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Confronting the Worldwide Epidemic of Vitamin D Deficiency

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Introduction

The term vitamin D actually refers to a pair of biologically inactive precursors of a critical micronutrient. They are vitamin D3, also known as cholecalciferol, and vitamin D2 also known as ergocalciferol. Cholecalciferol (D3) is produced in the skin by a photoreaction on exposure to ultraviolet B light from the sun (wavelength 290 to 320 nanometers). Erogcalciferol (D2) is produced in plants and enters the human diet through consumption of plant sources.

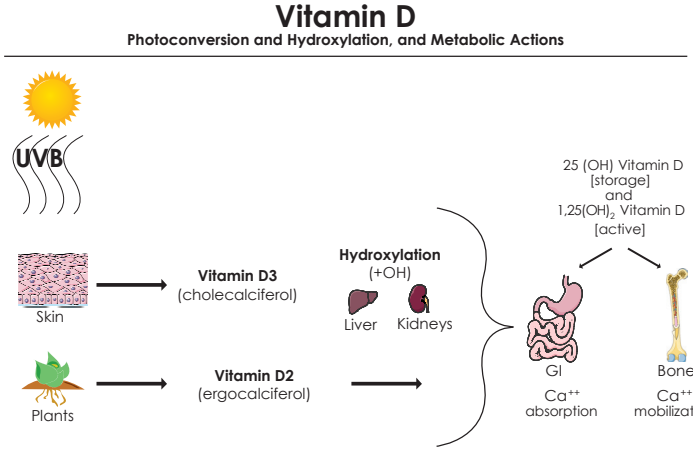

Figure 1. Sources and Photoconversion of vitamin D

Once present in the circulation, both D2 and D3 enter the liver and kidneys where they are hydroxylated to form both 25-hydroxyvitamin D and 1, 25 dihydroxyvitamin D. 25-Hydroxyvitamin D is relatively non-active and represents the storage form of vitamin D. By contrast, 1, 25 dihydroxyvitamin D is highly active metabolically and its levels are tightly controlled. Vitamin D has many critical metabolic functions. There has been recent confusion in the literature regarding differences in relative abundance, availability and effects of vitamin D2 vs. D3 which have been reconciled by thoughtful investigation [1].

25-Hydroxyvitamin vitamin D3 is the major circulating form of vitamin D3 in human blood, and therefore, it is the form measured by physicians to evaluate vitamin D status in people worldwide. However, it takes a long time for this form to work on calcium absorption and mobilization and it must be converted or metabolized to the more active 1, 25 Dihydroxyvitamin D for effectiveness in the body.

Knowledge of the role of vitamin D metabolic activity, its role in human health and identification of the forms and metabolic pathways for vitamin D had been building for many decades but only became fully elucidated during the 1970s. While nutrition is fundamental in human health, understanding of nutritional metabolism has generally lagged behind the pace of medical investigation and practice focusing on factors external to the host such as infectious micro-organisms.

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A D-Lightful History

Although vitamin D has been understood only relatively recently it has been a part of biology for a very long time. A micro-organism which is estimated to have lived in the oceans for 750 million years is able to synthesize Vitamin D, possibly making it the "oldest" hormone on the planet.

It was recognized over 150 years ago that people, especially children, who lived and worked in dark urban areas where there was little light were susceptible to bone diseases such as rickets. In Boston in 1889 it was estimated that 80% of infants had rickets. This pattern marked a shift away from a US population primarily engaged in agriculture (Thomas Jefferson's idea of an agrarian democracy) during the 1800s and exposed to plenty of light on the farms and in the fields. The lack of light in dank, dark urban environments was compounded by the unavailability of fresh foods and lack of food distribution. At that time it was noted that an extended visit to the country with clean air, water, abundant sunlight and the benefits of nature would often cure medical disorders. Thus the idea of the Nature Cure was born. One of the many famous beneficiaries of the Nature Cure in the late 1800s was future President Theodore Roosevelt, who was well known for saying that he was literally "Dee-lighted" with any number of things, including the results of his cure for his lung disease. One of the most common lung diseases in the late 1800s was tuberculosis. Sanitoriums and Solariums were created in wilderness areas away from the cities so that TB patients could benefit from the nature cure. Although there were no antibiotic treatments available at that time, many patients with TB benefitted from exposure to nature, including sunlight.

As early as 1849, cod liver oil was also used in the treatment of TB, according to the Brompton Hospital Records, Volume 38 [Table 1]. We now know cod liver oil to be one of the few dietary sources of vitamin D. We also now know that vitamin D activates the immune system cells that can fight TB. So the nature cure of sun and fish oil (also known to sailors as the "sun-fish" cure), which delivered increased vitamin D, was the right treatment for the times.

Table 1. Historic Milestones in Recognition of the Relations Among Sunlight, Vitamin D Activity and Health

Year	Observation	Vitamin D Pioneers
1849	Cod Liver Oil (vit D)Treats TB	Brompton Hospital
1889	Nature Cure Treats Rickets	S. Weir Mitchell, et al
1919	Mercury Arc Lamp (UVB) Treats Rickets	Huldschinksy
1921	Sun Exposure Cures Rickets	Hess & Unger
1920's	Vitamin D Discovered	Windaus
1920's	Vitamin D Photosynthesized in Lab	Windaus (Nobel Prize, 1928)
1940's	Sunlight Protects Against Cancer	Apperly
1970	25-Hydroxyvitamin D3 Isolated	Holick
1971	1,25 Dihydroxyvitamin D3 Isolated	Holick
1979	Vitamin D Receptors Found	De Luca et al
1980	Vitamin D Treats Psoriasis	Holick et al
2002	Vitamin D Regulates Blood Pressure	Li et al

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The direct connection between sun light and bone metabolism was also established in 1919 when Huldschinsky treated rickets with exposure to a mercury arc lamp. In 1921, Hess and Unger observed that sun exposure cured rickets.

In the 1920s medicine began to directly appreciate the connection between sunlight and the metabolic activities we now associate with vitamin D. This was also the decade that saw the actual identification and labeling of the many metabolically active constituents we now call vitamins. Vitamin D was discovered in the early 1920s by Windaus who was later awarded the Nobel Prize for his synthesis of vitamin D in the laboratory by replicating the photoactivation process that occurs in the skin.

In the 1930s the federal government set up an agency to recommend to parents, especially those living in the northeast, that they send their children outside to play and get some sun exposure. Foritification of milk with vitamin D also began at that time. Unfortunately, the last 40 years have actually seen a reversal of some of the sensible public health recommendations regarding adequate Vitamin D and sun exposure (see Vitamin D and Sun Exposure: There Goes the Sun).

Versatility of Vitamin D

The first major functions of vitamin D to be recognized were (1) enhancement of calcium absorption from the diet through the intestine and (2) mobilization and re-absorption of calcium from bone which represents the major store of calcium (or "calcium bank") in the body. See Figure 1. Calcium in turn is critical for cellular metabolism and membrane actions, enzymatic reactions, muscle function, skeletal structure and a host of activities needed to sustain life and maintain homeostasis. Since vitamin D has long been recognized for its role in calcium metabolism it has long been used to treat patients with renal failure and bone diseases. It is also important in postmenopausal osteoporosis for the current epidemic of bone fractures in the elderly [2].

However, in 1979 DeLuca found that vitamin D is actually recognized by every tissue in the body. Every cell has receptors for vitamin D. Since then it has been used to treat hyperproliferative skin diseases such as psoriasis.

For the immune system, the large white blood cell macrophages activate vitamin D. The activated vitamin D in turn causes macrophages to make a peptide that specifically kills infective agents such as tuberculosis mycobacteria. Vitamin D also has a role in autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes type 1. Given vitamin D's long recognized activity in the kidney it was also found to effect renin/angiontensin production in the kidney, the major regulators of blood pressure. There is a direct correlation between higher (more northern) latitudes and higher blood pressure (where both sunlight and vitamin D levels are lower) in both northern and southern hemispheres of the earth. People at high latitudes with high blood pressure experience a return to normal blood pressure levels following UVB light exposure, and restoration of active vitamin D levels, in a tanning bed three times per week for three months (and you thought it only worked if the sunlight was captured on a beach in the Bahamas!). Multiple sclerosis also shows a marked association with higher latitudes worldwide and there may be a similar role for protection by vitamin D.

Vitamin D is also thought to have an important role in cancer [see Sidebar]. As early as the 1940s it was noted that living at higher latitudes is associated with a higher incidence of several cancers (while only skin cancer specifically has a lower incidence at higher latitudes). Recent epidemiologic observations have continued to bear out this association. A high frequency of sun bathing before age 20 reduced the risk of non-Hodgkin lymphoma [3]. And, while sun exposure is related to an increased incidence of malignant melanoma, it was also associated with increased survival from melanoma in a recent study [4]. In some of the sunniest spots on earth, both the Australian College of Dermatologists, the Cancer Council of Australia, and the New Zealand Bone and Mineral Society, have concluded that a balance is required between avoiding an increased risk of skin cancer and achieving enough ultraviolet light to maintain adequate vitamin D levels.

As in all things involving nutrition, achieving a balance is a good goal and guide for optimal health. It was thought that a balanced approach to this problem could be achieved through thoughtful

dermatologic screening for skin cancers. Thus, most skin cancers should be detected and treated early since they are by definition visible on the surface of the skin, unlike cancers of other tissues which begin growing hidden and undetected deep inside the body.

However, dermatologic intervention also took another, different direction. Rather than just focusing on early detection and treatment of skin cancer, they began fighting against the sun. That in turn, has had profound effects on vitamin D nutrition and deficiency over the past 40 years now.

Vitamin D and Dermatology: There Goes the Sun

Many physicians and public health organizations, including the biomedically oriented World Health Organization, have been trying to go one better on Moby Dick's Captain Ahab, who "would strike the sun if it insulted" him. For 40 years there has been a concerted campaign to make people avoid sun exposure. Since ultraviolet B light from the sun is responsible for the photoactivation of vitamin D in the skin, sun blockers that "protect" the skin also virtually eliminate photoactivation of vitamin D. A sunscreen with SPF of 8 is supposed to absorb 92.5% of UVB while doubling the SPF to 16 absorbs 99%. This essentially shuts down vitamin D production. (It also demonstrates that SPF formulations above 16 have little marginal utility and calls into question the appropriateness of ever-increasing SPF numbers found on the pharmacy shelves)

People have become photophobic and dermatologists have been on a campaign to "strike the sun."

A study in Australia which has high levels of sunlight and high rates of skin cancer found 100% of dermatologists to be deficient in vitamin D [5]. In fact, most people should go outside in the sun for reasonable periods of time in order to get the many benefits of sunlight [Table 2]. It is always wise to protect the face and head with a hat and sunglasses since less than 10% of UVB light absorption happens above the neck and the face is the most cosmetically sensitive. It is best to expose the entire body in a bathing suit for 10 – 15 minutes at least three times per week. African-Americans require more sun exposure since their natural skin pigmentation accounts for an SPF-equivalent of 8 to 15.

Table 2. Get Some Sun: Benefits of Sun Light

Benefits of Sunlight
• Improves Bone Health
• Improves Mental Health
• Improves Heart Health
• Prevents Many Common Cancers
• Alleviates Skin Disorders
• Decreses Risk of Autoimmune DIsorders
• Decreases Risk of Multiple Sclerosis
• Decreses Risk of Diabetes

Global D-mensions of D-ficiency

There is essentially little or no active vitamin D available from regular dietary sources. It is principally found in fish oils, sun-dried mushrooms, and fortified foods like milk and orange juice. However, many countries worldwide forbid the fortification of foods. There is potentially plenty of vitamin D in the food chain because both phytoplankton and zooplankton exposed to sunlight make vitamin D. Wild caught salmon, which feeds on natural food sources, for example, has available vitamin D. However, farmed salmon fed food pellets with little nutritional value have only 10% of the vitamin D of normal fish. The "perfect storm" of photophobia, lack of exposure to sunlight, and insufficiency of available dietary vitamin D has led to a national and worldwide epidemic of vitamin D deficiency.

It is estimated that at least 30% and as much as 80% of the US population is vitamin D deficient. In the US, at latitudes north of Atlanta, the skin does not make (photoconvert) any vitamin D from November through March (essentially outside of "daylight saving time"; so while we shift the clock around, it does not salvage vitamin D synthesis). During this season the angle of the sun in the sky is too low to allow ultraviolet B light to penetrate the atmosphere and it is absorbed by the ozone layer. Even in the late spring, summer and early fall, most vitamin D is made between 10 AM and 3 PM when UVB from the sun penetrates the atmosphere and reaches the earth's surface.

It might be expected that vitamin D deficiency would be a problem limited to northern latitudes.

In Bangor, Maine, in young girls 9 to 11 years old, nearly 50% were deficient at the end of winter and nearly 20% remained deficient at the end of

summer. At Boston Children's Hospital, over 50% of adolescent girls and Black and Hispanic boys were vitamin D deficient year round. In another study in Boston 34% of Whites, 40% of Hispanics and 84% of Black adults over age 50 were found to be deficient [5].

However, vitamin D deficiency is also a national problem. The US Centers for Disease Control and Prevention completed a national survey at the end of winter and found that nearly 50% of African-American women ages 15 to 49 years were deficient. These represent the critical childbearing years. A growing fetus must receive adequate vitamin D from the mother, especially since breast milk does not provide adequate Vitamin D. A study of pregnant women in Boston found that in 40 mother-infant pairs at the time of labor and delivery, over 75% of mothers and 80% of newborns were deficient. This observation was made despite the fact that pregnant women were instructed to take a prenatal vitamin which included 400 IU vitamin D and to drink two glasses of milk per day [5].

Further, vitamin D deficiency is a global problem. Even in India, home to one billion of the earth's people, where there is plenty of sun, 30 to 50% of children, 50 to 80% of adults and 90% of physicians are deficient. In South Africa, it is also a problem although Cape Town is situated at 34 degrees latitude.

While there are many new bilateral and multilateral governmental and private efforts to export western medical technology and pharmaceuticals to the Third World to combat infectious disease, such as AIDS, there is no comparable effort to acknowledge and address the global dimensions of the vitamin D deficiency epidemic. The US Congress and President just signified it as a great achievement to give $40 billion in tax dollars to US pharmaceutical companies to send expensive drug treatments for AIDS (a preventable disease) overseas. By contrast, addressing the vitamin D deficiency epidemic could be accomplished with much safer and less expensive nutritional supplements together with sun light, the only source of energy that is still free.

Vitamin D Dose, Toxicity and Formulation

It has been well established that giving 100 IU of vitamin D daily to children will prevent rickets [Table 3].

As with most of established thinking about RDAs the doses are those that prevent the development of frank nutritional deficiencies and associated pathology. The idea of levels for optimal health does not enter the picture. Even the capricious RDA process raised the recommendation from 200 IU to 400 IU per day in 1997 (although technically it is not an "RDA" but an "IA"- or adequate intake). Currently, those more knowledgeable about human nutrition than the outdated RDA/IA process, recommend 1000 IU daily for both children and adults in order to maintain blood levels of 25-hydroxyvitamin D above 30 ng/ml. It is now recognized that each 100 IU of vitamin D ingested raises blood levels by only 1 ng/ml [Table 4].

Although a typical recommendation is in the range of 1000 – 2000 IU per day, it is a reasonable recommendation to take up to 5000 IU per day.

Table 3. The Evolving Picture of Vitamin D Daily Intake

Daily Intake	Associated Effects
100 IU	Prevents rickets, frank nutritional disease Amount in one glass of milk, or fortified orange juice
200 IU	"Adequate intake" per RDA pre-1997
400 IU	"Asequate intake" per RDA post-1997 Reduces risk of rheumatoid arthritis in women by 50%
1000 IU	Reduces risk of cancer (breast, colorectal, ovarian, prostate) by 50%
2000 IU	Reduces risk of Type 1 diabetes by 80% Reduces upper respiratory tract infections in elderly by 90%
30,000 IU	Minimum to develop toxicity over several months/ years

It is not easy to become vitamin D intoxicated. Sunlight actually destroys any excess vitamin D that is made in the body, so it is not possible to become vitamin D intoxicated from too much sunlight alone. In a world where dangerous and expensive drugs are doled out like candy, it is ironic to witness the degree of concern in the medical establishment over exposures to physiologic levels of natural

substances such as vitamins, and even sunlight!

Nonetheless a medical lore has developed over the possible risks of excess vitamin D intake although vitamin D intoxication is one of the most rare medical conditions in the world. If vitamin D were considered as a drug it demonstrates a remarkable therapeutic index of at least 300 for disease treatment (minimum toxic dose/dose to treat rickets) and at least 20 for chronic disease prevention. However, if the patient has a chronic granulomatous disorder such as histoplasmosis, sarcoidosis or tuberculosis, a vitamin D blood level above 30 ng/ml will cause hypercalcemia and hypercalciuria. Therefore, supplementation should be avoided in these cases.

Since the only pharmaceutical preparation of vitamin D is in 50,000 IU doses, one therapeutic regimen is 50,000 IU per WEEK for 8 weeks to treat deficiency; with 50,000 IU EVERY TWO WEEKS thereafter for maintenance of adequate vitamin D levels. Dietary supplements are also good choices for vitamin D.

Table 4. Blood Levels of Vitamin D (25, hydroxyvitamin D)

Level (ng/ml)	Associated intakes and effects
1	Amount blood level is raised by 100 IU intake
1-20	Deficiency
21-29	Insufficiency
30-150	Sufficiency, reached by 50,000 IU weekly for 8 weeks
50	Reduces risk of breast cancer by 50% (vs. 20 ng/ml)
150-200	Onset of toxicity

Despite the inadequacy of the RDA/IA process there is ample evidence and clinical experience indicating that vitamin D blood levels and daily intakes should be much higher than they are not only for prevention of bone diseases but for optimal health and helping reduce the risk of many common chronic diseases, disorders and medical conditions. Together with healthy sun exposure Vitamin D supplementation can be accomplished safely and effectively and should be a first line consideration in any clinical practice and for the general population.

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Vitamin D, Calcium and Cancer
Recently, vitamin D and its analogues have been shown to inhibit the proliferation of some neoplastic cells (Albert et al., 2004). Suppression of growth of these malignant cells point to involvement of vitamin D in cell proliferation and differentiation and suggest that analogues of the vitamin D hormone may be of interest as possible cancer preventive agents. The mechanism of action of vitamin D hormone remains largely unknown.

The function of vitamin D in cellular differentiation may relate to its action on intracellular calcium metabolism. Several studies provide indirect evidence of a possible involvement of calcium in cancer based on the effects of this mineral on the activity of carcinogens and on the ability of carcinogens and tumor proliferation to induce disturbances in calcium homeostasis. Whatever the mechanism, calcium seems to have an active role in cancer.

Vitamin D
Basic research investigations of the anticancer properties of vitamin D have appeared in light of its metabolic regulatory effects on calcium. Another facet of the function of vitamin D must be considered: its potential function alone as a steroid hormone. Receptors for vitamin D have been found in the small intestine, kidney, pituitary, parathyroid, and bone, all considered target organs. Through a series of metabolic steps in liver and kidney, vitamin D3 is transformed into the active metabolite 1,25-dihydroxyvitamin D3, which functions in calcium and phosphorus homeostasis. The suggested functions in cellular growth and differentiation distinguish the action of the active vitamin D metabolite.

Anticancer effects have been reported for vitamin D in leukemic cells and in cancer cells derived from sarcoma and melanoma. A high degree of receptivity for vitamin D was shown in human colon tumors. Vitamin D has a marked effect on cellular membrane composition and the fluidity of membranes. Vitamin D-deficient rats undergo changes in the fatty acid composition of cellular membranes, incorporating more saturated fatty acids. Whether vitamin D has pronounced effects on the colonic epithelium remains to be confirmed.

Topical application of 1,25-dihydroxyvitamin D3 inhibited proliferation in skin cells. Whether the parenteral form of the vitamin D3 shows the same antiproliferative effects has yet to be resolved. Analysis of the diets and the intensity of sunlight (and thus vitamin D levels) at various latitudes in the United States showed increased rates of many common cancers with increasing latitudes. Public health officials have deferred on recommending vitamin D supplementation to the public until confirmation of the benefit of added calcium has been shown more convincingly. At least one study has indicated an anticancer effect for calcium. Further testing of calcium could include this element in trials featuring reduction of human cell proliferation or precancerous lesions. Human studies of the cancer prevention effects of vitamin D have yet to be proven, and nutritional supplementation is still considered as a prospect of the future by the biomedical and oncology establishment.

Calcium
Calcium figures prominently in many cell functions and is important in survival of the cell through the regulatory nature of this elemental mineral on cellular proliferation and synthesis of DNA. Imbalances in calcium concentration have been correlated to aberrant cellular behavior. From the perspective of calcium/cell interactions, there are a least two mechanisms by which calcium could prevent tumor promotion. The first concerns the active role of dietary lipids and their chemical affinity for calcium. The second concerns the physiological and molecular aspects of cellular proliferation.
In the intestines, the digestion of fat yields aggregates of fatty acids, glycerides, and cholesterol intermixed with bile acids that function to solubilize these compounds. In the upper jejunum glycerols interact with pancreatic lipases to yield free and bound fatty and bile acids. Bound lipids are largely in the form of calcium soaps that are reported to be biologically inert. Unbound fatty and bile acids have a high affinity for calcium. Addition of calcium to the diet does not change serum triglyceride levels, but incorporation of high levels of calcium in the diet significantly increases fecal excretion of saturated fatty acids. Thus, with entry of dietary fat into the colon a significant loss of calcium could occur.

Loss of calcium from colonic epithelial cells could have a number of effects contributing to initiation of the tumor process. For example, in skin, the level of ionized calcium is suspected to regulate the balance of growth of skin cells and induce differentiation.
That calcium could offset abnormal cellular

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proliferation has been tested clinically. Investigations found that supplementation by 1,250 mg of calcium/day significantly reduced cell proliferation in patients at high risk for large bowel cancer. Epidemiological studies also support the hypothesis that a higher calcium intake may reduce risk for colon cancer. One large study showed that people who took calcium supplements of 1200 mg/day showed a decreased risk of colorectal polyps (Baron et al., 1999), a preneoplastic lesion.

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