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Abstract

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It was as early as the mid-1600s that Whistler (1) and Glisson (2)independently published scientific descriptions (in Latin!) of rickets, caused, we now know, by a vitamin D deficiency. However neither treatise recognised the crucial role of diet or exposure to sunlight on the prevention of this disease. Around 200 years later, in 1840, a Polish physician called Sniadecki realised that cases of rickets occurred in children living in the industrial centre of Warsaw but did not occur in children living in the country outside Warsaw. He surmised that lack of exposure to sunlight in the narrow, crowded streets of the city where there was considerable pollution due to the burning of coal and wood, caused the disease. Such a view was poorly received at the time as it seemed inconceivable that the sun could have any useful benefit on the skeleton. The prevalence of rickets increased as industrial processes and labour expanded and, by the end of the nineteenth century, this bone disorder was estimated to affect more than 90% of children living in such urban polluted environments in Europe. Similarly, as Boston and New York City grew in the late 1800s, so did the number of cases until, in 1900, more than 80% of children in Boston were reported to suffer from rickets.

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A Short Circular History of Vitamin D from its Discovery to its Effects

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The discovery of vitamin D

It was as early as the mid-1600s that Whistler[1] and Glisson[2] independently published scientific descriptions (in Latin!) of rickets, caused, we now know, by a vitamin D deficiency. However neither treatise recognised the crucial role of diet or exposure to sunlight on the prevention of this disease. Around 200 years later, in 1840, a Polish physician called Sniadecki realised that cases of rickets occurred in children living in the industrial centre of Warsaw but did not occur in children living in the country outside Warsaw. He surmised that lack of exposure to sunlight in the narrow, crowded streets of the city where there was considerable pollution due to the burning of coal and wood, caused the disease. Such a view was poorly received at the time as it seemed inconceivable that the sun could have any useful benefit on the skeleton. The prevalence of rickets increased as industrial processes and labour expanded and, by the end of the nineteenth century, this bone disorder was estimated to affect more than 90% of children living in such urban polluted environments in Europe. Similarly, as Boston and New York City grew in the late 1800s, so did the number of cases until, in 1900, more than 80% of children in Boston were reported to suffer from rickets.

In 1918 Sir Edward Mellanby discovered that beagles, housed exclusively indoors and fed a diet of oatmeal, developed rickets but that the addition of cod liver oil to the food treated the disease successfully[3]. He wrote in 1921 *"The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin"*. Various experiments by Hess, Steenbock and Black in the 1920s followed in which excised pieces of rat skin were UV-irradiated or rat food was UV-irradiated. It must have been astonishing at the time to establish that both could be used as a dietary source to treat rats with rickets. Concurrently the first fat-soluble vitamin (A) and water-soluble vitamins (B and C) were being discovered; the factor protecting against rickets was known to be fat-soluble and was given the next letter in the alphabet – D. It was classified as a vitamin although it was recognised from the beginning that it was not necessarily required as a dietary constituent.

The chemical structures of the various forms of vitamin D were determined in the 1920s and 1930s by Windaus and colleagues[4] in Goettingen, Germany. Windaus was awarded the Nobel Prize in Chemistry in 1928 "for services rendered through his research into the constitution of the sterols and their connection with the vitamins". The biologically active form of vitamin D, found in the skin and called D_3, was characterised in 1936 (see *Figure 1*), and was shown to result from the ultraviolet (UV) radiation of 7-dehydrocholesterol. Thus vitamin D was established as a steroid. Very soon after this, the component in cod liver oil that prevented rickets was identified as vitamin D_3.

Vitamin D in the diet is present as either vitamin D_2 if the source is plant, or D_3 if animal. Few foods naturally contain vitamin D. Most is found in oily fish such as salmon, meat and eggs. Fat spreads and breakfast cereals are fortified with vitamin D. In the States orange juice, milk and some breads are also fortified. In the 1930s, vitamin D was added to many more American food-stuffs including peanut butter and hot dogs and even to a beer, marketed as having "sunny energy".

For most people living "normal" lives, more than 90% of their vitamin D requirement is derived from exposure to the UV radiation in sunlight. The body has a huge capacity to produce vitamin D: for example, exposure of 6% of the skin surface to summer sunlight for approximately 30 minutes around noon on a clear day in the UK would be equal to ingesting about 10 mg vitamin D. A 25(OH)D blood level of between 50 and 125 nmol/L (20-50 ng/mL) is considered optimal, with levels below 25 nmol/L indicating severe deficiency. An interesting study published in 1995[6] involved the crew of an American submarine and revealed a steady decline in the 25(OH)D concentration from a starting level of 78 nmol/L to 48 nmol/L after 2 months under the sea. This was despite a Navy diet that included milk and breakfast cereals fortified with vitamin D. Since the 1960s, a daily dietary allowance for children of 10 mg vitamin D has been recommended – this was based on nothing more scientific than the vitamin D content of a teaspoon of cod-liver oil! In adults 5mg daily was recommended. Many experts today believe that these values are too low by several-fold.

Too much vitamin D does you no good

It has been recognised for more than 50 years that too much vitamin D can result in intoxication, possibly due to the increased activity of $1,25(OH)_2D$. This is manifest by nausea, vomiting, poor appetite, weakness and weight loss. Calcium levels are raised in the blood leading to a confused mental state and heart rhythm abnormalities. Calcinosis can also occur. There is no evidence that sun exposure, even at high levels, can cause vitamin D intoxication, and diet is also unlikely to either, although this can happen on occasion. After the second World War, excess amounts of vitamin D were added to some milk products and this resulted in sporadic outbreaks in Britain of vitamin D intoxication in infants and young children[7]. Such an outcome is not entirely past history as vitamin D toxicity was reported as recently as last year to occur in babies in Japan who had received prolonged feeding of premature infant formula with a high vitamin D content.

With increasing interest by the general public in a "healthy" diet, it is possible that toxicity could occur nowadays from a high intake of vitamin D in supplements, such a multi-vitamin pills. The safe upper limit recommended for the ingestion of vitamin D is generally considered to be 25 mg/day for infants and 50 mg/day for all other ages, although some reports suggest that amounts considerably higher than these would still not represent a health hazard[8].

Too little vitamin D does you no good

As vitamin D plays a major role in the growth, development and maintenance of bone health, any deficiency leads to mineralization defects with an increased risk of osteoporosis, osteomalacia and fractures in adults, and rickets in children with a decrease in their genetically programmed height. An exciting discovery was made in 1979 by Stumpf and colleagues[9] that vitamin D receptors are present in many part of the body, in addition to the obvious locations associated with calcium metabolism - the gastro-intestinal tract, bone and kidney. This work led to the idea that vitamin D deficiency may be important in various non-skeletal disorders. Subsequently $1,25(OH)_2D$ was demonstrated to inhibit the proliferation of several cell types, to stimulate them to differentiate and, most recently, to act as an anti-apoptotic factor. As a result of these various properties, many physiological functions have been attributed to vitamin D, including stimulation of insulin production, modulation of antigen presenting cell and T lymphocyte activities, prevention of inflammatory bowel disease, photoprotection of skin and reduction in blood pressure (*reviewed in* [10]).

In addition to this remarkable list, vitamin D has been proposed to lower the risk of several types of internal cancers and autoimmune diseases. Evidence to support this hypothesis has been gathering over the past 20

years or so with Cedric Garland and colleagues in the States being the first to note the association[11]. More recent work along similar lines has been carried out by William Grant[12]. The main indications have come from epidemiological studies at a population level in which a latitude gradient has been established for various tumours, such as colorectal, large bowel, breast and prostate. The results revealed that the lower the latitude, and hence the higher the ambient sun exposure, the lower the risk of developing or dying from these cancers. Similar studies reached the same conclusion when the autoimmune disease, multiple sclerosis, was considered[13]. For example, in Australia where the genetic background of the population is similar throughout the whole country, the prevalence of multiple sclerosis per 100,000 people is 12 in N.Queensland at latitudes of 12-23°S and 76 per 100,000 people in Tasmania at latitude 45°S. It seems that high exposure to the sun during childhood and early adolescence is particularly related to a reduced risk of multiple sclerosis. Further reports have associated the consumption of vitamin D supplements with a lowered risk of cancer development.

So, how common is vitamin D deficiency? Many experts agree that babies who are entirely breast-fed (there is little vitamin D in human milk) and the elderly who seldom venture outdoors are frequently vitamin D deficient. For the ages inbetween, much controversy exists at present. Some argue that many working adults and children who do not spend much time outdoors or who rarely exposure their skin to sunlight may be at high risk of vitamin D deficiency, especially during the winter period. Astonishing figures have been published recently, such as 40% of the US population, 48% of girls aged 9-11 years old and 80% of nursing home ofpatients suffer from a vitamin D insufficiency. Even in areas of the world intense insolation such as Queensland, high rates of vitamin D insufficiency have been reported. Indeed the lack of vitamin D has been called "an unrecognised epidemic" in adults over 50 years of age.

How do we ensure a "perfect" amount of vitamin D?

As almost all of our vitamin D normally comes from the action of sunlight on our skins, attempts have been made to calculate how much exposure is required to maintain adequate vitamin D levels for good health. For several reasons, such estimates are very difficult to establish.

First the amount of UV radiation in sunlight varies markedly depending on factors such as the time of day, season, latitude, cloud cover and aerial pollution. Because of the zenith angle of the sun to the earth in the early morning and late afternoon and in winter, most UVB photons are efficiently absorbed by the ozone layer. As a result, little or no UVB reaches the skin and so the production of vitamin D_3 does not occur. Therefore sun exposure between the hours of 10 am and 3 pm in the spring, summer and autumn is crucial. As vitamin D_3 is fat soluble, it can be stored in the body fat, thus providing a means of seeing us through the winter months when there is essentially no solar UVB irradiation.

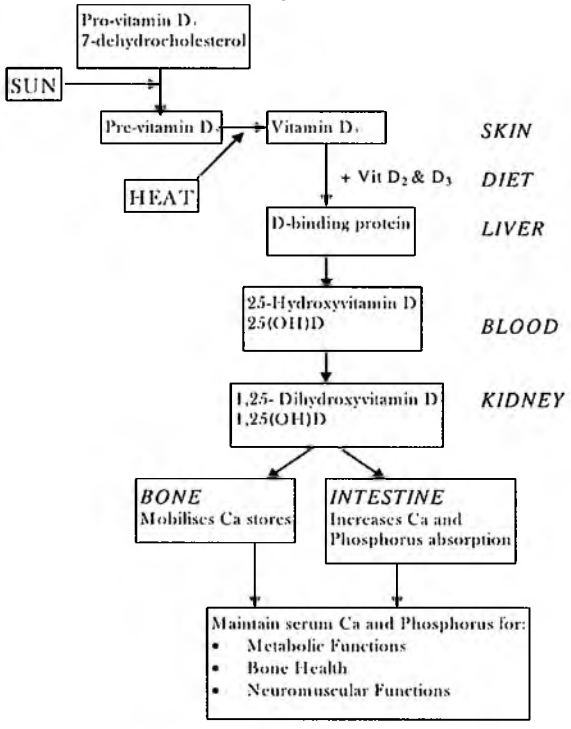

Figure 1. The metabolic pathway and functions of vitamin D

Secondly human behaviour with respect to sun exposure is very variable. In some cases, clothes are thrown off and lying in the full sun to develophe increased risk of skin cancer induction due to excessive sun exposure is taken into account with the wearing of protective clothing, hats, sunglasses and use of sunblocks. For example a sunscreen with a sun protection factor of 8 (thus allowing 8x greater time in the sun without burning) reduces the capacity of the skin to produce vitamin D_3 by more than 95%. What a dilemma – how to exposure yourself to sufficient sun to ensure the production of vitamin D while, at the same time, not increasing your chances of developing skin cancer!

Michael Holick, in particular, has put forward the view that the population at large in developed countries may be becoming vitamin D deficient. He published a book in 2004 called "The UV Advantage". In it, he explained how we need solar irradiation on unprotected skin to create vitamin D. This point was considered contrary to government health warnings regarding the dangers of being out in the sun, and Holick was asked to resign late in 2004 from the Department of Dermatology at the Boston School of Medicine.

The consensus view at present is that we should expose ourselves to an "intelligent" amount of sunlight. The dose should certainly be less than that required to redden the skin. Indeed as little as exposure of the hands, arms and face 2-3 times weekly for 15 minutes on each occasion when the weather allows is probably sufficient[14,15].

So the history of vitamin D is certainly not at an end. The story continues to unfold, even after 400 years of research, and more revelations will surely follow as further knowledge regarding this intriguing molecule emerges.

References

[1] Whistler D. Morbo puerili Angorum, quem patrio idiomate indigenae vocant The Rickets. *Lugduni Batavorum,* 1-13 (1645).

[2] Glisson F. De Rachitide sive morbo puerili, qui vulgo The Rickets diciteur, London 1-416 (1645).

[3] Mellanby E and Cantag MD. Experimental investigation on rickets. *Lancet* 1919: **196**, 407-412

[4] Windaus, Linsert O, Luttringhaus A and Weidlinch G. Uder has krystallistierte Vitamin D_2. *Justis Liedigs Ann Chem* 1932: **492**, 226-231

[5] Holick MF. Vitamin D: new horizons for the 21st century. McCollum Award Lecture, 1994. *Am J Clin Nutr* 1994: **60**, 619-630

[6] Dlugos DJ, Perrotta PL and Horn WG. Effects of submarine environment on renal-stone risk factors and vitamin D metabolism. *Undersea Hyperb Med* 1995: **22**, 145-152

[7] Bauer JM and Freyberg RH. Vitamin D intoxication and metastatic calcification. *J Am Med Assoc* 1946: **130**, 1208-1215

[8] Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations and safety. *Am J Clin Nutr* 1999: **69**, 842-856

[9] Stumpf WE, Sar M, Reid FA et al. Target cells for 1,25-dihydroxyvitamin D in intestinal tract, stomach, kidney, skin, pituitary and parathyroid. *Science* 1979: **206**, 1188-1190

[10] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* **80 (suppl)** 2004: 1678s-1688s

[11] Garland CF, Shekelle RB, Barrett-Connor E et al. Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men. *Lancet I* 1985: 307-309

[12]. Grant WB. An ecologic study of dietary and solar UV-B links to breast cancer mortality rates. *Cancer* 2002: **94**, 272-281 (2002).

[13] Ponsonby A-L, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 181, 71-78 (2002).

[14] Holick MF. Vitamin D: a millennium perspective. *J Cell Biochem* 2003 **88**, 296-307

[15] Garland CF. More on preventing skin cancer. Sun avoidance will increase the incidence of cancers overall. *Br Med J* 2003: **327**, 1228