October 2003 Issue |Michael Holick, MD, PhD Boston University School of Medicine

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Welcome to *Functional Medicine Update* for October 2003. It may seem premature to start talking about our 11th International Symposium on Functional Medicine, which will be held in the spring of 2004. However, I want to give you some information about where the Institute for Functional Medicine is headed next year. Selection of the topic for the 11th symposium is based on many responses we received from participants who attended the 10th International Symposium on Functional Medicine in Tucson in May 2003.

In 2004, we will focus on aspects of the pandemic of type 2 diabetes—its origin, its interrelationship with other age-related disorders, and how to develop effective management programs for children and adults. We are putting together a world-class roster of plenary speakers and workshop facilitators who will speak on this topic from a functional medicine perspective across disciplines from science and research to clinical implementation. You will hear more about the program and presenters over the course of the next few months. I want to give you an opportunity to mark the dates on your calendar—May 11-15, 2004, in Vancouver, British Columbia at the Westin Bayshore Resort & Marina.

Vitamin D and Type 2 Diabetes
Over the course of the next several months in *FMU*, I am going to bring some of the symposium topics into discussion so those of you who attend the symposium will be well prepared. Those of you who may not plan to attend the symposium will receive some of the information we will be discussing next May.

This month we will be discussing a topic that may appear to be only indirectly related to type 2 diabetes. That topic is vitamin D and its relationship to medicine and disease. The vitamin D connection to chronic age-related diseases other than osteoporosis may not be obvious. You will understand that connection, however, after you listen to our Clinician/Researcher of the Month, Dr. Michael Holick. Dr. Holick has been a primary investigator of vitamin physiology and medicine for more than 25 years. He will present some valuable news to use.

Type 2 Diabetes and Cell Signaling Processes
I would like to begin by looking at the long-term objective of understanding the etiology of type 2 diabetes from the standpoint of cellular signaling processes. Cellular signaling is becoming a “hot topic” in basic science and physiology research. Each day, new information becomes available that helps us understand the importance and complexity of the signaling process. Signal transduction, as it is called, occurs in different ways in different types of cells, tissues, and organs. We cannot simply talk about

global cell signaling. We must, instead, discuss specific processes within specific organs, organ systems, or tissues that give rise to specific functional or phenotypic changes.

A new term is emerging in medicine. We have used the terms “genomics,” “proteomics,” and “metabolomics.” The new term is “phenomics.” It describes the interrelationship between gene expression and mRNA translation into protein. It is concerned with the way proteins control function, how metabolism ultimately gives rise to the outcome in the cell, and how that all works together to give rise to what we observe as the phenomic outcome in that patient, organ, or organ system. Phenomics assumes a functional change in the organism that is a consequence of the mixture or interrelationship of metabolomic, proteomic, and genomic factors.

Phenomics
This is a heavyweight topic. I believe, though, that you will understand not only what Dr. Holick is going to discuss later in this issue, but also where we will take this discussion over the next several months. We will take the latest discoveries about signal transduction and cell signaling and apply them to clinical procedures that personalize treatment to individual need and improve patient outcome.

That is a big promise, but we will follow through on it over the next several months. This month we will look at some of the cell signaling interrelationships that connect bone, brain, heart, kidney, colon, prostate, and breast. Those may seem strange areas to be connected. Through cell signaling, we begin to understand shared physiological processes in phenomics that may become the sentinel systems, or the fulcrum. Remember that, like Atlas, if we put the right lever in the right place, we can move the earth. Perhaps we want to make sure we are putting the lever at the right place with regard to these systems

We begin with osteoporosis, a condition we all know something about. This condition is of significant concern, particularly for women as they go through menopause. Colles’ fractures, spinal compression fractures, and disability can lead to hospitalization and even death. Many people who end up in the hospital with spontaneous fractures from osteoporosis never return home. It is considered the 11^{th} to the 7^{th} cause of death in the older-age population. That statistic is significant. It is more than simply an orthopedic problem.

To understand the etiology of osteoporosis is to better understand the interrelationship between skeletal mass and the appendicular skeleton, and how various forms of bone are either resorbed or regenerated in the dynamic process of maintaining the osteolysis and osteogenesis equilibrium. Bone cell mass, sometimes called bone reserve, is an important attribute to maintain as we age.

Bone Reserve
Bone reserve is the skeletal mass one must keep intact to withstand the normal wear and tear of life. Every time one twists, turns, stumbles, or trips, it results in strain on the skeleton that has to mobilize its reserve, its tensile strength, like a bridge. As bone reserve is compromised over time, the inevitable stress and strain the skeleton is subjected to may decrease reserve. This organ reserve derives from the James Fries model we have spoken about many times in *FMU*.

Eventually, if one dips below the threshold, or the zone of fracture, simple daily mechanical activities one never thinks about may exceed the resilience of one’s bone mechanical resistance and lead to spontaneous fracture. An older individual does not fall down and break a hip; instead, he or she suffers a

spontaneous hip fracture and then falls down. The normal strength of the bone is so compromised that it cannot respond to the stress and strain of daily living, which might include tripping or stumbling.

Maintaining Skeletal Reserve

The goal is to maintain a high skeletal reserve, a high skeletal mass. One has to build that reserve in one's younger years. If one has it, one wants to hold onto it. Therefore, one must try to build bone mass in youth with appropriate exercise, nutrition, and a healthy lifestyle, and try to maintain it. This is a classic model of functional aging, the functional medicine concept, the organ reserve concept.

How is that accomplished? One needs to look at the dynamics of calcium into the bone, calcium out of the bone, the hydroxyapatite matrix, the proteinaceous skeletal framework upon which the calcium hydroxyapatite phosphate is crystallized. To do that, consideration must be given to the many complex factors that play a role in that balance, not just calcium nutrition itself. It has to do with the way the protein is synthesized, and the anabolic and catabolic factors that lead to protein synthesis and degradation. It also relates to the way calcium moves into cells and magnesium moves out of cells, the calcium/magnesium dynamic. There is a strong endocrine relationship through the parathyroid and thyroid glands. There is a gastrointestinal absorption component with calcium-binding protein and the absorption of calcium. There is a relationship to various hormonal factors related to aspects of the bone-remodeling process.

Estrogen's Role

Postmenopausal estrogen loss in women appears to increase the risk of bone loss, as it does in men who have low estrogen levels, or who have estrogen receptors that are genetically unable to receive the estrogen message from their bodies. Men are also at risk for osteoporosis. We tend to forget about spontaneous fractures in older men. Although these fractures occur less frequently in men than in women, it is still a troubling problem in men. All these hormonal, endocrinological, gastrointestinal, and nutritional lifestyle variables play roles in maintaining bone reserve.

The Role of the Immune System

What is more interesting in terms of new evidence is the role the immune system plays in this process. This information does not negate or diminish the significance of the endocrine system, the parathyroid and thyroid, and kidney and liver function that we will be speaking about in greater detail later, but it hints at an immunological cascade.

Why am I suggesting this? Individuals who have increased bone turnover, particularly in cases of arthritic conditions associated with increased loss of bone reserve, may have increased levels of interleukin-6 in their blood. This proinflammatory cytokine appears to play a role in the developmental stage of the osteoblasts and osteoclasts. The osteoclast is the bone-resorbing unit; the osteoblast is involved in bone formation or osteogenesis. Inflammatory cytokines appear to play a role in the developmental physiology of the osteoblast, the bone-forming unit, being converted to the osteoclast, the bone-resorbing unit. Therefore, high levels of inflammatory mediators increase the relative population of the bone resorbing units at the expense of lowered levels of the bone formation unit. That trips the equilibrium balance toward increased bone resorption.

Inflammatory Cytokines in Arthritis and Bone Turnover

A report in the journal *Arthritis & Rheumatism* is titled "The Role of the Interleukin-6 Family of

Cytokines in Inflammatory Arthritis and Bone Turnover." [1] According to the authors of this paper, interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6) appear to be involved with increasing cell signaling and bone resorption. Skeletal mass is composed of active, dynamic tissue, reflecting all sorts of neuro-endocrine-immunological changes over time. Therefore, it is not just the absorption of calcium, or the dietary calcium, or even the endocrine control of calcium, but it is also the immunological control of where calcium is placed or how it is mobilized, based on cell-signaling processes at the osteoblasts and osteoclasts.

Proinflammatory Th-1 cytokines like IL-1, TNF, and IL-6 appear to participate in the activation of bone resorption. Autoimmune clinical conditions like rheumatoid arthritis, in which significant elevations of these cytokines occur, are associated with increased risk of bone loss.

Osteoporosis as Part of the Web of Health Relationships
From previous discussions, we might postulate that increased evidence of these inflammatory cytokines is related to other disorders associated with age, such as coronary heart disease, cancer, and neurological problems such as dementia. I am implying that osteoporosis might be connected to other degenerative, age-related conditions. It is here that functional medicine comes into play. It would be misleading to regard disorders as individual, compartmentalized diseases unrelated to one another, as if every page of the diagnostic-related groups (DRG) reflects independent variables having no dependence on any other condition. In so doing, we are led to the false belief that heart disease is not connected to osteoporosis, arthritis, cancer, or dementia.

Instead, we should look at underlying mechanisms associated with cell signaling processes that alter the phenomics of the cells, tissues, and organs, and the outcome of the patient. These interrelated mechanisms give rise to different predictive abilities and perhaps different strategies for treatment than we would conclude if we looked at each disease as if it was independent from all others. This point is a central feature that distinguishes functional medicine from a traditional pathophysiology-based medicine, which is rooted in diagnosis as the primary key to understanding.

Inflammatory Mediators in Various Diseases
Inflammatory mediators such as IL-1, TNF, and IL-6 are the same signal transduction modulators involved as associated risk factors in conditions like coronary artery disease and presenile dementia. The names of the players have not changed; they are the mediators, the cell-signaling activators that send signals at a distance in the body from one tissue to another. They are commonly shared across different diseases.

This means that we may have distinguished diseases artificially, one from the other, rather than looking at the commonality of mechanisms and tying that together with unique genetic susceptibilities or sensitivities. Why does one person have osteoporosis, another heart disease, and another dementia? They do not necessarily have all three all the time. The answer would be related to and rooted in the genetic uniqueness of the way these tissues express their different characteristics, but they can share similar mechanisms

That leads to a discussion of IL-6 and coronary artery disease. The *Journal of the American Medical Association* featured a paper titled "Inflammatory Markers in Coronary Artery Disease." [2] According to the authors of this paper, an elevated IL-6 level is a strong and independent predictor of mortality for

patients with acute coronary syndromes in both the invasive and conservative treatment arms of the clinical trial. It appears that elevated IL-6 is related to elevated inflammatory markers like C-reactive protein (CRP), particularly high-sensitivity CRP and myeloperoxidase levels, which I will discuss in more detail.

IL-6, the signal transduction agent, is an intercellular mediator involved with cell signaling in bone turnover, which leads to increased conversion of osteoblasts to osteoclasts and the resorption of bone. IL-6 is also involved with signals related to coronary artery disease.

Myeloperoxidase
Similarly, activation of cell signals involved with inflammatory processes triggers other cascades of events. This is where the process becomes exciting, because the cascade of these events may differ from tissue to tissue in the way they play themselves out into the phenotype. Both elevated IL-6 levels and increased levels of myeloperoxidase are associated with coronary artery disease, and myeloperoxidase levels are independently associated with coronary artery disease risk.

Myeloperoxidase is an enzyme some people have called the Klebanoff reaction, named for its discoverer, Dr. Seymour Klebanoff, at the University of Washington. He is the pathologist who found that the immune system works in defending the body against invaders like bacteria through a form of chemical warfare that involves bleaching the invaders to death. Bleaching refers to the production of hydrogen peroxide and, subsequently, other oxidants from the immune system. This is a selective microbiocidal mechanism in which cell-mediated immune defense participates. It entails the release of hydrogen peroxide at a special area of contact with a cell-surface reactive material like a gram-negative bacterium or a virus.

Bleaching Process
This bleaching event, like conducted oxidation, causes destruction of the cellular machinery, lyses the cell, or causes something of that nature. It is a part of the defense mechanism. One of the enzymes involved with the production of these oxidants is called myeloperoxidase. It is found in high levels in white cells. As a byproduct of its reaction, myeloperoxidase is an enzyme that produces an activated form of oxygen called hypochloride (HOCl). HOCl is found in bleach. Sodium hypochloride is the basic component of chlorine bleach.

When we talk about bleaching the cells, we are referring to the hypochloride ion, which can undergo secondary conversion into a variety of other oxidants, including superoxide, singlet oxygen, and hydrogen peroxide. Elevated myeloperoxidase activity in white cells is associated with an increased risk of coronary artery disease, suggesting that an overactive Th-1 immune system can increase the risk not only of bone loss, but also of atherogenesis. I refer to a paper titled “Association between Myeloperoxidase Levels and Risk of Coronary Artery Disease.” [3]

Processes may exist that connect different types of diseases, and understanding these processes may help us proceed with therapy. This understanding may be preferable to simply treating the individual disease as if it works independently in isolation from other disorders. This is the functional medicine concept and strategy.

Let’s take an example of a therapeutic agent that might cut across diseases and speak more to

mechanisms. Glycine is one such agent that has received considerable attention recently in the scientific press. Glycine is the simplest of all the amino acids in which the R group of that amino acid is a hydrogen. It is the one amino acid that does not have a D and an L form. Despite its simple organic chemical structure, glycine has demonstrated antiinflammatory, immunomodulatory, and cytoprotective effects. Glycine influences cellular physiology across a wide range of function.

I have previously described the way the immune system works—the Th-1 proinflammatory cytokines as cell messengers, and their ability to activate components of oxidative processes. Perhaps we could develop a hypothesis to explain how glycine might cut across conditions associated with inflammation, immune dysfunction, and cell death. It must have something to do with the cell-signaling process. Perhaps we should be looking at all the disorders associated with cell-signaling processes that have gone awry. Perhaps glycine would be a central therapeutic agent that might be useful for those conditions. This is reverse logic for evaluating therapies for a functional medicine strategy.

Glycine Functions

Glycine protects against shock caused by hemorrhage, endotoxin, and sepsis. It prevents ischemic reperfusion injury and cold-storage reperfusion injury in a variety of tissues and organs, including liver, kidney, heart, intestine, and skeletal muscle. It is known to diminish renal and liver injury caused by hepatic and renal toxicants and drugs. Glycine also protects against induced arthritis in animals, inhibits gastric secretion, and protects the gastric mucosa against chemical- and stress-induced ulcers. How can one simple amino acid have all those remarkable effects? How can one agent affect all of those independent diseases?

Perhaps it is not the diseases, but the mechanisms that relate to the etiology of altered cell signaling for which glycine has some effect on normalizing cell signals. That is a hypothesis I want to explore. Glycine appears to exert protective effects that cut across its antiinflammatory potential, its immunomodulatory potential, and its direct cytoprotective actions. It appears to act on inflammatory cells such as macrophages in the immune system. These are the cells engaged in hand-to-hand combat, secreting the Th-1 cytokines, the various chemical signals like IL-1, TNF, and IL-6. Glycine acts on these macrophages to suppress their activation, which results in the suppression of transcription factors and reduced formation of free radicals and inflammatory cytokines.

Modifying Gene Expression

A simple amino acid may have the ability to influence the genes in such a way as to modify gene expression patterns and therefore alter protein synthesis and activation of metabolism into the phenomics—that is, the phenotype of the cell or tissue. It may be able to arrest an out-of-balance immune system that is shifted toward proinflammatory states, with increased release of cell signals associated with oxidative injury and oxidative stress. That is a huge step forward in understanding how nutrients or agents can modulate function beyond filling the gap of deficiency.

Nowhere in the development of the original minimum daily requirements or RDAs for any nutrient was this discussion ever raised, because no one knew about it. This is remarkable breakthrough information that has evolved over the last 10 to 15 years with the unlocking of the human genome and factors that modify its expression. Glycine appears to act on inflammatory cells such as macrophages, to influence cell signaling, which alters the activation of transcription factors that subsequently produce molecules such as inflammatory cytokines that increase oxidative free radicals and oxidative stress.

An Influence on Numerous Disease States

In one model of its mechanism, glycine appears to activate a chloride channel that stabilizes and polarizes the plasma membrane. In the neurological system, glycine has an agonist-induced effect on the L-type voltage-dependent calcium channels, resulting in suppression of intercellular ions, which may account for its immunomodulatory and antiinflammatory effects and its potential role in animal models for prevention of neurologic injury. Several years ago, an article in the *American Journal of Psychiatry* described the benefits of glycine in a group of schizophrenic patients who did not respond well to traditional anti-schizophrenia medications. When these patients were placed on oral glycine, they experienced significant improvement in their function, and glycine potentiated the action of their medications. [4]

This is a simple example of one nutrient that cuts across mechanisms that influence many different functions across different disease states. We can consider the whole system as a complex transportation system, such as the railroads of days gone by. We may have a problem with the transportation system: the cars are not reaching their final destinations; they are breaking down. A management team is brought in to determine exactly who is at fault. Someone needs to examine the rails to see if they are intact and whether the cars are either flying off the rails or having a rocky trip and cannot achieve normal speed. They are producing a lot of heat on the tracks or having flameouts in their tinder boxes. The rails represent the mechanism of transportation. That is where we are going in this discussion of these cell-signaling substances.

Glycine in Clinical Application

From a clinical perspective, what amount of glycine are we talking about? Doses of glycine can vary depending on different applications. For example, to improve the detoxification in the liver, intakes of 3 to 12 grams have been reported in the literature. When talking about the effects of glycine on brain biochemical function, doses may be as high as 10 to 20 grams. There can be a wide range of glycine intake, but it has a broad safety range.

Individual characteristics determine who could benefit from an increased intake of glycine. No single size fits all. The fact that it has been shown useful for some does not mean everyone should start taking large amounts of glycine. That is not the object of this discussion. Glycine is a novel antiinflammatory, immunomodulatory, and cytoprotective agent. For those of you who want to follow up on this topic, a review article on glycine appeared in *Current Opinion in Clinical Nutrition and Metabolic Care*. [5]

Peroxisome proliferator-activated receptors (PPARs) are a family of signaling molecules related to diabetes, insulin, and possibly obesity. These newly recognized nuclear orphan receptors are transduction agents that are important in the cell-signaling process related to energy economy, mitochondrial function, fatty acid metabolism, and insulin sensitivity.

There is a growing pandemic of maturity-onset diabetes, or type 2 diabetes. We call it a pandemic because it cuts across all ages, affecting an estimated 16,000,000 people in the United States alone. [6] Researchers believe an additional 16,000,000 Americans have a pre-diabetic condition, or impaired glucose tolerance (IGT). In both type 2 diabetes and IGT, cardiovascular disease is the leading cause of morbidity and premature death. Increased risk of macrovascular disease in both type-2 diabetes and IGT is associated with insulin resistance.

As we know from discussions with Dr. Gerald Reaven, the father of syndrome X, insulin resistance refers

to an impaired ability of the body to respond appropriately to insulin and utilize glucose. Our 2004 symposium will deal extensively with the increasing amount of basic and clinical science underpinning the understanding of the etiology of type 2 diabetes.

PPARs

The PPAR family is one cell-signaling contributor in this case, specifically through its influence on gene expression. The mechanism of some aspects of insulin resistance might occur by altered signaling through PPAR substances. There are both agonists that activate PPARs—the *alpha*, *beta*, and *gamma* forms—and there are antagonists that inactivate selectively. This process may be tissue-specific.

How does this relate to the emerging model of insulin resistance, hyperinsulinemia, and type 2 diabetes? Once again, it is the genes/environment model we have talked about so many times. Genetic and environmental influences connect to give rise to the expression of insulin resistance. Insulin resistance increases insulin levels, leading to a hyperinsulinemic state that has an adverse impact on glucose tolerance and triglyceride synthesis, leading to hypertriglyceridemia. It decreases HDL synthesis, leading to lowered HDL levels.

PPAR Influences

The increased small, dense atherogenic LDLs lead to an adverse effect—an increase in plasminogen activator inhibitor 1. That increase has a direct effect on chemotaxis of white cells and attachment to the endothelium, which becomes an etiological factor leading ultimately to transmigration, foam cell formation, LDL oxidation, and, using the Steinberg model, atherosclerosis.

We see a complex interweaving of genes, environment, endocrine function, immune function, and, ultimately, the expression of cardiovascular disease.

Thiazolidinediones

The PPAR family is a series of signaling molecules that play a role in this process. Researchers have become increasingly interested in their respective roles in the past few years, particularly as a consequence of the discovery of a family of drugs called thiazolidinediones. The first of these to come to market was Rezulin, which was subsequently removed because of its potential for liver toxicity.

Thiazolidinediones activate or serve as agonists for the PPARs. Researchers are also discovering a number of other substances that can serve as partial agonists or activators of PPARs. They have selectivity among the *alpha*, *beta*, and *gamma* families of PPARs. Many of these are nutritionally derived. They include omega 3 fatty acids, for instance, and possibly conjugated linoleic acid, or CLA.

Considerable attention is being focused on PPAR-modulated pathways. The PPAR pathways are nuclear receptors that appear to be at the crossroads between lipid metabolism and inflammation. This role suggests, once again, a mechanism for conditions that cut across a number of organs, such as bone, brain, heart, kidney, prostate, and breast. Pathology in all of these organs has inflammatory components. All may be related to insulin signaling, PPAR signaling, and their interrelationship with these inflammatory mediators.

A PPAR Review

PPARs are ligand-activated transcription factors that belong to the nuclear receptor family.[7]They have been called orphan receptors because their function was not understood. They are not members of the steroid hormone family of receptors, as it was first believed. PPARs function as regulators of lipid and lipoprotein metabolism. They are also involved in glucose homeostasis. They influence cellular proliferation, differentiation, and apoptosis (the death of transformed cells).

PPARα is highly expressed in tissues such as the liver, muscle, kidney, and heart, where it stimulates the β oxidation of fatty acids and leads to their metabolism. PPARγ , on the other hand, is predominantly expressed in intestine and adipose tissue. It triggers adipocyte differentiation and can promote lipid storage. The hypolipidemic fibrates, for example, as well as other anti-diabetic glitazone drugs, are synthetic ligands for PPARα and PPARγrespectively. Furthermore, fatty acids and eicosanoids of the omega 3 family are natural PPAR ligands. Therefore, we can see some relationship between diet and environmental factors and cell signaling through the PPAR receptor family.

Modulatory Role of PPARs
PPAR activators exert antiinflammatory activities in different immunological and vascular cell types, such as monocytes, macrophages, endothelial, epithelial and smooth muscle cells, in which PPARs are known to be expressed. These findings indicate a modulating role of PPARs in the control of the inflammatory response. This role has potential implications across a number of diseases that may only secondarily be associated with insulin, dysinsulinism, or hyperinsulinemia. These conditions are associated with bone formation, neurological functional difficulties, cardiovascular disease, and kidney, colon, and breast cancer.

These conditions make interesting but strange bedfellows. All of these pathologies, however, may be connected under a single cell-signaling mechanism. It would be unduly simplistic to suggest that if we understand PPARs, we understand everything about those diseases. It is only a part of the complex network of cellular signaling. Certainly, however, PPARs are an important part of this understanding. A review of this topic appeared in *Inflammation Research*. [8]

PPARs and Atherosclerosis
PPARs play an important role in the etiology of atherosclerosis, again emphasizing the connection between heart, insulin, and type 2 diabetes. A review of this topic, in the journal *TRENDS in Molecular Medicine*, discusses the emerging understanding of PPARα and PPARγ , and the protection against atherosclerotic disease that appears to be part of a major research emphasis. [9]

Vascular inflammation is modified both *in vitro* and *in vivo* as a consequence of PPARγactivators. [10] Strong evidence indicates that these PPARγ activators inhibit the expression of adhesion molecules such as vascular adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 2 (VCAM-2), molecules we talked about at our symposium in Tucson that are associated with atherogenesis. I hope you see the beginnings of a model that uses cell signaling to define new therapeutic strategies

INTERVIEW TRANSCRIPT

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JB: This month, in our Clinician/Researcher of the Month interview, we are fortunate to speak with a researcher who also has clinical interests. Dr. Michael Holick teaches at the Boston University School of Medicine and has been an active investigator for over 20 years in vitamin D physiology, biochemistry, and its application in clinical medicine. Welcome to FMU, Dr. Holick. Would you begin this discussion by reviewing the history of vitamin D?

MH: The vitamin D story really began 300 years ago as the Industrial Revolution began to take hold in Northern Europe. Children lived in sunless alleyways and developed rickets. It would take another 200 years for science to appreciate the fact that exposure to sunlight is critically important for the production of vitamin D in the skin and that it can ultimately prevent rickets in children. It also helps to maintain good bone health, and it may even prevent cancer in adults.

The Many Roles of Vitamin D

JB: As we look at the interesting evolution of vitamin D, the photochemical connection is fascinating. In your role at the Boston University School of Medicine, you are also a professor of medicine in dermatology and physiology. Some people may not understand how that is connected to your directorship of a bone healthcare clinic. Those roles all interrelate with the history of vitamin D.

MH: That's correct. In fact, we did some studies showing that even some of the earliest life forms—cytoplankton—have been photosynthesizing vitamin D on the earth for over 750 million years. We now realize that when one is exposed to sunlight, it's the ultraviolet B portion, the most energetic portion of the sun that penetrates to the earth's surface, that converts the precursor of cholesterol, 70-hydrocholesterol, not directly to vitamin D, but to pre-vitamin D.

Once pre-vitamin D is formed, and it's formed specifically in the membrane of the skin cell, it immediately transforms into vitamin D, and is kicked out of the cell into the extracellular space. As you are aware, most vitamin D is produced in the epidermis, which is bloodless, and then it enters into the bloodstream where it journeys for its first hydroxylation in the liver.

SPF Creams and Photochemistry

JB: I have heard people bring up a clinical question in relation to this process. If photochemistry is involved in the formation of vitamin D in the skin, what is the effect on this process of high SPF sunscreen creams designed to reduce the risk of skin cancer?

MH: That's a very good point. We know, for example, typically for natural sunscreen, i.e., skin pigmentation, melanin, most African Americans are deficient in vitamin D because they have such good sun protection. We did a study that showed if you wear sunscreen with an SPF of 8 properly, it reduces your ability to make vitamin D by more than 95 percent. It's very similar to African Americans, and puts people at risk for vitamin D deficiency.

So what do we do? It's very simple. You don't need to bake in the sun to make lots of vitamin D. Five to 10 minutes of exposure, two to three times a week, is usually more than adequate to make enough vitamin D.

Skin Exposure Needed for Vitamin D Production
JB: What surface area of the skin needs to be exposed to produce that effect?

MH: We did a study with medical students. We had them in bathing suits in the winter and brought them upstairs to our clinical research center where we put them in a tanning bed to mimic sunlight. If you're wearing a bathing suit, and you expose your body to what's called a minimal erythemal dose (MED), a light pinkness to your skin, not a sunburn, it's equivalent to taking 20,000 units of vitamin D a day.

If you expose 6 percent of your body surface to 1 MED, it's equivalent to taking about 600 to 1000 units of vitamin D a day. That is the amount that most experts, including myself, believe you need if you're not exposed to sunlight.

Early Research
JB: That gives us some clinical perspective. I presume you must have become interested in this topic at some level because of your place of residence. I note you received both your MD and PhD at the University of Wisconsin. I recall that a lot of your early work was done there.

MH: That's correct. I was very fortunate to work with Dr. DeLuca, and my PhD thesis was "The Isolation and Identification of 1,25-dihydroxyvitamin D3." In the two years we spent together, my roommate and I were the first to chemically synthesize it.

Then, while I was in medical school, I had the opportunity to collaborate with other investigators. We were the first to report the efficacy of 1,25-dihydroxyvitamin D to treat renal osteodystrophy.

Hydroxylation of Vitamin D
JB: That research takes us in a direction that is different from considering vitamin D as a vitamin to the more contemporary view that it is a prohormone. Conversion of its prohormonal form, cholecalciferol, into the hydroxylated derivatives is where it mitigates its action. Would you describe that hydroxylation?

MH: Once you make vitamin D in your skin, or you ingest it in your diet, it has to go to the liver, where it's converted to 25-hydroxyvitamin D, the major circulating form of the vitamin. It is the form of vitamin D that clinicians should be using to measure vitamin D status in their patients. It then leaves the liver, enters the circulation, and goes to the kidney where it is activated in the 1 position to form 1,25-dihydroxyvitamin D.

It is 1,25-dihydroxyvitamin D that is recognized by its specific receptors in the intestine to increase the efficiency of intestinal calcium absorption, and it goes to your bones to mobilize calcium stores from the bone. Contrary to what people think about vitamin D as being critically important for bone health, and that it has a direct action on causing the mineralization of bone, the true function of vitamin D is to make sure your blood ionized calcium is normal. If you're not getting enough calcium from your diet, you will remove it from your bone, and vitamin D helps in that process.

Hydroxylase Enzymes
JB: Of those two hydroxylase enzymes, the one in the liver and the one in the kidney, do we know which is more sensitive to metabolic acidosis or various inhibitors that could interfere with the transformation?

MH: The liver has a large capacity to hydroxylate vitamin D. Unless you have severe fat malabsorption and are not absorbing vitamin D, or more than 90 percent of your liver is dysfunctional, you are capable of metabolizing vitamin D to 25-hydroxyvitamin D. The kidney, on the other hand, is different. It is quite sensitive and tightly regulated in its ability to make 1,25-dihydroxyvitamin D. Parathyroid hormone is certainly a good example. High blood phosphorus will shut down this hydroxylation and low-blood phosphorus will turn it on.

Chronic Kidney Disorders and Vitamin D Status
JB: Is there a correlation between chronic kidney disorders and the relationship to vitamin D status?

MH: In fact there is. We now know that phosphorus is critically important. Patients who develop mild to moderate renal failure often have elevated blood phosphorus level because they can't clear it. This shuts down the renal production on 1,25-D. That results in a decrease in intestinal calcium absorption, which leads to an increase in the production and secretion of parathyroid hormone, leading to secondary hyperparathyroidism.

Controlling the level of phosphorus is critically important in early to moderate renal failure. That is usually done by giving oral calcium carbonate with meals to bind it so it doesn't get absorbed. Once kidney function is reduced by more than two thirds, the kidney can no longer make an adequate amount of 1,25-D to satisfy the body's requirement. Therefore, one needs to be on either 1,25-dihydroxyvitamin D3 or one of the new active vitamin D metabolites that have recently hit the market.

Geriatric Vitamin D Management
JB: In the geriatric medical population, particularly in nursing homes, administration of vitamin D metabolites, or salmon calcitonin, is a common occurrence. Is that a consequence of kidney-related functional problems, or is it just a complication of many other factors?

MH: For the most part, nursing home residents should not be getting vitamin D metabolites; they should be getting vitamin D. Physicians often order 1,25-dihydroxyvitamin D erroneously because they think it's the active form that should be used to measure and determine vitamin D status. It often comes back normal or even high. It does not give any insight into the vitamin D status of the patient.

Only if they have poor renal function should they be getting one of these vitamin D-active compounds because, first of all, they're very expensive, and second, they can cause hypercalcinuria, hypercalcemia, and other complications.

Vitamin D and Immune Function
JB: Let's move to a discussion of the emerging understanding of the role of vitamin D in the immunological system.

MH: It turns out that activated B- and T-lymphocytes have receptors for 1,25-D. We also know that 1,25-D will alter the immune system in various ways. I think a more important question is how it relates clinically. The first insight was made in what are called NOD mice. These mice routinely get type 1 diabetes after 200 days of life. If you pre-treat them with 1,25-D, in 80 percent of the cases you prevent them from developing type 1 diabetes. Hypponen in Finland looked at children from 1 year of age on and followed them for more than 20 years. [11] The risk of developing type-1 diabetes decreased by 80

percent in the children who received 2000 units of vitamin D a day.

We also know there is a latitudinal association with multiple sclerosis. If you live in a higher latitude, you have a higher risk of developing multiple sclerosis. It has been shown in a mouse model that multiple sclerosis could be prevented when the mice were pretreated with activated vitamin D. [12] We think 1,25-dihydroxyvitamin D is a very important immune modulator, and having adequate vitamin D status is critically important for maximum immune function.

Role of Vitamin D in the Immune System
JB: Is vitamin D's role in the immune system part of the innate immune system modulation, say the Th-2 versus Th-1, or do we know anything about that?

GH: It seems to be innate in the sense that it regulates both antibody production and T-cell function.

Vitamin D in Pregnancy or MS
JB: When a clinician asks you if that means a pregnant woman or an individual with relapsing MS should be supplemented with vitamin D, what do you say?

GH: Two things are relevant here. First, all women who are pregnant should have their 25-hydroxyvitamin D levels assessed. We've just done a study at Boston Medical Center and found, at least in African American and Hispanic women, that in more than 86 percent of cases both the infant and the mother were severely vitamin D-deficient as the infant was being born.

In terms of MS patients, they often have muscle weakness. Vitamin D deficiency is often associated with muscle weakness and bone aches and pains. When we see patients with MS, we make sure they have adequate vitamin D. We maintain their 25-hydroxyvitamin D levels of at least 30 nanograms per mL.

Vitamin D and Psoriasis
JB: In regard to the immunological effect of vitamin D and its metabolites, I know you have looked into its relationship to psoriasis. Would you tell us about that?

MH: We now know there are receptors for 1,25-D in almost all tissues in the body. Why would that be? Since I was interested in the skin and its ability to make vitamin D, it was a big surprise, back in the early 1980s, to learn that skin cells have 1,25-D receptors. We took skin cells, incubated them with 1,25 D, and showed it is one of the most potent inhibitors of skin cell growth.

When I put my MD hat back on and asked if it had a practical application, psoriasis came to mind. It is a hyperproliferative disorder of the epidermis. We initiated the first clinical trials and demonstrated the therapeutic efficacy of topically applying the active form of vitamin D to treat psoriasis. It is now considered to be one of the best treatments, if not the best treatment of choice world-wide. Pharmaceutical companies have now developed a variety of active vitamin D analogs specifically to treat psoriasis.

Ichthyosis
JB: That's fantastic. Does this include things like congenital ichthyosis? That's not strictly a psoriasis, but I've seen some anecdotal reports that vitamin D and A have been useful for that, as well.

MH: You're correct. Ichthyosis comes in various forms and, in fact, we treated some patients with ichthyosis with activated vitamin D. Some responded extremely well and others didn't respond at all.

Vitamin D as a Nuclear Receptor Family Regulator

JB: Because of my interest in molecular biology, I was interested to learn of another new chapter in our understanding of vitamin D. That is its role as a member of the orphan nuclear receptor family of regulators, along with retinoic acid. How is that research is evolving? Will it help us understand these mechanisms clinically?

MH: We know that 1,25 D interacts with its specific vitamin D nuclear receptor. To unlock genetic information, however, it has to combine with retinoic acid X receptor. Then this complex sits on what is called a vitamin D-responsive element on the DNA; it specifically recognizes this complex. A variety of transcriptional factors begins piling on top. This activity sets up the engine that will transcribe DNA into mRNA, which ultimately is the way new protein synthesis occurs.

This is really important, because we now realize that 1,25 D is probably one of the most potent inhibitors of cell growth and, more importantly, of cancer cell growth. As early as 1941, Apperly published a paper on this association in a cancer research journal. If you live in higher latitudes, you have a higher risk of dying of the many common cancers, like prostate, breast, colon, etc. People who live in Massachusetts and New Hampshire have a higher risk of dying of those cancers than folks who live in Texas, for example.

We have done studies looking at this in more detail. What we found was that many cells in the body have the machinery to activate vitamin D. We think that activation process is responsible for the production of 1,25 D that regulates cellular growth and decreases risk of cells becoming cancerous, such as those in the breast, colon, and prostate.

Clinical Application

JB: That discovery takes the understanding of vitamin D to a new level. Do you feel we understand this relationship well enough to begin applying the research in the clinic, or are we still at the research level?

MH: It's actually getting into the clinic. We asked another simple question, about cancer patients. They are often not feeling well; they don't go outside; they're on chemotherapy. Are they at risk of vitamin D deficiency? First, is that vitamin D deficiency making them not feel well? And second, could it actually be preventing their chemotherapy and other therapies from maximally working?

Last year I had a group of medical students collect blood from cancer patients. We found that almost 50 percent of patients with cancer at the end of the summer were vitamin D deficient. We think, in effect, this has a direct relationship with human cancer and metastatic disease. We've also done a study in mice and have shown that if you give them colon cancer, and you make them vitamin D deficient, they have very aggressive tumor activity. On the other hand, if you give the same tumor to animals that are vitamin D sufficient, it reduces metastatic activity by 55 percent.

Hydroxylation in Tumor-Bearing Animals

JB: Do tumor-bearing animals still retain the appropriate hydroxylation pathways in their liver and kidney?

MH: Yes.

Thyroid/Vitamin D Relationship
JB: I recall seeing a couple of reports on the relationship between thyroid function and the retinoic acid receptor, and interrelationship with the vitamin D metabolites. Is a thyroid/vitamin D connection emerging as well?

MH: What we know is that the thyroid hormone nuclear receptor can interact with the vitamin D receptor in a heterodimeric fashion, just like with RxR. So people are now beginning to think that if you had a lot of vitamin A around, and it's taking away the RxR, the retinoic acid X receptor, that maybe you can't have the vitamin D effect, and that the same thing may be happening with thyroid hormone. There is this very complex interaction with many of these steroid-like hormones, and it's the super family of nuclear receptors, i.e., the vitamin D receptor, retinoic acid receptor, thyroid hormone receptor, and glucocorticoid receptor, etc.

25-Hydroxyvitamin D Assessment
JB: If a patient has some indeterminate endocrinological disturbances, would it be wise for the clinician to evaluate his or her 25-hydroxyvitamin D to see if it may be playing a role in this process?

MH: I would go one step further. Along with other experts, I now think vitamin D plays a very important role in overall health and welfare. We know that clinicians should be getting a 25-hydroxyvitamin D measurement in their patients once a year, just like a cholesterol level.

Broad Vitamin D Applications in Public Health
JB: We have talked about the osteoporosis connection, but perhaps you can tell us how you think these vitamin D discoveries relate to CVD risk, osteoporosis risk, and menopausal female health risks. If we were able to address these, how could we impact some of these major public health issues?

MH: In simple terms, vitamin D deficiency will, of course, cause secondary hyperparathyroidism. Both calcium and matrix are being removed from the bones. Therefore, you're putting more holes in your bones. Therefore, vitamin D deficiency will precipitate and exacerbate osteoporosis. In addition, vitamin D deficiency causes a mineralization defect of your skeleton, i.e., osteomalacia. Osteomalacia, unlike osteoporosis, which is a silent disease, can cause muscle aches and pains, and both isolated and global bone pain.

Many patients who have seen lots of different physicians have a normal sedimentation rate. They have a very large work-up only to find nothing wrong. They wind up with a diagnosis of fibromyalgia. Our own experience and that of others is that probably 40 to 60 percent of patients with these types of symptoms are chronically vitamin D deficient. When they are treated with vitamin D and adequate calcium, it sometimes results in as much as a 25 percent increase in their bone density in 2 to 3 years, because you are finally mineralizing all of this osteoid that had been poorly mineralized because of vitamin D deficiency.

Fibromyalgia Connection
JB: How about some of the clinical symptoms that may have been assessed as nonspecific fibromyalgia? Do you see any improvement in those clinical pain scores?

MH: What we tell patients is that it often takes months to years to become severely deficient in vitamin D and develop osteomalacia. It often will take months, up to a year, to correct that deficiency and realize significant improvement. I've had patients who have been totally bedridden or wheelchair-bound who, after 6 months to a year, are walking again, totally free of their bone pain, and back to work.

As an explanation to clinicians, the way we treat vitamin D deficiency is not by giving a mouthful of multivitamins. First, it's not going to work and second, they're going to become vitamin A-intoxicated. What should be done is to give 50,000 units of vitamin D once a week for eight weeks to fill up the tank, and then put them on 50,000 units, perhaps once or twice a month, depending on their vitamin D status.

Vitamin D Delivery Method
JB: Do you give that intramuscularly?

MH: No, we give it orally. It's a pill and each one costs $1. For about $15 you can correct vitamin D deficiency.

Dosage
JB: Let me make sure we got that right. It was 50,000 IU per week, once a week for eight weeks, and then grading down to once every month for the next couple of months.

MH: Right.

Plant-Derived Vitamin D Derivatives and Hypercalcemia
JB: Could you discuss hypercalcemia and plant-derived vitamin D derivatives?

MH: It was known for 30 years that cattle in South America, especially at the end of the summer, were dying because their hearts and their major blood vessels were calcified, and they had severe hypercalcemia. This was due to their eating a plant called Solanum. This plant makes activated vitamin D and puts sugar on it. Why this plant does this, nobody knows, but it is an interesting natural source for 1,25-dihydroxyvitamin D.

Toxic Solanum in Edible Plants
JB: That plant family has other members that are edible, such as tomato and potato. Are any of these vitamin D derivatives found in those edible plants?

MH: It's in the leaves, not in the fruit or the vegetable. As a result, it's of little consequence. As you are probably aware, especially for tomatoes and potatoes, the leaves are often very poisonous and that's probably part of the reason for it.

Future Vitamin D Research and Application
JB: What is the current direction of vitamin D research and clinical application?

MH: I think what's really exciting is that analogs of vitamin D are now being made that have little effect on calcium metabolism, but have major regulatory activity on cellular growth. It's likely that vitamin D compounds will be developed to prevent and treat some common cancers. It may be useful in preventing and treating autoimmune diseases like rheumatoid arthritis, multiple sclerosis, and type-1 diabetes. Most

recently, it's been shown that 1,25-dihydroxyvitamin D will inhibit the production of renin in the kidney.

For many years we have known about the association between higher latitudes and a higher risk of hypertension and cardiovascular heart disease. We think that may, in fact, be related to activated vitamin D regulation of one of the major blood pressure hormones, renin.

Vitamin D and Metabolic Syndrome
JB: That would take us into a discussion of metabolic syndrome and whether there was any relationship between vitamin D physiology and the exacerbation of hypertension, and the renin/aldosterone/angiotensin connection found in metabolic syndrome.

MH: An interesting thing about metabolic syndrome is that the patients are often obese. We have shown that if you are obese, you are more likely to be vitamin D deficient. The reason is that whether you ingest vitamin D or make it in your skin, it gets deposited in your fat and is not available in your body.

The UV Advantage
JB: Thank you for spending this time with us. I've often said we need to have news to use, and you have certainly delivered on that requirement. I wish you the very best in your continued research. It sounds like the research is proceeding full speed ahead, and that we will be seeing a lot more about the vitamin D connection to clinical medicine.

MH: Thank you very much, Jeffrey. Because of my interest in getting this message out, not only to clinicians, but to the public, I've recently written a book titled The UV Advantage, which will be published next spring. It goes into great detail about all of these issues, and about how you can actually get safe sun. In tables at the end of the book, I point out how long you need to stay outside to get enough sunlight to make an adequate amount of vitamin D, anywhere on the globe, anytime of the year, in any season.

Future Success
JB: Thank you, once again, and the best to you in your continued work.

MH: Thank you so much, and to you, too.

Cell Signals in Disease States

Dr. Holick introduced an interesting concept in medicine beyond the specificity of vitamin D and its metabolites—the hydroxylated derivatives. It was a general theme that small molecules, when activated, can send signals across different tissues that result in either the prevention or increased prevalence of specific diseases. These diseases may be varied in type.

In his discussion on vitamin D, Dr. Holick referred to the same family of organ-related disorders I have been speaking about in regard to the PPARs. He talked about problems in bone, brain, heart, kidneys, colon, prostate, and breast. Are there shared similar signaling mechanisms that require multiple agents for their support and control? For instance, in inflammation, we need both first- and second-signal messengers to elicit a phenotypic inflammation. First-signal messengers would be those that come from the Th-1 cytokines, like IL-1, TNF, and IL-6. The particular outcome of inflammation requires first-signal

messengers to trigger a second-signal process involving nitric oxide (NO), activation of cyclooxygenase, and the release of the proinflammatory eicosanoids, leukotrienes, and prostaglandins. The relationship of all of those together ultimately gives rise, at the cellular level, to the phenotype we call inflammation.

Cell-Signaling Processes

A number of cell-signaling processes take place, not just a single messenger. This is where the story becomes confusing. What is it that triggers the expression of genes to start this process? We are beginning to learn about nuclear regulatory factors and gene activators. These are specific agents that can start the processes through the release and elaboration of first signal messengers like NFκB or AP-1, protein molecules that can initiate specific cascades of events through gene expression, proteomic outcome, and metabolic functional changes that create the phenotype of altered cellular physiology.

It is a whole new era, particularly when we start adding to the recognition that lifestyle variables and thoughts, beliefs, attitudes, and environment can all serve as modulators of the regulatory factors involved in cellular signaling.

Vitamin D and Insulin Signaling

Dr. Holick's discussion of vitamin D and the prevention of disorders of bone, skin, and heart, as well as colon, prostate, and breast cancers, also relates to insulin signaling and the PPAR family.

These PPARs are part of a complex orchestration of altered cellular physiology in response to a stressor. PPAR receptors, ligand-activated transcription factors (a subfamily), the nuclear receptor family, including the vitamin D receptor and the retinoic acid receptor RxR all tend to work together as a team. PPAR activators have effects on metabolic risk factors and on vascular information related to atherosclerosis. PPARs also have a profound effect on the metabolism of lipoproteins and fatty acids and therefore cut across type 2 diabetes and the hypertriglyceridemia seen in metabolic syndrome and hyperinsulinemia.

Activation of PPARs

PPARs are activated by specific fatty acids, particularly omega 3 fatty acids, and also by CLA. The fact that PPAR can be activated by fat seems paradoxical. Can specific fats increase the metabolism of fats? That appears to be the case, that there is a signaling capability with certain kinds of dietary fats. Omega 3 oils then signal the metabolism of other types of dietary fats to be used as calories for mitochondrial oxidative phosphorylation, or energy source.

A complex, dynamic, varied relationship exists among all the signaling factors, messengers, triggers, agonists, and antagonists. That relationship affects expression into the genes and ultimately to the proteins and metabolism. The end result is what we observe clinically as the phenotype of the individual, and our simplistic disease categories. We are apt to attribute a disease to a patient on the basis of the bias or the preconception we developed in our training, from our degree, and from our mentors. In one family of investigators or clinicians, it might be seen as arthritis; in another it might be seen as a condition related to increased monocyte stickiness and pre-atherosclerosis. In yet another it may be seen as preclinical dementia, depending upon where an individual looks.

Benefits of Improving Insulin Sensitivity

What we are really talking about is taking this esoteric information from the research laboratory and

trying to apply it in the clinic. We know that if we improve insulin sensitivity or reduce serum circulating insulin levels, we will increase cell-signaling stability to lower the inflammatory mediators. As a result we see proper regulation of things like metabolism of vitamin D.

As Dr. Holick pointed out, we should be evaluating patients by looking at the 25-hydroxy vitamin D levels in the plasma of patients on an annual basis, to see where they are in relation to this important signaling molecule. This is the presaging of a new form of medicine using the functional medicine model.

PPARs and Atherosclerosis

In terms of the relationship between PPARs and atherosclerosis, I emphasize that these cell-signaling messenger molecules do not have just single action effects. PPARγ , for example, has profound effects on the differentiation and function of adipose tissue where it is highly expressed in the adipocyte. PPARγ is also expressed in atherosclerotic lesions in macrophage. The negative regulatory effects of NFκB and activator protein 1, or AP1, which are also signaling pathways, interconnect the PPAR pathway with gene expression pathways and lead, downstream, to the expression of oxidant stress mediators such as myeloperoxidase with its production of hyperchloride and hydrogen peroxide. The endpoints are the oxidants. The upstream regulators are the cell signal messengers, production of which is modifiable through environmental and physiological factors.

PPARγ affects the recruitment of monocytes in vascular endothelial cells. The involvement of PPAR in atherosclerosis, a disease with chronic inflammatory character, suggests that PPARs play a role in other inflammatory-related diseases and help quench inflammation. PPAR agonists may, in fact, serve as general antiinflammatory modulators. Are omega 3 fatty acids useful in arthritis, for example? Are they useful in preventing neurological diseases? Do they help prevent heart disease? Are they useful in coagulation disorders? Might all of these factors relate to the omega 3 role, in part, through modulation of PPAR families and other immune modulation that leads to gene expression of these inflammatory mediators?

A Functional Medicine Model of Disease

This strategy differs from simply finding a disease and a drug to modify its symptoms. We are looking at shared, common mechanisms that are tied together with common cell-signaling substances. 25-hydroxy-vitamin D is a common signaling substance shared among disorders of the bone, brain, heart, kidneys, colon, prostate, and breast, as are PPARα and PPARγ . In preparation for next spring's 11th International Symposium on Functional Medicine on type 2 diabetes, we will be discussing other cellular signaling molecules which can be modified environmentally. For those of you who are interested, the review article I have been referring to in describing the interconnectedness of PPARs to all these inflammatory conditions is one that appeared in *Biochemical Pharmacology*.

From the Lab to the Clinic

Let's take this discussion from the abstract to the applied. What does this information mean to clinicians? In a hypothetical patient, you may take plasma measurement of high-sensitivity CRP or the triglyceride/HDL ratio. Let's say you see an elevated CRP level of 4 mg/L, and the upper normal limit is around 1.5 – 2.5 mg/L. Let's further assume you find a 25-hydroxy-vitamin D level of 15 nanograms per milliliter, below the 30 nanogram-per-milliliter cutoff that Dr. Holick talked about. You can then begin to develop a model for that patient that maps back against his or her clinical signs and symptoms.

This takes us back to the patient-centered assessment model of functional medicine. Rather than simply looking at pathophysiology, we are looking at antecedents, triggers, and mediators leading to signs and symptoms with which the patient presents. These signs and symptoms can be of different severity, intensity, and duration.

Finding the Mechanisms of Disease
It helps us to develop a model based on mechanisms, not just on trying to find the diagnosis in that patient. From the mechanism, we begin to determine the ways we can modify it based on what we know, using the tools we have available. Those tools could include drugs, nutrients, alteration of lifestyle variables, and environmental factors that can help modify the single molecules that create the outcome we categorize as disease.

That is the functional medicine model Dr. Holick described in this month's *FMU*. Whether he knows his concepts and research of 25 years are consistent with the functional medicine model we have been describing is a subject for further discussion. But you can see that in the minds and dedication of many confident researchers and clinical investigators, the concept of functionality preceding pathophysiology is emerging as a dominant theme.

We look forward to being with you in November and to your attendance at the 11thInternational Symposium on Functional Medicine in Vancouver, British Columbia, May 11-15, 2004. We will focus on "The Coming Storm: Reversing the Rising Pandemic of Diabetes."

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