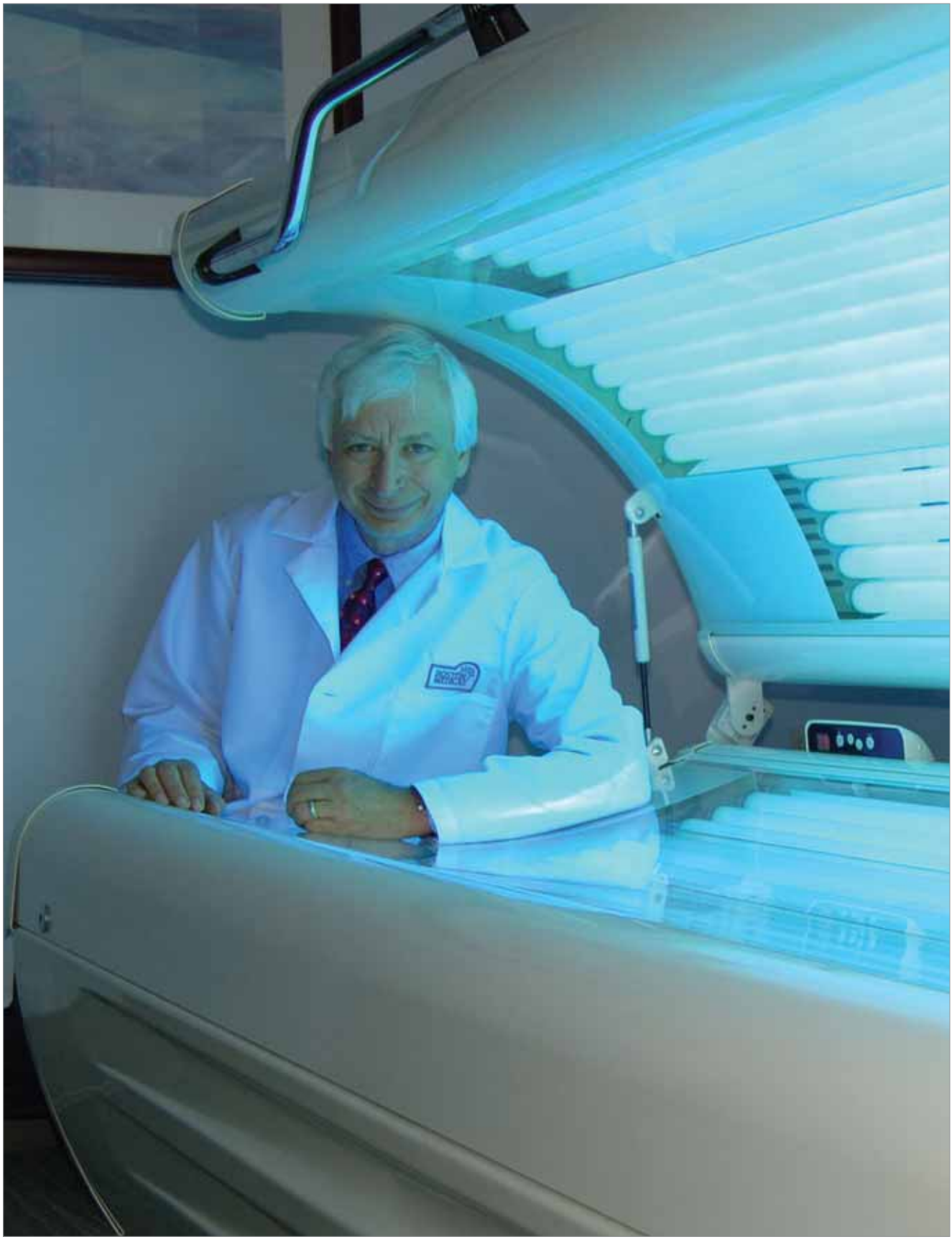


MICHAEL HOLICK, PHD, MD: VITAMIN D PIONEER

Interview by Frank Lampe and Suzanne Snyder • Photography by David Keough

Michael F. Holick, PhD, MD, is professor of medicine, physiology, and biophysics; director of the General Clinical Research Center; and director of the Bone Health Care Clinic and the Heliotherapy, Light, and Skin Research Center at Boston University Medical Center.

After earning a PhD in biochemistry and a medical degree and completing a research postdoctoral fellowship at the University of Wisconsin, Madison, Dr Holick completed a residency in medicine at Massachusetts General Hospital in Boston.

Dr Holick has made numerous contributions to the field of the biochemistry, physiology, metabolism, and photobiology of vitamin D for human nutrition. He determined the mechanism for how vitamin D is synthesized in the skin, demonstrated the effects of aging, obesity, latitude, seasonal change, sunscreen use, skin pigmentation, and clothing on this vital cutaneous process. Dr Holick has established global recommendations advising sunlight exposure as an integral source of vitamin D. He has helped increase awareness in the pediatric and medical communities regarding the vitamin D deficiency pandemic and its role in causing not only metabolic bone disease and osteoporosis in adults, but in the increasing risk of children and adults developing common deadly cancers and autoimmune diseases, including type 1 diabetes, multiple sclerosis, and heart disease.

Dr Holick is a diplomate of the American Board of Internal Medicine, a fellow of the American College of Nutrition, and a member of the American Academy of Dermatology and the American Association of Physicians. He has received numerous awards and honors, including the American Skin Association's Psoriasis Research Achievement Award, the American College of Nutrition award, the Robert H. Herman Memorial Award in Clinical Nutrition from the American Society for Clinical Nutrition, the Annual General Clinical Research Centers' Program Award for Excellence in Clinical Research, and most recently, the Linus Pauling Functional Medicine Award from the Institute for Functional Medicine. Dr Holick serves on a number national committees and editorial boards and has organized and/or co-chaired several international symposia. He has authored more than 300 peer-reviewed publications, more than 200 review articles, and numerous book chapters. He has acted as editor and/or co-editor on 10 books and authored The UV Advantage *(iBooks New York), which is available at uvadvantage.org.*

Opposite: Shown here in the General Clinical Research Center at Boston University Medical Center, Dr Holick contends that healthcare professionals, the government, and world health organizations need to consider recommending sensible sun exposure as an excellent source for satisfying people's vitamin D requirements.

***Alternative Therapies in Health and Medicine* (ATHM):** Please give us an overview of how you came to study vitamin D.

Michael F. Holick, PhD, MD: You would think that I was very careful and thoughtful in my consideration of what I wanted to specialize in as I was working toward my PhD, but there is nothing further from the truth. Most students want to work in the hottest area of scientific investigation because they think that that will make them successful. In the late 1960s, when I went to the University of Wisconsin, the hottest topic was how your body uses energy, how it generates energy in the mitochondrion. At the time, everybody wanted to study that. It was mainly post-doctoral fellows who were working with the greatest experts in that particular field. When I tried to get into the field, I was told to go to talk to this young investigator who was working in vitamin D.

I couldn't think of a more boring subject than vitamin D. It prevents rickets in kids, and we don't see rickets anymore, so why would I be interested? But at the time, they made the observation that vitamin D was converted in pigs to 25-hydroxyvitamin D_3. When I came on board, I needed to get a master's degree. My project was to demonstrate that what they found in pig blood was found in human blood. I started my research and identified 25-hydroxyvitamin D_3 as the major circulating form of vitamin D_3 in human blood. As a result of that, as I was doing the study, I realized that there was a contaminant in human blood that was not found in pig blood. So you couldn't simply follow the procedure for pig blood. I introduced a whole new chromatographic separation system that permitted me to identify 25-hydroxyvitamin D_3.

After only 3 months of research, I had completed my master's degree research activity. Then it was realized that 25-hydroxyvitamin D_3 took too long to work on the body in terms of enhancing intestinal calcium absorption and mobilizing calcium from the bones, which were the major functions of vitamin D. It was thought that maybe 25-hydroxyvitamin D_3 had to be converted or metabolized to an active form. The hunt was on by 3 different laboratories to be the first to identify the active form of vitamin D. The DeLuca Laboratory, where I worked, was one of the laboratories interested in identifying the active form of vitamin D_3.

Long story short: for my PhD thesis, which I completed about a year later, I was responsible for the first isolation and identification of the active form of vitamin D_3, 1,25-dihydroxyvitamin D_3.

ATHM: That was your dissertation, in essence?

Dr Holick: Yes. I identified 25-hydroxyvitamin D_3, which is the major circulation form used by physicians to measure vitamin D status in patients worldwide, and I also identified the active form of vitamin D_3. Two years later, my roommate and I were the first to chemically make it. Once it was appreciated that the activation of vitamin D occurred in the kidneys, it instantly became obvious while working in Dr DeLuca's and Dr Schnoes' laboratories why patients with kidney disease had severe bone disease and had a resistance to vitamin D.

When I was in medical school when we gave patients who were wheelchair-bound the active form of vitamin D that I had made in the test tube because they had kidney disease and associated bone disease, they began walking again. That was my introduction to the translational benefit of vitamin D research, and I have worked in that area ever since.

ATHM: It sounds as though the state of research around vitamin D in the late 1960s was not very advanced.

Dr Holick: That's correct. I isolated 25-hydroxyvitamin D_3 in 1970 and 1,25-dihydroxyvitamin D_3 in 1971. For the next decade or so, it was thought that we would figure out how active vitamin D enhanced intestinal calcium absorption, how it could be used to treat patients with renal failure and bone disease, and maybe postmenopausal osteoporosis. Thus, most thought that probably that would be the end of the vitamin D story—until 1979, when the DeLuca Group reported that essentially every tissue in your body appeared to recognize the active form of vitamin D. We and others went on to show that every tissue and cell in your body has a receptor for vitamin D. We began to appreciate that maybe vitamin D had other biologic actions. One of the first insights was by a former post-doc that worked with me in the DeLuca Group. His name is Dr Tatsuo Suda, DDS, PhD. When he went back to Japan, he showed that if you take leukemic cells that have a vitamin D receptor and incubate them with the active form of vitamin D, it inhibited their growth and induced differentiation. That was the first insight into the potent biologic action of vitamin D and its potential role in preventing cancer. After that observation, in the early 1980s we showed that 1,25-dihydroxyvitamin D_3, the active form of vitamin D, could be used to treat the hyperproliferative skin disorder psoriasis. I introduced the concept of using activated vitamin D compounds to treat psoriasis, which is the first line therapy for psoriasis.

IT'S ESTIMATED THAT ANYWHERE FROM 30% TO 80% OF THE US POPULATION IS VITAMIN D DEFICIENT.

ATHM: So it was the work of your Japanese colleague that brought the awareness that there was more going on with the therapeutic use of vitamin D than simply prevention of rickets?

Dr Holick: Exactly. All of a sudden, we recognized that the cells that had a vitamin D receptor had a wide variety of genes that were being turned on and turned off by 1,25-dihydroxyvitamin D_3. These genes controlled cell growth and induced cells that were malignant to either become normal or die.

ATHM: Would you talk about the statistics around vitamin D deficiency in the United States?

Dr Holick: It's estimated that anywhere from 30% to 80% of the US population is vitamin D deficient. We did a study in Boston at the end of the summer—at a time when you would expect the blood levels to be the highest—and we found that 40% of Hispanics, 34% of whites, and 84% of African-American adults over the age of 50 were vitamin D deficient. We did a study in young girls in Bangor, Maine, ages 9 to 11. Forty-eight percent were vitamin D deficient of at the end of the winter. They wore sun protection all summer; 17% remained vitamin D deficient at the end of the summer.

The Centers for Disease Control and Prevention did a study in the United States at the end of the winter and found that 48% of African-American women, during their childbearing years of 15 to 49 years of age, were vitamin D deficient. A study done at Boston's Children's Hospital by Dr Gordon reported that 52% of adolescent Hispanic and African-American boys and girls were vitamin D deficient throughout the year. That theme is carried out whether you live in Florida or Alaska. Vitamin D deficiency is an extremely common problem that has very serious health consequences.

ATHM: Those numbers would lead any normal person to say that this is a pandemic within the United States.

Dr Holick: Absolutely. I just came back from India and physicians there didn't believe that vitamin D deficiency could be a health problem. They decided to do a study to measure blood levels on themselves. Ninety percent of the Indian physicians, whether they lived in Bombay or in New Delhi, were vitamin D deficient. They now have reported that 50% to 80% of adult Indians are vitamin D deficient. Upwards of 30% to 50% of Indian children are vitamin D deficient.

ATHM: Why are people deficient in vitamin D at this level?

Dr Holick: To me, it's not a surprise at all because people assume that if you have a well-balanced diet you're getting all the nutrients you need. There is essentially no vitamin D from any dietary source. It's principally found in oily fish or in sun-dried mushrooms and in fortified foods, like milk and orange juice. But there are only 100 international units (IU) in a glass of milk or vitamin D-fortified orange juice. We now recognize that for every hundred IU you ingest, you raise your blood level of 25-hydroxyvitamin D by 1 nanogram per milliliter (ng/mL).

What better way to get it than from exposure to sunlight? Our hunter-gatherer forefathers were always exposed to sunlight. Their skin pigment evolved and devolved specifically for the environment in which they lived in order to produce enough vitamin D and yet protect them from excessive, damaging effects of sun exposure.

ATHM: Have you seen some differences in terms of segmentation between age, gender, race, and where people are located geographically on the planet?

Dr Holick: Yes. We've done studies globally. I was just in South Africa and even there, they're finding vitamin D deficiency very common. I pointed out something that they didn't realize. In Cape Town (34° S), for instance, if you compare your skin's vitamin D synthetic activity in the summertime to what it is in the wintertime, there's an 80% reduction in vitamin D synthesis in the wintertime compared to summertime.

If you live north of Atlanta, Georgia, you can't make any vitamin D_3 in your skin from about November through March. In the early morning or late afternoon, even at the equator with the sun shining, you're still not making vitamin D_3 because the zenith angle of the sun is so oblique that most of the UVB photons that make vitamin D are absorbed by the ozone layer.

That's why most humans obtain from sun exposure their vitamin D requirement between the hours of about 10 AM and 3 PM and mainly in the late spring, summer, and early fall. They store it in their body fat and it is released throughout the winter months, allowing them to be vitamin D sufficient throughout the year.

ATHM: How much vitamin D does a person get from exposure to the sun?

Dr Holick: We did a study that showed that if you expose a person in a bathing suit to what we call 1 minimal erythemal dose, which is a light pinkness to the skin 24 hours after sun exposure, it's equivalent to taking between 15 000 and 20 000 IU of vitamin D_3. For a white adult, that would be equivalent to being exposed to sunlight in June at noon for about 10-15 minutes on a Cape Cod beach. Your body has a huge capacity to make vitamin D. What's interesting is that the sunlight destroys any excess vitamin D that your body makes, so you could never become vitamin D intoxicated from sun exposure.

ATHM: Is there a danger of vitamin D intoxication when it is taken orally?

MOST HUMANS OBTAIN FROM SUN EXPOSURE THEIR VITAMIN D REQUIREMENT BETWEEN THE HOURS OF ABOUT 10 AM AND 3 PM AND MAINLY IN THE LATE SPRING, SUMMER, AND EARLY FALL.

Dr Holick: Absolutely. If you take more than 10 000 IU per day of vitamin D orally for more than 6 months, you are at risk of becoming vitamin D intoxicated. In fact, we reported a case in *The New England Journal of Medicine* in which a lawyer who had heard about all the beneficial effects of vitamin D went on the Internet and bought it in powder form. A teaspoon was supposed to contain 1000 IU of vitamin D. He was taking 2 teaspoons per day, and he presented to a local emergency room severely vitamin D intoxicated. When he called me, I told him to send the powder over and we would do an analysis because I found this hard to believe he could be vitamin D intoxicated from the amount he believed he was taking. Sure enough, the company forgot to dilute it. He was taking a million IU a day—that will cause vitamin D intoxication, which can increase the blood calcium and calcify blood vessels and kidneys.

ATHM: Can you talk a bit about vitamin D deficiency, how and when it began, and its consequences?

Dr Holick: In the 1930s, when people began to appreciate the connection between sun exposure and vitamin D, the US government set up an agency to recommend to parents, especially those living in the northeast, that they send their kids outside to be exposed to some sunlight because that was a major source of vitamin D. They also began to fortify milk with vitamin D at the same time. Of course, all of that has gone by the wayside because

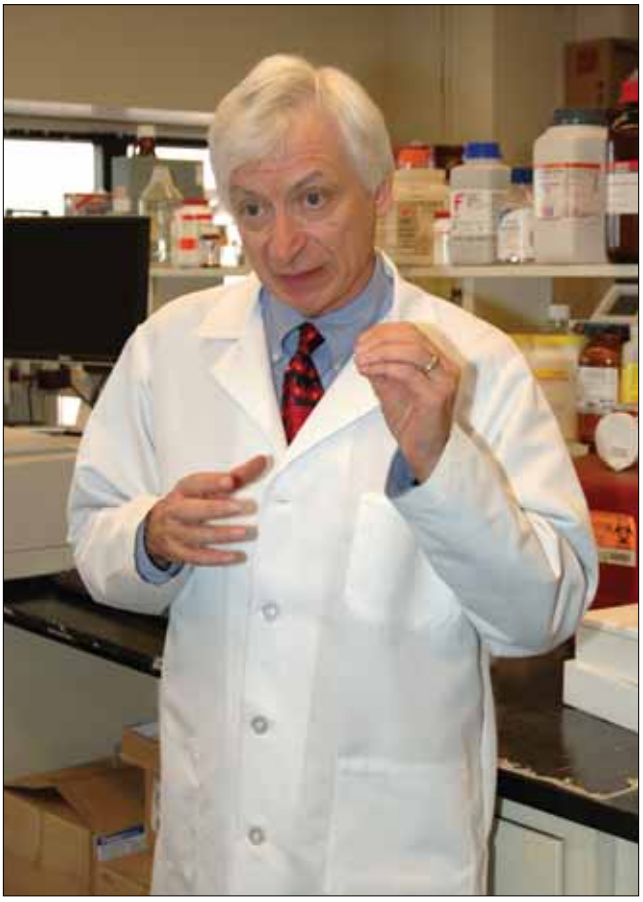
for 40 years the dermatology community and the World Health Organization have recommended that people never be exposed to direct sunlight. That has been a major cause of this worldwide pandemic of vitamin D deficiency.

What are those consequences? As early as the 1940s it was appreciated that if you lived at higher latitudes, you were at greater risk of dying of cancer—even though it was appreciated that, yes, if you lived down south and were exposed to more sunlight, you could increase your risk of non-melanoma skin cancer. But the argument even back then was that it was easy to detect and easy to treat non-melanoma skin cancers, unlike the lethality of colon, prostate, and breast cancer which seemed to be associated with lack of sun exposure.

In the 1980s and 1990s, the Garland brothers began looking at the map of the United States and related it to cancer incidence. They first looked at colorectal cancer incidence and showed that people living in the northeast had a 10% increased risk of developing colorectal cancer. Then they did further studies showing that the higher the latitude a person lived in, the higher his risk of colorectal, breast, and several other cancers. Other investigators, including Dr Schwartz and Dr Grant, also looked at prostate cancer and found a similar association.

The Garland brothers and their colleagues and Dr Grant have shown that if you look at blood levels of 25-hydroxyvitamin D, from both prospective and retrospective studies, if you start out with a 25-hydroxyvitamin D of at least 20 ng/mL, you reduce your risk of developing colorectal, breast, and a wide variety of other cancers by 30% to 50%. It's estimated that if you take 1000 IU of vitamin D per day, which most experts recommend everybody, both children and adults, be on, you reduce your risk of developing colorectal, breast, prostate, and ovarian cancer by approximately 50%. A study was done by the Harvard Group showing that women who had a blood level of 48 ng/mL on average for 25-hydroxyvitamin D had a 50% reduced risk of developing breast cancer.

Based on the knowledge that people who live at higher latitude are at higher risk of developing type 1 diabetes, Dr Hypponen did a study in Finland in which she looked at the records of children who back in the 1960s took 2000 IU of vitamin D_3 a day during the first year of life. She followed their medical records for 31 years and found that they had a 78% reduced risk of developing type 1 diabetes. Children who were vitamin D



"For 40 years the dermatology community and the World Health Organization have recommended that people never be exposed to direct sunlight. That has been a major cause of this worldwide pandemic of vitamin D deficiency."

"Soon to be published is a study showing that if you hinder the ability of the body to activate vitamin D, it results in an enlarged heart and hypertension, consistent with all the earlier observations."

deficient and had rickets had a 2.4-fold increased risk of developing type 1 diabetes.

Pittas reported from the NHANES III database that if you increase your calcium and vitamin D intake, you reduce your risk of developing type 2 diabetes. Wang recently showed a 50% reduction in having a heart attack in people who are vitamin D sufficient. It's also known that if you live at higher latitude—north of Atlanta, Georgia—for the first 10 years of your life, you have a 100% increased risk of developing multiple sclerosis for the rest of your life. And studies have shown that women and men who have the highest levels of 25-hydroxyvitamin D reduce their risk of developing MS by about 42%.

A similar observation has been made for rheumatoid arthritis in women: about a 44% risk reduction for women who ingest more than 400 IU of vitamin D a day. It has been known for more than 150 years that cod liver oil helped in the treatment of tuberculosis. At the turn of the last century, solariums were set up specifically for TB patients. We have always known that macrophages activate vitamin D, and that potentially is a problem for patients with chronic granulomatous disorders like sarcoidosis because, the macrophage makes 1,25-dihydroxyvitamin D_3,

"People are now using sunscreen with an SPF of 45. So even if you put on half or one third of it, you're still getting an SPF of 15, which is reducing your ability to make vitamin D in your skin by 99%."

which enters the circulation and causes an increase in calcium in the urine and high blood calcium. But we never understood why your macrophages activated vitamin D until recently, when Liu published in *Science* in 2005 that the reason your macrophages activate vitamin D is because the 1,25-dihydroxyvitamin D tells the macrophage to make cathelicidin, which is one of the defensin proteins. It's a peptide that specifically kills infective agents such as TB. So we now are beginning to realize why vitamin D is so important in innate immunity. A study in postmenopausal women who took 2000 IU of vitamin D_3 a day had a 90% reduction in upper respiratory tract infections compared to women who took 400 IU of vitamin D_3 a day.

We also know that activated T and B lymphocytes have receptors for 1,25-dihydroxyvitamin D, and 1,25-dihydroxyvitamin D modulates their activity, which is why it's important in auto-immune diseases like multiple sclerosis, rheumatoid arthritis, and type 1 diabetes. In 1979, Rostand published a study showing that people who live at higher latitudes have a higher risk of having hypertension—that is true whether you live in Europe, Australia, or the United States. If you take hypertensive patients and put them in a tanning bed to simulate sunlight 3 times a week for 3 months and increase their blood level of 25-hydroxyvitamin D by 180%, their blood pressure becomes normal. We also took a group of hypertensive patients and put them in a tanning bed that had only UVA radiation—so they did not make any vitamin D—and there was no change in their blood level of 25-hydroxyvitamin D and no change in their blood pressure.

Li published a study in the *Journal of Clinical Investigation* in 2002 showing that the active form of vitamin D is one of the most potent regulators of renin production. And soon to be published is a study showing that if you hinder the ability of the body to activate vitamin D, it results in an enlarged heart and hypertension, consistent with all the earlier observations.

ATHM: Can increased intake of vitamin D lead to the mitigation of or remission of specific health conditions?

Dr Holick: Because every tissue and cell in your body has a vitamin D receptor, we think that vitamin D acts as a sentinel for your health in that it will control cell growth. If the cell growth becomes malignant, it will either return the cell to normal or induce apoptosis, cell death. Once the malignant process begins, unfortunately, cancer cleverly develops systems to become resistant to the beneficial effect of the active form of vitamin D. This is why it is so important to be vitamin D sufficient throughout your life.

Thus, it is not a surprise to me that if you just increase vitamin D intake, you are not going to treat cancer. Although there was a 21-month study in men with prostate cancer who received 2000 IU of vitamin D a day had a 50% reduction in their PSA levels. Lappe and colleagues reported that postmenopausal women who took 1400 to 1500 mg calcium and 1100 IU vitamin D_3 a day for 4 years reduced their risk of developing all cancers by 60% compared to the placebo group.

We did a study in cancer patients and showed that most cancer patients are vitamin D deficient. This is not a surprise because they don't feel well, so they're not outside, and they often have upset stomachs so they are not eating very well and as a result they're malabsorbing whatever little vitamin D may be in their diet. We found that when we give them vitamin D, they feel better. Their muscle strength is improved, their overall feeling of well-being is improved, and that in and of itself is beneficial.

ATHM: Is it true that there has never been a science-based recommended daily allowance (RDA) established for vitamin D?

Dr Holick: I was on the Institute of Medicine Committee. It was formed in 1995, and we deliberated for 2 years. We were asked by the National Academy of Sciences and the Food and Nutrition Board of the Institute of Medicine to come back with recommendations based on published literature. Dr Heaney, Dr Hughes, Dr Weaver, Dr Specker, and I were the experts in the field of calcium and vitamin D. We realized even back then, based on our own work that had yet not been published, that our recommendations were probably going to be inadequate. But we were obligated to make recommendations based on published literature. There was essentially none that was very useful at that time.

Most of the literature showed that giving 100 IU of vitamin D to a child will prevent rickets. But that's the most gross manifestation of vitamin D deficiency. That was kind of the hallmark back then. Before 1997, when the new recommendations came out, the recommendation was not 400 IU/d, but 200 IU for everybody. [Editor's note: It was determined by the Institute of Medicine in 1997 that there was insufficient evidence to establish an RDA for vitamin D. Instead, an adequate intake (AI)—a level of intake sufficient to maintain what was perceived then as healthy blood levels of 25-hydroxyvitamin D—was established and remains unchanged.] So we felt that we made at least some contribution because we could, based on the published literature before 1995, show that at least 400 IU was needed to benefit adults over the age of 50 to 70, and 600 IU for people aged 70 and older. But now many experts agree that both children and adults need a minimum of 1000 IU of vitamin D a day to maintain a blood level of 25-hydroxyvitamin D that we consider to be healthful, which is above 30 ng/mL.

ATHM: If that committee were adjourned today, would the results be different?

Dr Holick: No question about it. There is so much published literature now to demonstrate that even 1000 IU a day will not raise your blood level above 30 ng/mL. We just published a study in healthy adults living in Boston during the wintertime that 1000 IU vitamin D_2 or vitamin D_3 a day did not raise their blood level above 30 ng/mL.

ATHM: So is the issue of vitamin D deficiency really around lack of exposure to the sun?

Dr Holick: In a word, yes. The data are clear. The literature shows that your blood levels of 25-hydroxyvitamin D are maximal at the middle to end of summer and at their nadir in the wintertime. That's for both children and adults worldwide. Humans have always depended on the sun for their vitamin D requirement. The diet provides little, if any, vitamin D.

People think that if you eat oily fish, you'll get the necessary vitamin D. A year ago we did a study that compared farmed salmon to salmon caught in the wild. It turns out that wild-caught salmon get vitamin D from the food chain, and there is plenty of vitamin D in our food chain because phytoplankton and zooplankton, exposed to sunlight, make vitamin D. In fact, we think vitamin D is probably the oldest hormone made on this earth because there's an organism that has lived in the Atlantic Ocean for more than 750 million years that we cultured and showed made vitamin D. Farmed salmon, on the other hand, are fed pelleted food that has very little basic nutritional value. There is essentially no vitamin D in it. When we compared the wild-caught to farmed salmon, we found farmed salmon had 10% to 25% percent of the vitamin D content of wild-caught salmon.

ATHM: Please talk about the use of sunscreen as it relates to vitamin D synthesis.

Dr Holick: Ultraviolet B radiation is responsible for making vitamin D. So a sunscreen with an SPF of 8 is supposed to absorb 92.5% of UVB radiation. If you put a sunscreen with an SPF of 8 on your skin properly, which is a certain amount per unit area, it will absorb 92.5% of UVB and decrease your ability to make vitamin D in your skin by 92.5%. SPF of 15 reduces the ability by 99%.

It has been argued that most people don't put a sunscreen on properly. I agree with that, but the problem is that people are now using sunscreen with an SPF of 45. Even if you put on half or one third of it, you're still getting an SPF of 15, which is reducing your ability to make vitamin D in your skin by 99%. Farmers in the mid-West who had a history of non-melanoma skin cancer were told to always use sun protection, and they did. We measured their blood levels of 25-hydroxyvitamin D at the end of the summer, and most were vitamin D deficient.

What do I recommend? I typically recommend people go out for a period of time—depending on the time of the year, the time of day, the latitude, and the degree of skin pigmentation—if you know you're going to get a mild sunburn after 30 minutes, I typically recommend about 10, no more than 15, minutes of arms and legs exposure, or if you're in a bathing suit, abdomen and back exposure as well, 2 to 3 times a week. Always wear sun protection on your face because that's the most sun-damaged area and it's only about 9% of your body surface, so it doesn't provide you with that much vitamin D. Go out, enjoy yourself, get some sensible sun exposure, then put sunscreen on if you plan to stay out for a longer period of time.

People with a higher degree skin pigmentation, such as African Americans, are walking around with an SPF of 8 to 15. That's why they need to be exposed for much longer periods of

time and why people of color are at especially high risk of having vitamin D deficiency.

ATHM: This leads to a question about the body's ability to retain a proper amount of vitamin D. Based on the number of units you said one gets from sun exposure, there must be some shelf life within the body of vitamin D retention before it is depleted.

Dr Holick: Yes, the body is very clever. What happens is, you don't actually make vitamin D, you make previtamin D. Previtamin D is thermally labile and it rapidly converts to vitamin D, which then is released from your skin cells into your bloodstream. But on the way it's going through your subcutaneous fat and being stored. The half-life of 25-hydroxyvitamin D in your circulation is 2 to 3 weeks. As a result, you're increasing your blood levels of 25-hydroxyvitamin D and storing of vitamin D in your body fat. Thus, one sensible sun exposure is probably lasting you for at least 1 to 2 weeks.

ATHM: That speaks to how badly we're missing the sun in our culture, in particular.

THERE IS A PHOTOPHOBIA OUT THERE THAT IS PALPABLE AND REMARKABLE. AND IT'S REALLY UNFORTUNATE.

Dr Holick: No question about it. There is a photophobia out there that is palpable and remarkable. And it's really unfortunate. We did a study in pregnant women recently at our hospital. Pregnant women are typically well cared for by their obstetrician, and they're always told to take a prenatal vitamin, which contains 400 IU of vitamin D, and drink 2 glasses of milk a day. The women at our hospital were doing just that. We found that in 40 mother-infant pairs, at the time they gave birth, 76% of moms and 81% of newborns were vitamin D deficient.

ATHM: How is that presenting, especially in the newborns with the deficiency? There are a variety of chronic illnesses that appear to be related to vitamin D deficiency.

Dr Holick: Including asthma and wheezing disorders, which are a major health problem for inner-city kids, especially children of color. We think it may increase their risk of type 1 diabetes. It will probably prevent them from attaining their genetically pre-programmed height and bone mineral density and increase their risk of many other serious, chronic diseases later in life including multiple sclerosis, rheumatoid arthritis, and deadly cancers.

ATHM: We just don't have the studies yet?

Dr Holick: That's right. There are no long-term prospective studies evaluating vitamin D intake and risk of these diseases.

ATHM: Considering that the key vitamins were all identified by the 1930s, why is the seminal work on vitamin D so recent?

Dr Holick: Vitamin D was discovered in the early 1930s; Windaus won the Nobel Prize for it—not for discovering vitamin D, but for chemically making it and making the vitamin D that is made in our skin, vitamin D_3. There is an interesting distinction between vitamin D_2 and vitamin D_3. What people don't realize is that vitamin D_2 was made first. Back then it was assumed that vitamin D_2, which comes from the yeast steroid ergosterol, was made by human skin. The way they figured out that it wasn't was an interesting observation: if you gave vitamin D_2 to chickens, it didn't prevent them from getting rickets. But if you took the vitamin D from pigskin and gave it to chickens, it prevented rickets.

So it was known back in the 1930s that vitamin D_2 could not have been what was being made in our skin. Ultimately, 7-dehydrocholesterol was made by Windaus and he irradiated it with ultraviolet radiation, isolated vitamin D_3, and demonstrated that vitamin D_3 was the vitamin D that was made in our skin.

ATHM: Has recent research shown that both vitamin D_2 and D_3 are equally effective at increasing the levels of 25-hydroxyvitamin D? This is in opposition with earlier studies, is it not?

Dr Holick: That's correct. There was a study done in Canada in which researchers gave a group of adults 4000 IU of vitamin D_2 or 4000 IU of vitamin D_3 in ethanol for a period of 2 weeks and showed wide variability, and there appeared to be a 50% reduction in the 25-hydroxyvitamin D levels in the adults who were taking vitamin D_2. This implied that vitamin D_2 was less effective than vitamin D_3. The second study that set this kindling on fire was the observation by Dr Heaney's group. They gave a single 50 000-IU dose of vitamin D_2 or a single 50 000-IU dose of vitamin D_3 to healthy adults in the summertime. When they followed their 25-hydroxyvitamin D levels, they found that the levels more rapidly declined in the group that got that single dose of vitamin D_2. But more importantly and alarmingly was that the 25-hydroxyvitamin D_3 in those same subjects more rapidly declined than the subjects who received a placebo, implying that the vitamin D_2 induced the destruction of vitamin D_3. Therefore, not only was vitamin D_2 less active, but it caused the destruction of vitamin D_3.

I decided to conduct a study in which we gave 1000 IU of vitamin D_2 or 1000 IU of vitamin D_3 to healthy adults at the end of the winter—Dr Heaney's study was done in the summer, and sun exposure may have influenced the outcome of the study. We found that vitamin D_2 raised the blood levels of 25-hydroxyvitamin D identically to the group that took vitamin D_3.

More importantly, to leave no stone unturned, we also made a capsule that contained 500 IU of vitamin D_2 and 500 IU of vitamin D_3 and showed that the 25-hydroxyvitamin D levels increased exactly the same degree for the 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 and that there was no alteration in the 25-hydroxyvitamin D_3 levels in the group that got vitamin D_2.

That, to me, proves that vitamin D_2 is as effective as vitamin D_3 in raising and maintaining 25-hydroxyvitamin D levels. That is consistent with the early literature that showed that 100 IU of vitamin D_2 was effective in preventing rickets in children.

ATHM: How would you characterize the state of research in vitamin D today, in terms of where it is, where it needs to be, and where you see it going?

Dr Holick: Because of the overwhelming scientific evidence of the health benefits of vitamin D, numerous investigators worldwide are investigating it robustly. I applaud them all.

BECAUSE OF THE OVERWHELMING SCIENTIFIC EVIDENCE OF THE HEALTH BENEFITS OF VITAMIN D, NUMEROUS INVESTIGATORS WORLDWIDE ARE INVESTIGATING IT ROBUSTLY. I APPLAUD THEM ALL.

Where we need to go is we need to convince the health maintenance organizations, as well as the people responsible for healthcare worldwide, to increase vitamin D fortification of foods and to recommend some sensible sun exposure and do away with this issue of being sun-safe by never being exposed to direct sunlight without sun protection.

ATHM: How realistic is acceptance of these recommendations?

Dr Holick: I heard about a study that was done evaluating at the vitamin D status of Australian dermatologists. Guess what? 100% were vitamin D deficient. What a surprise. Vitamin D is in the popular press almost on a weekly basis. *Forbes* magazine just had an article about it. *Mother Earth Magazine* had an article about it. *TIME* considered it one of the top 10 stories of the year. *Discover* magazine considered it number 8 of the top 100 stories of the year. The message is finally getting out. It's finally filtering down to healthcare professionals and the regulatory agencies about the need to take measures to increase public awareness of the epidemic and institute sensible sunlight and supplement recommendations.

Dr Holick: I think that within the next couple of years, hopefully, there will be a movement in the United States to markedly increase the recommendation for vitamin D supplementation. That's what is holding back the food industry and the multivitamin industry because they are basing supplementation levels on the Institute of Medicine recommendations from 1997, which are outdated. Europe still forbids the fortification of most foods with vitamin D. That's because of an early observation in the 1950s, which turned out to be incorrect, that vitamin D intoxication occurred in some neonates. They concluded it was due to the over-fortification of milk, and as a result, they banned fortification of dairy products with vitamin D.

ATHM: Is there an upper safe limit of supplementation with vitamin D?

Dr Holick: In my opinion, you could easily take 5000 IU of vitamin D a day, probably forever. I typically recommend taking 1000 to 2000 IU of vitamin D a day—that should be adequate. I personally take 1400 IU of vitamin D a day. In the spring, summer, and fall, I cycle without sun protection for a period of time and then put the sun protection on. We know from the literature that you can take up to 10 000 IU of vitamin D a day for at least 5 months without toxicity.

You would have to take probably 30 000 to 50 000 IU of vitamin D a day for long periods of time, months to years, to become vitamin D intoxicated. The typical vitamin D intoxication incident is inadvertent where usually, more than several hundred thousand units to millions of units a day for a prolonged period of time are ingested. Vitamin D intoxication is one of the most rare medical conditions worldwide.

ATHM: Where along the curve is the medical establishment in understanding the role and importance of vitamin D?

Dr Holick: Whenever I give a presentation, one of the first things that happens is all the attendees will go to their local pharmacy and buy all the vitamin D supplements. When they hear the story and appreciate what's going on, they get religion. I was in South

Africa, for example, giving some talks for a pharmaceutical company, and the president and CEO of the company was sitting in the audience and immediately after my talk, he went out and got 1000 IU of vitamin D for himself and his family members.

Once people hear the story and appreciate that there is no downside to increasing your vitamin D intake and there is a significant upside, everybody complies. But it's incomprehensible to most physicians that this simple vitamin that everybody has always taken for granted is present in adequate amounts in a healthy diet, can have all of these health benefits. There is still great skepticism.

We also find that if we can convince a physician to order 25-hydroxyvitamin D assay on a couple of their patients, they all come back as deficient. This often will convince them. They've got religion, and now they order it on all their patients. They realize that vitamin D deficiency is a major health issue.

We've got a long way to go, but those who are getting it really appreciate it. The assay for 25-hydroxyvitamin D is the most ordered assay now in the United States.

ATHM: In your work, you explore the link between vitamin D deficiency and prostate and some other cancers, but you also reference obesity, tuberculosis, hypertension, and MS. Where are we are in terms of the published research on those conditions, and how far along are we in our understanding of those connections?

Dr Holick: We know that if you're vitamin D deficient, you have an increased risk of 30% to 50% of developing some of the most deadly cancers. What is the mechanism? Over the past decade, both our lab and other labs have shown that your skin, prostate, colon, breast, brain—just for starters—all have the enzymatic machinery to activate vitamin D locally. That's a major new concept because what was a real conundrum was, if you're exposed to a lot of sunlight and make a lot of vitamin D in your skin, or you ingest a lot of vitamin D in your diet, you cannot get your kidneys to make more 1,25-dihydroxyvitamin D.

There is a simple reason: the kidneys are responsible for activating vitamin D specifically for having it travel to the intestine and bone to regulate calcium metabolism. So if your kidneys were to make a lot more, then you would have had negative health consequences, such as hypercalcemia (high blood calcium) and hypercalciuria (high urine calcium). What the body cleverly does instead was to have all of the other tissues in your body activate vitamin D. It was shown by us and by others that if you have a patient who has no kidneys, he has no circulating blood levels of 1,25-dihydroxyvitamin D. Therefore, it was assumed that only the kidneys made it. What we didn't realize was that the body was clever and it could activate vitamin D locally in the prostate, colon, and breast. 1,25 D, locally produced, can regulate up to 200 different genes to regulate among other cellular functions cell growth, produce insulin in the pancreas, and regulate production of renin in the kidneys. Once it carries out these functions, 1,25-dihydroxyvitamin D induces the expression of the gene, called the 25-hydroxyvitamin D 24-hydroxylase, which is an enzyme that rapidly destroys 1,25-dihydroxyvitamin D. 1,25-dihydroxyvitamin D never leaves the cell and therefore its signature is never picked up in the bloodstream.

Obesity is a separate issue because as we discussed before, vitamin D is stored in your body fat. If you have normal body fat, your fat is being recycled and the vitamin D in the fat is released into the circulation so it can satisfy your body's requirement. But what if you have so much fat that vitamin D gets sequestered, so it can never get back out?

It's well-documented by Norman Bell and by others, including us, that most obese people are vitamin D deficient. Most obese people have muscle weakness and aches and pains in their bones and muscles and are lethargic. They're vitamin D deficient. Vitamin D deficiency is associated with all of those symptoms.

We did a study to prove the point. We took obese and non-obese people and put them in a tanning bed. Obese subjects raised their blood levels of vitamin D only 50% as much as a normal-weighted individual. To be sure that this had nothing to do with body surface, we also gave an oral dose of 50 000 IU of vitamin D_2 to obese and to non-obese individuals and saw exactly the same phenomenon—that vitamin D levels rose about 50% in the obese individuals compared to the non-obese individuals.

In terms of the other diseases, especially autoimmune diseases, activated T and B lymphocytes have receptors for 1,25-dihydroxyvitamin D. There's evidence to suggest that the macrophages activate vitamin D to produce 1,25-dihydroxyvitamin D. These are 2 reasons why this happens. The first is that 1,25-dihydroxyvitamin D tells the macrophage to express cathelicidin which is a protein that kills infective agents like tuberculous. The macrophage also secretes it to influence the immunological functions of activated T and B lymphocytes. And so both antibody production and cytokine production by B and T lymphocytes, respectively, are influenced by 1,25-dihydroxyvitamin D.

Not only does 1,25-dihydroxyvitamin D regulate innate immunity to decrease your risk of infectious diseases, but it also probably regulates your autoimmune response system, which may explain why you're less likely to develop type 1 diabetes, rheumatoid arthritis, Crohn's disease, and multiple sclerosis if you receive adequate sunlight or vitamin D. It has also been suggested that the mechanism of MS, as well as type 1 diabetes, is due to an infectious disease possibly, a slow virus, and there is some speculation that 1,25-dihydroxyvitamin D, by inducing innate immunity, may inhibit this kind of infectious activity. 1,25-dihydroxyvitamin D may have a dual role in preventing the viral infection or limiting the viral infection while also regulating your immune response, all for the purpose of preventing autoimmune diseases.

In terms of heart disease, we know that blood vessels have vitamin D receptors. The active form of vitamin D will enhance contraction of the heart muscle, as Dr Simpson from Michigan showed many years ago. We know that 1,25-dihydroxyvitamin D alters inflammatory activity, which is a major component for developing atherosclerosis. There is evidence that the active form of vitamin D regulates the major blood pressure regulating hor-

mone renin in your kidneys.

ATHM: Here in the Rocky Mountain region, even considering our northerly latitude, we're at altitude and have much more exposure to UVA and UVB, yet this area is known to have a high incidence of both MS and cancers. How would you explain that, based on everything we have discussed?

Dr Holick: You need to know what the population's vitamin D status is. You would think that in India, for example, there is no vitamin D deficiency, yet 50% to 80% of children and adults were found to be vitamin D deficient. It may be that because people in Denver are aware of the high intensity of UVB inducing sun burning, they are more likely to wear sun protection. A sunscreen with an SPF of 15 reduces vitamin D production by 99%.

I am not suggesting that vitamin D is a cure-all for everything, but I think that there is a lot of evidence to suggest that vitamin D deficiency is associated with many serious, chronic diseases. They have even associated living at higher latitude, or being born in the wintertime with a higher risk of developing schizophrenia later in life.

ATHM: Research shows that people who get skin cancer are less likely to develop other cancers and that the melanomas that they do develop are generally in non-sun-exposed areas. How do you explain that?

Dr Holick: Most melanomas occur on the least sun-exposed areas. That's well-documented. Occupational sun exposure decreases your risk of developing malignant melanoma. There's a very interesting study by Dr Berwick reporting that the more sun exposure you have as a child and young adult, if you develop melanoma, you're less likely to die from the cancer.

ATHM: At the clinical level, how best can practitioners take advantage of all this information in their practices in terms of diagnosing, testing protocol, and beyond?

Dr Holick: The only way to know a patient's vitamin D status is to measure 25-hydroxyvitamin D. I tell physicians to never measure the active form of vitamin D, 1,25-dihydroxyvitamin D. It is normal or elevated in a vitamin D deficient state—which is kind of incomprehensible until you realize that the active form of vitamin D circulates at 1000 times less concentration than 25-hydroxyvitamin D. 25-hydroxyvitamin D has a half-life in your circulation of 2 to 3 weeks. The active form of vitamin D is only 2 to 4 hours.

As you become vitamin D deficient, the body immediately responds by increasing the production of parathyroid hormone, which tells your kidneys to activate vitamin D, which is why your 1,25-dihydroxyvitamin D levels are either normal or elevated. How is that possible? And how can you be vitamin D deficient? Our guess is that your target tissues, namely the intestine and bone, still can't get enough, even though your blood levels are normal. Serum calcium is usually normal in the vitamin D deficient state. Most physicians think that if the calcium is normal, the patient is not vitamin D deficient, but in fact it tells you nothing about vitamin D status.

ATHM: With so many seemingly divergent symptoms, how can practitioners best diagnose vitamin D deficiencies?

Dr Holick: Patients who have non-specific complaints of aches and pain in their bones and muscles with a normal sedimentation rate—meaning that they don't have a rheumatologic or immunologic disorder—should think about vitamin D deficiency and osteomalacia.

Based on my experience and others' as well, we estimate that anywhere from 40% to 60% of those patients benefit by correcting their vitamin D deficiency. I also point out to physicians that it takes a long time to become osteomalacic, usually months to years. It takes an equally long time to resolve all those symptoms, so don't expect to correct it overnight.

I recommend that the vitamin D tank is empty, thus, you need 50 000 IU of vitamin D once a week for 8 weeks. This treatment usually will fill the tank and increases the blood levels of 1,25-dihydroxyvitamin D above 30 ng/mL. But physicians have to realize that this doesn't correct the cause of the vitamin D deficiency. So I put my patients on 50 000 IU of vitamin D every other week forever. My experience in more than 100 patients after 72 months of this therapy is that their blood level of 1,25-dihydroxyvitamin D is approximately 40 ng/mL.

Why give them 50 000 IU? That's the only pharmaceutical capsule form available in the United States. It's relatively inexpensive, and if you give it as a prescription, the patients will recognize it as a medication that they have to take. If you simply tell patients to go to the local drugstore and buy a supplement and take 1000 IU of vitamin D a day, their response often is, "It's a supplement, so if I forget it a couple of times, it's not a big deal." If you give it as a prescription, compliance is usually better.

Typically, 2 to 3 months later, patients will come back saying that they feel better—just an overwhelming feeling of improved well-being. Often a lot of the aches and pains in bones and muscles are resolved. I also tell physicians that the easiest way to make the diagnosis of osteomalacia is to press with thumb or forefinger on the sternum or the anterior tibia of the lower leg with moderate pressure, and if they wince in pain, in my opinion, this is classic periosteal bone discomfort consistent with osteomalacia.

ATHM: What other research are you currently engaged in?

Dr Holick: We're doing a study in men with metastatic prostate cancer. We're investigating 4000 IU of vitamin D a day on their overall feeling of well-being and their PSA (prostate-specific antigen) and, ultimately, the outcome of their disease. Will it prolong their lives?

Since we had been discussing the issue of sun exposure and association with living at higher latitude with an increasing risk

of cancer, is it possible that when you make vitamin D in your skin, it's different than the vitamin D that you take in orally? The reason for the question is that when you're exposed to sunlight, you not only make previtamin D_3 and vitamin D_3, but you make at least 5 and up to 10 different additional photoproducts that you would never get from dietary sources or from a supplement. So the obvious question is, why would Mother Nature be making all of these vitamin D photoproducts if they weren't having a biologic effect?

We're in the process of identifying the photoproducts to see if they have a special biologic function. In the meantime, we're going to expose men with prostate cancer to simulated sunlight to raise their blood levels of vitamin D to the same degree as patients who are taking oral vitamin D and see whether there is some additional benefit.

Since we know that many common cancers including colorectal cancer have vitamin D receptors and they will respond to active vitamin D compounds, we are also interested in the possibility of whether we can develop an analog of active vitamin D that would thwart the cancer from developing a resistance to it, so that you could use its antiproliferative activity to either kill the cancer cell or to put the cancer cell back into its normal growth. We're doing a study that we hope can identify a compound that we can test in clinical trials in patients with colon cancer.

We recently published a study with Dr Lisa Bodnar showing that preeclampsia, which is a major problem for pregnant women, is associated with vitamin D deficiency. The more vitamin D deficient pregnant women were, the higher their risk of developing preeclampsia. We also recently reported that C-sectioning is more common in women who are vitamin D deficient. This is not a surprise because, muscle strength is associated with vitamin D, and if you're vitamin D deficient, you have less muscle function and probably less ability to control birthing.

ATHM: Do you see any issues or problems with OTC supplementation versus pharmaceutical- grade vitamin D_3?

Dr Holick: At the moment, no. We've done an analysis on some of the products. They look to be quite good. People don't realize that manufacturers typically put in 50% more than what is on the label to maintain shelf life. Even 1000 IU tablet that could contain 1500 IUs is perfectly safe. There is one circumstance that physicians should be aware of: if a patient has a chronic granulomatous disorder, such as sarcoidosis, tuberculosis or histoplasmosis, then you can't raise the blood level of 25-hydroxyvitamin D much above 30 ng/mL because if you do, you will cause hypercalciuria and hypercalcemia.

ATHM: How long does it take for supplementation to increase blood levels of vitamin D to an acceptable level?

Dr Holick: When we give 50 000 IU once a week for 8 weeks, it usually gets the blood level of 25-hydroxyvitamin D to the desired level of greater than 30 ng/mL. People think that's too much vitamin D to take and it will cause vitamin D toxicity, but it's not. I joke with my colleagues when I give my presentation that what is remarkable to me is what physicians seem to remember more from their medical school days than anything else is, "Don't ever make your patient vitamin D intoxicated." They've never seen vitamin D intoxication. They don't know what vitamin D intoxication is, but they know that 50 000 IU is going to cause vitamin D intoxication. Fifty thousand IU taken once a week for 8 weeks then once every other week is safe. When you go outside in the sun one time in a bathing suit, your body makes about 20 000 IUs when you receive one minimal erythemal dose (light pinkness to the skin 24 hours after the exposure).

I have been traveling around the world not only lecturing about vitamin D but hearing from physicians how common vitamin D deficiency is. Whether you live near the equator, such as in South Africa, Saudi Arabia, India, Australia, Brazil, and Mexico, for example, it's been estimated that 30% and upwards of 80% of children and adults who have minimum sun exposure are vitamin D deficient. It's been estimated that people living at higher and lower latitudes especially in Europe and the United States that 50% to 100% of children are at high risk for being vitamin D deficient. People of color are especially at high risk because their skin pigment is a very efficient sun screen, which can reduce their ability to make vitamin D in their skin by upwards of 99%.

Most experts—myself included—agree that vitamin D deficiency is defined as 25-hydroxyvitamin D <20 ng/mL and that vitamin D insufficiency is between 21 and 29 ng/mL. To obtain the full benefits of vitamin D for health, many experts recommend that their blood level should be >30 ng/mL. Vitamin D intoxication is typically not seen until blood levels are above 150 to 200 ng/mL. For every 100 IU of vitamin D ingested, it increases the blood level of 25-hydroxyvitamin D by 1 ng/mL. This is why both children and adults need to be on at least 1000 IU of vitamin D a day when they are having inadequate sun exposure to satisfy their body's vitamin D requirement.

There needs to be a reevaluation by not only healthcare professionals but also government and world health organizations to reconsider recommending sensible sun exposure as not only an appropriate but an excellent source for satisfying a person's vitamin D requirement.