

AVENUES

THE NEWSLETTER OF THE PINE STREET FOUNDATION

29/30

SPRING/SUMMER 2010

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elcome to the spring issue of *Avenues*! 2010 is already off to an incredible start and this coming year promises to be our best yet, with new research projects and educational initiatives.

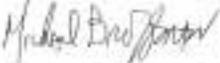
THE IMPORTANCE OF VITAMIN D

Vitamin D is crucial to immune health and general well-being, yet one out of every three Americans has very low levels of vitamin D in their blood. In this evidence-based review article, we examine vitamin D's history and discuss its role in helping us achieve optimal health. See opposite page for more.

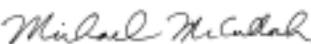
THANK YOU

We would like to gratefully acknowledge all the individuals, foundations, and companies who so generously supported the Pine Street Foundation during 2009. Your generosity is integral to the success of our mission and we hope you'll continue to support our work during the coming year. See page 13 for more.

With thanks and best wishes,



Michael Broffman, LAc



Michael McCulloch, LAc, MPH, PhD

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Vitamin D3: A Review of the Evidence for its Role in Human Health

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Vitamin D is crucial to our well-being. In this article, we discuss the history of its discovery, how we get it, and the evidence for its clinical effectiveness.

Vitamin D is made from cholesterol and plays an essential role in immune function. (Sigmundsdottir, Pan et al. 2007) Specifically, vitamin D regulates genes that facilitate several important body functions, such as (1) helping absorption of calcium and phosphorus in the intestines from food, (2) regulating reabsorption of calcium in the kidneys, (3) governing the transport of calcium into bone, (4) regulating bone growth and remodeling (repair), (5) helping regulate thyroid and parathyroid function, (6) modulating neuromuscular and immune function, and (7) reducing inflammation. (van den Berg 1997; Cranney, Horsley et al. 2007)

There are currently over 400 clinical research studies in progress focusing on vitamin D. These studies are all listed on the National Cancer Institute's website (www.ClinicalTrials.gov), and they range from studies seeking to understand how vitamin D works in the body, to those for the treatment of numerous different diseases.

Deficiencies of serum vitamin D can lead to many different health problems, including osteoporosis, (Cranney, Horsley et al. 2007; Macdonald, Mavroei et al. 2008) autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis, (Hayes and Acheson 2008; Holick 2008) prostate cancer, (Gupta, Lam-

mersfeld et al. 2009) infectious diseases, and several other forms of cancer. (Holick 2008; Perez-Lopez 2008) Vitamin D is also used clinically to prevent osteoporosis, muscle weakness, chronic obstructive pulmonary disease (COPD), cancer, asthma, and bronchitis. (Natural Medicines Comprehensive Database 2009)

WHAT IS VITAMIN D? WHAT ARE ITS VARIOUS FORMS?

Vitamin D goes through three different stages in its formation and metabolism: First from cholecalciferol to calcidiol and then to its active form, calcitriol.

The cycle of vitamin D's activity begins as cholecalciferol (vitamin D3), the naturally occurring form of vitamin D, which is made in large quantities in your bare skin when sunlight strikes it. It can be taken as a supplement and is also found in small amounts in some foods. Cholecalciferol is first transformed by the body into calcidiol (25-OH-D3, or 25D3), a pre-hormone.

The second step, calcidiol (also called 25-hydroxyvitamin D or 25-OH-D), is the form of vitamin D that is measured when your blood is drawn to test for deficiency. Vitamin D then goes through one more transformation before it becomes the active form in the body, calcitriol (1,25-dihydroxyvitamin D). It was once thought that this transformation happens primarily in the kidneys, but recent studies indicate most organs independently make and regulate calcitriol. Calcitriol is a potent seco-steroid hormone that has powerful anti-cancer properties. (Vitamin D Council 2009)

WHEN WAS VITAMIN D DISCOVERED?

The discovery of vitamin D resulted from the confluence of two different streams of research thinking that had been in progress for several decades: a search for understanding of the chemical nature of cholesterol, and the search for a cure for the crippling bone disease called rickets. Adolf Windaus (1876–1959) was a German chemist who devoted his entire career to the study of the molecular structure of cholesterol, for which he was awarded the Nobel Prize in 1928. Windaus was unusual among scientists in Germany in that he openly opposed the Nazi party and, in 1933, protected a Jewish graduate student from dismissal from his university.

His discovery of vitamin D was the result of a collaboration with two other researchers: Alfred Hess who, as early as 1926, had proposed the idea that “it would seem quite possible that the cholesterol in the skin is normally activated by UV-irradiation and rendered anti-rachitic [preventing rickets] – that the solar rays and artificial radiations can bring about this conversion. This point of view regards the superficial skin as an organ, which reacts to particular light waves rather than as a mere protective covering.” They worked together with researcher Otto Rosenheim in London, and together demonstrated that Hess’ theory was correct. Windaus contributed understanding of the structure of the cholesterol molecule, Hess discovered that cholesterol could be converted to a rickets-preventing compound, and Rosenheim conducted the laboratory experiment demonstrating that a component of cholesterol could be converted into vitamin D by exposing it to UV light. (Wolf 2004)

BLOCK THE SUN, BLOCK VITAMIN D

Our ancestors lived naked in the sun for several million years. 50,000 years ago, some of us migrated north and south to places with less sun. Then we put on clothes, started working inside, and began living in cities where buildings blocked the sun. Then we started traveling in cars instead of walking or riding horses. Glass windows, sunscreen, and heavy clothing block even more of the UVB in the sunlight. Then, only a few years ago, we started actively avoiding the sun and putting on sunscreen. All this time we humans have been steadily reducing the tissue levels of the most potent steroid hormone in our bodies, one with powerful anti-cancer properties. The really significant reductions in sunlight exposure have occurred since the industrial revolution, just the time the “diseases of civilization” like cardiovascular disease, diabetes, and cancer seem to have greatly increased. (Vitamin D Council 2009) Essentially, protecting yourself against the sun causes vitamin D deficiency. (Reichrath 2007)

Conversely, the use of supplemental vitamin D appears to be an effort to compensate for this lack of direct sunshine in our lives. (Vieth 1999)

It appears that sunlight is good for the entire body, as most tissues in the body have vitamin D receptors. (Holick 2008) The tongue-in-cheek dialogue line from the movie *Over the Hedge* (Dreamworks Animation, 2006) states, “humans are gradually losing their ability to walk.” This may be due not just to the fact that

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ON THE COVER
Detail of silk brocade on *thangka* painted and blessed by
His Eminence Kalu Rinpoche (1905-1989). India, circa 1971.

ABOUT *AVENUES*
Avenues are choices. When managing disease, there are many different possibilities to consider. Through this newsletter, the Pine Street Foundation seeks to illuminate some of these choices through evidence-based research in the hopes that by having more options, patients and health care providers will be able to make better, more informed treatment decisions.

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we travel more by car than by foot, but also because we're getting less sunlight; low levels of serum vitamin D are also associated with loss of knee joint cartilage. (Ding, Cicuttini et al. 2009)

Studies conducted by the US government have found that three out of every four Americans have very low levels of vitamin D in their blood (below 30 mg/mL). The ideal range is between 50 and 70 mg/mL. This is especially important to consider, given that there is virtually no vitamin D in most of the foods we typically eat. For example, the Vitamin D found in fortified milk is only 100 IU per glass, which is a clinically meaningless amount. (NIH: Office of Dietary Supplements 2009)

HOW DOES THE BODY MAKE VITAMIN D FROM SUNLIGHT?

Cholecalciferol, a form of vitamin D that is also called vitamin D₃, is formed in the skin when it is struck by ultraviolet light of the correct wavelength, UVB. (Vitamin D Council 2009)

Only 20 to 30 minutes of full-body noontime summer sun exposure stimulates the skin to produce as much as 10,000 IU vitamin D, which is 50 times higher than the US government's recommended 200 IU per day. (Vitamin D Council 2009) Or, one can obtain that same amount by drinking 100 glasses of milk.

The skin does another amazing thing with cholecalciferol: it prevents vitamin D toxicity. Once the body makes about 20,000 units, the same ultraviolet light that created cholecalciferol begins to degrade it. A steady state is reached that prevents the skin from making too much cholecalciferol. This is why vitamin D toxicity does not occur from the sun, though it is possible when taking vitamin D supplements orally. (Vitamin D Council 2009)

WHAT ABOUT THE HAZARDS OF SUN EXPOSURE?

With basal and squamous skin cancers, there is a large body of research including quantitative and mechanistic proof that sun exposure causes these diseases. These cancers are clearly linked to sun exposure in people with pale skin, are related to the amount of sun exposure and latitude of residence, and are successfully prevented by sun avoidance and exposure protection. (Shuster 2008)

With melanoma, however, the evidence is not so clear-cut, with most cases occurring on body areas with less sun exposure (according to two different meta-analyses of 24 studies including nearly 20,000 people.) (Siskind, Whiteman et al. 2005; Caini, Gandini et al. 2009) Although there is clear evidence that a history of intermittent sun exposure and sunburn significantly increase the risk of melanoma, conversely a high occupational history of sun exposure seems to reduce that risk. (Gandini, Sera et al. 2005) It appears that people who live further from the equator, and whose sun exposure is more intermittent than continuous, will be more likely to develop melanoma. However, more research needs to be done to evaluate the risk-benefit ratio of possibly increased risk of melanoma, versus the overall health benefits of extra vitamin D₃ achieved by increasing sun exposure.

ANIMALS FORM CHOLECALCIFEROL IN THEIR FUR & FEATHERS

Fur bearing animals, and many birds, make cholecalciferol in their fur or feathers since sunlight can not get to their skin. Interestingly, mammals and birds then eat the cholecalciferol by licking their fur (grooming) or rubbing their beaks on their feathers (preening). So, when you take cholecalciferol by mouth, you are doing what a number of other mammals do. (Vitamin D Council 2009)

WHAT HAPPENS NEXT IN THE MAKING OF VITAMIN D, AFTER SUNLIGHT STARTS THE PROCESS? CALCIDIOL MADE IN LIVER

After cholecalciferol is made in the skin, or taken by mouth, it is transported to the liver where it is metabolized into calcidiol or 25(OH)D. Calcidiol is now thought by some scientists to have steroid hormone properties. It certainly helps maintain your blood calcium levels, but calcidiol's main importance is that it is the form of vitamin D circulating in the blood. Calcidiol is what tells you if your vitamin D "gas tank" is full. If your serum calcidiol level is less than 40 to 50 ng/mL, your tank is low and should be filled up, keeping it that way unless you have a rare medical condition called vitamin D hypersensitivity. (Vitamin D Council 2009)

In order to understand why you should keep your vitamin D tank full, you need to understand the next step in the metabolism of cholecalciferol. After your liver turns cholecalciferol into calcidiol, calcidiol follows one of two pathways. The first pathway takes priority — as your life literally depends on it — but the second pathway is causing all the excitement among researchers today (discussed below). However, if your tank is low, most of your calcidiol takes the first pathway, leaving little to no vitamin D available for your immune system. (Vitamin D Council 2009)

FIRST PATHWAY: CALCITRIOL MADE IN KIDNEYS

The first pathway leads to the kidneys, where calcidiol is turned into calcitriol. Calcitriol is a potent steroid hormone, one of the most potent in the human body, active in tiny pictogram quantities. A steroid hormone is simply any molecule in the body that is made from cholesterol and that acts on specific receptors to turn your genes on and off and regulate cellular function. They are important to health, always need to be handled with care, and are often quite potent, which is why supplemental calcitriol is only available by prescription. (Vitamin D Council 2009)

Calcitriol made by the kidney circulates in the blood to maintain your blood calcium levels through its action on calcium absorption, excretion, and storage in bone. Calcium is vital to the function of the cells in the body. Without enough calcitriol in the blood, calcium levels will fall and a variety of different illness will develop. Therefore, the first priority for calcidiol is to go to the kidneys where it makes enough calcitriol to secrete into the blood in order to regulate serum calcium. (Vitamin D Council 2009)

SECOND PATHWAY: MORE CALCITRIOL PRODUCED IN TISSUES

The second vitamin D pathway leads to your tissues and that is the source of many of the important immune-regulating and inflammation-reducing capabilities of vitamin D. Virtually all of the health benefits of vitamin D discovered in the last 10 years are from vitamin D going down the second pathway. If any calcidiol is left over — that is, if your tank is full and your kidneys are getting all the calcidiol they need to maintain serum calcium — then calcidiol is able to take multiple other pathways, ones that leads directly to the cells. This path is only now being fully understood and is causing excitement among researchers and clinicians all around the world, especially concerning cancer. Specifically, these are the autocrine (inside the cell) and paracrine (around the cell) functions of the vitamin D system. (Vitamin D Council 2009)

These functions are crucial to understanding why you should keep your vitamin D tank full. If you only have a small amount of calcidiol in your blood, virtually all of it goes to your kidney, which then makes extra calcitriol to keep your serum calcium levels from falling. Almost no calcidiol gets to your tissues to make tissue calcitriol. (Vitamin D Council 2009)

TISSUE CALCITRIOL: A CANCER FIGHTER

But when your tank is full from the first pathway, the left over calcidiol goes down that second pathway to benefit the many cells in the body that are able to make their own calcitriol to fight cancer. The more calcidiol they get, the more calcitriol those cells can make. (Vitamin D Council 2009)

Other steroids limit their own production by inhibiting the very chemical reactions that make them. For example, a chemical reaction in the body turns cholesterol into progesterone, a female hormone. When enough progesterone is made, progesterone shuts down (inhibits) the chemical reaction so no more progesterone is made. This is called negative feedback. This occurs with all other steroids somewhere in the metabolic process. If it didn't, the body would not be able to precisely regulate steroid hormone levels. However, this process does not appear to occur with calcitriol in the tissues: throughout the entire range of average human calcidiol levels, tissue calcitriol levels continue to increase. (Vitamin D Council 2009)

This is a crucial piece of information, because it has such profound implications for human health. Just as modern humans have been living (and dying) with historically low levels of calcidiol in their blood, their tissues have been living (and dying) with historically low levels of calcitriol. And calcitriol is the most potent steroid hormone in the human body. It turns genes on

and off: genes that are either making proteins that are essential to fighting cancer or genes that are making proteins that are promoting diseases like cancer. (Vitamin D Council 2009)

BUILT-IN TOXICITY PROTECTION

What prevents tissue calcitriol levels from getting too high? Something has to or your tissues would make too much. One thing that helps is called catabolism, or breakdown. The more calcitriol made, the more metabolized and excreted in the bile. But that does not prevent too much from being made in the first place. In most humans, the more cholecalciferol in the blood, the more calcidiol the liver makes, until calcidiol levels reach about 50 ng/ml. (Vitamin D Council 2009)

The crucial rate-limiting step for the production of calcitriol for most humans in the tissues is the skin, or how much you go into the sun. The body has a fool-proof method of limiting cholecalciferol, in that only about 20,000 units can be made in the skin every day because the same sunlight that makes it, begins to break it down. After your skin turns dark (tans) even less cholecalciferol is made. Humans have a natural system in the skin that prevents toxicity. Another way of saying this is that the rate-limiting step for the production of calcitriol in the tissues is your behavior: how often you go into the sun or how much cholecalciferol you take as a supplement. This makes vitamin D unique. (Vitamin D Council 2009)

WHY IS THERE CONTROVERSY ABOUT RECOMMENDED LEVELS OF VITAMIN D?

In the United States, adult dietary requirements of 200 IU/day are established as just enough to prevent osteomalacia (softening of the bones due to a lack of vitamin D) in the absence of sunlight.

For the past decade, the number of research studies published every year on the health benefits of vitamin D has dramatically increased. Despite all this new evidence, however, the recommended level of vitamin D intake set by the Food and Nutrition board (an agency of the US government) has remained at 200 IU/day for those up to age 50 years, 400 IU for those age 51-70 years, and 600 IU for 71 years and above. (NIH: Office of Dietary Supplements 2009) The problem with waiting until age 71 to increase the intake is that most of the diseases associated with insufficient vitamin D3 intake have already occurred by that age. Inadequate vitamin D early in life can lead to long latency diseases such as autoimmune disease, bone disease, and certain types of cancers. (Kimball, Fuleihan Gel et al. 2008) Encouragingly, the Institute of Medicine (an independent, non-governmental, nonprofit organization that is part of the National Academy of Sciences) has undertaken a study to assess current clinical and laboratory research data and

update the recommended intake levels for vitamin D and calcium, including a focus on obesity, age-related chronic diseases, with results expected by May 2010. (Institute of Medicine 2009)

The upper tolerable limit of vitamin D established by the Food and Nutrition board is 2000 IU/day. These conservative dosing guidelines persist today, in spite of dozens of studies; these include a 2007 analysis that used the Food and Nutrition Board's own risk assessment approach to determine that, based on well-designed human trials that found no toxicity from vitamin D dose at or above 10,000 IU/day, this should be established as the new upper limit. Extended use of 10,000 IU/d of vitamin D3, even in people with a high physiologic background level of vitamin D, introduces no risk of toxicity for adults. (Vieth 2009) Perhaps not coincidentally, this level of 10,000 IU/day is the same amount of vitamin D that can be created by the body in response to sunshine. (Hathcock, Shao et al. 2007)

The growing weight of new evidence on vitamin D shows benefits far beyond its role in bone growth. The authors of the sunshine study wrote that in spite of the new evidence for a wide range of benefits, the established upper limits for vitamin D (2000 IU) "is not based on current evidence and is viewed by many as being too restrictive, thus curtailing research, commercial development, and optimization of nutritional policy." (Hathcock, Shao et al. 2007) Some of the most renowned vitamin D researchers have called for upward revisions of these limits. (Vieth 2006; Vieth, Bischoff-Ferrari et al. 2007)

Another controversy comes from physicians opposing the use of vitamin D because of interactions with medications. Fortunately, there are only a few recognized interaction problems with vitamin D and prescription medications, which are listed here:

Digoxin: The combination can increase risk of fatal cardiac arrhythmias, because of the possibility that high doses of vitamin D over 2000 IU/day may cause hypercalcemia. (McKevooy GK 1998)

Atorvastatin (Lipitor): The combination can result in lower than desired levels of atorvastatin, because vitamin D increases levels of the drug-metabolizing enzyme cytochrome P450. It should be noted, however, that even though atorvastatin serum levels decreased in a study of this drug combination, nevertheless there was no significant change in total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol. (Schwartz 2009)

Diltiazem (Cardizem, Dilacor, Tiazac): The combination may reduce the effectiveness of these medications in atrial fibrillation, because of the possibility that doses of vitamin D over 2000 IU/day may cause hypercalcemia. (Schwartz 2009)

Verapamil (Calan, Covera, Isoptin, Verelan): The combination may reduce the effectiveness of these medications in atrial fibrillation, because of the possibility that doses of vitamin D over 2000 IU/day may cause hypercalcemia. (Bar-Or and Yoel 1981)

Calcipotriene (Dovonex): This vitamin D analog is used topically for psoriasis and, like vitamin D, can cause hypercalcemia. (McKevooy GK 1998)

Thiazide Diuretics: The combination may cause hypercalcemia because these diuretics decrease urinary calcium excretion. (Parfitt 1972)

The following medications can cause vitamin D depletion: Carbamazepine (Tegretol), cholestyramine (Questran, Locholest, Prevalite), colestipol (Colestid), corticosteroids, mineral oil, orlistat (Xenical, Alli), phenobarbital, fosphenytoin (Cerebyx), rifampin (Rifampicin, Rifadin, Rimactane), stimulant laxatives such as senna (Senokot) or visacodyl (Dulcolax), and sunscreens. (Natural Medicines Comprehensive Database 2009)

WHY ARE THE LOW LEVELS OF RECOMMENDED INTAKE A PROBLEM?

The problem is several-fold: (1) vitamin D plays such an important role in human physiology and immune function, as described previously; (2) it helps the body in healing a wide range of illnesses; (3) we spend far less time outdoors than our ancestors; (4) many studies have shown low vitamin D blood levels, even in countries such as Pakistan which have plenty of sunlight; (Khan and Iqbal 2009) and (5) there is little vitamin D present in most foods, meaning that without additional supplementation, many people have very low vitamin D blood levels.

THE POLITICS OF VITAMIN D: HOW DID THIS HAPPEN?

The first established recommended dietary allowance of vitamin D in infants was 400 IU/day. (National Academy of Sciences 1989) Unfortunately, the scientific basis for how this dose level was established is cursory and somewhat arbitrary: (1) it is roughly equivalent to the vitamin D contents of a teaspoon of cod-liver oil, and (2) had been generally accepted as the amount needed to safely prevent rickets, a disease in which the long bones of the body become stunted and deformed. (Holick 2004) The recommended adult dosing levels were established in a similarly cursory manner: a committee of experts recommended adults take one-half the infant dose, 200 IU vitamin D per day, even though there were no research data demonstrating that this level of intake had any ability to affect serum blood levels of vitamin D. (Vieth 1999)

There are many other instances of the illogical and cursory manner in which vitamin D nutritional levels have been established. In the UK, for example, the basis for the adult dietary requirement of 100 IU/day was a small study with only of 7 adult women with osteomalacia, in whom there were increases in bone mineral density after being given that dose. (Dent and Smith 1969)

HOW IS DOSAGE OF VITAMIN D MEASURED?

Dosage of vitamin D is generally measured in International Units (IU), a system of units based on the biological effect of the substance in question. For vitamin D, 400 IU equals 10 micrograms (µg). Because IUs are specific to the substances they measure, one IU of vitamin D, for example, does not equal one IU of vitamin A.

WHAT ARE SOME OF THE BENEFITS OF VITAMIN D SUPPLEMENTATION?

IMPROVEMENT IN CONGESTIVE HEART FAILURE

Several clinical trials have shown a variety of benefits: In one randomized trial, patients with congestive heart failure (average age of 75) received a vitamin combination with vitamin D at a daily dose of 400 IU, or placebo. Patients in the vitamin D group had no difference in their levels of immune signaling molecules called cytokines, but did achieve significant improvement in their left ventricular function and quality of life. (Witte and Clark 2005)

Another randomized trial of men with congestive heart failure (in this study, they were younger, with average age of 55) gave patients either a placebo or vitamin D but at a higher dose of 2000 IU per day. By contrast, this study showed the opposite effect: a decline in serum cytokines levels, but no change in either left ventricular function or survival. The authors of this study acknowledged several possible reasons for the lack of clinical effectiveness: (Schleithoff, Zittermann et al. 2006) They saw an increase of 26.8 ng of vitamin D in the treatment group, which may have been insufficient to achieve any clinically relevant change. Additionally, patients' baseline levels prior to treatment were a very low 14 to 15 ng/ml. There was also a high number of dropouts in this study, probably related to the fact that patients were very ill. The researchers also gave calcium supplements to both the vitamin D and placebo groups, which may have improved heart function in both study groups. In neither did the researchers specify their reason for establishing vitamin D dose levels, one at 400 IU/day and the other at 2000. We are still lacking a well-designed study that includes a dose-finding phase monitored closely enough to clearly see how much vitamin D is needed to pro-

duce an immune response specific to inflammatory cytokines. (Vieth and Kimball 2006)

PREVENTION OF BREAST CANCER

One of the ways in which vitamin D may reduce the risk of developing breast cancer is by reducing hormone levels in premenopausal women. In a study designed to examine the relationship between vitamin D and hormone levels, 101 women aged 18 to 22 who were not using hormonal contraceptives, were recruited during summer and winter. For women recruited in summer, one blood sample was taken, and for those recruited in winter, an additional sample was taken after 4 weeks of daily vitamin D. The researchers found that for every increase in serum vitamin D levels of 4 ng/ml (10 nmol/l), progesterone decreased by 10% and estradiol decreased by 3%. (Knight, Wong et al. 2009)

Another study found that in comparing women with breast cancer to controls, higher intake of vitamin D through combined use of food, supplements, and sunlight exposure, reduced risk of developing estrogen receptor-positive/progesterone receptor-positive (ER+/PR+) breast cancer by nearly half, and both ER-/PR- and mixed (ER+/PR-) by nearly one quarter. (Blackmore, Lesosky et al. 2008) Another study published one year earlier found similarly strong results, although the researchers did not distinguish between types of breast cancer. (Knight, Lesosky et al. 2007)

Other compelling human trials data are available. A Phase II study conducted at Princess Margaret Hospital, Toronto, enrolled 40 women with bone metastases from breast cancer to receive 10,000 IU vitamin D3 and 1000 mg calcium daily for 4 months. There were several beneficial (and no harmful) outcomes of this treatment: while there were no significant changes in bone resorption markers or change in global pain scales, there was however a significant reduction in the number of sites of pain. This study also found two women with previously unknown diagnoses of primary hyperparathyroidism, who were found to have hypersensitivity to vitamin D3 supplementation (this was due to their underlying parathyroid abnormality, not to direct toxicity of vitamin D3). Intriguingly, vitamin D3 treatment also led to a reduction in elevated parathyroid hormone levels which may have been caused in women by long-term treatment with bisphosphonate drugs (such as Actonel, Aredia, Boniva, Fosamax and Zometa). (Amir, Simmons et al. 2010)

PREVENTION OF OSTEOARTHRITIS PROGRESSION

In older adults, maintaining blood levels of serum vitamin D above 75 nmol/L reduces risk of fracture. (Mocanu, Stitt et al. 2009)

IMPROVEMENT OF MULTIPLE SCLEROSIS

Abnormally low levels of serum vitamin D may be a significant risk factor for multiple sclerosis, and most people with this condition have low serum levels of vitamin D. The latitude at which a person resides affects their risk of developing multiple sclerosis, with higher rates of occurrence found in countries farther from the equator where they receive less sunlight. Vitamin D apparently helps to regulate immune function within the central nervous system. Results of phase I/II studies suggest that vitamin D can be helpful for people with multiple sclerosis. Furthermore, there are no studies which have shown a lack of benefit for vitamin D in people with multiple sclerosis. (Pierrot-Deseilligny 2009)

In fact, a small six-month open study of 12 people with multiple sclerosis found that calcium at 1200 mg per day, combined with progressively increasing of vitamin D3 from 28,000 to 280,000 IU per week led to a reduction in the number of brain lesions by over half (on nuclear magnetic brain scan), no toxicity and no changes in liver enzymes, serum creatinine, electrolytes, serum protein, or parathyroid hormone. (Kimball, Ursell et al. 2007)

SLOWING THE PROGRESSION OF PROSTATE CANCER

During the spring and summer seasons, when there is usually more sun exposure, men with localized, low- to intermediate-grade prostate cancer who are on watchful waiting experience a slower rise in PSA than during the fall and winter. (Vieth, Choo et al. 2006)

PREVENTION AND TREATMENT OF INFLUENZA

A significant contributor to winter-time flu susceptibility may be a combination of reduced exercise resulting in weaker respiratory fitness, and vitamin D deficiency induced in part by less exposure to sunlight. (See *Avenues* 27-28, 2009) Vitamin D3's ability to prevent flu infection was studied by Dr. John Cannell, Executive Director of the Vitamin D Council. Cannell has estimated that vitamin D plays a role in the repair and maintenance of more than 1000 human genes in a wide variety of tissues. Included in these genes is the one responsible for the polypeptide called cathelicidin, a naturally occurring broad-spectrum antibiotic made in your white blood cells. Cannell also cogently suggests that vitamin D deficiency may be one of the chief culprits behind seasonal influenza epidemics. (Cannell, Vieth et al. 2006) pointing out evidence from intervention trials that have shown vitamin D3 prevents respiratory infections in children. (Cannell, Zasloff et al. 2008)

HOW IS VITAMIN D MEASURED? WHAT ARE OPTIMAL BLOOD LEVELS OF VITAMIN D?

There are two measurement systems for monitoring levels of vitamin D in the blood. The first is a measurement of vitamin D by weight found in a given volume of blood: nanograms per milliliter (ng/ml). The second measures vitamin D by its molecular concentration for a given volume of blood: nanomoles per milliliter (nM/L). The Vitamin D Council recommends maintaining vitamin D blood levels between 50–80 ng/mL (or 125–200 nM/L) year-round. (Vitamin D Council 2009)

For people living in sunny areas, normal serum vitamin D levels are between 40-70 ng per ml. There are three ways to boost vitamin D levels: sunlight, artificial ultraviolet B (UVB) radiation, and vitamin D3 supplements. 2,000-7,000 IU vitamin D per day should be sufficient to maintain year-round levels of vitamin D in the blood. (Cannell and Hollis 2008)

Reinhold Vieth has recently addressed the question of long-term vitamin D dosing. The question of what represents optimal vitamin D levels in the blood is not a simple one. The human body has a regulatory capability that responds to fluctuations in dietary intake of vitamin D, and there is evidence that fluctuations in serum concentrations of vitamin D could be problematic. When levels of serum vitamin D decrease, the ratio of enzymes which regulate vitamin D levels must increase to maintain the optimal set-point of tissue 1,25(OH)2D. According to Dr. Vieth, this adaptive regulatory system of vitamin D is not well understood, and suggests that higher summertime vitamin D levels, when followed by much lower winter levels, can lead to body tissue levels of vitamin D well below the ideal set-point. Therefore, desirable vitamin D concentrations are both high and steady. (Vieth 2009)

WHO IS AT RISK FOR LOWER VITAMIN D LEVELS?

Most people, according to several studies, have vitamin D levels that are well below the optimum 75 nmol/L. Vitamin D inadequacy is described by experienced vitamin D researchers Reinhold Vieth and John Cannell MD as "an epidemic." (Cannell, Vieth et al. 2008) A study of 107 healthy adults in Toronto found that over 90% had blood levels below 75, and over three quarters had levels below 50. Vitamin D levels were lowest in non-Causians with darker skin pigmentation. (Gozzdik, Barta et al. 2008) Dr. Vieth has also identified that if sun-deprived adults want to maintain their levels of vitamin D above 75, they would need to take much more than the currently recommended dietary amounts. (Vieth 2007)

WHAT ARE OPTIMAL LEVELS OF DIETARY INTAKE OF VITAMIN D?

Safe levels of vitamin D appear to be much higher than the recommended daily allowance. In a study of vitamin D supplementation in older adults given 5000 IU/day for 12 months, serum vitamin D levels increased from an average baseline of 28.5 nmol/L to 125.6 +/- 38.8 nmol/L, and both lumbar spine and hip bone mineral density increased significantly. With respect to safety, serum parathyroid hormone was lower than at baseline, and there were no cases of hypercalcemia. (Mocanu, Stitt et al. 2009)

There has also been research that specifically compared the effectiveness of different doses and time intervals of vitamin D3 supplements in achieving higher serum levels of vitamin D. In one study, volunteers were given 600 IU/day, or 4200 IU/week, or 18,000 IU/month, or placebo. After 4 months, researchers found that daily vitamin D3 was more effective than weekly, and monthly dosing the least effective, in achieving higher serum vitamin D levels. (Chel, Wijnhoven et al. 2008) However, another study of women in their 80s found that vitamin D3 daily at 1,500 IU, weekly at 10,500 IU, or monthly at 45,000 IU provided similar increases in serum vitamin D levels. (Ish-Shalom, Segal et al. 2008)

There are differences between individual people in the body's ability to achieve higher serum vitamin D levels in response to taking it in supplement form. These differences appear to arise from a genetic trait called the vitamin D binding protein, of which there are three known genotypes. A dose evaluation study of 98 adults sought to identify what effect this protein would have on the body's ability to absorb two different doses of vitamin D: 600 or 4000 IU over a one-year period. The most common genotype (TT genotype, found in 48 of 98 people) achieved a 97% increase (nearly double the baseline). Slightly less common (31 of 98 people) is the TK genotype, where a 151% increase was observed (two and a half times baseline levels). The most rare genotype (KK genotype, found in 3 of 98 people) achieved a 307% increase in vitamin D levels from supplementation (reaching over four times their baseline levels). (Fu, Yun et al. 2009) This suggests that response to vitamin D supplements differs between individuals and, therefore, testing blood levels before and during supplementation is recommended.

SAFETY

The only known toxicities of vitamin D are related to its effect on metabolism of the mineral calcium. (Kimball, Ursell et al. 2007) To date, there is no evidence of toxicity with vitamin D up to 10,000 IU/day, except in cases of sensitivity such as those

with parathyroid disorders. Known cases of vitamin D toxicity in which hypercalcemia occurred all involve using over 40,000 IU per day. (Vieth 1999)

In a study assessing both short and long term safety, 25 teenage students were randomly assigned to receive either placebo or vitamin D3 at 14,000 IU per week, for 8 weeks, to test short-term safety. To assess long-term safety, 340 students received placebo, vitamin D3 at 1,400 IU per week, or at 14,000 IU per week for a one-year time-span. There were no adverse effects at any dose level or duration. In the short-term group, there was a modest 25% increase in vitamin D serum levels; in the long-term group, vitamin D levels also increased only modestly in the low-dose group receiving 1,400 IU per week, but more than doubled in the high-dose group receiving 14,000 IU per week. (Maalouf, Nabulsi et al. 2008)

It is nevertheless essential to recognize the importance of vitamin D toxicity in those with primary hyperparathyroidism and various granulomatous diseases like sarcoidosis. The parathyroid gland makes parathyroid hormone, which helps the body regulate calcium levels. When it malfunctions, it can cause primary hyperparathyroidism, and an exquisite sensitivity to vitamin D3 supplementation occurs. In an unusual case, a 77-year-old woman who had been taking vitamin D2 at 50,000 IU daily for two years developed dramatically elevated calcium levels. During her clinical evaluation it was discovered she had primary hyperparathyroidism. After stopping vitamin D, her serum 25-hydroxyvitamin D remained elevated years, most likely because her parathyroid disorder prevented adequate availability of an enzyme that normally metabolizes vitamin D-catabolizing enzyme, called 25(OH)D-24-hydroxylase. (Taskapan, Vieth et al. 2008)

In a study of smokers from Finland, higher blood levels of vitamin D (without supplementation) were associated with a three-fold increase in risk of pancreatic cancer. However, it is important to note that this study took place in the same group in which an earlier study found that beta-carotene caused an increase in the rate of developing lung cancers. (Stolzenberg-Solomon, Vieth et al. 2006) This suggests that in smokers, vitamin D supplementation may have a paradoxical effect, much like that seen with beta-carotene.

WHAT KINDS OF VITAMIN D SUPPLEMENTS ARE RECOMMENDED?

Although there are more than 5000 vitamin D containing supplements currently on the market, only 178 of these products have been verified by the USP (United States Pharmacopeia); they can be identified at the following website: www.naturaldatabase.com. (Natural Medicines Comprehensive Database 2009)

HOW CAN YOU DETERMINE WHAT YOUR VITAMIN D INTAKE IS?

The USDA's website contains an online reference for locating dietary nutrient levels of commonly eaten foods, the National Nutrient Database, providing an extensive list which can be sorted by alphabetically by food or in descending order of concentration: <http://tinyurl.com/ya6xvze> (USDA 2009)

HOW CAN YOU DETERMINE YOUR SERUM VITAMIN D LEVELS?

The best way is with laboratory tests. There are at least four types of laboratory tests available to determine vitamin D levels in serum: the classic calf-thymus receptor assay, DiaSorin radioimmunoassay (RIA), DiaSorin "LIAISON 25 OH Vitamin D TOTAL", and Roche Modular "Vitamin D3 (25-OH)". (Seiden-Long and Vieth 2007; Wagner, Hanwell et al. 2009) The DiaSorin LIAISON was the most accurate and precise automated tool for serum vitamin D testing. (Wagner, Hanwell et al. 2009)

Blood levels of 25-hydroxy-vitamin D (25-OH-D), the active form of Vitamin D, can be tested by most medical laboratories, with the order of a blood test from a medical provider.

Additionally, through a collaboration between the Vitamin D Council and ZRT Laboratories of Beaverton, OR (503-466-2445), individuals can order their own 25-OH-D test at www.zrtlab.com/vitamindcouncil. According to the Vitamin D Council, "This is a home test for 25(OH)D, requiring a finger or heel stick to get several drops of blood. You order the test kit, which ZRT will ship to you. After receiving your kit either you, or someone you know in the medical field, will do a finger or heel stick and put the blood on the blotter included in the kit. You will then send the blotter paper back to ZRT in the envelope provided. ZRT will perform the 25(OH)D test in their lab and send the results directly back to you. The Vitamin D Council has verified that results obtained by ZRT are accurate and correspond very well to the results given by both LabCorp and DiaSorin RIA." (Vitamin D Council 2009)

SUMMARY

Vitamin D plays an essential role in maintaining important body functions such as the immune system and bone health. While vitamin D supplementation is helpful in preventing and treating many health conditions, it is certainly not a substitute for going outdoors. We hope that this comprehensive examination of the evidence for vitamin D safety and efficacy will stimulate many engaging and productive dialogues between physician and patient about safe levels of vitamin D supplementation and the advisability of vitamin D blood level monitoring and therapy. 

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