, to alterations in skin integrity (xanthomas, for instance, are associated with familial hypercholesterolemia). That is an extreme example, but well before that we see many different cutaneous examples of dysfunctional signaling, inflammation, and hyperinsulinemia. With that in mind, it is a good time to move to our clinician of the month, Dr. Valori Treloar.

INTERVIEW TRANSCRIPT

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We are at the very "looked-forward-to portion" of Functional Medicine Update, our clinician of the month. I am really excited this month to speak with a board-certified dermatologist who is really a functional dermatologist. Her clinic is Integrative Dermatology-its own title gives the definition-and this is Dr. Valori Treloar.

I'd like to-in introducing her-talk a little bit about her background through the eyes and words of a colleague, Dr. Bill Danby, who is in the Section of Dermatology, Department of Medicine at Dartmouth University. Dr. Danby has recently written the forward to Dr. Treloar's book (which I think is mandatory reading) called The Clear Skin Diet.¹⁸ I think this-if I can be so bold as to kind of abstract from his forward-will give you a sense as to how remarkable Dr. Treloar is in this whole field of integrative dermatology.

An Introduction by Dr. Bill Danby

Dr. Danby says it is a very high compliment to be asked to write a forward. As he has gone down his path of discovery, he has gotten more and more interested about the concept of diet and how it interrelates with dermatological function (I'm kind of paraphrasing). "All this," he says, "led me eventually to approach, with considerable trepidation, the high priest of nutritional epidemiological studies [who we

have interviewed on FMU in the past], Dr. Walter Willett, the Frederick John Stare Professor of Epidemiology and Nutrition at the Department of Nutrition, Harvard School of Public Health. I think I detected some incredulity during our initial meeting, but for reasons we've never discussed, he must have wondered if there was something to it because he assigned Clement Adebamowo, a postdoctoral fellow, to the work. After a lot of heavy lifting, Clement had his Doctor of Science, I had a 30-year-old question answered, and the association between milk and acne was proven. The word 'association' is important because we are still puzzling over the molecular mechanisms involved, but the original work has led further, and following my presentation on the subject to the Massachusetts Academy of Dermatology a few years ago, Dr. Val Treloar quietly presented herself and we got talking, and talking, and talking. I found that Val, partly because of her additional training but more out of a deep and abiding interest, has an encyclopedic knowledge of the relationship of foods to our most important hormonal and inflammatory processes. This extends far and away beyond my grasp, and, as she points out, far beyond what is taught to (or learned by) today's (and yesterday's) medical students."

I think that is a very wonderful introduction of Dr. Treloar and what she brings to us today on Functional Medicine Update. Valori, welcome to Functional Medicine Update and I guess the first question is, how does a dermatologist end up becoming an integrative dermatologist, and having gone through the Applying Functional Medicine in Clinical Practice training program, and being a leader in functional medicine in this field? That is kind of an interesting path.

VT: I owe it all to you, Jeff. I am sure my story is the same one that you hear over and over again. After 10 years in clinical practice I was really getting kind of frustrated with the limitations of my conventional dermatology toolbox for my patients with chronic disease. I started sort of gently looking outside of the box and was handed The 20-Day Rejuvenation Diet. What doctor in their right mind would read a book with such a title? I was really astonished by what I read in that book, and then I went and signed up to take the AFMCP (Applying Functional Medicine in Clinical Practice--it was the last one that was offered over long weekends in two consecutive months). I made the transcontinental trip twice (October and November of the year 2000), and became more and more convinced and amazed as I went through AFMCP. I really came to an epiphany: I had a whole new toolbox to offer my patients.

Then, of course, I had to go and study a little bit. I bought a few nutrition text books. My kids were away at camp that summer and I would get up early before my workday and spend a few hours plowing through the textbooks. I sat for the certifying exam of the American College of Nutrition, and I really turned into a PubMed nerd because I was delighted to discover that there was this whole parallel universe of science and nutrition applied to cutaneous disease. Granted, much of it is biochemical and animal models and cell culture--there is not a large volume of human, double-blinded, placebo-controlled, randomized trials--but I really did feel that in discussion with my patients, when I told them about the biochemistry, the physiology made a lot of sense and that I really thought that we were taking very little risk by improving diets and adding prudent nutrient supplements and that we might get a real benefit. My patients (many of them) were wide open to this approach; they were as frustrated as I was with having been through the whole mill of conventional treatments with not much response.

I have really had that wonderful experience that a lot of us have of being exhilarated by the new ways that we can help people, and some life changes that we can really help people go through.

JB: When I look at your background, it reminds me of "the road less traveled," as I guess they say. It is a

more difficult path, obviously, for people to have done what you have done: a Bachelor of Science from the University of Michigan and your Medical Doctor degree from Boston University, then your residency at the VA in Boston and Tufts University, and a research fellowship with Syntex Dermatology Research Center, and then all of your years of clinical experience as a staff dermatologist at Harvard University Health Service, at the Marino Center for Progressive Medicine, and in private practice in Wellesley and now Newton, Massachusetts. That is a lot of years. One might say that could really put you in stead to be an excellent traditional dermatologist. But then you add on top of that all these other things that you are talking about that have to come from this internal drive to be a seeker, at some personal sacrifice, obviously, both in time and I would probably say maybe even in money, in the end-an aspiration to seek out and do better. What drives a person like you to this? What's the motivation?

VT: I think it is this whole idea of dreading certain patients darkening your door because you really are scrambling at the bottom of your toolbox and you are kind of running out of things, and then suddenly to have that now overflowing with new tools. And there is a lot of creativity, I think, to it. We, as clinicians, really recognize all that biochemical individuality is so real, that our patients are unique, and the art of medicine is exploring variations in treatment options to find the find the right match for the right patient. You have often spoken about the "mythical" average 70 kilogram man not being really representative of the vast majority of our patient population. It really does come from recognizing that people are different and you need to explore variations on treatment options to deal with that biochemical individuality.

JB: You know, there are three fields of healthcare that always struck me as being very interesting first-level understandings of functional medicine from what we see in the patient, as contrasted to things that might be buried deep within the anatomy, like internal medicine. Those fields are ophthalmology, dentistry, and obviously dermatology. As you talk to the traditional people in those professions-the ophthalmologist or the dentist or the traditional dermatologist-they may not see what they are dealing with everyday as being connected to the rest of the body. They may not think of the eyes as being kind of a window into the overall physiological status of the patient, or what is going on in the hard and soft tissue of the mouth as being related to other systemic factors, or, in the case of dermatology, the skin being an organ of vital barrier influence that has relationships to all these other functions. When you talk to your colleagues, how do you get them to see this broader functional aspect of dermatology?

VT: I think that a lot of my colleagues really enjoy being reminded about the basic science and biochemistry behind the diseases that we deal with in dermatology, in particular because we are so good at describing what we see and it has been a descriptive field for so long. We all recognize (those of use who are clinicians, anyway) that when we give a patient a name to their disease, much of the time we are not telling them anything. One of my favorite conditions to discuss with my patients is a rash called periorificial dermatitis. I say to them, "Oh yeah, you have periorificial dermatitis." It is pink, scaly, little bumps around the mouth, the nose, and around the eyes. And they say, "Oh, what is that?" And I say, "It's a rash around the eyes, nose, and mouth." So we have given it a great name. Do we have any idea why it happens? We have some approaches that, basically, have been empirically tried over the years that seem to be helpful, but I don't know why it happens.

My colleagues...we all share that frustration of "Yeah, I can give it a name but don't ask me what that means because I'm not really sure why it is happening to you now." What is fun about functional medicine is that you have the whole matrix to start exploring. What has changed in the patient's life that may have been relevant to causing this and to suddenly, at this point, become a problem? The nice thing

about being a board-certified dermatologist is that I can certainly offer them the conventional therapy that seems to be helpful in suppressing those symptoms and knocking them down, but at the same time, we can explore what seems to turn the processes on so that they will be less reliant on the medications.

My colleagues-a lot of them-are open to the question. They really understand that we don't know what is going on for a lot of the diseases that we are very good at describing. It is an interesting puzzle and I think a lot of us go into dermatology because we like puzzles. There is a lot of contact dermatitis that you get to explore. What is happening in the environment to bring that on? I think that a lot of people find it intriguing.

JB: That is a wonderful segue into the first thing that the reader of your book, *The Clear Skin Diet, a Nutritional Plan that Works*, is exposed to and that is the quote you have offered, which is: "This book is dedicated to the medical professionals and scientists who continue to think outside the box. Thanks for demonstrating that the only myth concerning acne and diet is that which states there is no connection between the two." That is a very provocative introduction. Tell us a little bit, if you would, about how you have kind of teased apart and understand this connection between diet and acne?

Two Disciplines, One Philosophy

VT: I have to give credit to my co-author, Alan Logan, who truly did the bulk of the writing and is certainly the one who came up with that, as you say, "provocative" comment. He actually had a few more comments that I think would have been taken by my colleagues as somewhat insulting. One of the things that he and I did together as we rewrote the book was calm down the rhetoric a little bit and that was done, in part, because I want my colleagues to see this as a resource.

When Alan and I started looking at this material, we found that we had come to the same position, starting from very different places (he is a naturopathic physician; I'm a board-certified dermatologist with an interest in nutrition), and we had found all of the same papers. We had found all the same references. When we sat down and started talking we realized that we really had a kernel of truth in here. We are really excited about providing the information not only to patients, for whom I think it is really useful (hopefully), but also as a place for our colleagues to go to really sort of begin to understand why the biochemistry and physiology of nutrition truly has an impact on the pathophysiology of acne. It is quite heavily referenced. I find that a lot of us have a tendency to do this in functional medicine when we try to write for the public. We reference a little more heavily than is comfortable for most of our readers who are patients, hoping that they will show it to their doctors, and their doctors will look and see that there is some compelling evidence to support the approach.

JB: I noticed that you have done a really nice job in the book, as I read it, in taking the complex concept of the functional medicine matrix, or the web, and breaking it down into component parts that can be kind of bitten off and absorbed one at a time. The thesis that you developed, which I think is very convincing (very compelling), is that if you look at a former clear skin nation, and you use Japan as an example, and look at what has happened to their skin as their diet has changed, you see very strong epidemiological and kind of statistical changes. Tell us a little about what this Japanese precedent suggests.

Former "Clear Skin" Nations and Peoples: Japan, the Inuit, Peru, and More

VT: I find that to be a fascinating story, and that is one that Alan is particularly good at describing (that is his chapter; he is married to a Japanese woman and spends a lot of time living in Japan-is very connected

with the culture there) and I think that the story of the Okinawans, which is pretty well described, is representative of a number of different cultures. It is not just Japan where we have seen that the encroachment culture (largely a Western diet, rich in refined carbohydrates and hydrogenated vegetable oils and other vegetable oils) is associated with an increase in inflammatory disease. It turns out that Schaefer really made a clear observation of the Inuit when he was up there in the 60s and the 70s as Western influence really started coming into that area. The Inuit were renowned for their gorgeous, clear complexions and complete lack of acne. It became very clear that as the kids started eating candy and the sodas and a much more Westernized diet started replacing their omega-3 fatty acid/protein-rich diet that the kids started getting acne. It was a very profound, very obvious change to the people who were there during those decades. A similar change could be described in Portugal and was also described in Peru. And there is the wonderful story that was published in the Archives of Dermatology in the year 2002 with Loren Cordain as the lead author (and no dermatologists as authors, by the way).¹⁹ It is a most amazing story, looking at the Ache and Kitavan people who are still living essentially Stone Age lives with that diet rich in fiber-wild game, small amounts of gathered vegetables, and fish (very omega-3-rich, fiber-rich, plant polyphenol-rich diet). These cultures had no acne. He went on to speculate about how their stable insulin levels, which had been documented, compared and contrasted sharply to the spiking insulin levels that we see with a typical American diet that results from several carbohydrate-rich meals and snacks throughout the day, and that the area under the curve is much higher for insulin, and then speculated about how insulin could perhaps be having an effect on testosterone levels because of a decrease in hepatic production of sex hormone binding globulin. It was a wonderful article, just sort of bringing together some of these observations-very rare observations-over the years about how Western culture seemed to have an influence on acne (or the Western diet seemed to have an influence on acne), sort of beginning the process of pulling it together and trying to figure out what the mechanisms were.

JB: It is very interesting. We had the privilege of interviewing Dr. Cordain on Functional Medicine Update on this whole Paleolithic Diet concept a number of years ago. He had just, at that point, completed and I think had accepted for publication the article you are referring to, and he was making, as you mentioned, as a non-dermatologist, some observations. But taking that from the observational level and moving it into the clinic obviously is the proof in the pudding, so to speak. What you are doing and how you have described it in your book is you are taking the concept of metabolic syndrome/dysinsulinemia and describing how that interrelates with hormones. We often say that in adolescence the reason that boys and girls get acne is because they are starting (if they are a girl) into their menstruating years, and if they are a boy they are starting to develop their testosterone levels, and these are just the natural consequences of their developmental process. But you have seen, clinically, obviously, a very different implication of that. It is not just necessarily the natural process of going through that first stage of development in becoming an adult. Could you tell us a little bit about your clinical experience in what some people say is just a natural association of hormones with acne versus the environment/genes association with acne?

An Integrative Approach to Teenage Acne

VT: We point out to the kids at the very beginning that there are people at all ends of the spectrum. There are kids who no matter what they eat are going to have gorgeous, clear skin. And there are kids who are going to do everything we tell them to do and they are still going to have acne, and that is (again) this biochemical individuality (a genetic variability among the kids). But the vast majority of kids are somewhere in the middle, where diet really does make a huge difference. Because of the name of my practice and the nature of my practice I get to see a lot of kids who get it-teenagers who really do take some responsibility for their health. Everybody says teenagers aren't willing to change their diet, but a lot

of these kids really are. They are smart. They get it. We find ways for them to snack that are healthier.

When I have a kid, I sit down with them and we talk: What is your typical breakfast, lunch, and dinner?; What do you usually snack on?; How well are you sleeping?; How many times a night do you wake up?; On a scale of 1 to 10 what number do you give the stresses that you are experiencing in your life?; What kind of exercises are you performing now-are you playing on a sports team?; What other exercises are you doing? We work our way through that, which is one of the worksheets in the back of the book, and the kids and I sit down together and say, "Here are places where maybe changes would make a difference." Sometimes kids are a little resistant. I say, "Look, you can take all this information and do with it whatever you want, but if I told you that if you are one of these lucky people who eliminates dairy from your diet and your acne goes away is it worth it for you?" Most of these kids are saying, "Yeah, that would be worth it for me."

And the other point we make-and Loren Cordain makes this point in a lot of his books-is if you cheat once a week you are still 90% compliant and you are probably still going to have excellent benefit. A lot of these kids will have a threshold. This is all pure speculation on my part, but we explore it individually. There are kids who can have a few dairy products. They can have cheese once or twice a week. They can have ice cream once a week mixed in with their otherwise really healthy diet and they tolerate it, and that is variable from kid to kid. It really is surprising how quickly you can go through this material with somebody and come up with a few places where they can instigate a few little changes and explore it on their own. Again, because I have the luxury of being able to prescribe, I will also give them some retin-A, and if they are really inflammatory nodular scarring, I will put them on an antibiotic to quiet that process down and minimize their scarring while they are incorporating their lifestyle changes. We almost always are able, then, to withdraw the antibiotics, continue them on their probiotics to help keep their gut in a healthier state, and find that they (because of the lifestyle changes they have made) no longer require the antibiotics to maintain control over their acne. It is a wonderful position to be in to say, "Okay, we are going to use these powerful tools. They have side effects so we will want you to not rely on them, so we are going to work on the lifestyle changes which take longer to give you a benefit, but we will be able to then withdraw the pharmaceutical medications and their risks, and leave you with better control of your health."

JB: I'm so impressed with the way that you have contextualized this. The two of you, in the book, I think have found that very-difficult-to-find balance between your clinical experience and your observations and the vast years of observations that you have made coupled with what the literature is saying and the trajectory. I notice there are over 300 references that you provide at the back of your book that really document all of these associations from a mechanistic level. It is like the Magna Carta of functional medicine dermatology. It is really very, very well done. When you talk about kind of using the matrix, or what we call the functional medicine web, it appears to me that you've really found the way that this applies very nicely to dermatology. I love the chapter on gut function as it relates to dermatological problems with the skin, kind of as a reflection of immune dysfunction -- and the use of pre- and probiotics. Has that been a difficult thing for you to describe to patients-how the gut might connect to the skin?

VT: I don't think so. You know, people know their bodies. I think people pay attention more than we think. A lot of people will say, "Well, of course," when you suggest there is a connection, and, "Yeah, that does make sense." A lot of people come to me saying, "Oh my God, it is so nice to find a

dermatologist who gets it; who confirms my impression-validates my impression-that when I eat this way I get better, when I eat that way I get worse." As I always say to them, "I don't argue with success."

JB: That's the proof of the pudding, no question. So this takes us, obviously, to a very pragmatic place. That is, integrative dermatology is a unique title that might raise the eyebrows of those who have some presumption as to what either integrative medicine or functional medicine is, and it also maybe makes it more complicated in terms of how you define fee-for-service and spend the time with your patients. How have you worked all these kind of real-world mechanistic issues out in your practice?

VT: I have to say I really have a lot of enthusiasm for what I do. A passion about it, really. My colleagues will comment, "You are so passionate about this," and they listen and I take a page out of your book. I always stand up in meetings (we have meetings at our local hospital; we have them in town here in Boston; there are a number of academic monthly meetings; there are regional meetings for the New England Dermatologic Society). I make a point of standing up. I try to stand up at all of these meetings. I cite references supporting some kind of nutritional intervention for one of the diseases that we are discussing. I get, for the most part, blank stares. Every once in a while I see people scribbling notes. At every meeting, someone comes up to me and asks for a little more information. And there are people who now recognize me and will come up to me and start asking me questions about their own personal nutrition or some patients in whom they have started exploring (fish oil is a real favorite these days and a lot of people are kind of exploring it).

So, I figure if I have one person scribbling notes from making a statement (which I try to have well-supported with literature) I am getting someplace. A lot of my colleagues will say now that they have patients who come to them and say, "Well, Doc, isn't there something I can do other than take these medicines?" and they will say, "I have just the dermatologist for you." And they will send these patients over to me. Those patients and I are a great fit. One of my colleagues says, "I am very happy to have someone who shares their mindset, who I know is well-trained and is not just flying by the seat of their pants, who is using really good science to try to make these decisions."

So, it is happening slowly-that people are hearing the message and at least beginning to open their minds a little bit. They are not quite ready to try to incorporate this into their own practice, but they are recognizing that they have value. It has been since 2000 (8 years) that I have been slowly working on them.

JB: I would like to acknowledge actually four things that seem to characterize what I have heard you say as to why you are a success and will continue to be a growing success, whereas others in our field may still be aspiring to find this level of success by implementing these concepts in their practice and are finding it awkward. It seems like there are four things that stand out to me. I am sure there are more than four, but these are the four that kind of stand high on the marquee.

Number one is you are really hard-working and diligent in your self education. You have not taken this lightly, you have taken it like going back to school and saying, "I'm going to really become a master to the level that I can of this new body of information and it is going to require some work and dedication," and cooperation in your family support because time is still 24 hours a day. That hard work/diligence component is one thing that really defines you and, I think, your success.

The second obviously kind of drives out of that and that is that you have used that hard work to get into the primary literature, to some extent, and ferret out a lot of the science that gives you the supporting documentation beyond your own experience that you can use on your side, both for patient education and for colleague education, and maybe even third-party reimbursement education, if necessary, about why you do what you do. It is pretty hard to argue 300 citations that are all from tier-one, peer-reviewed literature. I think the foundation in good science and, hopefully, functional medicine and AFMCP provided some part of that in your education.

And then three, obviously, is attitude. Anyone who listens to you sees the advocacy and the balance-what I would call your positive affirmation that there are things we can do. You are open-minded, you're a seeker, you're an explorer, you are working cooperatively with your patients, and you are very excited about the advocacy that you can bring to that patient's problems. You know, the best sales job is positive attitude and excitement about what you are doing. You certainly bring that.

And then lastly, fourth, is all of this is contextualized in balance, I think. You are not way out there on the limb of extremism. You are using the best tool, which is the basic concept, I think, of functional medicine-the right tool at the right place, getting away from the old maxim of "if all you have is a hammer, everything is a nail." It is using the right tool or tools at the right time, and that concept of balance really makes your outcome, I think, even more successful. Maybe there are some takeaways for all sorts of other listeners beyond that of the field of dermatology just as to how you are approaching this in your own field so successfully. As they would say in Australia, "Good on ya." It sounds like you are really doing a magnificent job.

VT: You have been very kind, Jeff, and I want to thank you for giving me this whole new way of looking at my work.

JB: Thank you and I would really recommend your book to our listeners because dermatology is part of what people carry around all the time on their outside and it reflects their inside function. I think *The Clear Skin Diet*, this book that I think you co-authored so beautifully with Alan Logan, in itself is a very unique combination of a naturopath and a board-certified dermatologist working together collaboratively. I think you brought the best of both worlds into this book. I want to thank you so much for spending the time with us. I know you've got to get to patients, but you have really given a lot of us some pearls to use, so thank you.

VT: Thanks so much.

I certainly hope that you had the same feeling that I had in listening to Dr. Treloar speak about her practice and her journey as a dermatologist. It was just so enriching. It reminds me of why the Institute for Functional Medicine and the whole functional medicine concept was really developed over the last 17 years and why it has evolved-because it is made up of people like Dr. Treloar who bring this exuberant commitment (as Dr. David Jones talks about, "a re-enchantment with medicine") to just continue to strive to do better every day and to bring the full weight of their skills and their thoughts and experience into the practice of healthcare delivery. You can really feel it, can't you, when you hear her speaking and talking about her experience?

One of the topics that Dr. Treloar addressed in the book *The Clear Skin Diet* in some greater detail has to

do with the gut-skin connection and this whole concept of pre- and probiotics. Isn't it interesting to watch the evolution of this field? It was probably 26 years ago, as I recall, that we first talked about probiotics and gastrointestinal-associated lymphoid tissue function (the gut-immune system, in other words) and how that influences systemic inflammatory markers. I didn't think at the time we were so far ahead of the pack, but I guess, really, when you look back a quarter of a century, we were pretty much an early adopter of this concept of looking at the gut from a different perspective (from a functional perspective) as part of the immune system, and how that influences the brain, the liver, the systemic circulating white cells, and ultimately every cell in the body.

Cochrane Collaboration Publishes Review of the Effects of Probiotics

I'm very pleased to see that recently the Cochrane Collaboration, which you probably know is this wonderful group of individuals who have collected together their expertise to evaluate the evidence-based medicine surrounding different types of medical therapies, some of which have to do with what has been traditionally called integrative medical therapies or complementary alternative medical therapies, or maybe even functional medicine therapies. Within that domain are some of the Cochrane Collaboration reviews of the effects of probiotics on gastrointestinal function and gastrointestinal disease. We might have thought 25 years ago, when we first talked about this on *Functional Medicine Update*, that this was not within the purview of traditional medicine. It is starting to actually be able to fulfill the criteria of support from groups like the Cochrane Collaboration. I'd like to just quickly review what they recently wrote about: probiotics for maintaining the remission of inflammatory bowel disease and Crohn's disease. You can find this, actually, in the 2007 publication of the Cochrane Collaboration.²⁰ This review is part of what you can find on www.thecochranelibrary.com, under the concept of Crohn's disease and probiotics.

As we review this kind of meta-analysis, we are coming to recognize this systematic review has taken us into a different level of support for this gut-immune connection to gut flora and how that influences, then, local and systemic immunological factors. I think it is a very, very interesting examination of this emerging view for how probiotics and prebiotics might influence gastrointestinal function and systemic inflammation. They talk about *Saccharomyces boulardii*, which has received more and more attention as a potential therapeutic probiotic for the management of inflammatory bowel disease. The authors go on to say, however, that if you looked at all the studies that have been published in the peer-reviewed literature, you are not led to recognize that there is an overwhelming support of probiotics in isolation as being therapeutically successful. In fact, they go on to say there is no evidence to suggest that probiotics are beneficial for the maintenance or remission of Crohn's disease unless there have been other things done, and so these are more complementary types of interventions, and that is, of course, the functional medicine model-it is not magic bullets, it is not one thing, it is changing diet, it is intervening with the appropriate therapeutic support agents, and it is the best medicine, so to speak, and that is what Dr. Treloar was obviously talking about.

Often I think we tend to think of some of these interventions as being green medicines or silver bullets: "Just do this instead of that." So we give probiotics instead of antibiotics, or probiotics instead of sulfasalazine. What we really should be looking at, as Dr. Treloar so beautifully stated in her presentation, is the use of these agents in combination as a consequence of the way we have evaluated that patient through the functional medicine matrix and personalized their therapy. They may be on antibiotics. They may be on immunoreactive compounds. They are also going to have to eat and so we are tailoring the diet correctly: we are giving them adjunctive nutrients where possible, we are reinoculating the bowel using

the 4R program, and the objective is to use as little medicine as possible for the shortest duration as possible while trying to improve, obviously, the rate of recovery and the prevention of recidivism or relapse.

I think that the studies that are often done, unfortunately, use agents just one at a time as kind of single agents against these diseases, and then we go back and we say, "The research doesn't support the use of probiotics in inflammatory bowel disease," or "The research doesn't support the use of probiotics for managing insulin resistance," or "The research doesn't indicate that probiotics are good for hepatocellular injury in inflammatory liver disease." That is because some of this research was done isolated, one agent at a time, rather than looking at the complex of that agent (in this case, pre- and probiotics) in the combination of personalized therapy for the patient. Obviously the reason that we don't have the data is it is very difficult to design these studies to look at combination therapies and do it in stratified ways that are individualized to the patient. So you start saying, "We can't even find a methodology to prove our hypothesis." You have to use inferential information, you have to use case studies, you have to use animal studies, you have to use epidemiological work, and you have to use intervention trials that have cohort analysis that have demonstrated success. In other words, it is the combination of information together that paints a picture towards support of improved patient outcome, rather than kind of a one agent against one outcome variable.

The Cochrane Collaboration evaluation, to me, shows there is definitely benefit to probiotics, but we can't unequivocally state that it is the magic bullet for Crohn's disease or inflammatory bowel disease as a single agent intervention against placebo. Once again, that calls for (in my mind) the kind of approach Dr. Treloar was describing, which is a functional medicine approach that uses a combination of variables for managing the patient's topography of their dysfunction or their disease, the architecture of their disease, which is more than just one agent influencing physiological function, and it requires more than one agent, then, to normalize their function. I believe this is a kind of nice specific example of a more general theme that you heard from her presentation about how to look at a whole organism as it pertains to a dermatological condition and say that the dermatological condition is a reflection of an imbalance in the whole organism, now let's look within the functional medicine matrix at where those balances may reside in that patient, be it insulin or stress hormones or food allergies or gut dysbiosis or imbalanced dietary intake of various agents or omega-6/omega-3 fatty acid imbalances-you start looking at that full mosaic to design the program that is individualized to the patient. From that, then, comes the treatment of choice, and ultimately the best medicine for that patient.

Thank you very much for your attention and we really, once again, thank Dr. Treloar for her very high skills in communicating how functional medicine works in a dermatological practice. We'll look forward to sharing with you next month.

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