

August 2004 Issue | Colleen Hayes, PhD Department of Biochemistry

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Welcome to *Functional Medicine Update* for August 2004. We were privileged last month to have Dr. Mark Hyman as our Clinician of the Month. He gave us a lens to see through as to how functional medicine applies to the management of complex patients with chronic conditions. Dr. Hyman is to be complimented for the way he articulates the vision.

I was impressed when I saw the most recent issue of the *Alternative Therapies* journal (May/June 2004), and read the editorial by Dr. Hyman titled “Integrative Health and Medicine: An Opportunity for Leadership and Collaboration.”^[1] Dr. Hyman has recently been appointed Editor-in-Chief of this journal, and his introductory theme was very prescient. It is certainly consistent with our view at The Institute for Functional Medicine about where medicine is going. I would like to quote some of the interesting features of Dr. Hyman’s editorial.

“Emerging and traditional models of alternative and integrative care have long fostered the understanding of the relationships between biological, psychological, social and spiritual forces that lead to the disequilibrium we call illness. Emerging from the very heart of conventional medical science is a call for action to discard antiquated concepts and build a science of health that is founded on understanding these relationships.

“The nature of practice must shift in the way we acquire information, in the structure of our days, in the tools we use to acquire history, in the tests we use to identify patterns that connect myriad symptoms into one story, in the way we educate our patients and discover with them the instruction manual for their bodies and minds, and in the way we engage, motivate and inspire our patients to change. Herein lies the opportunity for integrative health and medicine to lead the transformation of our disease care system into a healthcare system.

“The *good* medicine of the future will move beyond the tools of pharmacology and surgery to the modification of the infinite variables that create health or disease. The new medicine, based on a sound theoretical framework, will allow us to formulate with our patients sensitive instructions to modify gene expression through entry points in the new biological landscape and speak through the new biological language. We can communicate to our cells with precision and balance using new therapeutic tools that include nutrition, exercise, mind-body medicine, nutraceuticals, and traditional healing systems, as well as more refined pharmacogenomic and surgical interventions.

“Our tools of instrumentation are becoming more refined, peering not only into our anatomical structure, or the structure of cells, but into the very heart of dynamic functioning, into the very story of our life, and the potential held within our genetic code.

“The field of integrative health and medicine is at the center of this new vision; it is the compass along the new road we are traveling in medicine. As a community we need to stand together, build bridges and consensus, guide research, shape public policy, create new opportunities in medical education, and lead the way with a cohesive voice that both welcomes rigorously and examines all perspectives.”

Dr. Hyman is to be complimented for that insight. It is the theme we should hold onto as we move into this month's *Functional Medicine Update*, to talk about the extraordinary understanding that is evolving about vitamin D.

INTERVIEW TRANSCRIPT

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JB: Once again, it's time for our Clinician/Researcher of the Month. This month, we are pleased and privileged to have Dr. Colleen Hayes as one of our guests. Colleen Elizabeth Hayes is a professor of biochemistry at the University of Wisconsin-Madison. She has an extraordinary background, which includes a series of important contributions from her nearly 30 years of research experience.

Dr. Hayes received a Chemistry BA at DePauw University, and a PhD in biological chemistry at the University of Michigan. She was the Helen Hay Whitney Postdoctoral Fellow at Harvard Medical School, Department of Pathology, and the Helen Hay Whitney Postdoctoral Research Fellow at the University of Wisconsin-Madison, Immunobiology Research Center. She has been engaged in research having to do with nutritional interrelationships and the function of the immune system through work on retinoids and, more recently, in the area of vitamin D. Her bibliography is quite remarkable, and I would like to cite a couple of noteworthy papers that relate to the discussion we are going to have today.

In 1986, Dr. Hayes coauthored a paper with Hector DeLuca at the University of Wisconsin on monoclonal antibodies and their relationship to the receptor for 1,25-dihydroxyvitamin D₃ (1,25-[OH]₂D₃) in the pig model.[2] This might signal a change in thinking about the vitamin D connection and its relationship to the immune system, which she will be talking to us about today.

Ten years later, in 1996, she coauthored another paper with Dr. DeLuca that started down the fascinating road of looking at vitamin D and its relationship to multiple sclerosis (MS).[3] Just to show you where this work has gone as she has continued it, in 2004 she published a paper titled “Gene expression analysis suggests that 1,25-dihydroxyvitamin D₃ reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis.”[4] Here, we interface with what I have called “nutrigenomics,”

the interrelationship between various nutrients and gene expression—proteomic and metabolomic outcomes. I hope that gives our listeners an overview as to where we are going in this interview. It is with great privilege that I would like to introduce Dr. Hayes to FMU. Thank you so much for being with us.

CH: It's a great pleasure to be here, and thank you for inviting me.

Biochemistry of Vitamin D

JB: As background for our listeners, would you quickly review the biochemistry of vitamin D as a prohormone? I want to make sure everyone is on the same page.

CH: Yes. This is a so-called vitamin that isn't really a vitamin at all. It's a compound that derives from 7 α -hydrocholesterol in the skin when ultraviolet B radiation penetrates the epidermal layer. The photons cleave to one of the bonds in 7 α -hydrocholesterol and form previtamin D₃, which then isomerizes to vitamin D₃. It is transported on a vitamin D-binding protein out of the skin to the liver, where a 25-hydroxyl group is put on that compound. Now, we have the circulating form—25-hydroxyvitamin D₃, the form that a clinician should measure to determine a patient's vitamin D status. It is not the biologically active form, however. The final activation step occurs in the kidney, but also in many other tissues. One α -hydroxyl group is placed on the molecule to generate 1 α ,25-dihydroxyvitamin D₃. Another name for that is calcitriol, a hormone in the steroid hormone family. Although we call it a vitamin for historic reasons, it really is a hormone. We can talk more about how you get your vitamin D requirement and what that hormone does.

JB: Dr. Hayes, we were fortunate some months ago to have Dr. Michael Holick from Boston University Medical School talk to us about some of the work he has been doing on vitamin D physiology. He made the comment that from his experience in measuring 25-hydroxyvitamin D₃ levels in patients that it is commonly below what he considers important in maintaining proper function. He felt there was a lot of nascent insufficiency of this important prohormone. Have you experienced the same thing, and do you share some of those views?

How Latitude Affects Vitamin D Levels and Pervasiveness of Vitamin D Deficiency

CH: I share his view. I have read Michael Holick's work and it is excellent. There are other scientists who have made similar measurements and I've read their publications, as well. One of them was MK Thomas who surveyed patients in a hospital.[5] Vitamin D deficiency is very common. It's common in infants who are entirely breastfed. It's common in elderly people who have a slightly lower capacity for forming vitamin D in their skin. It's common in people of color because the pigment in their skin effectively absorbs the photons and prevents them from generating vitamin D. Another group of people that have deficiency are those who use sunscreen heavily, or who practice sun avoidance. We have a lot of groups of people that are at risk for vitamin D deficiency. Also, those of us who work a little too much indoors are at risk for vitamin D deficiency. The winter is a particularly difficult time of the year for those of us who live where I live (Wisconsin), or at latitudes similar to that. Above 35 degrees latitude, the photons don't have enough energy during the winter to break that bond and generate vitamin D. The ozone absorbs those photons and the sun angle is so low that there isn't enough energy. People who live in the northern United States or equivalent parts of Europe and around the world experience about a five-month period of time where they don't get high-energy photons, so they don't make any vitamin D. By the end of the winter term, they can fall well into the vitamin D-deficient range, unless they're supplementing their diets with vitamin D.

JB: If you were to go to the average practicing physician and ask her/him to do a quick association test with vitamin D, the response would probably be, “calcium and bone.” Yet, you and others are starting to identify that vitamin D has a much broader series of effects on physiological function beyond that of the relationship to calcium, through its immunological effects. Would you describe how we’ve emerged that view?

CH: Classically, vitamin D is known as the vitamin that’s important for forming and maintaining the skeleton, and controlling the calcium that is used in forming that skeleton. There has been a realization over the last 20 years that this is just the tip of the iceberg. The hormone binds to a receptor protein called the vitamin D receptor. You referred to one of my publications where we were actually measuring that receptor. But it turns out that receptor is in almost all cell types. In fact, I don’t know of a cell type that doesn’t express that receptor. That tells us that there are many, many cell types that use the hormone for some biological purpose other than skeletal maintenance and the mineral ion homeostasis.

A Possible Protective Role of Vitamin D in Diabetes, Arthritis, Inflammatory Bowel Disease, Systemic Lupus Erythematosus, Thyroiditis, and Psoriasis

To give you some examples from my area, we have been investigating the vitamin D receptor expression in lymphocytes and cells of the immune system. We have seen it function there, and we have good evidence from our own work in animal models that this hormone has a protective role in MS, diabetes, arthritis, and inflammatory bowel disease (IBD), to name just four autoimmune diseases. Others have shown an effect in systemic lupus erythematosus, thyroiditis, and psoriasis, as well. We are seeing a very broad spectrum of autoimmune diseases in animal models that can be prevented using the hormone 1,25-dihydroxyvitamin D₃. There is some evidence that our animal data is also applicable to humans. Vitamin D may be very critical in helping the immune system to maintain tolerance to prevent a broad spectrum of autoimmune diseases.

JB: I have heard that the 1,25-dihydroxyvitamin D₃ binds to a receptor that has been lumped into the family of orphan nuclear receptors. Would you tell us a little bit about what they are? I think that would be of interest.

CH: There is a family of proteins that has been called the steroid hormone receptor family. All of these family members have some common features. One is that they have a DNA-binding domain and they are found in the nucleus of a cell. Another common feature is that they have a ligand-binding domain, which binds to a ligand and then the receptor can stick to the DNA. Each member of the family has as its function the control of gene expression in a ligand-responsive manner.

To use the vitamin D receptor as an example, when this protein binds the ligand 1,25-dihydroxyvitamin D₃, and also binds DNA, it turns on the transcription of a nearby gene. It recognizes a particular site on DNA to bind, and that gives us a spectrum of genes that are responsive to the hormone. You mentioned the orphan receptors in that family. There are proteins that, by looking at their structure and sequence, we can tell they must belong to this family. They have a DNA-binding domain, but for some of them, we don’t know the ligand, and so they have been called orphan receptors because we’re searching for a ligand that will trigger their transcriptional control activity. The vitamin D receptor is not an orphan because we know its ligand. The important take-home point is that it functions in the nucleus to regulate gene expression, so it gives us a spectrum of genes that respond to this hormone, and the hormone, of course, is responding to light. It is a tool that our cells can use to tune certain cellular processes to light

availability. Again, that gives us a sense that there are many more biological processes tuned to sunlight than just the maintenance of our skeleton.

JB: I've been told that some of these are heterodimeric, meaning they have multiple ligands; for example, triiodothyronine, or T3, the thyroid hormone metabolite. Even fatty acids like eicosapentaenoic acid (EPA) or the vitamin A derivative, retinoic acid, seem to have binding affinity for some of these receptors. Are there interactions that occur among 1,25-dihydroxyvitamin D3 and some of the other agonists?

CH: Yes. The vitamin D receptor is a single protein, but it can't function as a single protein; it needs a partner. Its partner is the retinoid X receptor. That retinoid X receptor does partner with a number of the hormone receptors, and it does bind retinoic acid. There are interactions between these ligands in controlling gene expression. The retinoid receptor family is very interesting because it's a big family of receptors. There are retinoic acid receptors α , β , and γ , and these are controlled in a tissue-specific manner, so you may see the retinoid receptor γ expressed only in a limited spectrum of tissues, whereas the α form is expressed in nearly all cells. That large family of receptors can mediate gene expression control in a very tissue-specific way. The vitamin D receptor is an ancient molecule, we think, and there is only one form of it, unlike the retinoid receptors which have multiple isoforms. Again, it does partner with the retinoid X receptor, forming a heterodimeric protein. There are lots of possibilities for interactions between the retinoid family of compounds and the vitamin D hormone, in terms of tuning gene expression to achieve a certain biological outcome for the cell.

JB: About a year ago, I remember reading a paper coauthored by Dr. Walter Willett about vitamin A excess and bone fracture.[6] Is there a molecular association between overstimulation with vitamin A of these RXR receptors, or is that another mechanism?

CH: That's work I don't know, so I would hesitate to comment about it. I haven't read that paper, and I'm not familiar with retinoic control of bone metabolism.

JB: Let's move on to your extraordinary evolution of the model between vitamin D and MS. I remember in one of the talks I was privileged to hear you present, that you spoke of the history of how this whole association emerged.

Suggested Link Between Vitamin D and Multiple Sclerosis

CH: It's a very exciting history. The story begins with a very old observation that was made by an astute World War I Army physician in the United States. He noticed, in examining recruits, that those who had symptoms of MS came from the northern states, such as Maine, Vermont, New Hampshire, Michigan, Wisconsin, Minnesota, and Oregon. He never saw a recruit from the southern states, such as Florida, New Mexico, or Georgia, with symptoms of MS, so he began to collect data and wrote up a description of a latitude gradient in the incidence of this disease. That triggered four decades of epidemiological research around the world, attempting to find out if the latitude gradient that had been described in the United States was also a feature of other places. In fact, it was a very robust finding. MS does show a gradient of prevalence with latitude. The disease is almost unknown at the equator; it is very, very rare at the equatorial part of the world. As you move away from the equator, either to the north or to the south, the disease becomes increasingly prevalent. It reaches its peak of prevalence in northern Scotland and northern Canada, as you might expect. The same gradient applies in the Southern hemisphere, although there are not as many data about that.

The next piece of the puzzle came in 1960. A man named Donald Acheson was trying to sort out all the variables that might be associated with latitude and determine which one of the many variables might best explain the prevalence of MS. After a long and intense study, he determined that winter sunlight showed the best correlation. It was an inverse correlation. The more the winter sunlight, the lower the disease prevalence; the less the winter sunlight, the higher the disease prevalence. The chairman of my department, Dr. Hector DeLuca, discovered the active hormone 1,25-dihydroxyvitamin D₃ when he was a graduate student. He has researched that hormone ever since. We are steeped in the biology of vitamin D here and I knew, as did Hector, that sunlight catalyzes the first step in vitamin D biosynthesis. He and I were also interested in why the vitamin D receptor was in lymphocytes. We had been talking for some time about trying to figure out why lymphocytes had a receptor for this hormone, which was known at the time for its skeletal maintenance function. We put 2 and 2 together and formed a hypothesis that sunlight might protect people from getting MS because it might be catalyzing vitamin D synthesis, and the vitamin D might be essential for lymphocytes for some functions that would protect a person from MS. We went about testing that idea in an animal model of the disease called experimental autoimmune encephalomyelitis. In that mouse model, we can induce a disease that looks very much like MS if we force a mouse to make an immune response against myelin basic protein, which is a component of the axonal sheath allowing axons to transmit an electrical pulse. We treated some mice with the hormone 1,25-dihydroxyvitamin D₃, and other mice were given a placebo. I should also mention that Dr. Marguerita Cantorna worked with us on this project and was a key person in doing experiments. Then, we attempted to induce the disease and, to our astonishment, we found that when mice were given the hormone, we could not induce it. Furthermore, if we first induced the disease and then treated the mice with the hormone 1,25-dihydroxyvitamin D₃, the disease symptoms went into remission and didn't come back. We were very excited. That was back in 1996. We thought we had some evidence that it was, in fact, correct that sunlight protects against MS through the activity of sunlight generating vitamin D, and that was a starting point for my last decade of work, trying to figure out why that's the case.

JB: That is an unbelievably exciting story, which emphasizes taking advantage of the chance observation that leads to great progress and discovery. Let's fast-forward to 2004 and the most recent paper you submitted on gene expression analysis and 1,25-dihydroxyvitamin D₃ reversing the experimental autoimmune encephalomyelitis, and how it relates to the stimulation of inflammatory cell apoptosis.⁴ There's a lot of importance in that paper that is underneath the water line. Would you bring us up to speed?

CH: We are very excited that paper was finally published. It was a labor of love. It took us a long time to do that piece of work because, as you know, DNA microarray technology is relatively new. It's a technique that allows you to ask about control of gene expression on a genomic wide scale. I mentioned earlier that the vitamin D receptor controls gene expression in a ligand-responsive manner. We finally realized that what we needed to know was the range of genes that are controlled by this hormone in the central nervous system, where the pathology of MS is going on.

We established the encephalomyelitis disease in mice, and when the mice were severely ill (they were actually paralyzed from this disease), we treated half of them with 1,25-dihydroxyvitamin D₃ and the other half with a placebo. Within a few hours, we collected the central nervous system tissue, isolated the RNA, and applied the RNA to DNA microarray chips (which interrogate all the genes known to be expressed in any tissue, at any time) so we could see the spectrum of genes that were expressed in a placebo-treated diseased animal. We could also see the spectrum of genes that were changing within

hours after hormone treatment. In that experimental design, we applied the hormone treatment to start this process in a synchronous manner so we could actually define those genes. If we think about it in terms of a person who has adequate supplies of vitamin D, these processes would be going on all the time; it wouldn't be a matter of turning them on synchronously. We did that experimentally so we could learn what they were.

We looked at 12,488 genes in nine different samples—a massive amount of analytical work. I must tell you that without the help of our collaborators, that wouldn't have been possible. We had wonderful assistance from Dr. Tom Prolla in our Genetics Department here. He's an established expert in DNA microarray analysis and interpretation. We also had wonderful help from Dr. Brian Yandell, a mathematician and statistician. As you can imagine, wading through 12,488 genes in nine samples to determine what's statistically significant, was a challenge beyond me. At the end of the day, we saw a small number of genes change. The family was certainly less than 100 in that timeframe. What we found remarkable was that in the types of gene changes we observed we saw some themes. One theme was protection of the central nervous system (CNS) cells like the neurons, the astrocytes, and the oligodendrocytes. We saw them turn on genes that we know to be protective in terms of signaling their survival. Certainly, this hormone has some effects protecting the CNS.

Another family of gene changes that occurred, which we found very exciting, were those that signaled cells that were becoming sensitive to apoptotic signals. An apoptotic signal is something that can trigger a cell death program. Of course, when you think about an inflammation, you have a stimulus for the inflammation. It might be a virus; it might be a bacterial infection. In any case, you call in all the white blood cells and they do the work of eradicating the stimulus. And then, what happens to them? Somehow, you have to resolve this inflammation. An inflammation that is allowed to persist can do a lot of tissue damage. That is, in fact, the underlying pathology in MS. There's ongoing inflammation that damages the oligodendrocytes and the neurons.

What we saw was that in the presence of the hormone 1,25-dihydroxyvitamin D₃, the inflammatory cells were becoming sensitive to apoptotic signals. They were turning on pro-apoptotic genes and they were turning off genes that could signal survival. We think what it did was reset the threshold for apoptosis and allow us to ask those cells to die, now that their job was done, and return the CNS to its homeostatic set point without inflamed cells being present. We were able to take that genetic information from the genomics research and go in and look with a method that would actually keep a feature of a cell undergoing apoptosis; that feature is the fragmenting of the DNA. It's one of the late steps in the apoptotic program. We used a method to label them ("mixed ends"), and visualized it with an antibody to the label that we used, and we could see apoptotic cells appear in the portion that has infiltrating inflammatory cells. We could see those cells beginning to undergo apoptosis.

What we think this hormone helps the immune system do, at least in part (this is probably one mechanism of many), is that it resets the apoptotic threshold so these inflammatory cells are more sensitive to apoptotic signals and they will die at the end of the inflammatory process. With that knowledge, what would it look like if a person was vitamin D deficient and didn't have that hormone available? The outcome might be that these inflammatory cells are not going through apoptosis when the inflammation needs to be resolved. The inflammation would be going on much longer than is necessary, and long enough to do some tissue damage. We think this may be one explanation as to why so many autoimmune diseases are showing sensitivity to sunlight, and possibly to vitamin D, because they all involve an inflammation. In diabetes, it's an inflammatory infiltration of the pancreatic islets. In rheumatoid

arthritis, it's an inflammatory infiltration of the synovium of the joint. In thyroiditis, it's the thyroid.

The common theme of all these autoimmune diseases is an inflammation that is not resolved and goes on long enough to damage tissues. We think we may have a handle on one of the underlying mechanisms for all of these processes, and an explanation that sunlight is required to help resolve inflammatory lesions before they do damage. That paper, although it took several years to bring it all together, has opened a floodgate for us in terms of understanding mechanisms, and we're very excited about it. Now, we're going after the mechanism in a cell to see if we can prove that hypothesis, or test it.

JB: I want to compliment you and your group. I think this is stunning work. It combines so many different tools and techniques in a synthesis to uncover very complex mechanisms and give insight into qualitative observations that have been made, as you said, for over 40 years. This is one of those threshold breakthroughs. I have a great appreciation for the quality of the work that went into this paper. On behalf of all of us, thank you for this work; it's wonderful.

CH: You're entirely welcome. May I just take a minute and say that the National Multiple Sclerosis Society has been funding our work, and we're very grateful to them for the opportunity to do it. Without them, it wouldn't have been done.

The Suggested Link Between Vitamin D and Multiple Sclerosis

JB: That's a great team. Are you aware of any experimental clinical work that has gone on in applying some of these observations about 1,25-dihydroxyvitamin D₃ with human MS?

CH: That's a very important question and there isn't yet very much data in the literature. There is an important paper that came from Cassandra Munger (a graduate student) and her mentor, Alberto Ascherio at the Harvard School of Public Health.[7] We had a conversation some years ago about how one can test the idea that vitamin D might be protective in terms of lowering the risk of MS. Donald Atcheson pointed out that there was one database in the world that might shed some light on this, and that was the Nurses Health Study Database out of Harvard. Walter Willett is using that database to look at cardiovascular disease and various nutritional questions. This database contains work with a group of 200,000 nurses who have voluntarily allowed their health to be monitored over a period of 30 years. They've collected nutritional information from these nurses and they have a massive database. We realize that you could go to that database, if it had adequate nutritional information in it, and ask if those nurses that took vitamin D supplements had a lower risk of MS. Alberto and Cassandra have done that work and published it in January of this year. What they found was very exciting, that being that those nurses who took a multiple vitamin tablet of 400 IUs of vitamin D, plus other vitamins, had a 41 percent lower risk of MS than the nurses who didn't take a multiple vitamin supplement. We don't have any information on the vitamin D levels in their serum. That's something Alberto is looking for now. We also don't know which component of the multiple vitamin may have performed the protective function. That's why we need the serum data to see if we can get a closer look at how they achieved that protection. But the suggestion is there that vitamin D supplementation early on can reduce the risk of MS later.

There is also a beautiful study by Elina Hippunen in Finland.[8] She didn't study MS; she studied diabetes. She also had access to a national health database and was able to show that infants—children who received 2000 IUs of vitamin D daily in their childhood—had an 80 percent lower risk of diabetes as adults. That is also a very exciting outcome, suggesting that vitamin D supplementation reduces the risk

of diabetes.

In terms of what we can do for individuals who are already affected with MS, there is a study going on now in Canada that is addressing that question, but I'm not part of it and I don't know how far it has progressed. I think they will probably be announcing results soon. Reinhold Veith is the principal investigator of the study and they're trying to see if supplementary vitamin D might be able to lessen the symptoms of MS. There's a suggestive report that that's possible, something I found very exciting. It's well known that the severity of the disease varies during the year, so the most severe symptoms typically occur in the late winter and early spring. The disease lessens in severity by the end of the summer and the early autumn. As you know from my earlier comments about vitamin D biosynthesis and sunlight, by the end of the winter, most of us are vitamin D deficient. The severe symptoms were correlating with vitamin D deficiency, and the abatement of symptoms was correlating with the synthesis of vitamin D in the summer. That periodic variation in MS severity gives me some hope that we're going to be able to at least affect the severity of the disease. Even if by this time it's not possible to completely rid an individual of these difficult symptoms, we may be able to make it better. That's what the Toronto study under Reinhold Veith is trying to accomplish.

JB: As I listen to you talk of all the various potential implications of this extraordinary work, I'm reminded of your 1998 paper, looking at the effect of 1,25-dihydroxycholecalciferol on inhibition of the progression of arthritis in murine models of human arthritis. Even this suggests that what people say about their arthritis being worse in the winter and better in the summer may be true.[9] There are lots of interesting implications here.

CH: I hear from people all the time that they've been using a tanning booth, or they've been flying to Arizona or Florida during the winter months and feeling better. There's probably a very good reason they're feeling better. Many people have discovered their arthritis symptoms improve when they're exposed to the sun in the summer. I'm hopeful that we're going to be able to help people afflicted with that painful disease.

JB: When I look at the list that you provided—diabetes, MS, IBD, atherosclerosis, systemic lupus erythematosus, thyroiditis, and rheumatoid arthritis—I note that's a lot of age-related chronic illness.

CH: I haven't said that there is work by other people showing a protective effect of vitamin D on cardiovascular disease, breast cancer, colon cancer, and prostate cancer.

JB: I think this shows the implications of your work.

CH: It's a tremendous spectrum of biological activities that is just now opening up, so it's a very exciting time in translational medicine for this system that's classically been thought of in the context of bone, to be opening up in so many other areas.

JB: I want to thank you. We've taken more time than we probably deserve, but it's a great privilege to have you go through this story. We wish you continued success with your work. It's pioneering and it will make a difference at the clinical level.

CH: Thank you so much, Jeff, for inviting me. I've enjoyed this immensely and hope that you're correct

and we're on the track to better health.

JB: You're speaking to the right group. They will be very receptive to your message. Thank you, Dr. Hayes.

Clinician Of the Month

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JB: I hope you have been as stimulated with Dr. Hayes' presentation as I have been, as it relates to the implications of vitamin D chemistry and physiology and its impact on health and medicine. I thought it would be useful to move from the biochemical realm into the clinical realm by talking to an expert clinician who understands nutritional medicine, and who incorporates it into his practice.

Dr. Norton Fishman is a graduate of the Applying Functional Medicine in Clinical Practice (AFMCP) training program and is a functional medicine doctor of great distinction. He has been in practice for many years and is currently located in Rockville, Maryland. His practice bears the title, "Optimal Health Physicians," which certainly conveys the focus of his work. At a meeting of the American College of Nutrition that Dr. Fishman and I both attended, I was privileged to hear him talk about his clinical experiences with the vitamin D connection to health problems. I thought it would make a wonderful segue for our listeners to hear how such information gets woven into real practice. It is a great privilege to introduce you to Dr. Fishman. Norton, it's wonderful to have you with us today, and thanks so much for giving us some time.

NF: Indeed, Jeff, it's an honor to be on FMU.

JB: Would you tell us a little bit about how your experience led you to the AFMCP course and defining your practice as "Optimal Health Physicians?"

NF: I was a pretty regular primary care physician in Internal Medicine back in Chicago, where I had a practice for almost 27 years. It evolved into doing a lot of work in geriatric medicine, which included treating clients in nursing homes. Things began to change around 1993/1994. I always use the image of being on the Titanic, walking up to the ship's purser and asking why my ankles are wet, and getting the following answer: "Don't worry about it; go up to the deck; they're playing the violins." What I did instead was to get into a lifeboat. I saw this great big ship of medicine that I had been part of for several decades starting to sink. Getting into functional medicine is like getting into a lifeboat, and it's floating. The big ship is having a problem dealing with the chronic health conditions that we're seeing more and more of. Regular medicine is wonderful for delivering acute illness needs, but I stepped off the big boat.

To get into functional medicine, you need to be open minded, curious, and in my case, I had a personal experience that led me into it. I think a lot of doctors have had a personal experience that leads them into functional medicine. Sometimes, it's fortunate or unfortunate, but getting exposed to things that functional medicine has to deliver opened me up. Your programs, training with the American College for

Advancement in Medicine (ACAM), and training in environmental medicine, have been like taking a new residency. Over a couple of years here in Rockville, Maryland, and with several valuable mentors, I have been able to change the way I looked at medicine and recreate the joy I once had.

JB: That's a marvelous story. Have you found that patients have traveled with you on your journey? Do you have a new kind of patient population? How has this transition been for you in practice?

Vitamin D and Seasonal Affective Disorder

NF: Interestingly, some of it is because I changed cities. We went from the Midwest to the east coast, via the Olympic Peninsula for a short while, and I'll get back to that. Of course, I have a whole new cadre of patients who have stayed with me the past 10 years since I've been here. What I'm finding is that there is a difference between the word "patient" and "client." In medicine, we love the word "patient." When I looked it up in the Oxford Dictionary, I found it meant "somebody who lets you do something to them." So, my idea of a patient became someone who is on a gurney. When you're going into surgery or into the emergency room, you're a patient, but someone who sits across from you at your desk is a client. I found that my clients here wanted a consultant; they wanted advice and guidance. This has been a great area here in DC. People are very medically sophisticated. Many of them want to take good care of themselves. In many ways, it's been like preaching to the choir, which I enjoy. My clients are very grateful to have somebody listen to them, to be open minded to their ideas about nutrition, to give them guidance, and not to laugh at them.

JB: Being here in Gig Harbor, Washington, you've piqued my curiosity. Tell us a little bit about your travels from Chicago through the Olympic Peninsula to Washington, DC. That sounds like a very interesting, non-linear path.

NF: We actually moved to Port Townsend on the Olympic Peninsula, figuring that would be an ideal place to live, once we left the city. In many ways it was, but something came up. There's an area at Port Townsend that I'm sure you're aware of called the "rain shadow from Mt. Olympus," so we didn't get the rain you get in Seattle, and it was lovely. There was sunshine often. We moved in around January and my wife found out that she suffered from major seasonal affective disorder (SAD). When we looked on the map, because the weather is relatively warm, we realized we were further north than Montreal or Toronto. Although the sun was coming down, it was coming down at the wrong angle; it was very low. We spent six months there; it was beautiful, but we realized it wasn't going to work out and we became attracted to the Mid-Atlantic States.

That leads me to vitamin D because in October of 2000, I attended a symposium on osteoporosis. I think it was sponsored by John Hopkins. I had a takeaway that really changed my life and the life of my wife. It was one of those "by the ways." Dr. Michael Gloth was talking about using large doses of vitamin D—100,000 units a month for ladies with osteoporosis. The "by the way" was that the ladies taking vitamin D who had SAD got better. I don't remember much about the osteoporosis, but I came home, talked to my wife, and told her we had the "magic." I put her on a dosage of 100,000 units of vitamin D a month (a very large dose), and magic occurred. After a short while, Kathy noticed that her normal "dip" into SAD wasn't happening. I told her we needed to describe this. I began to realize, as I went over the symptoms, that SAD is not depression. I think we have depression/depression, and SAD is a separate disease. But the things that work for depression don't work for SAD. When Kathy described to me what was happening, and as I've talked to clients since, I got a very similar story.

They all say that as October and November approach (in the northern latitudes), they start feeling like they're going into a bed of molasses. There's inertia—physical, mental, and emotional. Everything is an effort; it's hard to get up. They start slowing down. They have a sense of social isolation; they tell people to go away and not bother them. Libido decreases. They're in a mental fog. Some people even say they're fattening up on sweets. They want more sleep. I've talked to some who say they feel confined, as if they're in a cave. They're just getting isolated.

After a while, I realized that these people were describing a pattern, which I'll call mammalian hibernation, and that it was occurring inappropriately in cognitively advanced primates called humans. I realized that SAD symptoms were indicative of someone who is inappropriately going into hibernation. My wife, Kathy had tried special lights designed for those with SAD, but they had a very minimal effect. The magic was the vitamin D, which gave her a new winter. I've talked to many people who find that lights help a little bit, but they're not the answer. The reason we moved away from the Olympic Peninsula no longer existed, but we love it in Maryland and plan to stay here.

JB: This is one of those extraordinary discoveries. Out of this comes some clinical replication, so an observation of one becomes the value for many. Have you had occasion to measure 25-hydroxyvitamin D3 levels in the serum? Do you follow serum calcium levels, or parathyroid hormone levels when you're giving that high a dose of vitamin D?

NF: What happened initially is that I started doing this enterically, and luckily I came across evidence, as you pointed out, from several people who had done some work at the University of Wisconsin, and there are several people who have been writing about these things. Actually, there's a certified nutritionist by the name of Krispin Sullivan whose website I came across, which has some very good material. I believe Dr. Michael Holick has written some books on this. I suddenly realized I'd better be checking this out, because it's nice to get a clinical response, but we need to make sure we're being safe. One can get into vitamin toxicity. I began measuring 25-hydroxyvitamin D3, and it's been well pointed out that's the test to get, not the 1,25. I've found that many people with SAD have low levels of vitamin D. I also learned that the lab values I was getting back were not correct in terms of what "normal" is. We've been working with lab values (what I'll call normal) of 30 to 60 nanograms, with the optimal probably being 40 to 45 nanograms of what I want to shoot for when I'm giving vitamin D. I've cut back the dosage for many people. I test after three months and I find that some people come back into a normal range in that length of time, so then I go to lower doses. For other people taking large doses, it might take a year before we see an improvement.

JB: That is fascinating. There's a general view, because we've all read in the textbooks that vitamin D is a toxic vitamin in excessive doses, that 100,000 units would immediately produce a toxic plasma level in all people. It's very interesting to hear of your clients' responses.

NF: I write a prescription for a 50,000-unit capsule of vitamin D. I caution clients that they are to take only one capsule every two weeks. I know people who have used higher doses, but I would be very cautious about that. I've noticed, interestingly, way before vitamin levels even rise, that there's a change in those with the SAD condition. There may be a particular UV band that is important regarding vitamin D and SAD. I know people have tried light boxes, but I think the key is vitamin D. It does something even beyond what we know it does for immunity and other factors. It must be affecting brain receptors in some way because we'll often see a very quick response, way before levels improve.

JB: Do you see any elevation in serum calcium when your clients are on this higher dose of vitamin D?

Importance of Periodic Testing of 25-hydroxyvitamin D Blood Levels

NF: No. I check 25-hydroxyvitamin D levels every three or four months initially, including a chemistry screen along with it to make sure we are checking calcium and phosphorus. I have found that it has no effect on serum calcium. If you have a client who's getting levels above 45 and you're supplementing, you'll want to go very easy. Then, a value to look at would be to use an over-the-counter form of vitamin D3 from a fish oil extract, perhaps in a dosage of 1000-2000 units a day. I don't see getting into any problem with that. You'd want to hold off getting past 60 nanograms because then you're moving toward toxic levels, but I personally have not seen any problems with getting the levels too high, or certainly the calcium rising.

JB: This is a very interesting observation. I'm doing a little speculation with you here, but let's assume that one of the reasons individuals have vitamin D-related SAD is because they have an inability to properly convert vitamin D into the 25-hydroxy or the 1,25-dihydroxy hormonal form. The block is at some level in perhaps gene uniqueness or some other metabolic effects that prevent the appropriate conversion. That is similar to the classic example Linus Pauling talked about in molecular medicine, or that Bruce Ames has recently talked about. By mass action effect—by increasing the concentration of the substrate—we push the reaction, in this case conversion of vitamin D into its active form, the 1,25-dihydroxyvitamin D3. When you don't see a significant elevation in the 25-hydroxy with very high doses of vitamin D, it raises the question about whether there is a metabolic block preceding the 25-hydroxy formation.

NF: That's exactly true. And it's because there's such variation between individuals. It does pay (this has been emphasized), to do frequent testing. I do testing on everybody coming in for an initial exam and for followup, not just for SAD. You may have looked into all the issues that are arising indicating that we probably have an epidemic of under-utilization of vitamin D that people are totally unaware of, which is very subtle. SAD stands out. People get better and they know it. It's real and it's great because it's very rapid and very specific. The general underlying low vitamin D that many people have no knowledge of is probably a factor affecting immunity. They're showing that it affects the potential for epithelial cancers like breast, prostate, and colon cancer, by helping to resist getting into that problem. Certainly, people have shown that it's affecting autoimmunity and multiple sclerosis specifically, and we're going to be looking at osteoporosis. This is a pretty important substance. In my testing, using the new standards, I've found a lot of people have lower levels than I ever would have expected. In people with SAD whom I'm not treating dramatically, I may use smaller doses, such as 2000 units of an over-the-counter vitamin D as a base, (60,000 units a month instead of 100,000), and then monitor them.

JB: I want to compliment you. This is doing both good observational and clinical medicine, coupling together the science that has emerged around this interesting hormone, vitamin D and its 1,25-dihydroxy form, and how it relates to clinical observation. This is historically how medicine has evolved. I really want to compliment you on the way you've assembled this information.

NF: Thank you, Jeff.

JB: Do you feel the observation you've made regarding vitamin D and your wife's SAD has been replicated in other clients? Is this something you think may be a cornerstone in SAD that all doctors

should be looking at?

NF: I definitely think so. Obviously, I took my case of one and expanded it. In the old days of medicine, treating chronic illness was an interesting experience because sometimes it takes a long while to see results. I used to love treating strep throats—give them penicillin and they call you up two days later and tell you you're a hero. What I've found in treating SAD is the same response. We take on a problem that is a severe disability for people. Many of them are knocked out of function for three or four months of the year. And the further north in latitude, the worse it shows up. Being able to ameliorate it in rapid fashion has been great. I'm finding clients responding who have true SAD. What's interesting is that we may even have a diagnostic test. If somebody doesn't respond to a good vitamin D dosage, they may not have SAD; they may have depression. I've found that people who have SAD don't respond to antidepressants unless they also have depression. I think we're dealing with two diseases that have different treatment protocols.

JB: That's tremendous insight. As you're talking, I'm sitting here with my colleague, Jay Johnson, in the studio we have shared for the last 25+ years. In the middle to late 1970s, when Jay and I were involved at the Northwest Academy of Preventive Medicine, we had a physician from Canada who spoke about the use of Aquasol (containing vitamin A and vitamin D) for the management of MS and autoimmune dysfunctions, and for what he called depression. I think he was practicing in Manitoba, and had experienced some big problems with the medical licensure board about the fact that he was audacious enough to use a vitamin A, vitamin D-containing nutritional supplement for the management of something on which the vitamins were not thought to have any impact at all. As I recall, he was an older-age physician and he retired rather than have to live with the insults of the medical licensure board. Sometimes, being a pioneer can have its price.

NF: Being a pathfinder is not an easy job. I'm not necessarily recommending it unless you have a real predilection for it. It's too bad, but I guess that's human nature. That reminds me of two points I want to make about dosing and vitamin D. First, make sure people are taking calcium. Vitamin D's job is to bring calcium up in the blood level and if there's not enough nutritional calcium available, it may rob the bones. Calcium supplementation is important. Also, people have pointed out that being on vitamin A in sufficient amounts with vitamin D is valuable. It makes an interesting point. We've talked about the fact that MS seems to be tied into the vitamin D story. One of the suggested treatments for MS is supplementation with fish oils. I suspect what may have been a factor is related not as much to the omega 3s as to the vitamin D they were getting.

JB: That is interesting. It goes back to the old cod-liver-oil-for-breakfast recommendation. We're learning old things in new ways and now calling it "modern." It's pretty fascinating.

Importance of Regular Exposure to Sunlight for Short Period in Maintaining Normal Vitamin D Levels

NF: There's one other point I'd like to make about people being confined and therefore cut off from light. Dermatologists are now telling everybody to stay out of sunlight and use sun block, but I think they're wrong. I'm a clinician so I can be audacious; I don't have to have my research. I think we need sunlight in proper amounts to help with vitamin D levels. We're looking at cancer protection, and perhaps even for melanoma. The UV band gives us vitamin D, and that only comes from direct sunlight. That's why the sun needs to be overhead. One needs to be out in the noonday sun for perhaps a short time if light-skinned, and perhaps a longer time if dark-skinned. Light is a nutrient, just like water and all our

foods are. I don't think locking people out of it is the right approach. Chronic, long-term exposure to ultraviolet light is what gets people into problems, and perhaps acute sunburns.

I was thinking about people in nursing homes who are locked up in bed, away from the sun. We might even look at people in prisons who are locked away. I'm willing to bet a great number of those people are going to be found to be vitamin D deficient. We see a lot of lethargy and inertia in our nursing home patients. I wonder if we checked them and then gave them vitamin D whether we might find more active people. I think we're opening a door at a nutritional level, to a whole new concept that we had no knowledge of before.

JB: Thank you for such extraordinary insight. What a great "1-2 punch," having Dr. Hayes talk about the fundamental science around vitamin D as a hormone, and for you to add clinical applications. I want to encourage you to continue on this great path. We see you as a pathfinder in the future of functional medicine. Thank you again, Dr. Fishman, for your extraordinary work and for your contribution to FMU.

NF: Thank you, Jeff.

We have been privileged to hear wonderful presentations by Dr. Hayes and Dr. Fishman concerning the underpinning of the bioscience in the emerging story of vitamin D and its clinical implications. This is a fascinating, evolving chapter in nutrigenomic-based functional medicine. I would like to amplify some of those thoughts about the emerging vitamin D connection, to better understand its application in the prevention, and perhaps even treatment, of chronic, age-related disorders.

Vitamin D and Prevention of Falls

Let us not forget about the role of vitamin D and bone in the prevention of osteoporosis. A recent paper appeared in the *Journal of the American Medical Association* titled "Effect of Vitamin D on Falls."^[10] This is a meta-analysis of a series of published papers from 1960 to February 2004 related to vitamin D and bone fracture.

Falls reportedly occur in 30 percent per year of those 65 years of age or older and 40-50 percent of those are 80 years or older. Falls are a big contributor to morbidity and ultimately to mortality, because many of these individuals go into the hospital and never come out after sustaining a fall with injury. Falls constitute the largest single cause of injury mortality in elderly individuals, and are an independent determinant of functional decline, leading to 40 percent of all nursing home admissions and substantial societal costs. It is certainly something we need to be more attentive to in geriatric medicine. Any way we can help prevent falls would not only be important for the individual, but would be significant in terms of public health and use of medical services.

Because of the increasing proportion of older individuals, annual costs from all fall-related injuries in the United States in people 65 years or older have been projected to increase from \$20.3 billion dollars in 1994 to \$32.4 billion dollars in 2020. Previously, the moderate protective effect of vitamin D on fracture risk has been attributed primarily to bone mineral density changes. However, vitamin D may also directly improve muscle strength thereby reducing fracture risk through fall prevention. It was found in a number of randomized controlled trials that vitamin D reduced fractures within eight to 12 weeks, a finding consistent with muscle strength benefits.

Now that we recognize that the hormonal form of vitamin D (the 1,25-dihydroxyvitamin D₃ you have heard so much about) has receptor sites on virtually every cell, and that it is related to gene expression patterns and outcome associated with both the proteomic and metabolomic function of the cell and tissue in that organ, it would not be too far-ranging to speculate that vitamin D might have an effect on sarcomere function or muscle cell function. The potential effect of vitamin D on falls, however, has not been well established. Several randomized controlled trials have addressed this, but results have been mixed, including several trials that reported non-significant results.

In the *JAMA* paper on the effect of vitamin D on falls, the authors looked at the cumulative literature published from 1960 through February 2004 to see how the vitamin D story has evolved relating to prevention of the frequency of falls. Based on five randomized controlled trials involving 1237 participants, vitamin D reduced the corrected odds ratio of falling by 22 percent, compared with patients receiving calcium or placebo. From the pooled risk difference, the number needed to treat was 15, or equivalently 15 patients would need to be treated with vitamin D to prevent one person from falling. The inclusion of five additional studies involving 10,001 participants in a sensitivity analysis, resulted in a smaller, but still significant effect size. Subgroup analyses suggested that the effect size was independent of calcium supplementation, type of vitamin D, duration of therapy, and gender, but reduced sample sizes made the results statistically nonsignificant for calcium supplementation.

It is concluded from the meta-analysis that vitamin D supplementation appears to reduce the risk of falls among ambulatory or institutionalized older individuals with stable health by more than 20 percent. This may be due to its effect not just on bone but also on muscle strength. Therefore, there may be other values of vitamin D beyond that which we have traditionally thought of in terms of the calcium connection to osteoporosis and bone fracture.

As we so eloquently heard from Dr. Hayes, the conversion of vitamin D to its hormonal form (first the 25-hydroxylation in the liver and then the 1-hydroxylation in the kidney to produce the 1,25-dihydroxyvitamin D₃, or calcitriol) is dependent upon a series of hydroxylating enzymes which are members of the cytochrome P450 family. These cytochrome P450 hepatic mono-oxidases and the renal mono-oxidase enzymes are those that deliver the hydroxyl groups that make the vitamin D into the hormonal form. You might ask what the specific oxidases are that engage in the process of vitamin D hydroxylation. That is now fairly well understood. CYP27A1 and CYP27B1 are the two cytochromes that appear to be engaged in the hydroxylation patterns of vitamin D. Therefore, one might speculate that lowered activities of these hydroxylating enzyme systems, or mono-oxygenases, would lead to underconversion, or slower conversion of vitamin D into its hormonal form, the rate-limiting step being the 25 hydroxylation of vitamin D itself.

How could one upregulate the hydroxylation in individuals who have sluggish or impaired hydroxylation; in other words, upregulate the specific cytochrome P450s involved in the production of the hormonal form of vitamin D? That goes back to the discussion we had with Dr. Fishman about why some people may have seasonal affective disorder (SAD) as a consequence of impaired vitamin D metabolism into the active 1,25 dihydroxy hormonal form. It turns out that recent work has suggested at least one pair of phytonutrients that can upregulate CYP27B1, thereby increasing the hormonal form from the vitamin D in cell culture systems. These are the soy isoflavones that we have heard so much about—genistein and diadzein—from soy concentrate.

Phytoestrogens and Vitamin D Metabolism—Prevention and Therapy of Colorectal, Prostate, and Mammary Carcinomas

In a recent paper published in the *Journal of Nutrition*, work from James Ambrecht and his collaborators at the Department of Pathophysiology, University of Vienna Medical School, Austria; the Institute for Preventive Medicine, Nutrition and Cancer, and Division of Clinical Chemistry, University of Helsinki, Finland; and the Geriatric Research, Education, and Clinical Center at the St. Louis Veterans Administration Medical Center found that soy isoflavones increased levels of CYP27B1.^[11] They suggest this may result in increased 1,25 dihydroxyvitamin D, which may be one of the reasons why soy consumption has been associated with reduced incidence of colorectal, prostate, and mammary carcinomas. By increasing the active hormonal form of vitamin D, which has an effect on epithelial cell regulation and differentiation through the processes Dr. Hayes talked about, through the immune system and favorable effects on apoptosis, there may be an indirect effect on reducing the incidence of these three forms of mucosal cell carcinoma—colorectal, prostate, and mammary. There may be an interrelationship of interest between consuming soy products and increasing vitamin D metabolism in individuals who have low levels of 25-hydroxyvitamin D₃, a very important potential observation coming out of the recent primary research literature. If a person is increasing dietary vitamin D level intake and does not see a concomitant increase in plasma 25-hydroxyvitamin D₃ level, he/she may want to increase soy isoflavone intake to see if that amplifies the conversion of the vitamin D into the active hormonal form.

Vitamin D, Bone Loss, and Inflammation

We have also started to look at the loss of bone from the bone remodeling unit and the production of osteoporosis from a slightly different perspective. In the past, it was a fairly simple model of calcium-in versus calcium-out, principally controlled by a dynamic relationship between parathyroid hormone, calcitonin, and dietary calcium, and how that influenced the osteoclast and the osteoblast. Now, we are starting to see a new component emerge that is important in bone loss, and that is inflammation.

“Inflammation and bone resorption often go hand in hand, a fact evident in conditions such as joint destruction in rheumatoid arthritis or periodontal disease.”^[12] The most common loss of teeth in the adult is that of alveolar bone associated with periodontal disease. Even in people with reasonably good oral hygiene, there can often be loss of alveolar bone. How does this work?

Arming the Osteoclast

Osteoclasts, the bone-resorbing cells of the organism, also share several features with macrophages and dendritic cells. Osteoclasts are derived from hematopoietic stem cells within the macrophage lineage, and they respond to several interleukins produced by activated T cells involved with the inflammation pathways. These include the receptor activator of nuclear factor κ B (NF κ B), the so-called RANKL. RANKL and tumor necrosis factor (TNF) stimulate osteoclast differentiation and bone resorption. In the case of high TNF levels or high RANKL levels, the osteoblast is converted to the osteoclast cell more rapidly, increasing the number of bone resorbing units, at the expense of lowering the number of bone formation units. The equilibrium is shifted in the bone-remodeling unit toward bone loss.

In the April 15, 2004 issue of *Nature*, work by Koga and Inui et al. tightens the link between bone resorption and the immune system.^[13] The authors show that cells of the immune system and osteoclasts

share requirements for costimulatory signals that are mediated by immunoreceptor tyrosine-based activation in osteoclasts, and this costimulation is needed for RANKL-induced differentiation and bone resorption. Therefore, high levels of inflammation or inflammatory mediators increase the relative risk of bone loss, or osteoclastic osteolysis.

We might also ask about the role of the hormonal form of vitamin D. We learned from Dr. Hayes' work that it is engaged in influencing macrophage apoptosis and attenuating an upregulated immunological system associated with inflammation. There may be another role that vitamin D plays other than the calcium connection in maintenance of bone integrity. It may serve as an antiinflammatory or an inflammation-balancing substance that has to do with the ability to reset the balance between the thymus-dependent 1 (Th1) and thymus-dependent 2 (Th2) lymphocytes. Dr. Hayes has made active contributions in this area over the last 20 years in our understanding of that relationship.

What I am describing is an interesting relationship between inflammation, bone loss, vitamin D in its hormonal form, immune cell activity, and the interrelationship between Th1 and Th2, or systemic inflammation versus tissue-specific inflammation. The vitamin D hormonal form, calcitriol, may have a central role in establishing the proper equilibrium or the cell system responsiveness to stimuli, so it is not shifted too much in terms of Th1 or Th2 predominance, but is able to maintain the proper equilibrium so it does not tip over into extended systemic inflammation or into extended or amplified tissue-specific inflammation that is often associated with disorders such as atopy, asthma, allergy, or eczema.

The Parathyroid Gland and Calcium and Phosphorus Dynamics

Let us not forget the relationship with the parathyroid gland, as well. The parathyroid gland plays an important role in the secretion of parathyroid hormone on the little tufts of tissue that sit embedded within the thyroid gland that produce parathyroid hormone, or PTH, and interrelate and counter-balance the release of calcitonin from the thyroid gland. The combination of those two establishes another equilibrium pertaining to calcium and phosphorus dynamics.

A number of individuals over many years have talked about the fact that as our diets became lower in calcium and higher in phosphorus; we started "tipping the thermostat" of the parathyroid hormone/calcitonin connection to more bone loss. High phosphorus intake and low calcium intake turns up PTH activity. There is a nutritionally-induced, secondary hyperparathyroid-like condition which causes more calcium to be pulled from bone as a source of maintaining plasma serum calcium levels. Phosphorus stimulates this process. The high soft drink-containing diets or lifestyles of many children may contribute to this nutritionally-induced, borderline or secondary hyperparathyroidism. Increasing calcium and lowering phosphorus in the diet helps to maintain the proper balance, one with the proper dietary signals that influence the proper regulation of calcitonin and parathyroid hormone. I do not want to exaggerate this connection. This is not the major source of bone loss, but it is another factor that can contribute to altered hormonal messages that interrelate with the dynamics of calcium and ultimately, soft tissue calcium deposition or hard tissue calcium loss; in other words, bone calcium loss.

The parathyroid gland takes its signals from many sources. For instance, when there is chronic renal failure, there are often alterations in hormonal messages from the kidneys, which alter parathyroid function so chronic glomerulonephritis can have adverse effects on parathyroid function that influences the calcium/phosphorus dynamic. I do not want to make the story so simplistic as to say that only dietary

calcium/phosphorus ratios control these hormones and ultimately, their impact on bone. I want to put that into the mix because when dietary recall studies with food-frequency questionnaires or diet diaries are done in many individuals, it is found that dietary calcium levels are fairly low (below 800 mg per day), and dietary phosphorus levels may be up in the several grams-per-day level, particularly if they are taking phosphate-containing foods and eating a lot of high-protein meals. Phosphorus in diets is generally associated with the nucleo-proteins or nucleic acids; the phosphorus in them is part of the triphosphate residues. Therefore, when we look at high protein diets, we often see high phosphorus, as well. A high protein diet is generally a low-calcium diet because calcium comes from vegetable products, whole grains, and things of that nature (along with dairy products, obviously). As a consequence, that can shift dietary calcium/phosphorus intake to a higher phosphorus/lower calcium basis, which then increases the parathyroid output of PTH and decreases calcitonin, leading to bone loss.

Fooling the Parathyroid Gland

There are several researchers now working on secondary hyperparathyroidism, particularly in individuals who have renal failure and who are on hemodialysis. There are some new medications now being released that “fool” the parathyroid gland and prevent secondary hyperparathyroidism. Certainly, the pharmacological world is working on how to manipulate parathyroid function in the pathophysiology of renal failure.

Those among what I call “vertically diseased” individuals suffering from the blues, lack of energy, some muscle weakness and fatigue, sleep disturbances, modest bone loss, and tissue calcification—the complex of what we call the trajectory-toward-ill-health type of person, may be the candidates for whom dietary calcium/phosphorus ratios play an important role. Vitamin D and its conversion into its hormonal form are very important in “putting them back on the trail,” so to speak. If you are interested in the parathyroid connection to renal failure, there are a couple of recent papers in *The New England Journal of Medicine* you might want to look at. There is a nice editorial titled “Fooling the Parathyroid Gland—Will There Be Health Benefits?”^[14] Another paper discusses the management of secondary hyperparathyroidism in patients receiving hemodialysis titled “Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis.”^[15] There is also a paper on a good case history of a patient with asymptomatic primary hyperparathyroidism, if you would like to review the role of the parathyroid in controlling a variety of different functions beyond bone.^[16]

I hope we have given you some “news to use” in this edition of FMU relating to the exciting, emerging story around vitamin D in its hormonal form and its effect on the immune system.

We look forward to visiting with you in September.

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