November 2007 Issue | Michael Holick, MD, PhD Boston University

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Welcome to *Functional Medicine Update* for November 2007. In this issue, we are going to focus on a topic on which we have been doing quite a bit of work (because I think it deserves it): nutritional endocrinology. Our nutritional endocrinological discussions will focus on a couple of areas of topical and clinical importance; one of which has to do with the vitamin D story, which we have become more knowledgeable about over the last two years in*Functional Medicine Update*. There is some new "news-to-use" in this area that I think you are going to be very excited to learn about from a world leader in this area. The other area--which we are going to start with--is the relationship of insulin signaling, insulin sensitivity, and gene expression patterns. The list of the many disorders of chronic age-related diseases related to this topic continues to grow: type 2 diabetes, coronary heart disease, autoimmune disease, bone loss, dementia. Even cancers of the colon, breast, and prostate are associated with dysfunctional insulin signaling.

In some senses, this story is evolving beyond metabolic syndrome. Probably most *Functional Medicine Update* subscribers are aware of this, but I just want to give a quick reminder that we have recently put out a new product under the Synthesis banner: our seminar titled *Beyond Metabolic Syndrome: Dementia, Diabetes, Cardiovascular Disease, Hypertension, and Autoimmune Disease*. This is a product we put together in 2007, and it includes both the CD audio and the visuals that are associated with the seminar. For those of you who are not familiar with it, you can learn more about it by either going to our website, (www.jeffreybland.com) or you can give our Synthesis office a call at 1-866-272-5789. Just ask about the education product titled *Beyond Metabolic Syndrome*. I think you will find it very educational and clinically valuable.

Let me also say one other thing that I think you are aware of (we want to continue to fertilize the soil): We love questions. We actually thrive on being challenged. We would love you to send in your thoughts about what you want to hear on *Functional Medicine Update*--controversies, things you have heard about in the news, or things I have said that you don't agree with or would like to have revisited. I think we take to challenges very well and receive them in the spirit in which they are intended, so if you have any questions or areas you want us to focus on, or concerns about something that I said that you would like to revisit, give us a call. Again, let me give you the number: 1-866-272-5789 (it's toll free). You can also send an email through the website, www.jeffreybland.com. I'm looking forward to hearing about the interest areas that can make this FMU even more effective in meeting your needs.

Let's talk about the basic underpinning of nutritional endocrinology. I'll just spend a moment speaking of theory. I know most of you may not be as interested in theory, and are much more interested in what this

means to your patients. But, what it means to your patients often starts with a theoretical framework, so I want to share that with you quickly.

The connection between genes and environment really relates to the birth of the functional medicine concept. Each person possesses their own unique genome of 23 pairs of chromosomes; but these are pluripotential, which means they are not hard-wired to give a certain expression pattern. Rather, their expression over time depends on the exposure to certain environmental signals, and we view this as the origin of chronic disease.

Environmental signals include things like diet, lifestyle, thought patterns, water, air, and sunlight (which we will be speaking about in greater detail in this issue). All of these things are picked up as information units by the body and translated through intercellular signal transduction pathways (signals) into physiological actions. Those actions (what we call the phenotype) are translated through the genotype by way of the gene expression patterns.

Certain genes get turned on and others get turned off. We are shaped by a combination of these hard-wired genes, which we don't change (hopefully-they are not becoming mutated), and how they pick up information from the environment and translate it into the phenotype of the organism. This occurs over decades of living. And so we shape ourselves over time by our experiences. We shape ourselves psychologically, physiologically, spiritually, and physically as a result of our experiences, which probably occur from the moment of conception.

How does that relate to nutritional endocrinology, the theme of this month's *Functional Medicine Update*? "I think you can probably speculate about what direction I am going. The takeaway is that the endocrine system is connected to the immune and nervous systems, so we have this super system we call "psycho-neuro-immuno."

The Role of Intercellular Signal Transduction Pathways
Endocrinology is a system that exists to translate outside information into inside physiological function, and it occurs through pathways of gene expression and intercellular signal transduction. Nutritional endocrinology would imply, then, that there are substances within our diet (macro- and micronutrients, and accessory nutrients) that, when consumed, have some impact on regulating the functional status of the endocrine system through this gene-environment interaction and intercellular signal transduction pathways (intercellular communication). That would mean if we eat a polyphenol from some food, somehow there must be a mechanism that changes androgen or estrogen levels, or has an impact upon metabolism of hormones, and that it must work through some process of regulating function at the cellular level through this transduction process (this intercellular signal transduction).

I am saying this very simply-as if it's matter of fact-but in fact, this is a pretty remarkable change in our view of how nutrients may influence physical and physiological function: through transduction pathways that modulate gene expression. To date, over 500 regulating factors for these processes have been discovered, which include cytokines, chemokines, kinase enzymes, and all sorts of interesting molecules.

If you think about the future of personalized medicine, what we need to do is understand more about the interesting gene array that is in each person. What do they possess in their hard-wired book of life-their genome-and how do those unique characteristics get modified in their function, or their expression, by

environmental factors? It is a combination of understanding the uniqueness of that patient, which has to do with their SNPs (single nucleotide polymorphisms)-those changes in their book of life that cause them to be a little bit different by one later substitution than someone else-and then how those uniquenesses are modified in expression by the environment to produce a functional outcome: a person's health. I hope that is an understandable framework. This is what we are going to be contextualizing in this discussion of nutritional endocrinology.

Just recently, in the *American Journal of Clinical Nutrition*, an interesting editorial was published titled "The End of the Beginning." [1] Authors Shelly Cole and Anthony Comuzzie write about what gene studies are now telling us about the relative risk people might have to later stage diseases. They focus on gene uniquenesses, like the adiponectin gene. Adiponectin, which we have talked about, is an insulin-stimulating anti-inflammatory messenger molecule that is produced by adipocytes. The uniqueness of the adiponectin gene can be correlated with differing relative risk to things like type 2 diabetes and metabolic syndrome. But adiponectin genes don't work just by themselves; they work in concert with many other genes that regulate a symphony -- an orchestration -- to regulate insulin. So it is not just one gene at a time; it is genes in the context of family members that create outcomes.

The authors of this this editorial state that identification of well-supported candidate genes (such as adiponectin) is a necessary first step in genetic studies and understanding, say, the relative risk to things like metabolic syndrome or type 2 diabetes. In addition, we need to go on and connect those to the variation in phenotype by looking at other genes in the family.

The authors actually quote Winston Churchill: "Now is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." I think that is kind of where we are now in this whole gene expression story. We don't know where this story is going to take us, and people who presume they know are probably being premature because this is only the first stage in our understanding of how gene diversity (the SNPs) really regulate ultimate phenotype and sensitivity to our environment.

There is an interesting paper about Wilson's disease that appeared in *Clinical Chemistry* just recently that I would like to mention to you.[2] I have spoken about Wilson's disease for years and years--in fact, all the way back to my start in this field with trace mineral nutriture, back to the early 1970s. There was actually a best-selling book, *Mental and ElementalNutrients*, by Dr. Carl Pfeiffer, that talked about trace elements and the important role they have in regulating function (zinc and chromium and copper).

Wilson's disease is a genetic disorder that is associated with higher levels of ceruloplasmin in the liver that captures copper and leads to copper toxicity, in which people end up with liver failure and dementia. I remember seeing an incredible video (actually, it was a movie-this is pre-video, back in the early 70s) of a patient at NIH Hospital in Bethesda, who had Wilson's disorder. It was a young woman-very attractive and eloquent-and she was talking to the physician on camera, saying she was having these early-stage signs and symptoms. Then they tracked her--on film--over the course of a year. You could watch her, before your eyes on this kind of compressed time video, losing her mental function. She became totally unable to speak and unable to control her limbs. They put her on penicillamine-cuprimine-which was the treatment of choice at the time and you could watch her, then, over the last several months, come out of it and regain her function; this was all a consequence of copper toxicity associated with this genetic uniqueness called Wilson's disease.

You might recall that it has been found that counter-acting nutrient to copper excess is zinc. There were studies supported by the NIH that showed zinc is able to drive the uptake of copper down, and this has led to one approach to management of Wilson's disease -- not just with cuprimine alone, but also with oral zinc supplementation at high dose.[3]

Our early view of most genetic metabolism disorders was that you either had them or you didn't; there wasn't a variation of a theme. But now, with the availability of SNP analysis, we are finding that many people have some level of vulnerability to a genetic metabolic disorder-not just Wilson's, but Gaucher's, Fabray's, Tay-Sach's, and even phenylketoneuria-show variant forms because they are multiple gene loci. It is not just you have it or you don't; there are variations on a theme, similar to what we know with Gilbert's syndrome (that varying degrees of hyperbilirubinemia are associated with different penetrants of glucuronidase enzyme alteration).

In a *Clinical Chemistry* article, the author reports that by doing SNP analysis in Wilson's disease, you find a variegated number of SNPs that are associated with the condition. Within this condition, you might have a person with mild Wilson's, or you might have a person with much more severe Wilson's, meaning their ability to concentrate copper from their diet. A person with Wilson's is not being exposed to toxic levels of copper; they are concentrating the normal level of copper found in a diet into tissues, creating the toxicity. There are four SNPs that have been identified with Wilson's showing variation on a theme.

This complicates our story a little bit, doesn't it? We cannot just name each condition, find a gene for that condition, and then find the nutrient to modify it. It's a variation of themes and these things work in families.

Ultimately, all of this will lead us down the road towards personalized nutrition and using nutritional genomics as a tool for targeted medical nutrition therapy. But I think it's very important for us to recognize we are still early on in this process. As Winston Churchill said, we are at the end of the beginning, not at the beginning of the end yet. There is still a lot to be learned.

For those of you who want to follow the evolution of the topic of personalized nutrition through nutritional genomics, there is a nice article that appeared in *Nutrition Reviews* in 2007 titled "Personalized Nutrition: Nutritional Genomics as a Potential Tool for Targeted Medical Nutrition Therapy."[4] The authors of the review say that the best area we have now to apply this concept (looking at various SNPs as a family of gene uniquenesses) is in cardiovascular disease risk evaluation and coronary artery disease risk.

In the August 2, 2007 issue of the *New England Journal of Medicine*, there was a multiple-authored paper that looked at modern genotyping and the analysis related to coronary artery disease risk.[5] There are a variety of gene SNPs that cluster together (in fact, there were nine loci that were strongly associated with coronary artery disease) which had less than a 50{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} chance of being falsely positive. You can see that this field is starting to emerge to be pattern recognition rather than looking at single genes at a time. In this case, nine loci, when together, give rise to increasing relative risk to coronary artery disease. I want to emphasize that these genome-wide association studies are looking at risk related to families of genes that seem to encode for altered physiological function and give rise to

relative increasing risk to various diseases. Cardiovascular disease is probably the one that we now know the most about. I think we will follow this very closely in *FunctionalMedicine Update*. Now let's move from the abstract to the clinical reality. Where does this information take us in terms of nutritional endocrinology? What it says is that we really cannot, at this point, define specifically the genomic risk that a patient may have and the relative specificity of his or her nutrient needs based upon a genome screen to optimize endocrinological function. But we can use inferences from family and personal health history, from various types of traditional endocrinological markers, and from some endocrinological stress tests. Taken together, these elements would paint a picture-a mosaic-of that patient, and then we would use, in part, a slightly empirical diet approach by modifying the diet and following the patient's response to that diet.

I'm going to take this concept and specifically focus on metabolic syndrome, just to show you how this works. Is there the perfect diet for all patients with metabolic syndrome or hyperinsulinemia? Obviously, from what I have just said, if there is a variegated genotype for any condition, then there may not be a single diet that is optimal for all people within that family; there may be variations on a theme. I think that is part of the bane of our approach, but it is also part of the beauty because it allows us to have the diversity (or let's call it plasticity) of clinical approaches based on the patient presentation.

You may say, "How do I know what the right diet is?" Part of finding the answer is to start with what you think is as close to the center of the bull's-eye as possible. If you don't hit the center, then modify it slightly and use an iterative approach (working with a patient to get optimal outcome).

With that as a conceptual framework, let's get more specific. Let's ask the question that I was asking, in part, in the audio course *Beyond Metabolic Syndrome*: Is there an optimal diet for metabolic syndrome? Or, what are the diet diversities that are useful for the clinical management of the patient?

I'm very pleased to say that after I did this audio course, both the *New England Journal of Medicine*, and more recently the *AmericanJournal of Clinical Nutrition*, followed up with papers that supported the thesis I had presented. The title of the paper I am going to be reviewing is "Comparative Review of Diets for the Metabolic Syndrome: Implications for Nonalcoholic Fatty Liver Disease."[6] I think this is a very good article for those of you who want to dig a little deeper; it's got an excellent bibliography.

This was work that was done at the Department of Food Science and Technology at the University of California, Davis, and also the Nestle Research Center in Lausanne, Switzerland. The researchers used NASH as a marker for severe insulin resistance. People with NAH generally have triglyceride accumulation within their livers and elevated liver enzyme profiles. It used to be a very esoteric condition back when I was in my training. I recall that it was thought of as a very unusual situation. But now we are seeing it more and more, even in adolescents. It is not unusual to see modest elevations of liver enzymes that are not associated with hepatitis or cirrhosis of the traditional type.

In this particular article, what the researchers are looking at is elevated liver enzymes associated with non-alcoholic fatty liver disease. This condition has been speculated to now affect (and I know this number, for those of you not familiar with it, is going to shock you) 70 million Americans. Seventy million Americans (which is 30{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of the adult population, by the way) have evidence of non-alcoholic steatohepatitis. Let me just let that set in for a minute.

I wasn't in school that long ago. I started in '66 and finished in '70 with my PhD. For maybe some of you that sounds like a lifetime ago, but for me it doesn't seem that long. If I would have said that something like 70 million Americans in 2007 were going to have this condition back in the '60s, I probably wouldn't have gotten farther than being in school; I would have never graduated because I would have been considered more polemic than I actually already was. I think that this is a pretty staggering number.

An estimated 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of these individuals end up having the severe form of non-alcoholic fatty liver disease, which is this NASH condition. So, 70 million total with nonalcoholic fatty liver disease, of which 20{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of these individuals have NASH, which increases relative risk to not only severe type 2 diabetes and cardiovascular disease, but also liver failure and the need for liver transplant.

The question is what diet should these patients be on if this is a marker for insulin resistance and hyperinsulinemia? This question is the focus of this particular paper. There is some really interesting supporting information that follows directly from what I was speaking to in the *Beyond Metabolic Syndrome* audio course that I discussed earlier.

The issue can be described by comparing the lipotoxicity model as contrasted to the glucotoxicity model. Lipotoxicity is the infiltration of fat (triglyceride) within tissues that normally don't accumulate fat. We know that the adipocyte cell (the fat cell) is evolved to accumulate fat. That is where fat is normally found: the subcutaneous or visceral adipocyte. But when fat ends up spilling over out of the adipocyte, it ends up going into places where it normally shouldn't be and in high levels, which include liver cells, muscle cells, and pancreatic beta cells. This is called lipotoxicity. Fat can also get into the cardiac endothelium and into the vasculature. These conditions that are associated with NASH are reflective of fatty spillover and triglyceride imbalances, and have been called lipotoxicity (or fat toxicity).

What are the dietary treatments? First of all, you might say, "Shouldn't we be cutting total fat down in the diet because it's a fat problem?" Remember, the fat problem comes from an insulin-driven mechanism. It is not necessarily that a person was just consuming a huge amount of fat in their diet (although there is strong evidence that high saturated fat diets aggravate, as you might expect, the non-alcoholic steatohepatitis and non-alcoholic fatty liver disease). Certainly you want to cut down saturated fat. Of the fats that remain in the diet, however, clearly you want to increase-what do you think? Being a student of FMU, you immediately say, "Omega-3 fatty acids." And that's right. Omega-3 fatty acids (the eicosapentaenoic, the alpha-linolenic, and the docosahexaenoic acid family of omega-3 fatty acids) have been found to be good sources of lipids in nonalcoholic fatty liver disorders to improve insulin sensitivity and reduce (paradoxically) fatty liver infiltration, so here is a fat that lowers a fat, basically, is what the clinical evidence would suggest.

What do we want to stay away from? Partially hydrogenated trans-vegetable fats, because they increase fatty liver infiltration and increase insulin resistance, says the data. How about glycemic index? Glycemic index is a very important determinant of relative severity of nonalcoholic fatty liver disease, so what do we think? Low glycemic index, right? And low glycemic load.

Now, you might say, "Well that means taking carbohydrate out of the diet." It may mean that, but it probably means preferentially taking white carbohydrate out of the diet because that seems to have the

highest glycemic response. The fiber-rich flotsam-and-jetsam-containing whole grain carbohydrate generally has a much lower glycemic index than the highly refined, white, "close-to-godliness" type of carbohydrate. It is, again, increasing the fiber, decreasing the white carbohydrate (the highly refined carbohydrate).

What about sucrose and fructose? That's a very interesting question. There is still some interesting controversy about glucose, sucrose, and fructose. I think we can say, just as a general rule, too much simple carbohydrate increases lipotoxicity in a person with nonalcoholic fatty liver disease. What is too much? Does that mean take all simple carbohydrate out of the diet? No honey, no fruit? The answer is no. It really means when you get above a threshold where you are using additive amounts of white carbohydrate (meaning, simple sugars), you start to get into a problem (this is where we start getting up into the hundred pounds per person per year of added sugars).

So then you might say, "Is there a difference between fructose and sucrose and glucose?" The answer is yes. The real problem may be high fructose-containing corn syrup sweeteners (soft drinks have moved from sucrose as the sweetener into high fructose corn syrup sweeteners), because it is not just fructose alone, it is fructose in combination with a variety of other partial hydrolyzed oligosaccharides and monosaccharides that come in high fructose corn syrup sweetener. You can get a lot of simple carbohydrate very conveniently in liquid sugar as high fructose corn syrup sweeteners, so I think getting soft drinks out of the diet obviously is a very, very big issue.

Getting synthetic sweetener-added materials out of the diet is very important, but again, it doesn't mean cut out fruit. There is an interesting recent report that looked at sugary drinks linked to insulin resistance (this was a component of the Framingham Offspring Study examining the effects of sugar-sweetened drinks, diet soda, and fruit juice consumption on insulin sensitivity in 2500 subjects).[7] The study found that people who consume no sugar-sweetened drinks had fasting insulin of 188 pmol/L compared to 206 pmol/L for those drinking at least 2 servings of sugar- sweetened drinks per day. Sugar-sweetened drink consumption was not associated with a change in fasting glucose, and the author concluded that in these healthy adults, sugar-sweetened drink consumption appears to be unfavorably associated with surrogate markers reflecting hepatic, more than peripheral, insulin sensitivity.

Of course, that's what nonalcoholic fatty liver disorder is. It is an hepatic insulin insensitivity, right? So you may not see it, peripherally, but it is happening in the liver and that has been leading to the accumulation of fat in the liver. This study is pointing a finger towards soft drinks and bringing into question the health of kids who are going after school (or whenever) and getting these huge containers of soft drinks that they always seem to carry around; these kids are candidates for nonalcoholic fatty liver disease. Getting away from the additive sugary drinks is another part of diet modification.

What about protein? It is interesting because this question is about both protein quantity (I mean, the percent calories as protein) and also protein quality. Is there a difference between, say, vegetable protein and animal protein? Is there a difference between cooked protein (like charred protein) versus baked protein or broiled protein. We have all sorts of interesting questions about dairy protein, egg protein, vegetable protein, animal protein. Is there a difference between fish and beef?

This is a pretty interesting topic because each one of those sources of protein carries different information to the genomic receptor system. Did you hear what I just said? Each one of those different proteins carries

different information to the genomic receptor systems. That idea is probably flying in the face of everything you learned about gastric physiology and digestive physiology. What we learned early on was that proteins are all broken down to their requisite amino acids before they are absorbed, and therefore it doesn't matter, really, about the source of the protein because in the end they all end up in their building blocks anyway.

What we have learned over the last 10 to 15 years is that this story of digestive physiology is only partially correct. There are intact, proteomic fragments that are released by partial digestion and by pepsidases in the gut. These proteomic fragments may have effects on receptor sites within the GI epithelium, which sends signals to the body and they may be immune stimulant. Or they may be perceived as foreign invaders and initiate an inflammatory response. Or they may be proteomic fragments that (by micropinocytosis and in-cell vesicle formation) get absorbed into the blood at such a level at to induce, then, action at a distance (systemic effects, because they still have information content within them).

So, these different proteins are not necessarily inducing the same effects upon the enteropatic system or on the gastrointestinal associated lymphoid tissue system. I think we should not just generalize, and say "percent calorie protein" and assume that all proteins have the same impact on endocrine regulation-it's just not true. Many papers have demonstrated that vegetable protein and beef protein, for instance, have different effects on postprandial glycemia and insulin levels. So it is a more complicated topic than just saying, "Well, let's get the proper percent calorie/carbohydrate, fat, and protein." Within each of those compartments of macronutrients, there are a variety of different effects on the endocrine signaling system based upon the personality of the fat, or the personality of the protein, or the personality of the carbohydrate.

Is simple carbohydrate different in its information signaling than a complex carbohydrate at the same caloric amount? Yes. So is vegetable protein different in its signaling, at the same number of calories, as dairy protein (let's say, casein)? And the answer is yes, it is. So the point I am trying to get you to understand is that when we are designing a diet to modulate nutritional endocrinology and insulin sensitivity in the patient, we must be mindful not only of the percent calories of each of the macronutrients, but the personalities that each of those components have on modifying gene expression and the phenotype of the patient.

I hope this is getting through because, you might say it is in the complexity of understanding that ultimately better clinical specificity will result. Some patients don't do well on a high protein diet because you didn't choose the right protein. Other people don't do well on a high carbohydrate diet because the carbohydrate that was chosen may have contained some fragment, like a glutinous grain protein, that had an adverse effect on their immune system and induced an increase in their insulin levels Whereas if you change to another vegetable protein, maybe you would have a favorable effect. So it is, again, really looking at the patient and their individual response.

Going back to diets for metabolic syndrome and nonalcoholic fatty liver disease paper that I was describing, the authors say that one of the most beneficial diets for patients with nonalcoholic fatty liver disease and metabolic syndrome is the Dietary Approaches to Stopping Hypertension (or the so-called DASH diet). The DASH diet is a diet that has a high amount of fresh fruits and vegetables, whole grains, minimally processed, low-sodium foods, lean cuts of meat and fish, and increased omega-3 fatty acid

intake. So this concept that carbohydrates are bad with nonalcoholic fatty liver diseases is not necessarily true if the carbohydrate is built into the context of the proper diet with the right signaling molecules present.

The authors go through and discuss the Atkins diet, and the Ornish diet, and the Zone diet, as well as the Weight Watchers and the South Beach diets, and ultimately they come to a specific recommendation. I was very pleased to see that the specific recommendations they are describing are almost exactly coincident with the recommendations I derived in the *Beyond Metabolic Syndrome* course. It looks like we are all following the same lead.

An interesting add-on to the above article is a paper titled "Low Carbohydrate Nutrition and Metabolism," also published in the *American Journal of Clinical Nutrition*.[8] In this article, the authors say that this persistent epidemic of obesity and type 2 diabetes suggests that nutritional strategies are needed if the epidemic is to be overcome. I think we can all agree with that. And they go on to say a promising nutritional approach is to be engaged in carbohydrate restriction. Then they go through this whole discussion of how recent studies indicate under conditions of carbohydrate restriction, fuel sources shift from glucose and fatty acids to fatty acids and ketones and that ad libitum-fed, carbohydrate-restricted diets lead to appetite reduction, weight loss, and improvement in surrogate markers of cardiovascular disease.

That's all true. There is nothing I just said that is in this thematic review that would be considered untrue. But what I found philosophically disagreeable in this article is that they never differentiate the type of carbohydrate. They never talk about all that flotsam and jetsam that comes along with a partially processed, mostly unrefined, carbohydrate-rich diet. Nor do they address the things we call phytochemicals, and accessory nutrients: flavonoids, polyphenols, and the whole rich array of things that come with a modestly refined diet. This kind of a natural diet has signals that it sends to these gene receptors beyond that which you get from a diet of white. To not differentiate in this article between a carbohydrate diet that has high information content (i.e. minimally processed, phytochemically rich diet) and a carbohydrate diet that is highly processed and sending only carbohydrate calories as white, is to me (in this day and age of nutritional genomics) irresponsible. It looks like it is speaking to something that we have gone by, passed by, the door/threshold has been crossed, and we shouldn't be going back over it. So, this review paper, to me, on carbohydrate restriction, which does not mention anything related to phytochemicals that are found in a minimally processed, high complex carbohydrate diet, is irresponsible. I would rather champion the theme that was developed in the comparative review of diets for metabolic syndrome article that I described earlier that takes into account the full array of information molecules that modulate nutritional endocrinology in patients.

In the past, we have looked at various ways of evaluating the impact of diet on the endocrine system, including using lipid markers. Of course, the most common lipid markers used in clinical practice are triglycerides (cholesterol), and if you are going to fractionate a cholesterol lipoprotein panel, you look at things like HDL and LDL. We know that as a surrogate marker for metabolic syndrome, elevated triglyceride-to-HDL ratio is associated with increasing relative indication of insulin resistance. As we get above 3-to-1 triglyceride-to-HDL ratio (so 4-to-1, 5-to-1, 6-to-1, and so forth), it indicates increasing relative risk to metabolic syndrome/insulin resistance (until you get up to 10-, 11-, and 12-to-1, and then you get in a frank type 2 diabetes-type of situation). So we have used this, clinically, as a marker.

Within the last few issues of *Functional Medicine Update*, I have discussed other surrogate markers that may be earlier warning signs of alteration in the endocrinological pattern that leads to risk to nonalcoholic fatty liver disorders (or NASH, or even diabetes). One of those I talked about was the use of the apolipoprotein A-I-to-apolipoprotein B ratio. Remember the apolipoproteins are the protein fragments, or protein components, of these lipids that we measure in the blood that we call LDL, HDL, VLDL, IDL, or cholesterol.

Cholesterol is a fat, and therefore it doesn't circulate in the blood, which is principally water, in the absence of some transporter (something to move it along, to carry it, that is able to solublize it). We call that an emulsifying agent, or a detergent (if you want to use washing your clothes as an example). A detergent washes the oil out of your clothes by tricking it into thinking that it is like oil and getting it into the water; that is an emulsifier. The emulsifiers in our blood that help to allow cholesterol and fats to circulate are called apolipoproteins. They have names like apolipoprotein A, B, D, E.

Lipoproteins are formed in the liver as a consequence of different endocrinological signals. If you have high estrogen, you get a different family of apolipoproteins formed than if you have high androgens. Or if you have high insulin, which is an endocrine hormone, you have different lipoproteins formed than if you have lower or normal insulin. Some people have said that the early precursor marker for dysfunctional nutritional endocrinology is to look at the apolipoproteins that then later get into the pathological states of altered serum lipids and altered tissue lipids.

Apolipoprotein A-I-to-apolipoprotein B ratio can be analyzed by a laboratory. When this ratio is reduced (when you have a low level of apo A-I-to-apo B), there is an increasing risk to cardiovascular disease associated with metabolic syndrome; this has been called cardiometabolic syndrome.

To put things in context, recently a paper appeared in the *Journal of the American Medical Association* titled "Clinical Utility of Different Lipid Measures for the Prediction of Coronary Heart Disease in Men and Women," which looked at apolipoprotein A-I and apo B as predictive markers for cardiovascular disease.[9] This particular study looked at all patients and did not screen for those with insulin resistance. In this large, population-based cohort (minus a propective screen), the overall performance of apo B-to-apo A-I ratio for prediction of coronary heart disease was comparable to that of traditional lipid ratios, but did not offer incremental utility over cholesterol HDL ratio. The study authors concluded that the data do not support measurement of apo B-A-I in clinical practice when total cholesterol and HDL measurements are available.

I think that conclusion is correct if you look at all patients, but the question we should ask is how about if you segment for those patients with insulin resistance? Would you get higher diagnostic specificity and predictive value if you measured apo A-to-apo B-I ratios in those patients who were the subset of people at cardiovascular risk, who had lipotoxicity and metabolic syndrome? I just want you to understand that this is an area of some controversy. I believe that the combination of cholesterol HDL ratio, and triglyceride HDL, and apo B-to-apo A-I ratio gives a more composite view of the endocrinological state of the web, and allows you to titrate, then, the nutritional status of the patient to improve outcome.

With that in mind, let's take this concept of nutritional endocrinology and move into looking at vitamin D and how, as a nutritional endocrinological agent, it modifies function.

INTERVIEW TRANSCRIPT

Clinician/Researcher of the Month
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We're at that portion of Functional Medicine Update again that I know you look forward to-so do I. It's our clinician or researcher of the month and this month we are fortunate to have one in the same. He is both a researcher and a clinician. He has a PhD in biochemistry, as well as an MD. You know him because his name is in the news all the time and he has also been very kind to be a previous clinician of the month on Functional Medicine Update. He is also the recipient of the 2007 Linus Pauling Award, presented by the Institute for Functional Medicine.. I'm speaking of no one other than Dr. Michael Holick. The name, I'm sure, is very familiar to you.

I want to give you a quick update without going into the really dramatic and voluminous accomplishments that Dr. Holick has had over his years of contribution, both as a scientist and as a clinician. He was educated at Seton Hall originally, with a BS in chemistry, and went on to get his PhD and MD at the University of Wisconsin, where he worked within a world-renown group in the area of vitamin D, that of Dr. Hector DeLuca.

In 1970, Dr. Holick published a paper with his colleagues that would be considered a landmark paper, which he may mention because it is the start of this vitamin D story (from a publication perspective). This is the paper that appeared in Biochemistry that year titled "21,25-dihydroxycholecalciferol. A Metabolite of Vitamin D3 Preferentially Active on Bone."10 That is probably a pretty good place for us to start. Dr. Holick is a research professor as well as a professor at BU Medical School in the area of bone. He also works in the area of dermatology.

Michael, I'd like to start the discussion, if you would, talking about the evolution of this anti-ricketic vitamin (which is the way many of us learned of it in school) to become a major part of the story of nutritional endocrinology. You were really at the forefront of this. Could help us understand how that intellectual evolution occurred?

MH: Well, once again, Jeff, it is a real pleasure to be on your program. I think the information that you have been getting out to physicians for so many years, you know, has just been so crucial in patient care, and I really congratulate you and your colleagues for a really outstanding job.

In terms of vitamin D, you are quite right. I mean everybody had thought that vitamin D, the anti-ricketic vitamin, is for the prevention of rickets in children. We don't see rickets in children anymore, and so we really have not thought of vitamin D deficiency as a significant health problem. But in 1970 and 1971, we began to appreciate that once you make vitamin D in your skin or you inject it in your diet, that it has to go to the liver, and it is converted to 25-hydroxyvitamin D; it's the major circulating form. But it, too, is biologically inactive, and must go to your kidneys, where it gets activated to 1,25-dihydroxyvitamin D. It is 1,25-dihydroxyvitamin D that is the biologically active form of vitamin D, and it interacts with specific receptors in the intestine, bone, and kidney to regulate calcium, phosphorus, and bone metabolism.

A Major Vitamin D Breakthrough

The major breakthrough, however, came when we began to appreciate, as early as 1979, that every tissue and cell in your body has a receptor for vitamin D. And so you have to ask yourself, why would Mother Nature put receptors in your skin, brain, heart, and pancreas if they weren't having a function? That led, then, to a very interesting observation by Dr. Suda. What he found was that pre-leukemic cells (and leukemic cells) had a vitamin D receptor, and when you incubated leukemic cells with the active form of vitamin D, not only did it inhibit their growth, but it induced them to become mature and to terminally differentiate.

One clinical application for this observation was made by us in the mid-1980s when we showed that not only do skin cells have a vitamin D receptor, and that skin cells respond to active vitamin D by inhibiting proliferation and inducing maturation, but that when we topically applied 1,25-dihydroxyvitamin D to patients with psoriasis, a skin disease that afflicts probably about 1 to 2 percent of the world's population caused by an overproliferation of skin cells, that it was effective in basically treating that disease. And so active vitamin D compounds are now used as a first-line treatment for psoriasis.

The Link between Latitude and Cancer Incidence

And one final comment in terms of the endocrine aspect: What has always been puzzling, and has been a remarkable observation, is that as early as 1941, it was appreciated that if you lived at a higher latitude in the United States, such as Massachusetts, New York, or Vermont, you were more likely to die of cancer than if you lived down south, like in Georgia, South Carolina, and Texas. It was speculated by Dr. Apperly in 1941 that by being exposed to sunlight, and even if you developed non-lethal (non-melanoma) skin cancer, it somehow imparted an immunity to prevent you from developing more deadly cancers. And we now know why. The other major story in the vitamin D field now is not only do your kidneys activate vitamin D, but it appears that most tissues in your body also have that capability. But it does it in a very clever way.

What happens is that as you raise your blood levels of 25-hydroxyvitamin D, the molecules go to cells, and these cells can then activate it to 1,25-dihydroxyvitamin D, which will probably modulate cell growth and have a wide variety of other cellular effects. It has been estimated up to 200 different genes are controlled by 1,25-dihydroxyvitamin D. But what the body cleverly does, is that after 1,25-dihydroxyvitamin D does all of these functional activities within the cell, it then induces its own destruction, and therefore, it has no effect on calcium metabolism, nor does it have any effect on your blood levels of 1,25-dihydroxyvitamin D.

So the bottom line is that we now know that not only is vitamin D critically important for bone health throughout life, but probably it is incredibly important for prevention of common cancers, has major effects on the immune system, and also has major effects on our cardiovascular system.

JB: There are so many pearls that you put into that introduction. That is the most dense introduction I think we have had. It's amazing how many ways we could go in the next question. I will start with a common theme that I'm sure is on the mind of many people. In school, we learned that vitamin D is a fat soluble vitamin like vitamin A, and if you give a little bit too much you get toxic, so we have always been very reserved about vitamin D. Tell us a little bit about the toxicity story.

Vitamin D Toxicity

MH: Sure. I'll put it, again, into perspective because you are quite right. I mean, I always joke about this when I give my presentation. That is, I always tell the physicians in the audience that the one thing they probably remember from medical school more than anything else is: don't ever make your patient vitamin D intoxicated.

Now they have never seen vitamin D intoxication. They probably don't even know what vitamin D intoxication is. But if I tell physicians to treat their patients with 50,000 units of vitamin D, they just look starry-eyed and they are concerned that they are going to cause vitamin D intoxication. And this actually comes about because in the 1950s there was an outbreak of hypercalcemia in infants in Great Britain and they related it to overfortification of milk with vitamin D (although that was never proven). And based on that observation alone, in Europe, they passed laws forbidding vitamin D fortification in most dairy products, which continues to be on the books today.

But that concept has so permeated the medical community-that everybody is concerned about vitamin D intoxication-but what we now know, based on Dr. Vieth, and Dr. Heaney and our own work, is that you can give as much as 10,000 units of vitamin D a day for at least a half a year and not see any untoward toxicity. Typically, vitamin D intoxication occurs when you are taking more than 50,000 units of vitamin D daily for at least 6 months to a year. I'll give you one example. We saw a case where a gentleman was taking a vitamin nutrient that he had purchased off the internet. The company had forgotten to dilute it. He was taking a million units of vitamin D a day. He was severely vitamin D intoxicated.

JB: So if a physician is measuring in their patient that they are supplementing with D-they are measuring their serum calcium and their 25-hydroxy D levels and they are within normal range-can we assume they are not toxic?

MH: Unequivocally. If fact, by definition, vitamin D intoxication is a markedly elevated level of 25-hydroxyvitamin D, and typically it is above 150 nanograms per mL. So even though the normal ranges are coming back from laboratories at 20 to, say, 100 nanograms per mL, that is only for safety reasons. But we typically don't see vitamin D intoxication until they are above 150 to 200 nanograms per mL. So if the calcium is normal, with a level of 25-hydroxyvitamin D even of 1,25, that would not be considered to be vitamin D intoxication.

JB: So let's go back to your previous--really eloquent--point concerning this emerging understanding of how 25-dihydroxy can be converted in situ, even away from the kidney, into the 1,25 and then how that can be detoxified within the cell. That raises the question, what plasma level of 25-hydroxy do you need to get into in order to drive 25-hydroxy into these tissues that might have benefit in terms of the conversion into 1,25, or do we not know the kind of range?

Optimal Range of Vitamin D

MH: It is an excellent question. Most experts are now agreed that at a minimum, your patient should be above 20 nanograms per mL. But we now are considering you to be insufficient between 20 and 29 nanograms per mL. It is only when you get above about 30 nanograms per mL do we believe that all of the benefits of vitamin D can occur in the body.

I'll give you one example. There was a very nice study published by Dr. Liu, Dr. Meinken, and Dr. Adams in Science in March of last year.11 What they observed was the following. It has always been

known that macrophages activate vitamin D. They convert 25-hydroxy D to 1,25-dihydroxyvitamin D, and that is the reason for the hypercalceuria and hypercalcemia seen in patients with sarcoidosis. But we have never understood why these macrophages activate vitamin D. Well, they proved why.

It turns out that when a macrophage becomes infected (say, with TB, for example), what it does is it immediately upregulates the toll-like receptors, and the toll-like receptors get turned on in the macrophage. And the gene that gets turned on first is the enzyme to convert 25-hydroxy D to 1,25-dihydroxyvitamin D. Then the obvious question is, why is the macrophage making it? It turns out that 1,25-dihydroxyvitamin D tells the macrophage to increase the gene expression for cathelicidin, which is a peptide that specifically is made by the macrophage to kill infective agents, including tuberculosis.

So they cleverly went ahead and did the following study. They took African-American blood, which typically runs in the range of about 8 to 10 nanograms per mL. They added monocytes and TB, and showed that the TB infected the monocytes and killed them. They then took they same African-American blood and added to it 25-hydroxy D, and raised it to the level of about 26 to 30 nanograms per mL. They showed that those monocytes made 1,25-D, increased the production of cathelicidin, and killed the TB. So this proves that indeed you need to raise your blood levels of 25-hydroxyvitamin D, at least to 30 nanograms per mL to get the full benefits of vitamin D.

JB: Well that is really a fascinating observation, so here's the connection between the endocrine and immune system as it relates to vitamin D physiology. That raises a question in my mind about periods of a person's life where they may be more temporally at risk to vitamin D insufficiency. I'm thinking pregnancy.

I know that you have recently-in May of this year, 2007-your group published a paper in the Journal of Clinical Endocrinology and Metabolism that looked at maternal vitamin D deficiency and the risk to preeclampsia.12 I think that followed on a paper that I saw in the Journal of Nutrition in February of 2007-Bodnar's group, et al.-looking at the high prevalence of vitamin D insufficiency in black and white pregnant women residing in the United States and their neonates.13 Tell us a little bit about the pregnancy-vitamin D connection.

Pregnancy and Vitamin D

MH: Sure. Yes, in fact, we had published also, in January of this year. We looked at 40 mother-infant pairs at our medical center, and looked at their vitamin D status at the time that mom gave birth.14 Seventy-five percent were African-American; twenty-five percent were Caucasian. We found that 76{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of moms and 81{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of infants, at the time of birth, had a blood level of 25-hydroxyvitamin D of less than 20 nanograms per mL. Most of these women were taking a multivitamin (a prenatal vitamin) that contained 400 units of vitamin D, and drank (on average) 2.3 glasses of vitamin D-fortified milk a day, and they and their infants were still vitamin D deficient.

Lisa Bodner also has confirmed this. In fact, you are right. It was, in fact, Lisa Bodner, who made the observation, and we helped her with that, in showing that when you look at the incidence of preeclampsia and relate it to the blood level of 25-hydroxyvitamin D in the mom, that the higher the 25-hydroxyvitamin D, lower was the risk of developing preeclampsia.

I have recently talked with many of my OB/GYN colleagues, and they made a very interesting comment. They said, "You know, we see preeclampsia principally in the winter and early spring." And that is at the time when the moms, of course, are not getting any vitamin D and are at the highest risk of having severe vitamin D deficiency. So there may be a very significant association with the two.

And it also made one other kind of connection with the immune system, and that is that there has been this concept out there-Hope-Simpson was a physician, and in the 1980s he had suggested that it is curious that influenza occurs at the equator sporadically throughout the year, but influenza only occurs in temperate climates in the wintertime. He had suggested that there was a seasonal stimulus for this. Dr. Cannell and several other experts, including myself, wrote a recent paper to suggest the possibility, at least, that maybe indeed that seasonal stimulus is vitamin D deficiency.15 You become vitamin D insufficient and deficient around October/November because you no longer can make any vitamin D in your skin.

This was followed up by a very nice study by Dr. Aloia, who looked at African-American women receiving 2000 units of vitamin D a day compared to a group receiving only 400 units of vitamin D a day, and looked at their risk of developing upper respiratory tract infections throughout the wintertime, and showed a dramatic-almost 90{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36}--reduced risk of developing upper respiratory tract infections in the women that were taking 2000 units of vitamin D a day.16

Vitamin D is Linked to Many Conditions

JB: So that, then, leads to kind of an interesting general question. If vitamin D has this great array of impact on cellular function, then it might suggest that there would be a connection between vitamin D nutriture and physiology and overall longevity because we are talking about so many diseases. And, of course, this year in Archives of Internal Medicine we learned a little bit about that.17 Could you tell us that connection?

MH: Yes, it is a very interesting study. They looked at a large number of studies and looked at the vitamin D intake and then evaluated those manuscripts for longevity. What they concluded was that there was about a 7{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} increase in longevity for those that had the highest intake of vitamin D. Turning it around another way is that there was a 7{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduced risk of dying if you increased your vitamin D intake.

JB: These all sound extraordinarily positive, and, in fact, I saw a report that appeared-actually a couple of reports-since you gave your stellar performance and presentation at the Institute for Functional Medicine Symposium in May of 2007 that talked about vitamin D nutriture and type 2 diabetes risk, and even (maybe) metabolic syndrome and insulin sensitivity, so there is a whole other area of clinical implication.

But then I thought I saw a report about a month ago that said that investigators found no association between vitamin D status and autoimmune disease, which I found kind of contradictory to some of the trajectory that we have been seeing in the literature before. Do you have any comments about the diabetes/vitamin D and the diabetes/autoimmune connection?

MH: Sure. What we can say for sure is that there was a very interesting study that was published in 2001 by Dr. Hypponen.18 And what she did was she looked at children in Finland in the 1960s that were routinely getting 2000 units of vitamin D a day (that was what the recommendation was at that time) during the first year of life. And then she looked at their medical records for the next 31 years, and looked at their risk of developing type 1 diabetes. And she concluded that there was an 80{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} reduced risk in those children that took 2000 units of vitamin D a day during the first year of their life. The children that were vitamin D-insufficient had rickets, had a 2.4 fold increased risk of developing type 1 diabetes.

We know that beta eyelet cells have a vitamin D receptor. We know that if you incubate beta eyelet cells with the active form of vitamin D it stimulates those cells to make insulin. And since it is believed that this autoimmune disease for type 1 diabetes may in fact be due to a viral infection, that being vitamin D-deficient may increase your risk of that infection, and because vitamin D plays such an important role in both T and B cell function, that, in combination, may be the explanation for why vitamin D has been protective for type 1 diabetes.

Regarding type 2 diabetes, it is probably a little bit different story. Like I said, we know that 1,25-D will stimulate beta eyelet cells to make insulin. And there is some evidence that your fat cells have vitamin D receptors. We don't exactly know why, but it may very well be that part of the insulin resistance that is seen, especially in obesity, may in part be also due to vitamin D deficiency. Obesity is associated with vitamin D deficiency because the body fat sequesters the vitamin D and doesn't make it bioavailable to the body, and so typically obese people probably need twice as much vitamin D. So there are now several studies underway in patients with type 2 diabetes, and we are doing one of them, to see whether or not increasing their vitamin D intake to levels where we are getting the 25-hydroxy D above 30 nanograms per mL will be of any benefit.

JB: And how about the autoimmune/rheumatoid arthritis/multiple sclerosis connection with vitamin D? Is that still in an area of controversy?

MH: Yes, it's a good question. Again, it is curious, but true. If you are born above about Atlanta, Georgia, and live there for the first ten years of your life, you have a 100{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} increased risk of developing multiple sclerosis for the rest of your life, no matter where you live. People have always thought that multiple sclerosis may, in fact, occur either in utero or during early childhood, and may be, in fact, due to an infectious disease. You know, we just don't know what MS is due to. But there is a study done by a group where they looked at both men and women in the armed forces and their vitamin D intake and their relative risk of developing multiple sclerosis, and concluded that there was about a 40{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} decreased risk of developing multiple sclerosis, especially in women who were taking in more than 400 units of vitamin D a day. And then a more recent study by the same group suggested that both men and women had a lower risk of developing MS the higher their 25-hydroxyvitamin D was, so that the two were indirectly related.19

JB: I'd like to go just one step farther in your discussion about diabetes to look at the unfortunate epidemic that we are dealing with in medicine and health, which is renal failure and renal dialysis, which the centers are now growing rapidly to meet the growing need of people with renal failure. So that raises a

question about the vitamin D status of people who are in renal failure. I know that Amgen has a new drug out called Sensipar® that is a calcium agonist for managing problems with hypercalcemia, renal dialysis patients, and hyperphosphatemia. What is the status on a person with kidney problems and their vitamin D physiology?

MH: Yes, there are a couple of things going on. We believe that all patients with renal failure, no matter what the stage of the renal failure is, need to have a 25-hydroxyvitamin D of greater than 30 nanograms per mL. There are two reasons for it. The first is that we now know that the parathyroid glands also can activate vitamin D, and that they can make 1,25-dihydroxyvitamin D locally to suppress PTH production. And as you are well aware, patients with mild to moderate renal failure begin to develop secondary hyperparathyroidism. The second reason is that by raising your blood levels of 25-hydroxyvitamin D, it may have all these additional benefits on the body for patients who have stage 4 and 5 may be on renal dialysis and taking an active vitamin D analog or even the active form of vitamin D, calcitriol. Many physicians think that that is all that they need; that they are maintaining their vitamin D status. They are not. They are certainly satisfying the calcium and bone metabolism part of the equation, but they are not taking advantage of the local production of 1,25-dihydroxyvitamin D made in all the tissues in the body, including the parathyroid glands. Because it is likely that that production is making the concentration of 1,25-dihydroxyvitamin D within the cell much higher than it would ever be by giving it exogenously, either intravenously or orally, for preventing metabolic bone disease and secondary hyperparathyroidism. So, for example, pericalcitol, or calcitriol (given orally or intravenously), won't raise target tissue levels to those degrees.

JB: That's fascinating. That's very, very helpful. That's, I think, one of the areas where there seems to be quite a bit of misunderstanding within the field of vitamin D nutriture. I have talked to a number of diabetologists and nephrologists and it seems like that is still an area of confusion.

MH: Yes, and so the bottom line is that for everyone there is never a reason not to have a 25-hydroxyvitamin D above 30 nanograms per mL unless you have a chronic granulomatous disorder, such as sarcoidosis, in which case, you have to be a little bit more careful because of this extra renal production (the macrophage production) of 1,25-D that can get into your bloodstream.

Plant Cognates of Vitamin D

JB: One last question, and this is kind of a wild card question. A number of years ago-this is probably now 20 years ago-I recall meeting a biochemist/investigator by the name of Saul Wasserman who was doing work in animal science in hypercalcemia in animals that were grazing animals. He discovered (found) what he thought was a plant cognate of vitamin D that (if animals grazed on these plants and had this vitamin E analog) would create a condition that was hypercalcemia in those animals leading to joint calcification, soft tissue calcification, and then they would not be able to bend over and they would die of starvation. Are there, as far as you know, any plant cognates of vitamin D from certain plant foods?

MH: Right. It's a very good question. It turns out that as early as 1920, when they were starting to irradiate animals with ultraviolet light and sunlight, if you irradiate grass, if you irradiate, say, rye grass, you can, in fact, make the grass make vitamin D2 and vitamin D3. The observation by Dr. Wasserman--in fact, we made a similar observation and had published it almost simultaneously with him-is the plants called solanum, which are relatively toxic, make a 1,25-dihydroxyvitamin D that has attached to it a line of sugars.20 And it is because the cattle were ingesting such huge amounts of this compound and the

sugars were removed in their gut, that they became severely hypercalcemic. But there is little evidence that most of the plant foods that we ingest have any of the active form of vitamin D, and it is really only tiny, tiny amounts of vitamin D because they have not been exposed to a lot of ultraviolet radiation.

JB: Very interesting, and the solanum family is like potato, eggplant, and tomato, is that correct?

MH: Exactly correct.

JB: So I'd like to close with a philosophical question. This, I think, is almost like asking the obvious, but I'd like to get your very sage perspective, and that is, from all that you have said and published in your years of contribution to the field, it would seem, to the outside observer, that if there was a drug that had been developed by a pharmaceutical company that would accomplish all the things that vitamin D has been ascribed to be beneficial for that it would be a blockbuster drug and that company would be mega-successful and it would be a high investment opportunity on the stock exchange. But yet, we are still seeing reluctance to accept a lot of this information that you have shared within medicine as clinically valuable. Would you like to share your opinion as to why?

Recommendations for Supplementation and Sun Exposure
MH: Sure. I think that the problem is that they consider vitamin D to be a vitamin. To be a boring, fat soluble vitamin found in cod liver oil. But what we need to have a better appreciation of is that we were born, and we evolved, and we have been bathed in sunlight, and it really is sunlight production of vitamin D that has sustained vertebrate evolution and human evolution, and we have not really appreciated why.

One of the major reasons is because of the photo-production of vitamin D. And because of our civilization of being indoors and the paranoia about being exposed to any direct sunlight has put the entire world's population at risk of vitamin D deficiency, so vitamin D deficiency is really a disease of civilization and we need to appreciate the beneficial effects of the sun. If you are not getting adequate sunlight, I would encourage all of your listeners and family members-because I do it and my entire family does it-is to take a thousand units of vitamin D supplement everyday because that will help to maintain your 25-hydroxyvitamin D levels at around 30 nanograms per mL. And certainly sensible sun exposure, that is, no more than probably 5, 10, 15 minutes between the hours of 10 am and 3 pm, and that's during the spring, summer, and fall in temperate climates, followed by good sun protection, is really more than adequate. And it is typically arms and legs, two to three times a week; you can always protect your face.

JB: Well, Dr. Holick as I said in your introduction at the Institute for Functional Medicine meeting, if Nobel Prizes are given on the basis of making contributions to society that will change the course of history, I would say that your work stands tall and strong as being certainly a candidate for that kind of an award. We want to thank you for your absolute eloquence and championship/leadership in this whole area to alert the community as to the importance of this nutrient and its relationship to health. Thank you very, very much.

MH: Jeff, thank you so very much. It is always a pleasure to be on your program and continue your great work.

JB: You do the same. Talk to you soon.

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