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A global perspective for health

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# Sunlight and Vitamin D

## A global perspective for health

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Vitamin D is the sunshine vitamin that has been produced on this earth for more than 500 million years. During exposure to sunlight 7-dehydrocholesterol in the skin absorbs UVB radiation and is converted to previtamin D<sub>3</sub> which in turn isomerizes into vitamin D<sub>3</sub>. Previtamin D<sub>3</sub> and vitamin D<sub>3</sub> also absorb UVB radiation and are converted into a variety of photoproducts some of which have unique biologic properties. Sun induced vitamin D synthesis is greatly influenced by season, time of day, latitude, altitude, air pollution, skin pigmentation, sunscreen use, passing through glass and plastic, and aging. Vitamin D is metabolized sequentially in the liver and kidneys into 25-hydroxyvitamin D which is a major circulating form and 1,25-dihydroxyvitamin D which is the biologically active form respectively. 1,25-dihydroxyvitamin D plays an important role in regulating calcium and phosphate metabolism for maintenance of metabolic functions and for skeletal health. Most cells and organs in the body have a vitamin D receptor and many cells and organs are able to produce 1,25-dihydroxyvitamin D. As a result 1,25-dihydroxyvitamin D influences a large number of biologic pathways which may help explain association studies relating vitamin D deficiency and living at higher latitudes with increased risk for many chronic diseases including autoimmune diseases, some cancers, cardiovascular disease, infectious disease, schizophrenia and type 2 diabetes. A three-part strategy of increasing food fortification programs with vitamin D, sensible sun exposure recommendations and encouraging ingestion of a vitamin D supplement when needed should be implemented to prevent global vitamin D deficiency and its negative health consequences.

### Prehistoric Perspective

Life forms began to evolve in the oceans over 1 billion years ago. They took advantage of sunlight and used it as an energy source to generate carbohydrates. Curiously some of the earliest phytoplankton including *Emiliania huxleyi* (which is a coccolithophore, i.e., has a calcium carbonate exoskeleton) which has existed unchanged in the Sargasso Sea (Atlantic Ocean) for more than 500 million years when exposed to sunlight not only

photosynthesized glucose but also produced vitamin D<sub>2</sub> (Fig. 1).<sup>1</sup> This phytoplankton produces a large amount of ergosterol that when exposed to sunlight absorbs ultraviolet B (UVB) radiation and undergoes a photolysis reaction to form previtamin D<sub>2</sub>. Once formed this thermodynamically unstable isomer is transformed into vitamin D<sub>2</sub>. Similarly yeast and fungi also contain high amounts of ergosterol and when exposed to sunlight produce vitamin D<sub>2</sub>.<sup>1-4</sup>

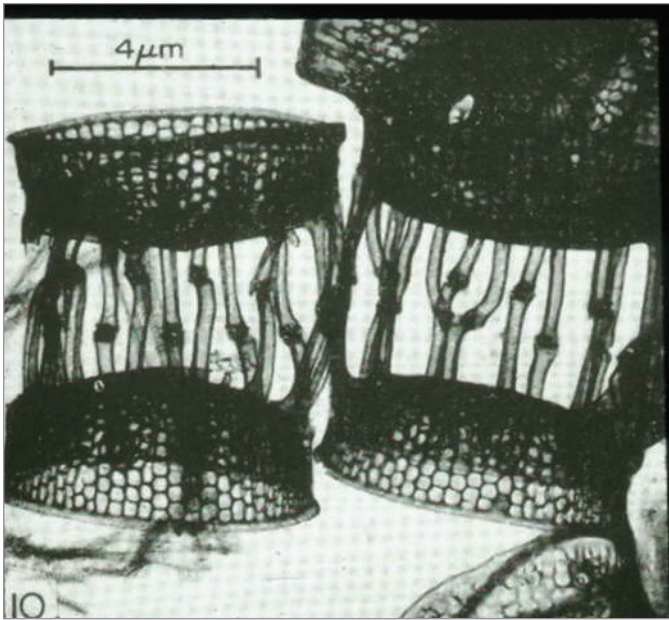
Although the functions of ergosterol and vitamin D<sub>2</sub> are unknown in these primitive unicellular photosynthesizing factories there are at least three possible functions that have been proposed. Ergosterol can efficiently absorb UVB radiation, which would make it an ideal natural sunscreen to protect UVB sensitive macromolecules in the organism including its proteins, RNA and DNA (Fig. 2).<sup>1,2</sup>

After absorbing UVB radiation previtamin D<sub>2</sub> is produced. Its absorption spectrum with a wavelength maximum at 260 nm overlaps the UV absorption spectrum for both DNA and RNA and thus would be able to protect DNA and RNA from photo-damage (Fig. 2).<sup>2</sup> When previtamin D<sub>2</sub> is exposed to UVB radiation it is converted to tachysterol<sub>2</sub> which has a UV absorption spectrum with a wavelength maximum at 282 nm which overlaps the UV absorption spectrum for amino acids in proteins that have conjugated double bonds including tryptophan and tyrosine (Fig. 1 and 2).<sup>1-4</sup> Thus early in evolution as organisms began to utilize solar energy for photosynthesis they needed a sun protection factor to absorb solar UVB radiation to minimize damage to UVB sensitive molecules. Ergosterol, previtamin D<sub>2</sub>, and its photoproducts could have acted as an ideal UVB sunscreen since they could absorb UVB radiation and dissipate its energy by the rearrangement of the double bonds.<sup>2</sup>

The amount of previtamin D<sub>2</sub> and photoproducts produced during sun exposure could also have been a photochemical signal (actinometer) to tell the organism that it has been exposed to enough solar UVB radiation and to signal it to leave the surface into deeper water where it would no longer be exposed to UVB radiation due to the ocean's ability to absorb this solar energy.<sup>2</sup>

It has also been speculated that if ergosterol was principally present in the plasma membrane and contained within the lipid bilayer that this rigid planar structure after exposure to solar UVB radiation would be transformed into a more flexible vitamin D<sub>2</sub> molecule that would likely be released into the extracellular space. This process could alter membrane permeability and possibly open up a pore to permit the entrance and exit of ions

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**Figure 1.** Microscopic picture of *Emiliana huxleyi*, which is a coccolithophore i.e., has a calcium carbonate exoskeleton. Holick, copyright 2013. Reproduced with permission.

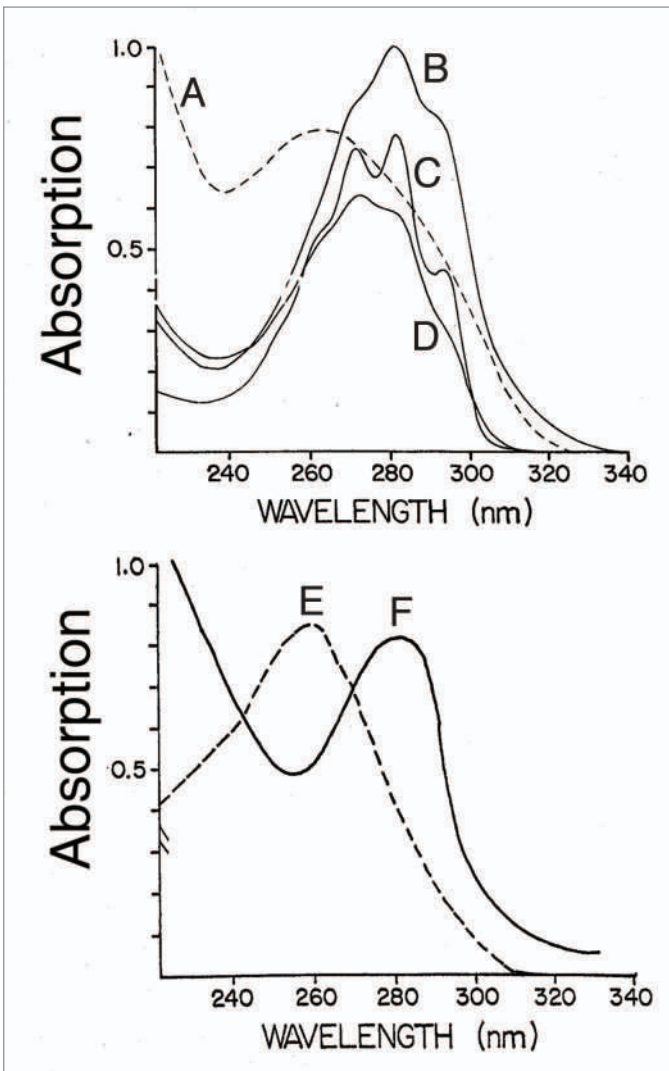
including calcium. This could be the connection for why vertebrates including humans have depended on sun exposure for the maintenance of their calcium metabolism.<sup>2,5-7</sup>

### Historical Perspective

As the industrial revolution swept across Northern Europe in the 1600s resulting in buildings built in close proximity and coal burning causing a pall of air pollution (Fig. 3) so too appeared a bone deforming disease rickets in children that had devastating health consequences (Fig. 4).<sup>8,9</sup>

The first insight into the possible relationship between the industrialization of Northern Europe and rickets was made by Sniadecki<sup>10</sup> (Fig. 5A) in 1822 when he concluded that children who lived in the inner city of Warsaw had a high incidence of rickets because of their lack of sun exposure. This was based on his clinical observations that children living in rural areas outside of Warsaw did not suffer from rickets while children born and raised in Warsaw were plagued with the disease. More than 70 y later Palm<sup>11</sup> came to the same conclusion based on reports from his colleagues in third world countries including India and China that rickets was uncommon compared with the high prevalence of the disease in children living in London. Another 30 y would pass before Huldchinsky<sup>12,13</sup> (Fig. 5B) would report that rachitic children exposed to a mercury arc lamp had dramatic radiologic improvement of their rickets several months later. He cleverly also realized that exposing one arm of a child with rickets had the same dramatic radiologic improvement in the forearm of the arm not exposed to the mercury arc lamp. He therefore correctly concluded that it was likely that something was being made in the skin and entered into the circulation to improve the global bone health of the child (Fig. 6).<sup>12,13</sup> Finally in 1921 Hess and Unger<sup>8,14</sup> (Fig. 5C) exposed rachitic children to sunlight on the roof of their hospital in New York City and demonstrated significant radiologic improvement in the children's rickets. These physicians also realized that children of color were at much higher risk for rickets and concluded that they needed longer exposure to sunlight to both treat and prevent rickets.

By turn of the 20th century it was estimated that upwards of 80–90% of children living in Northern Europe and in Northeastern United States had evidence of rickets.<sup>8</sup> Steenbock and Black<sup>15</sup> (Fig. 5D) and Hess and Weinstock<sup>16</sup> exposed various foods including cotton seed oil, corn oil, and milk to UVB radiation and demonstrated that this process imparted antirachitic activity for rodents. This led to the addition of ergosterol to milk followed by UVB irradiation or the addition of ergosterol that had been previously exposed to UVB radiation or to the addition of vitamin D<sub>2</sub> to the milk (Fig. 7).<sup>8</sup>



**Figure 2.** UV absorption spectra for (A) previtamin D<sub>2</sub>, (B) tachysterol, (C) provitamin D<sub>3</sub> (7-dehydrocholesterol), (D) lumisterol, (E) DNA, and (F) albumin. Holick, copyright 2007. Reproduced with permission.

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This process was quickly embraced by the dairy processors and in the early 1930s essentially all milk in the United States and in most industrialized countries including Great Britain and other European countries had vitamin D fortified milk. The United States government also established an agency in 1931 whose goal was to promote sensible sun exposure of young children to prevent rickets and improve their bone health (Fig. 8).<sup>9,14</sup> Within a few years these interventions essentially eradicated rickets.<sup>8,17-19</sup>

Vitamin D became so popular that in the 1930s and 1940s a wide variety of foods and beverages as well as personal care products were fortified with vitamin D.<sup>19</sup> They included not only milk and other dairy products but also soda pop, beer, hot dogs, custard and even soap and shaving cream (Figs. 9A-D).<sup>19</sup>

However in the early 1950s an outbreak of hypercalcemia in infants who had elfin faces, heart problems, and mental retardation led to an investigation by the Royal College of Physicians. The experts concluded that this was most likely due to vitamin D intoxication since a similar presentation had been observed in neonatal rodents born of mothers who were fed high doses of vitamin D.<sup>20-22</sup> Legislation quickly followed banning the fortification of any food or personal use products with vitamin D in Great Britain.<sup>8,17,22</sup> This ban quickly spread across Europe and for the most part remains in effect today with the exception of a few foods including margarine and some cereals being fortified with vitamin D.<sup>8,19-22</sup> It is however likely that these children had Williams syndrome which is associated with elfin faces, mental retardation, heart problems, and hypercalcemia due to a hypersensitivity to vitamin D.<sup>23</sup> Sweden and Finland now permit milk to be fortified with vitamin D.<sup>22,24</sup> It is worth noting that milk has been fortified with 100 IU vitamin D/8 oz for the past 80+ years without any reports of toxicity in infants. In the past 10 y juice products including orange juice have been fortified in the United States with 100 IU vitamin D/8 oz without any reports of toxicity.<sup>22</sup>

### Photochemistry of Provitamin D<sub>3</sub>

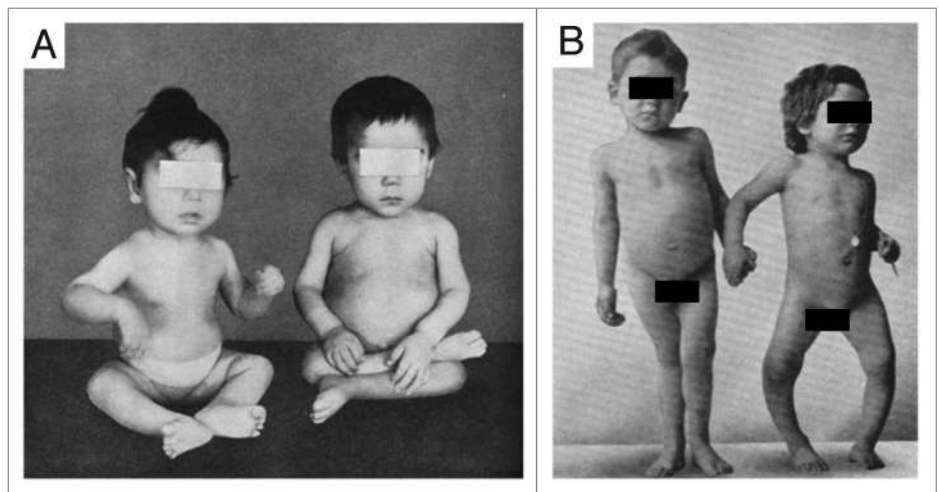
During exposure to sunlight solar radiation with wavelengths of 290–315 nm penetrate into the skin and are absorbed by proteins, DNA and RNA as well as 7-dehydrocholesterol.<sup>1,2</sup> Most of this UVB radiation is absorbed in the epidermis and as a result when exposed to sunlight most of the vitamin D<sub>3</sub> that is produced in the skin is made in the living cells in the epidermis. This is the reason why after exposure to sunlight vitamin D<sub>3</sub> remains in the skin even when the skin is washed with soap and water immediately after the exposure to sunlight.

When epidermal 7-dehydrocholesterol absorbs solar UVB radiation with energies of 290–315 nm (Fig. 10), it causes an activation of the double bonds

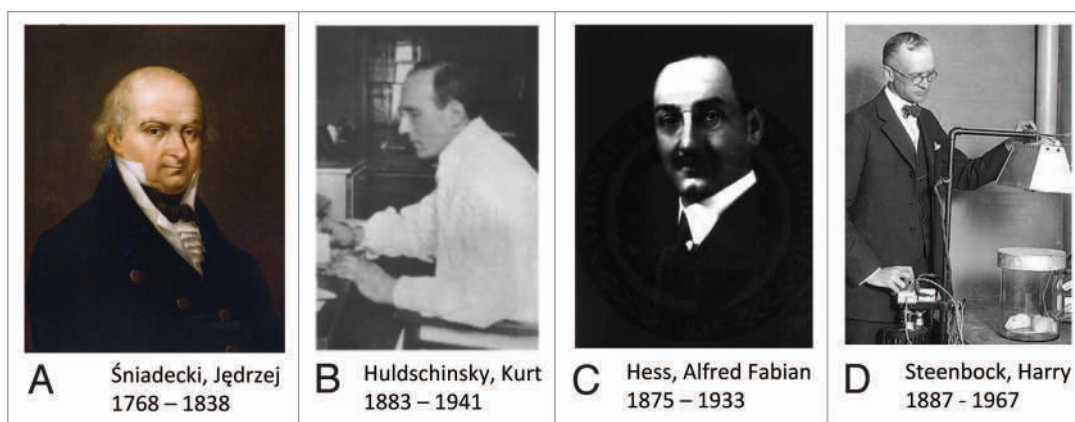


DARK ALLEY in Glasgow, photographed in about 1870. It is typical of the tenement houses for the synthesis of the hormone that prevents rickets.

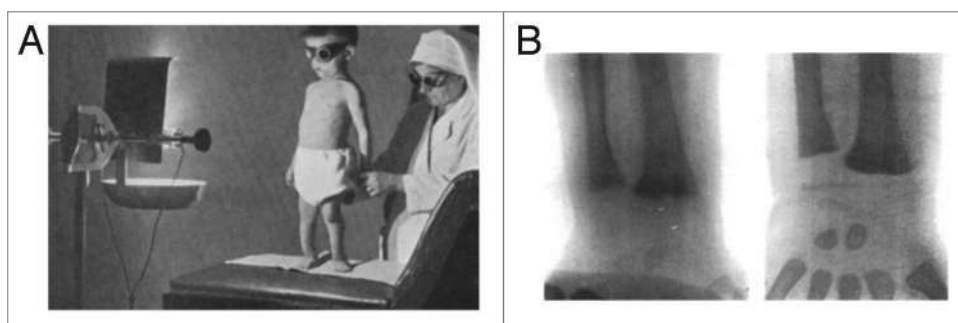
**Figure 3.** Photograph from Glasgow, Great Britain, in about 1870 showing that the buildings are built in close proximity to each other. Holick, copyright 1994. Reproduced with permission.



**Figure 4.** Skeletal deformities observed in rickets. (A) Photograph from the 1930s of a sister (left) and brother (right), aged 10 mo and 2.5 y, respectively, showing enlargement of the ends of the bones at the wrist, carpedal spasm, and a typical "Taylorwise" posture of rickets. (B) The same brother and sister 4 y later, with classic knock-knees and bow legs, growth retardation, and other skeletal deformities. Holick, copyright 2006. Reproduced with permission.



**Figure 5.** Photographs of researchers who made crucial contributions to vitamin D and rickets research. (A) Jędrzej Śniadecki, (B) Kurt Huldschinsky, (C) Alfred Hess, (D) Harry Steenbock. Holick, copyright 2013. Reproduced with permission.



**Figure 6.** UV radiation therapy for rickets. (A) Photograph from the 1920s of a child with rickets being exposed to UV radiation. (B) Radiographs demonstrating florid rickets of the hand and wrist (left) and the same wrist and hand taken after treatment with 1 h UV radiation 2 times a week for 8 weeks. Note mineralization of the carpal bones and epiphyseal plates (right). Holick, copyright 2006. Reproduced with permission.

causing them to rearrange and open up the B ring to form the seco-steroid (split steroid) previtamin  $D_3$  (Fig. 11).<sup>25</sup>

Previtamin  $D_3$  when made in a test tube exists in two conformeric forms, a 5,6-sec-cis-s-cis (czc) and a 5,6-sec-trans-s-cis (czt) form. The czt conformer is the most thermodynamically stable form and thus most of the previtamin  $D_3$  when produced in a test tube exists as this conformer. This conformer however being stable cannot isomerize to vitamin  $D_3$ . However the less thermodynamically stable conformer czc does undergo a 1-7 antarafacial sigma shift of a hydrogen from C-19 to C-9 causing rearrangement of the double bonds to form vitamin  $D_3$ . As a result it takes several days in a test tube at room temperature and even at body temperature for the czt conformer to isomerize to the czc conformer which then is converted to vitamin  $D_3$  (Fig. 12).<sup>6,7,26,27</sup>

From a physiologic perspective it made little sense for it to take several days for previtamin  $D_3$  to convert to vitamin  $D_3$  in the skin as it does in a test tube. Furthermore this was a significant problem for poikilothermic (cold blooded) vertebrates since a lower outside temperature would make it take a much longer time

for previtamin  $D_3$  that was produced in the skin to convert to vitamin  $D_3$ . Studies of lizard skin exposed to simulated sunlight revealed that the conversion of previtamin  $D_3$  to vitamin  $D_3$  was 10 times faster when compared with previtamin  $D_3$  in a isotropic organic solution (Fig. 12).<sup>6</sup> A similar observation was made in human skin (Fig. 13).<sup>7</sup>

This suggested that the skin had some property that accelerated the conversion of previtamin  $D_3$  to vitamin  $D_3$ . One possible explanation was that an enzyme existed that catalytically converted previtamin  $D_3$  to vitamin  $D_3$ . Skin homogenates incubated with previtamin  $D_3$  did not result in an enhancement in its

conversion to vitamin  $D_3$ . Thus another explanation needed to be found. It was hypothesized and finally proven with several studies that 7-dehydrocholesterol in the skin cell principally existed in the plasma membrane and was incorporated within the fatty acid hydrocarbon side chain and polar head group of the triglycerides (Figs. 11 and 14). The rigid planar structure of 7-dehydrocholesterol sandwiched in between the triglyceride fatty acid hydrocarbon tails could only be transformed into the planar czc conformer of previtamin  $D_3$  upon exposure to solar UVB radiation (Fig. 11).<sup>6,26-28</sup>

Once formed, this unstable conformer rapidly converted to vitamin  $D_3$ .<sup>6,7,26-28</sup> To confirm this hypothesis studies were done in liposomes that mimicked the plasma membrane and it was demonstrated that adding double bonds to the triglyceride's side chain or shortening or lengthening of the side chain resulted in a decrease in the kinetics for the conversion of previtamin  $D_3$  to vitamin  $D_3$  (Fig. 15).<sup>27</sup>

Because vitamin  $D_3$  is thermodynamically more stable and also more flexible it is ejected out of the plasma membrane into the extracellular space and diffuses into the capillary bed in the



dermis where it is bound to the vitamin D binding protein (DBP) for transport to the liver.<sup>2,5,6,22,29,30</sup>

There has been a lot of discussion as to whether ingesting vitamin D from the diet or from a supplement is the same as producing vitamin D<sub>3</sub> in the skin. Because it takes approximately 8 h for previtamin D<sub>3</sub> in the skin to fully convert to vitamin D<sub>3</sub><sup>26,27</sup> and it takes additional time for the vitamin D<sub>3</sub> to enter the dermal capillary bed there are at least 2 of the explanations for why it was observed that vitamin D<sub>3</sub> produced in the skin last 2–3 times longer in the circulation when compared with ingesting it orally (Fig. 16).<sup>29,30</sup> Furthermore when vitamin D<sub>3</sub> is produced in the skin 100% of it is potentially bound to the vitamin D binding protein (Fig. 17). When vitamin D<sub>3</sub> is ingested from the diet or supplement it gets incorporated into chylomicrons which are transported into the lymphatic system and then into the venous system were approximately 60% of the vitamin D<sub>3</sub> is bound to the vitamin D binding protein and 40% is rapidly cleared in the lipoprotein bound fraction.<sup>29</sup>



**Figure 7.** (A) Seal of a milk bottle that denoted that the milk was irradiated with UV radiation and contained vitamin D. (B) Cap of a milk bottle stating that activated ergosterol has been added to the milk. (C) Cap of milk bottle stating that the milk had been fortified with vitamin D. (D) Seal of a bottle of milk that denoted that the milk had been irradiated and contained vitamin D. Holick, copyright 2013. Reproduced with permission.

### Sun Controlled Cutaneous Production of Vitamin D<sub>3</sub>

During exposure to sunlight after previtamin D<sub>3</sub> is produced it will absorb solar UVB radiation and isomerize into two major photoproducts, lumisterol<sub>3</sub> and tachysterol<sub>3</sub> (Fig. 17).<sup>31,32</sup>

Neither of these two photoproducts has any effect on calcium metabolism.<sup>32</sup> Thus when the skin is exposed to sunlight it can only convert approximately 15% of 7-dehydrocholesterol to previtamin D<sub>3</sub> (Fig. 18).<sup>32</sup> Any further exposure will result in a photoequilibrium whereby previtamin D<sub>3</sub> is converted into lumisterol<sub>3</sub> and tachysterol<sub>3</sub> as well as revert back to 7-dehydrocholesterol (Fig. 17). In addition when vitamin D<sub>3</sub> is made from previtamin D<sub>3</sub> in the skin if it is exposed to solar UVB radiation it will absorb UVB radiation and be converted into several suprasterols and 5,6-trans-vitamin D<sub>3</sub> (Figs. 17, 19). In addition previtamin D<sub>3</sub> can also be converted to several toxisterols (Fig. 20).<sup>33–36</sup> Therefore no matter how much sun a human is exposed to vitamin D intoxication will not occur because any excess previtamin D<sub>3</sub> and vitamin D<sub>3</sub> is photodegraded into products that have no calcemic activity.<sup>31,32</sup>

This however does not mean that these myriad of photoproducts don't have other biologic effects such as regulating epidermal cell growth and reducing risk of skin cancer. One product, lumisterol<sub>3</sub>, if converted to 1,25-dihydroxylumisterol<sub>3</sub> may have anti-tumor effects in the skin.<sup>37</sup> Some of the suprasterols also have antiproliferative activity in cultured human keratinocytes (Fig. 21).

Therefore sensible sun exposure to produce previtamin D<sub>3</sub>, vitamin D<sub>3</sub> and its photoproducts may have some additional benefits above and beyond simply taking a vitamin D<sub>3</sub> supplement or ingesting vitamin D<sub>3</sub> from dietary sources.

### Factors that Influence Cutaneous Vitamin D<sub>3</sub> Synthesis

a) **Zenith angle.** Only about one percent of solar UVB radiation ever reaches the earth's surface even in the summer at noon time.<sup>38</sup> The reason is that all of the UV C (200–280 nm) and all of the UVB radiation up to approximately 290 nm is efficiently absorbed by the stratospheric ozone layer.<sup>38,39</sup> In addition the ozone layer absorbs approximately 99% of the UVB radiation with wavelengths 291–320 nm. Therefore increasing the path length by which solar UVB has to travel through the ozone layer will result in a decrease in the number of UVB photons that reach the earth's surface (Fig. 22).<sup>40</sup> This is the explanation for why during the winter when living above and below approximately 33° latitude very little if any vitamin D<sub>3</sub> can be produced in the skin from sun exposure. People who live farther North and South often cannot make any vitamin D<sub>3</sub> in their skin for up to 6 mo of the year.<sup>41</sup> For example in Boston at 42° North essentially no vitamin D<sub>3</sub> can be produced in the skin from November through February. Inhabitants living in Edmonton Canada at 52° North, Bergen Norway at 60° North,



**Figure 8.** Brochure of the US Department of Labor promoting sensible sun exposure in children in 1931.

or Ushuaia Argentina at 55° South are unable to produce any significant vitamin D<sub>3</sub> for about 6 mo of the year (Figs. 23 and 24).<sup>2,39,41</sup>

People who live in the far Northern and Southern hemispheres had apparently appreciated this fact and were able to satisfy their vitamin D requirement by eating vitamin D rich foods including oily fish, seal blubber, polar bear liver and whale blubber and liver all of which contain large amounts of vitamin D.<sup>42,43</sup>

In the early morning and late afternoon the zenith angle of the sun is also more oblique similar to winter sunlight and as a

result very little if any vitamin D<sub>3</sub> can be produced in the skin before 10 a.m. and after 3 p.m. even in the summer time (Figs. 23 and 25).<sup>44</sup>

Air pollution including nitrous oxide and ozone is common in many large cities including Los Angeles and San Diego (Fig. 26) and will absorb solar UVB radiation and therefore reduce the effectiveness of sun exposure in producing vitamin D<sub>3</sub> in the skin (Fig. 27).<sup>40,45</sup> The amount of UVB radiation available for cutaneous vitamin D<sub>3</sub> production is markedly reduced by the increase of sulfur dioxide in San Diego and Los Angeles, offsetting the fact that both cities are at lower latitudes.<sup>45</sup>



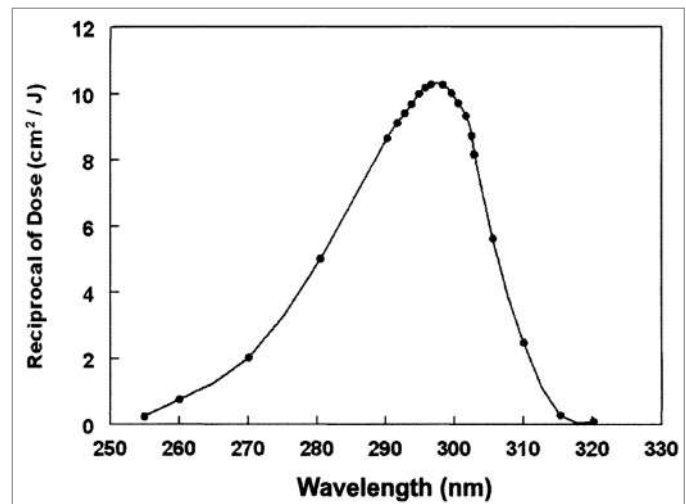
Altitude can also have a dramatic influence on the amount of solar UVB that reaches the earth's surface because the higher the altitude the shorter the path length that UVB has to travel through the atmosphere and thus the skin can produce more vitamin D<sub>3</sub>. This was dramatically demonstrated in Agra (169 M altitude), Katmandu (1400 M), and Mount Everest base camp (5300 M), India (27° North). An analysis of sun-induced vitamin D<sub>3</sub> synthesis in vitro was conducted at higher altitudes at the same latitude during the same month. In November in Agra very little previtamin D<sub>3</sub> was produced during exposure to the sun. It was observed that there was a direct correlation with increased previtamin D<sub>3</sub> production with increased altitude. At Mt Everest base camp (5300 M) there was almost a 5-fold increase in previtamin D<sub>3</sub> production compared with what was observed in Agra (Fig. 28).<sup>46</sup> Since glass absorbs all UVB radiation, exposure of the skin to sunlight that passes through glass, plexiglass, and plastic will not result in any production of vitamin D<sub>3</sub> in the skin (Fig. 29).<sup>31</sup>

Sunscreens were designed to absorb solar UVB radiation.<sup>47</sup> A sunscreen with a sun protection factor (SPF) of 30 absorbs approximately 95–98% of solar UVB radiation. Therefore the topical application of a sunscreen with an SPF of 30 reduces the capacity of the skin to produce vitamin D<sub>3</sub> by the same amount i.e., 95–98%.<sup>22</sup> This was confirmed with the report that the application of sunscreen with a SPF of only 8 dramatically reduced the blood level of vitamin D<sub>3</sub> after exposure to simulated sunlight in a tanning bed (Fig. 30).<sup>47,48</sup> Farmers in the Midwest who had a history of non-melanoma skin cancer and who wore a sunscreen all the time before going outdoors for more than a year demonstrated that at the end of the summer their blood levels were significantly lower (most were vitamin D deficient) than the levels of the control group (Fig. 31).<sup>48</sup>

**b) Skin pigment.** Humans evolved at the equator. They were constantly exposed to sunlight and developed an efficient natural sunscreen melanin,<sup>49</sup> which has an absorption spectrum of 290–700 nm and thus can effectively absorb solar UVB radiation (Fig. 32).<sup>45</sup> However even though Africans have extremely dark heavily pigmented skin a small amount of UVB radiation is able to penetrate into the epidermis to produce vitamin D<sub>3</sub>. This was demonstrated when adult whites (skin type 2) and blacks (skin type 5) were exposed to the same amount of UVB radiation in a tanning bed. Whereas the white adults raised their blood levels of vitamin D<sub>3</sub> more than 30 fold the black adults demonstrated no significant increase in their blood levels of vitamin D<sub>3</sub>. However when the black adults were exposed to 5 times more UVB radiation, they increased their blood level by about 15-fold (Fig. 33).<sup>50</sup> This was confirmed when surgically obtained white and black skin was exposed to sunlight in Boston in summer. After 30 min approximately 3% of cutaneous 7-dehydrocholesterol was converted to previtamin D<sub>3</sub> in the white skin sample



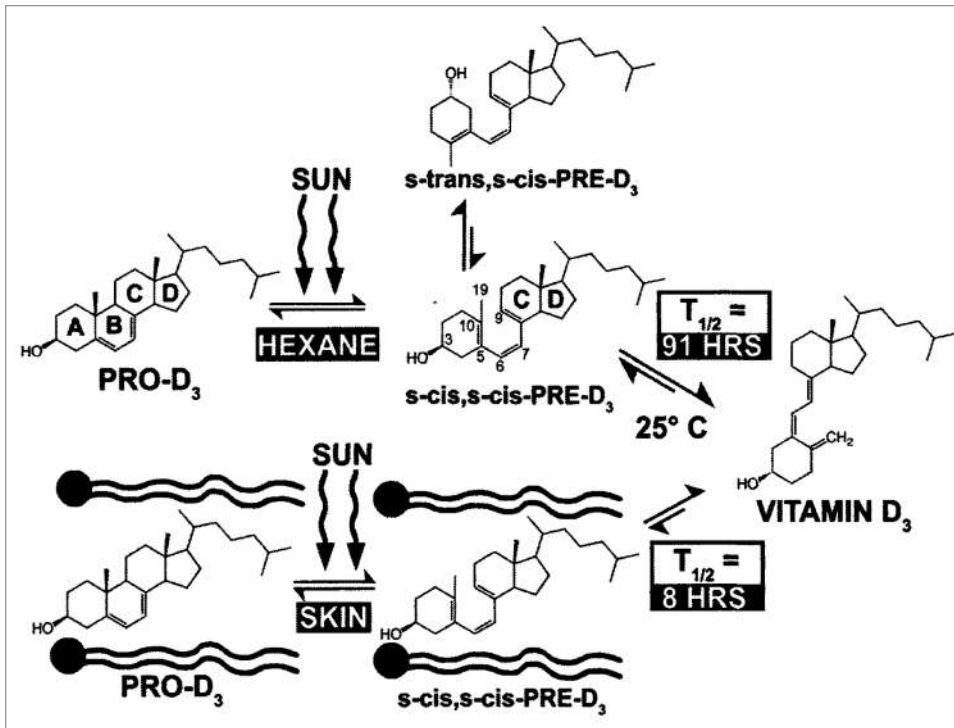
**Figure 9.** (A) Seal denoting that this product was fortified with vitamin D. (B) Bottle of oil denoting that it contained irradiated ergosterol. (C) Beer can denoting that it was fortified with vitamin D. (D) Advertisement denoting that Bird's custard contained vitamin D. Holick, copyright 2013. Reproduced with permission.



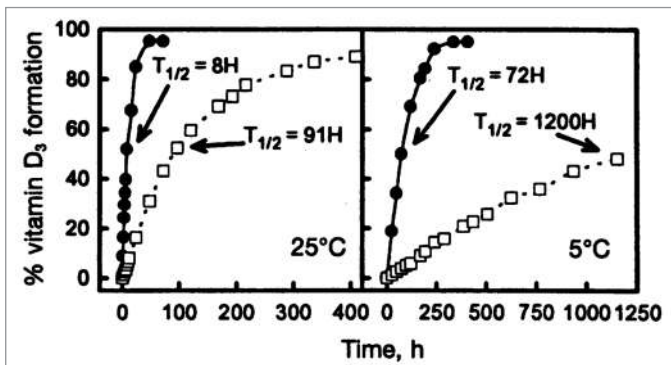
**Figure 10.** Action spectrum for the conversion of 7-dehydrocholesterol to previtamin D<sub>3</sub> in human skin. Holick, copyright 2007. Reproduced with permission.

whereas only about 0.3% of 7-dehydrocholesterol was converted to previtamin D<sub>3</sub> in the black skin (Fig. 34).<sup>51</sup> These findings could explain the positive association between skin lightness and





**Figure 11.** Photolysis of provitamin D<sub>3</sub> (pro-D<sub>3</sub>, 7-dehydrocholesterol) into previtamin D<sub>3</sub> (pre-D<sub>3</sub>) and its thermal isomerization to vitamin D<sub>3</sub> in hexane and in lizard skin at 25°C. In hexane pro-D<sub>3</sub> is photolyzed to s-cis,s-cis-pre-D<sub>3</sub>. Once formed, this energetically unstable conformation undergoes a conformational change to the s-trans,s-cis-pre-D<sub>3</sub>. Only the s-cis,s-cis-pre-D<sub>3</sub> can undergo thermal isomerization to vitamin D<sub>3</sub>. The s-cis,s-cis conformer of pre-D<sub>3</sub> is stabilized in the phospholipid bilayer by hydrophilic interactions between the 3β-hydroxyl group and the polar head of the lipids, as well as by the van der Waals interactions between the steroid ring and side-chain structure and the hydrophobic tail of the lipids. These interactions significantly decrease the conversion of the s-cis,s-cis conformer to the s-trans,s-cis conformer, thereby facilitating the thermal isomerization of s-cis,s-cis-pre-D<sub>3</sub> to vitamin D<sub>3</sub>. Holick, copyright 1995. Reproduced with permission.



**Figure 12.** Thermal isomerization of previtamin D<sub>3</sub> to vitamin D<sub>3</sub> as a function of time in lizard skin (●) and in hexane (□) at 25°C (left) and 5°C (right). Each point represents the mean value from three separate analyses. Holick, copyright 1995. Reproduced with permission.

25-hydroxyvitamin D [25(OH)D] levels as found by Armas et al.<sup>52</sup> (Fig. 35). The associations between skin lightness, UVB dose and 25(OH)D are documented in Figure 36.

Skin pigmentation or the lack thereof was important in the evolution of humans as they migrated North and South of the equator. Africans such as the Maasai (Fig. 37) living outdoors exposed to sunlight daily throughout the year have robust circulating concentrations of the major circulating form of vitamin D, 25(OH)D, in the range of 46 ng/mL.<sup>53</sup>

Although there have been several explanations for why skin pigment evolved as humans migrated North and South of the equator one of the most likely explanations is as humans migrated farther North and South of the equator the zenith angle of the sun increased resulting in a decrease in the amount of solar UVB radiation reaching the earth thereby reducing vitamin D<sub>3</sub> synthesis. A decrease in the amount of skin pigment resulted in a decrease in the sun screening protection permitting more of the UVB radiation to reach the epidermal cells. This provided an evolutionary advantage by being more efficient in producing vitamin D<sub>3</sub>.<sup>49</sup> It had long been speculated that our Neanderthal ancestors were heavily pigmented hairy creatures. This however did not make a lot of sense since having heavy pigmentation and excessive hair would markedly reduce cutaneous production of vitamin D<sub>3</sub> which was essential for maximizing skeletal health throughout life thereby reducing risk of life-threatening fractures. However, more important is the fact that vitamin D deficiency in utero and during the first few years of life would have caused infantile rickets resulting in a flat deformed pelvis with a small pelvic outlet. Furthermore vitamin D is important for muscle function which is also crucial for birthing.<sup>22,54</sup> These conditions caused by vitamin D deficiency would have made it difficult for females to give birth. Therefore in order to survive and procreate skin pigmentation had to markedly decrease in order to permit more UVB photons to enter the skin to produce sufficient amounts of previtamin D<sub>3</sub>.<sup>54,55</sup> Recent evidence has suggested that Neanderthals had a mutation of their melanocyte stimulating hormone receptor resulting in them being redheaded and having Celtic-like fair skin.<sup>56,57</sup> This is the likely explanation for why people in Northern Europe have skin types 1 and 2.

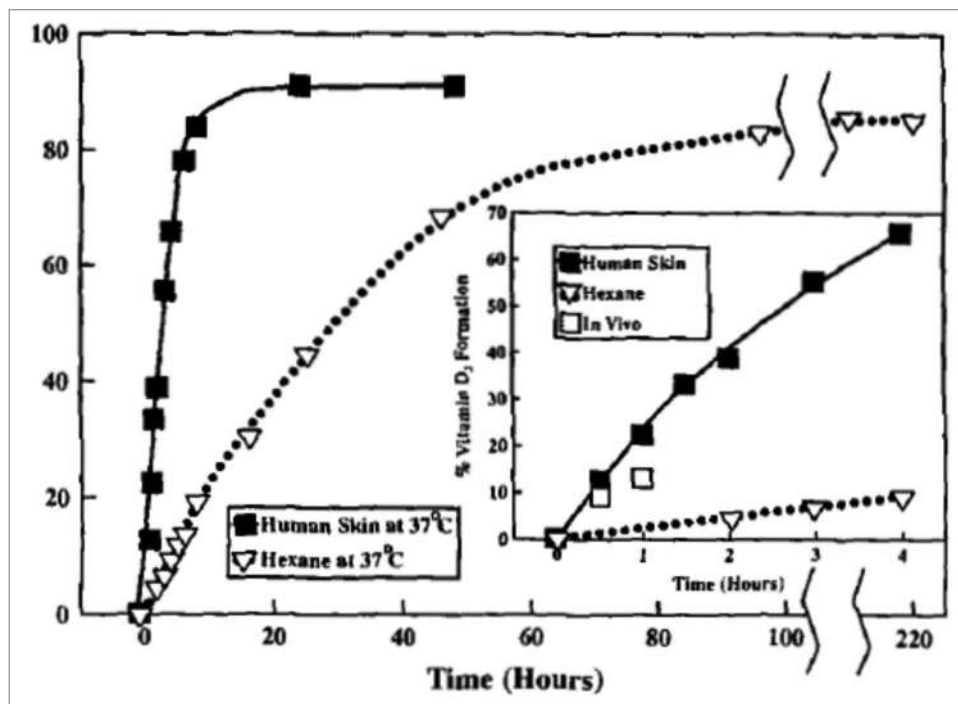
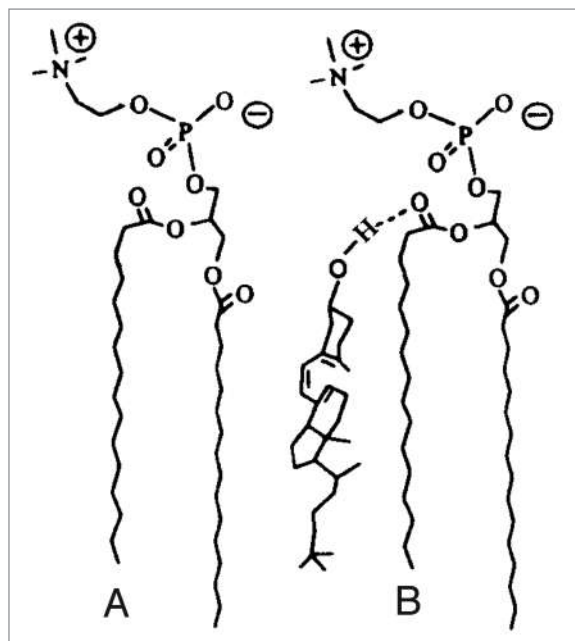
c) **Aging.** It was observed that 7-dehydrocholesterol concentrations in human epidermis were inversely related to age (Fig. 38).<sup>58</sup> The effect of aging on the cutaneous production of vitamin D<sub>3</sub> was demonstrated in a study that exposed healthy young adults and older adults to the same amount of UVB radiation

in a tanning bed. The increase in the blood level of vitamin D<sub>3</sub> in six young adults aged 20–30 was at least 3-fold higher compared with the six older adults aged 62–80 demonstrating that aging significantly decreased the capacity of the skin to produce vitamin D<sub>3</sub> (Fig. 39).<sup>59</sup> With this marked age-related decrease in the cutaneous production of vitamin D<sub>3</sub> could the elderly benefit from being exposed to sunlight or UVB radiation? The skin has a large capacity to produce vitamin D<sub>3</sub>. Exposure of a young adult in a bathing suit to one minimal erythemal dose (MED) of UV radiation in a tanning bed was equivalent to ingesting approximately 20,000 IUs of vitamin D<sub>2</sub> (Fig. 40).<sup>25</sup> When a healthy 75 y old male in a bathing suit was exposed to UVB radiation in a tanning bed three times a week for 7 weeks he was able to raise and maintain his blood levels of 25(OH)D into the healthy normal range of ~50 ng/ml (Fig. 41C). The percent increase in circulating 25(OH)D concentrations was similar to what was observed in healthy young adults (Fig. 41B). Ampoules containing 7-DHC that were also irradiated served to demonstrate the efficacy of the tanning bed in producing previtamin D<sub>3</sub> (Fig. 41A).<sup>5</sup> A study in elderly in a nursing home that had an activity room with an UVB emitting lamps on the ceiling (Fig. 42) reported that this was effective in raising and maintaining 25(OH)D levels in these residents (Fig. 43).<sup>60</sup>

### Influence of Latitude and Season on Vitamin D Status

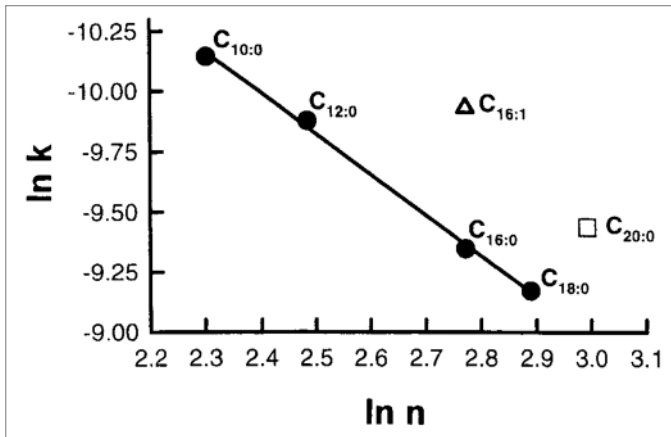
It is well documented that seasonal differences in cutaneous vitamin D<sub>3</sub> production have a dramatic influence on both children's and adults' vitamin D status (D represents vitamin D<sub>2</sub> or vitamin D<sub>3</sub>).<sup>22</sup> A study of 7437 Caucasian men and women from the 1958 British birth cohort at age 45 y revealed that the peak blood levels for 25(OH)D were observed in September

**Figure 14.** Proposed theoretical structural model for the localization of the cZc-previtamin D<sub>3</sub> in the phospholipids of a membrane. Based on the amphipathic nature and conformational mobility of previtamin D<sub>3</sub> we proposed the following model to show the spatial relationship between previtamin D<sub>3</sub> and phospholipids. We postulated that in the membrane, the cholesterol like cZc-previtamin D<sub>3</sub> is aligned parallel to its neighboring phospholipids, with its polar 3β-hydroxy interacting with the polar head groups of the phospholipids through hydrogen bonding, and the hydrophobic rings and side chain interacting with the nonpolar acyl chains of the lipids through hydrophobic and van der Waals interactions. A, phosphatidylcholine; B, cZc-previtamin D<sub>3</sub>. Reproduced with permission from ref. 27.

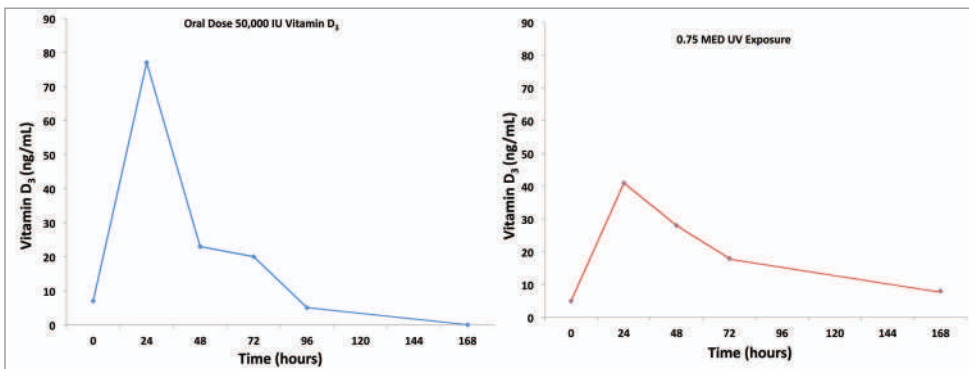


**Figure 13.** Thermoconversion of pre-D<sub>3</sub> to vitamin D<sub>3</sub> as a function of time in human skin and in n-hexane at 37°C. The inset depicts the thermoconversion of pre-D<sub>3</sub> to vitamin D<sub>3</sub> in human skin in vivo (■) and compares them with those in n-hexane (▽) and in human skin in vitro (◻) at 37°C. Reproduced with permission from.<sup>7</sup>

(~30 ng/mL) and the nadir was observed in February (~14 ng/mL) (Fig. 44).<sup>61</sup> A similar observation was made in postmenopausal women in Denmark. Those who had regular sun exposure achieved a blood level of 25(OH)D of ~45 ng/mL compared with women who avoided direct sun exposure had a 25(OH)D of ~23 ng/mL. This was also supported by the fact that hours of sun exposure was directly related to circulating concentrations of 25(OH)D (Fig. 45).<sup>62</sup>



**Figure 15.** Effects of phospholipid carbon chain length and saturation on the rate of pre-D<sub>3</sub> to vitamin D<sub>3</sub> isomerization in liposomes. k, rate constant; n, carbon number of phospholipid chain. Reproduced with permission from ref. 27.



**Figure 16.** The same healthy 31 year old female received a whole body exposure (in a bikini bathing suit) to 0.75 MED of ultraviolet B radiation and 4 weeks later received 50,000 IUs of vitamin D<sub>3</sub>. Blood samples were collected for 168 hours and the blood was measured for vitamin D<sub>3</sub> by high-performance chromatography. Reproduced with permission; Holick copyright 2013.

Latitude also has a dramatic influence on the cutaneous production of vitamin D<sub>3</sub> and therefore on a person's vitamin D status (Fig. 46).<sup>39,63</sup> Mean circulating 25(OH)D in children, adolescents and adults at various latitudes revealed that there was a significant inverse relationship with the highest levels for those living near the equator with blood levels of 25(OH)D ~40 ng/mL compared with those living far North and South of the equator with blood levels of 25(OH)D ~15 ng/mL (Fig. 46).<sup>64</sup>

However another study reported that those living at the highest latitudes in Europe had higher circulating concentrations of 25(OH)D.<sup>65</sup>

The likely explanation is that some people living far North and South of the equator who could not make any significant amount of vitamin D<sub>3</sub> in their skin for more than half of the year (Fig. 24) adapted by eating foods rich in vitamin D including oily fish<sup>22,42,43</sup> while others did not.<sup>39,44,66</sup>

## Sunlight and Non-Calcemic Health Benefits

**Historical perspective.** People have a feeling of wellbeing when exposed to sunlight. This may be due to the fact that keratinocytes produce β-endorphin when exposed to UV radiation.<sup>67</sup> In the early 1900s Finsen (Fig. 47) observed that exposure to sunlight (Fig. 48) dramatically improved cutaneous skin lesions caused by a tuberculosis infection (lupus vulgaris) and received the Nobel Prize in 1903 for his enlightening observations. This led to the use of solariums as a way to treat patients with tuberculosis and gave rise to the use of heliotherapy to improve health.<sup>19,68,69</sup> Heliotherapy was used to treat a wide variety of chronic illnesses in the early 1900s and it is still practiced throughout the world and especially in Northern Europe.<sup>19,70-72</sup> The rise in the use of pharmaceuticals to treat acute and chronic diseases led to the demise of heliotherapy especially in United States.<sup>19,68,69,73</sup>

## Sunlight and Vitamin D: The Cancer Connection

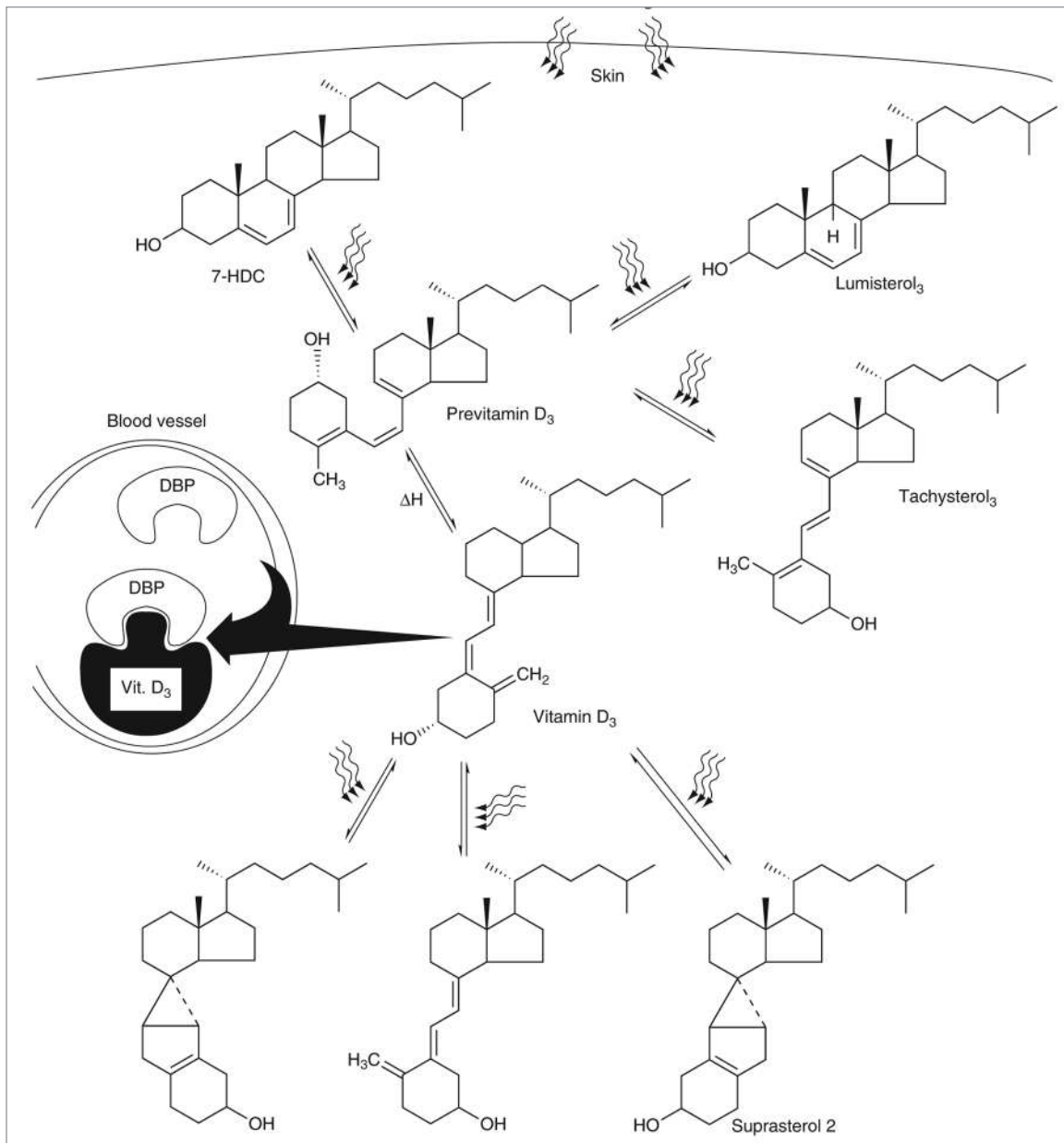
One of the first association studies relating sun exposure with reduced risk for cancer was reported in 1916 by Hoffman,<sup>74</sup> who found that living at a higher latitude was associated with an increased risk for mortality from cancer. He compared cancer mortality between 1908 and 1912 and observed that cancer mortality increased with increasing distance from the equator (Fig. 49). In 1937 Peller and Stephenson<sup>75</sup> analyzed the incidence of cancer in navy personnel in the United States Navy who were documented to have increased

exposure to solar UV radiation with age matched controls and reported that the rate of skin cancer was eight times higher in the navy personnel while the total number of deaths from other cancers was 60% less than the civilian population.<sup>75</sup>

Four years later, Apperly<sup>76</sup> compared total cancer mortality in the populations studied with the percentage of Americans and Canadians in the same population who were engaged in agriculture. He concluded that cancer mortality was highest in farmers living in the Northeast compared with those living in the South (Fig. 50).<sup>76</sup> He also reported that farmers living in the South exposed to more sunlight were at a higher risk for nonmelanoma skin cancer which he noted was easy to detect and easy to treat. He concluded that the fact that these Southern farmers had non-melanoma skin cancer resulted in them developing an immunity to the skin cancer which also resulted in an immunity to all cancers including those with high mortality rate.<sup>76</sup>

These observations essentially went unnoticed and the curious relationship of increased sun exposure and living at a lower latitude reducing risk of cancer mortality was buried in the





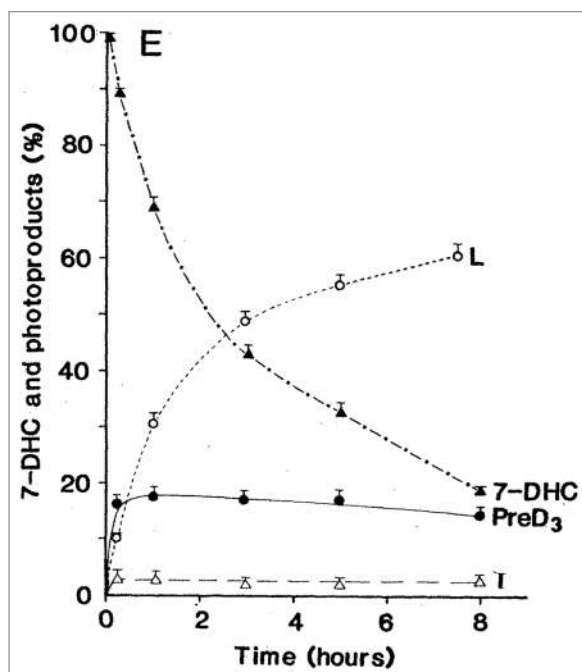
**Figure 17.** A schematic representation of the photochemical and thermal events that result in the synthesis of vitamin D<sub>3</sub> in the skin, and the photodegradation of previtamin D<sub>3</sub> and vitamin D<sub>3</sub> to biologically inert photoproducts. 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D<sub>3</sub> by the action of solar UV B radiation. Once formed, previtamin D<sub>3</sub> is transformed into vitamin D<sub>3</sub> by a heat-dependent ( $\Delta H$ ) process. Vitamin D<sub>3</sub> exits the skin into the dermal capillary blood system and is bound to a specific vitamin D-binding protein (DBP). When previtamin D<sub>3</sub> and vitamin D<sub>3</sub> are exposed to solar UV B radiation, they are converted to a variety of photoproducts that have little or no activity on calcium metabolism. Holick, copyright 1995. Reproduced with permission.

literature. Forty years would pass before Garland et al.<sup>77</sup> reported that there was a strong significant negative correlation with colon cancer mortality and mean daily solar radiation in the United States (Fig. 51).

They followed up these findings with an eight-year prospective case-control study of adults living in Washington County and reported that the risk of getting colon cancer decreased 3-fold in people with a serum 25(OH)D > 20 ng/ml. These results together suggested that living at higher latitudes meant less exposure to vitamin D producing sunlight and therefore the

connection with the association with latitude and cancer mortality could be linked to an inverse relationship with cancer mortality and vitamin D status.<sup>78</sup> Even in California where there is a large difference in latitude there was a positive association with colorectal cancer prevalence with latitude (Fig. 52).<sup>45</sup>

A multitude of epidemiologic studies followed these initial observations not only in the United States and Canada but worldwide. Grant<sup>79</sup> reported a dramatic inverse relationship between premature mortality due to cancer with UV exposure in both men and women (Fig. 53). In the United States, inverse



**Figure 18.** An analysis of the photolysis of 7-dehydrocholesterol (7-DHC) in the basal-cell layer and the appearance of the photoproducts previtamin D<sub>3</sub> (Pre-D<sub>3</sub>), lumisterol<sub>3</sub> (L), and tachysterol<sub>3</sub> (T) with increasing time of exposure to equatorial simulated solar UV radiation. Bars above data points show the standard error of the mean of three determinations. Holick, copyright 1981. Reproduced with permission.

associations with exposure to solar UVB radiation and cancer risk and mortality were reported for ovarian<sup>80</sup> and breast cancer,<sup>81</sup> cancers of the digestive system<sup>79,82</sup> and prostate cancer.<sup>83,84</sup> A meta-analysis of studies reporting cancer incidence rates for more than 100 countries including Australia, China, Japan, Spain among others revealed an inverse relationship with solar UVB exposure for 15 types of cancer including bladder, breast, cervical, colon, endometrial, esophageal, gastric, lung, ovarian, pancreatic, rectal, renal and vulvar cancer as well as Hodgkin's and non-Hodgkin's lymphoma.<sup>85</sup> Boscoe and Schymura<sup>86</sup> found that the relative risk of cancer incidence and mortality for numerous malignancies was strongly related to solar UVB exposure (Fig. 54). Giovannucci et al.<sup>87</sup> conducted a prospective study in men relating predictors of vitamin D status and cancer incidence and also found an inverse association (Fig. 55). Luscombe et al.<sup>88</sup> reported men who worked outdoors had a 3-y hiatus before developing prostate cancer compared with indoor workers (Fig. 56). It was also reported that adults who developed lymphoma had a decreased risk for mortality if they had more sun exposure as a teenager.<sup>89</sup> Knight et al.<sup>90</sup> asked women in Canada who had breast cancer how much sun exposure they had during their teenage and young adult life and compared this sun exposure to women matched for age, ethnicity and place of residence. She concluded that women who had the most sun exposure from ages 10 to 19 y reduced their risk of developing breast cancer by more than 60% when comparing the highest quartile of outdoor activities with the lowest. Also women over 40 y who had the most

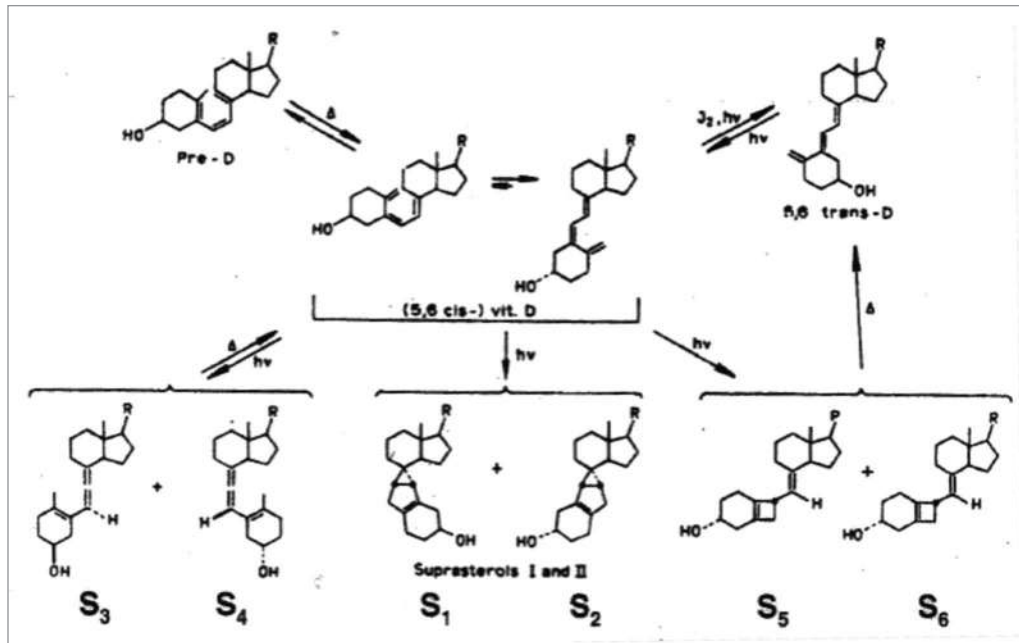
sun exposure lost the benefit since their risk was no different than those who had the least sun exposure.

The observational and epidemiologic studies relating increased latitude with increased risk for cancers suggest a possible role of sun induced vitamin D<sub>3</sub> synthesis as the beneficial factor responsible for these observations.<sup>87</sup> It is known that exposure to sunlight also has other physiologic effects on the skin including altering the immune system,<sup>91-93</sup> increasing production of  $\beta$  endorphin<sup>67</sup> and nitric oxide.<sup>94</sup> There are however a variety of studies including interventional studies and association studies supporting the notion that improvement in vitamin D status reduced risk of many deadly cancers.<sup>73,87,95-104</sup> Woo et al.<sup>105</sup> reported that more than 50% of men with completed local treatment of prostate cancer and rising PSA levels in the absence of symptoms had a decrease in their PSA serum levels when commencing the supplementation of 2000 IUs vitamin D<sub>3</sub> per day had a statistically significant decrease in the rate of PSA rise (Fig. 57).

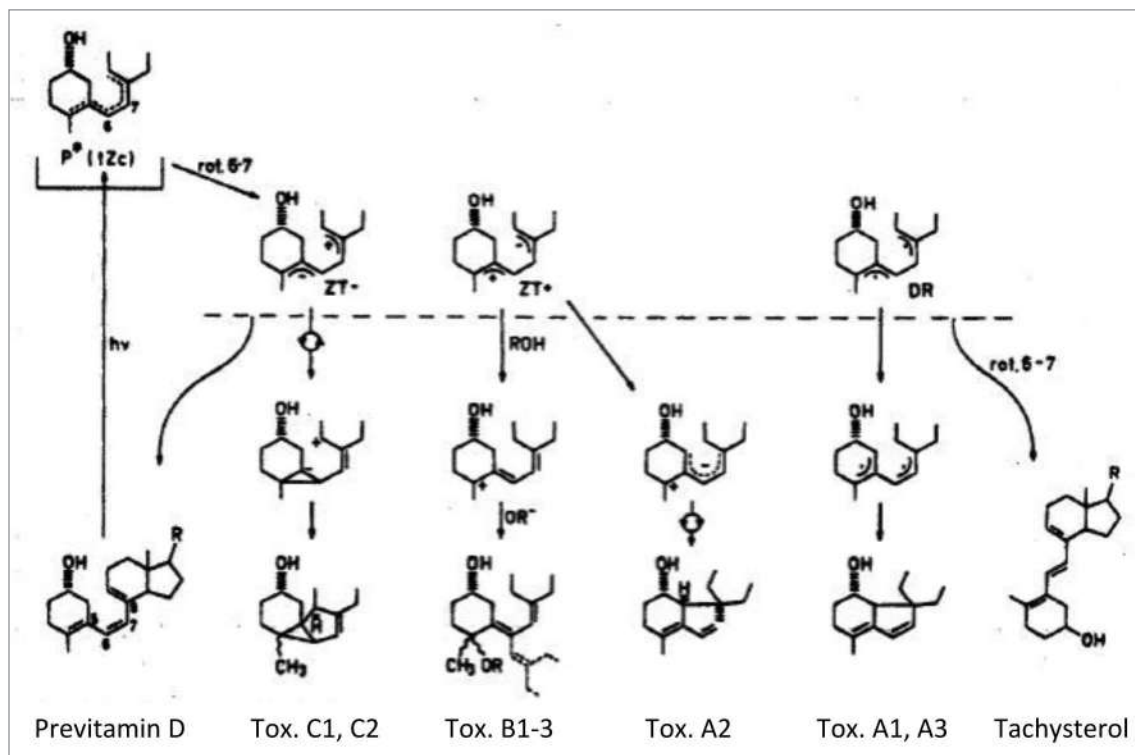
Lappe et al.<sup>101</sup> reported a more than 60% reduction in the development of all cancers in a small study of postmenopausal women who received calcium supplementation (1500 mg) along with 1100 IUs of vitamin D<sub>3</sub> daily compared with women who received placebo (Fig. 58). The Women's Health Initiative (WHI) initially reported that women who took 1000 mg of calcium and 400 IUs of vitamin D<sub>3</sub> daily for up to 8 y had no reduced risk for colorectal cancer.<sup>106</sup> However the women in this study who had a baseline 25(OH)D < 12 ng/mL had a 253% increased risk for developing colorectal cancer compared with women who had a baseline 25(OH)D of at least 23 ng/mL. Further scrutiny of the data from the WHI revealed that only 60% of the women admitted taking their calcium and vitamin D supplement at least 80% of the time. However those women not on personal calcium and or vitamin D supplementation but who took 400 IUs of vitamin D<sub>3</sub> daily along with calcium supplementation as part of the WHI study for 8 y had a 14–20% reduced risk for developing breast cancer and a 17% reduced risk for developing colorectal cancer.<sup>107</sup> The importance of vitamin D in reducing risk of colorectal cancer has also been supported by the observation that the vitamin D receptor polymorphisms were associated with colorectal cancer<sup>108</sup> and a quantitative meta-analysis on the optimal status for colorectal cancer prevention showed that a 25(OH)D level of 34 ng/ml was associated with a 50% reduced risk of developing colorectal cancer.<sup>109</sup> Another study showed that the 25(OH)D level and the risk for developing colorectal adenoma were inversely correlated and that the association was modified by the TaqI polymorphism of the VDR.<sup>110</sup> The United States Preventative Services Task Force evaluated vitamin D supplementation and risk for colorectal cancer and concluded that for every 4 ng/ml increase in circulating concentrations of 25(OH)D was associated with a 6% (95% CI 3–9%) reduced risk for colorectal cancer.<sup>111</sup>

### Sunlight and Vitamin D: Innate Immune Health

Cod liver oil was used in the mid-1800s to treat tuberculosis.<sup>73,112,113</sup> In the early 1900s heliotherapy was promoted for treating both



**Figure 19.** When vitamin D<sub>3</sub> is irradiated, it is converted to 5,6-trans-vitamin D<sub>3</sub> and at least 6 photoproducts known as suprasterols. Holick, copyright 2013. Reproduced with permission.

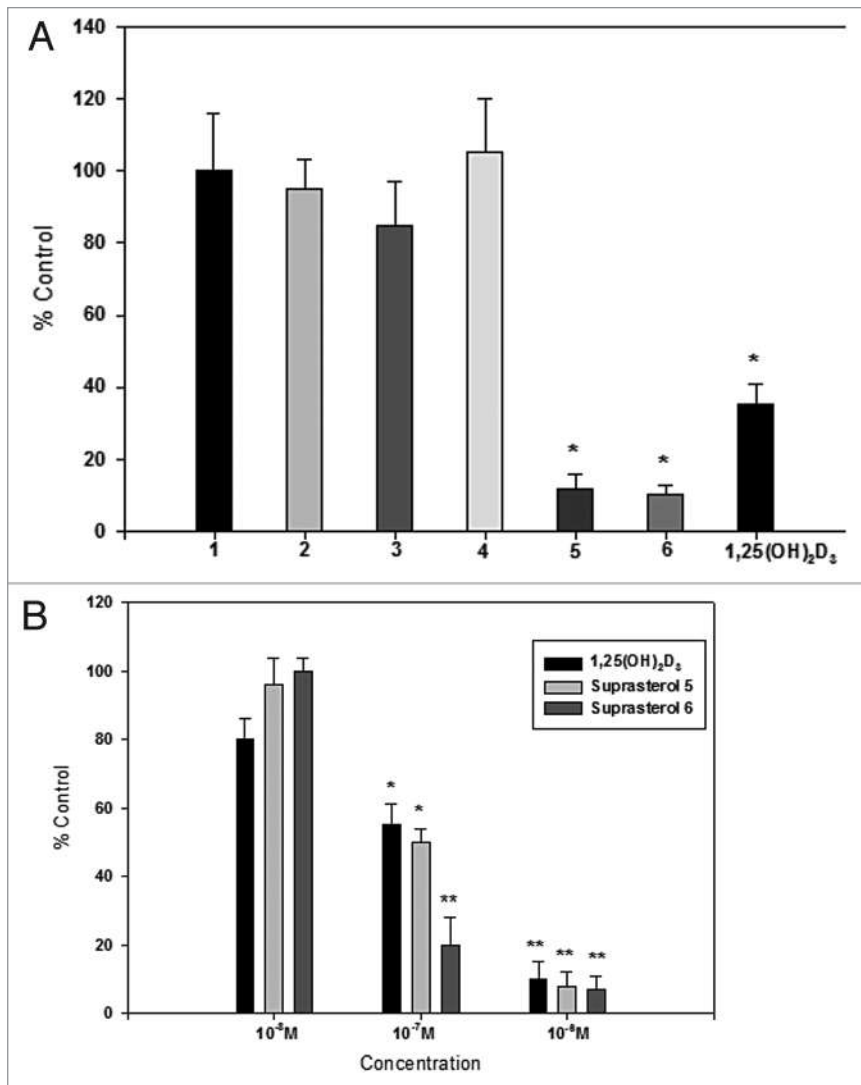


**Figure 20.** Once previtamin D<sub>3</sub> is formed, it has the ability to rotate around the 6-7 bond. Relaxation via rotation about the 6-7 bond followed by UV irradiation can give rise to a wide variety of toxisterols and tachysterol. Holick, copyright 2013. Reproduced with permission.

skin and pulmonary tuberculosis.<sup>69,114</sup> It was also recognized that young children with rickets had a much higher risk of developing pneumonia and upper respiratory tract infections and were more

likely to die of them.<sup>8,14,115,116</sup> Therefore sun exposure and vitamin D were used in the early 1900s to treat and prevent tuberculosis<sup>113,114,117</sup> and upper respiratory tract infections.<sup>72</sup>





**Figure 21. (A)** Proliferation of human keratinocytes after incubation with different suprasterols compared with negative control (100%). Suprasterols 5 and 6 show a strong antiproliferative activity as well as the positive control 1,25(OH)<sub>2</sub>D<sub>3</sub>. **(B)** Dose dependent antiproliferative activity of suprasterols 5 and 6 compared with 1,25(OH)<sub>2</sub>D<sub>3</sub> in keratinocytes. Mean ± SEM \*p < 0.01, \*\*p < 0.001 compared with control 100%. Holick, copyright 2013. Reproduced with permission.

Hope-Simpson<sup>118</sup> had speculated that there was a seasonal stimulus responsible for reducing infectious diseases during the summer. It is known for example that influenza infection is most prevalent in the winter months at latitudes North and South of the equator but is sporadic throughout the year in children and adults who live near the equator (Fig. 59). It has been hypothesized that the seasonal variation could be due to a seasonal variation in circulating levels of 25(OH)D.<sup>119</sup> Several observational and intervention studies have helped to support this hypothesis. Healthy adults living in New England who had 25(OH)D blood levels of ~38 ng/mL approximately halved their risk of developing acute viral respiratory tract infections.<sup>120</sup> School children in Japan who received 1200 IUs of vitamin D<sub>3</sub> daily for 4 mo during the winter reduced their risk of developing influenza infection

by 42%.<sup>121</sup> A study of 156 neonates revealed that the risk for acquiring respiratory syncytial virus (RSV), a pathogen causing severe lower respiratory tract infection, was 6-fold higher in infants who had a blood level of 25(OH)D < 20 ng/mL compared with infants who had a blood level of 25(OH)D > 30 ng/mL.<sup>122</sup>

Macrophages play an important role in fighting infectious diseases by ingesting and then destroying them.<sup>123</sup> When a macrophage ingests an infectious agent like tuberculosis toll-like receptors are activated to initiate an innate immune response.<sup>124</sup> One of the first responses is signal transduction to the nucleus to increase the expression of the VDR and the 25-hydroxyvitaminD-1-hydroxylase (CYP27B1). This results in the conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D. 1,25(OH)<sub>2</sub>D interacts with the VDR and increases the expression of cathelicidin<sup>125</sup> which is a member of the defensin proteins and rapidly permeabilizes susceptible infectious agents resulting in their destruction (Fig. 60). This is one of the mechanisms believed to be responsible for vitamin D reducing risk of infectious diseases. Liu et al.<sup>125</sup> also reported that the extent of antimicrobial activity of a monocyte exposed to *Mycobacterium tuberculosis* depended on the 25(OH)D levels of the medium in which the monocytes were cultured. Monocytes cultured in serum of African-American individuals who were vitamin D deficient (mean ~8 ng/mL) mounted an ineffective cathelicidin mRNA response upon exposure to *M. tuberculosis*, however the supplementation of the sera with 25(OH)D (mean ~30 ng/mL) restored the toll-like receptor mediated induction of cathelicidin mRNA. This was substantiated by Adams et al.<sup>126</sup> who not only showed, that the expression of cathelicidin by monocytes exposed to *M. tuberculosis* lipopeptides was significantly enhanced by addition

of exogenous 25(OH)D to the vitamin D deficient serum but that serum from vitamin D-supplemented subjects had the same effect. This data added support for the importance of maintaining a serum 25(OH)D > 30 ng/mL to generate an effective cathelicidin response following activation of monocytes/macrophages.

It has also been suggested based on studies in mice and in vitro that the local keratinocyte production of 1,25(OH)<sub>2</sub>D<sub>3</sub> from 25(OH)D<sub>3</sub> in the skin and oral pharynx enhanced the production of cathelicidin supporting the concept that maintaining serum 25(OH)D above 30 ng/ml may also be important in fighting infections in both the skin and oropharynx.<sup>127-130</sup> This may also help explain the observation that the risk for periodontal disease is higher in adults who have the lowest circulating concentrations of 25(OH)D.<sup>131</sup> Calcium and vitamin D supplementation

was associated with a lower risk of tooth loss in elderly men and women<sup>1</sup> respectively and with better periodontal health.<sup>132,133</sup>

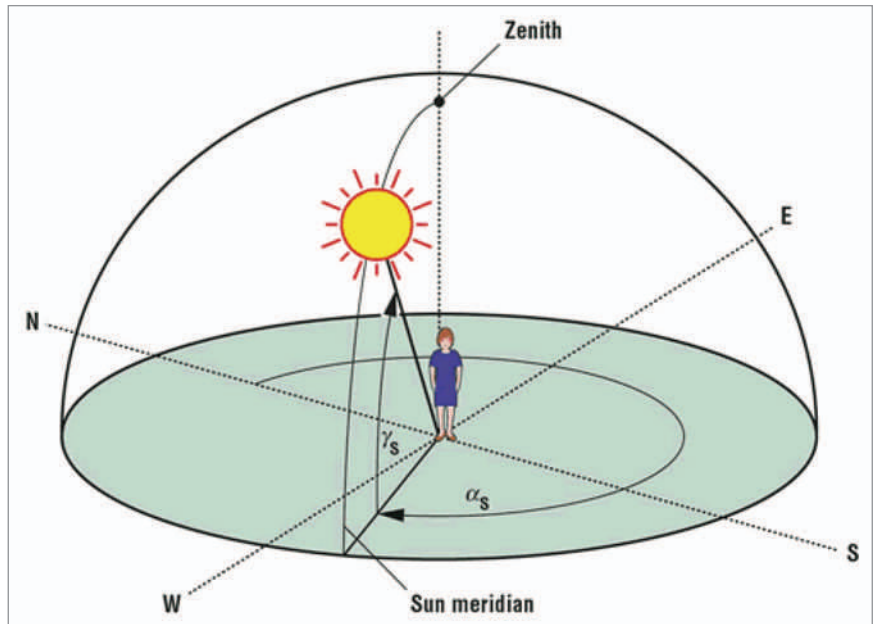
### Sunlight and Vitamin D: Autoimmunity Protection

There are a variety of association studies demonstrating that being born or living near the equator reduces risk of several autoimmune diseases.<sup>73,134-139</sup> Being born and living for the first 10 y at a latitude of  $\sim 40^\circ$  North compared with  $\sim 33^\circ$  North increases a person's risk of developing multiple sclerosis by 100% (Fig. 61).<sup>134,140,141</sup> Munger et al.<sup>142</sup> made the observation that high circulating levels of 25(OH)D were associated with a lower risk of multiple sclerosis and that women who had an intake of vitamin D of  $\geq 400$  IU vitamin D per day reduced their risk of developing multiple sclerosis by more than 40%.<sup>143</sup>

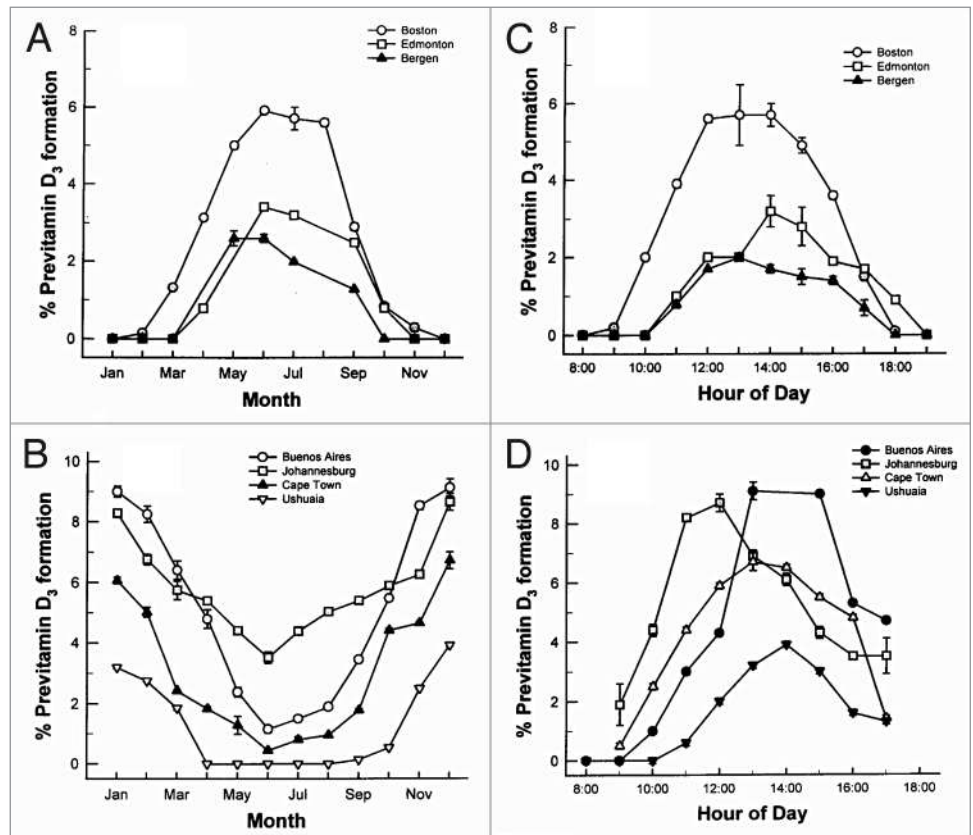
A plot of the incidence of type 1 diabetes vs. latitude demonstrated an impressive U-shaped curve. Children younger than 14 y during 1990–1994 in 51 regions worldwide demonstrated a 10–15 fold increase in risk for developing type 1 diabetes if they were born in far Northern and Southern latitudes (Fig. 62).<sup>144</sup>

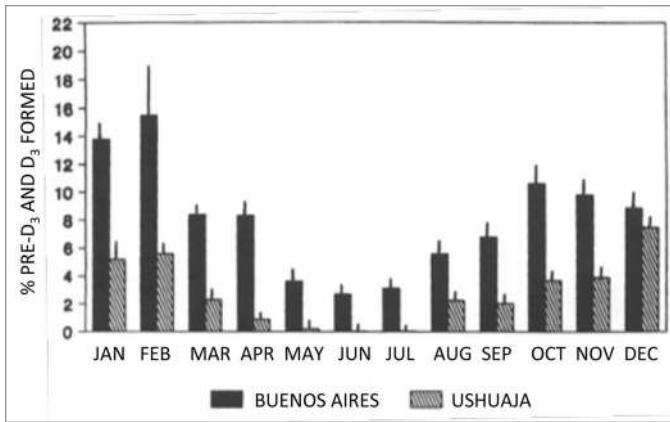
It was also reported that spring births were associated with increased likelihood of developing type 1 diabetes. These findings indicate a potential role of vitamin D in the pathogenesis of type 1 diabetes mellitus. This hypothesis is supported by an observational study that children in Finland who received 2000 IUs of vitamin D daily during their first year of life in the 1960s reduced their risk of developing type 1 diabetes 31 y later by 88%.<sup>145</sup> Because of concern about vitamin D toxicity the amount of vitamin D recommended for infants in Finland was reduced first to 1000 IUs daily and then to 400 IUs daily. Interestingly as a result of this decrease in vitamin D intake

**Figure 23.** Influence of season, time of day, and latitude on the synthesis of previtamin D<sub>3</sub> in Northern (A and C) and Southern hemispheres (B and D). The hour indicated in C and D is the end of the 1 h exposure time. Holick, copyright 1998. Reproduced with permission.

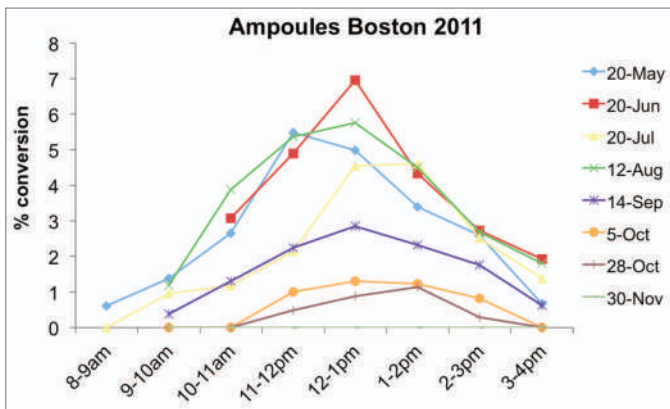


**Figure 22.** The solar zenith angle is the angle made by the sun's light with respect to the vertical (the sun being directly overhead). This angle is increased at higher latitudes, early morning and late afternoon when the sun is not directly overhead, and during the winter months. As the solar zenith angle increases, the amount of UVB radiation reaching the earth's surface is reduced. Therefore, at higher latitudes, greater distance from the equator, more of the UVB radiation is absorbed by the ozone layer thereby reducing or eliminating the cutaneous production of vitamin D<sub>3</sub>. Holick, copyright 2006. Reproduced with permission.

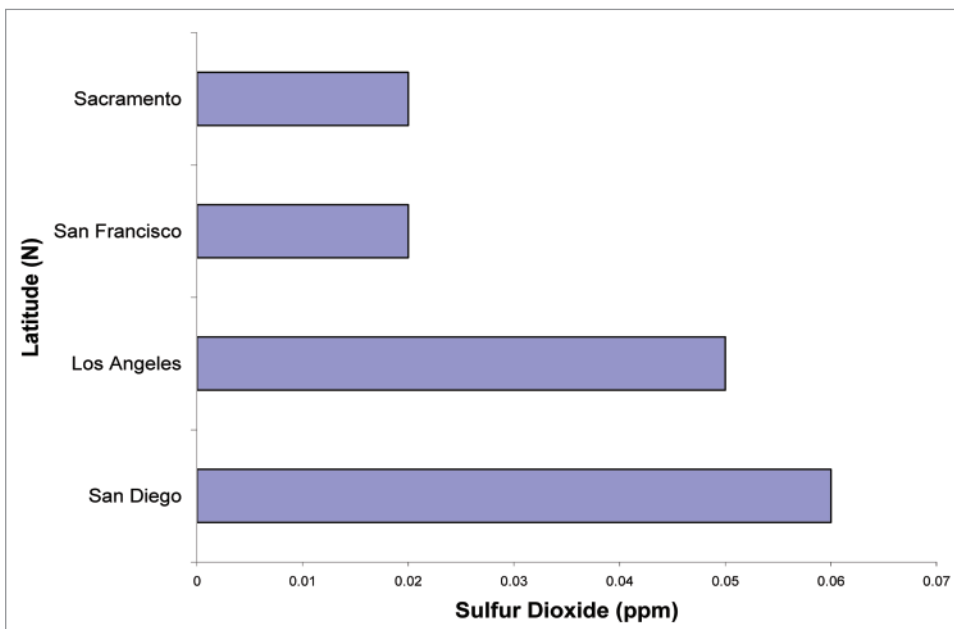




**Figure 24.** Photoproduction of previtamin D<sub>3</sub> and vitamin D<sub>3</sub> from 7-DHC throughout the year in Ushuaia, Argentina (slashed bars, 55 degrees South) and Buenos Aires (closed bars, 34 degrees South). Values are percentages of initial 7-DHC. Each bar represents the mean ± SEM of three determinations of the sample ampoules. Reproduced with permission from Ladizesky.<sup>41</sup>



**Figure 25.** Conversion rate of 7-dehydrocholesterol (7-DHC) to vitamin D depending on time of the day and season in Boston (42° North). The measurements were conducted after exposing ampoules filled with 7-DHC to sunlight. Holick, copyright 2013, reproduced with permission.



**Figure 26.** The amount of sulfur dioxide (ppm) measured over a one hour period in San Diego, Los Angeles, San Francisco, and Sacramento on the same day. Holick copyright 2005. Reproduced with permission.

there is an impressive increase in the incidence of type 1 diabetes occurring in Finland over the past 3 decades (Fig. 63).<sup>145</sup>

A pronounced North-South gradient has also been reported for inflammatory bowel disease, in particular Crohn's disease (Fig. 64).<sup>138</sup> A complete data set including demographic data and lifestyle factors based on the two prospective Nurses' Health Studies (NHSs) and comprising almost 240,000 nurses, also showed that women from lower latitudes had a consistently lower risk of developing ulcerative colitis and Crohn's disease compared with women living in higher latitudes.<sup>139</sup> These observations were supported by a prospective cohort study of 72,719 women enrolled in the Nurses' Health Study showing that a higher predicted vitamin D status was associated with a reduced risk of Crohn's disease.<sup>146</sup>

A case-control study investigating the association between latitude and rheumatoid arthritis using data from the Nurses' Health Study suggested that women living in higher latitudes were at greater risk for rheumatoid arthritis (Fig. 65).<sup>147</sup> These latitude-dependent differences in the prevalence of rheumatoid arthritis could be explained by differences in the vitamin D status. Merlino et al.<sup>148</sup> showed in a study in Iowa that women with the highest intake of vitamin D reduced their risk of developing rheumatoid arthritis by more than 30%.<sup>73</sup> However, other investigators did not find such an association when reviewing the data from this study.<sup>149</sup>

Although the exact mechanisms by which vitamin D may reduce risk for autoimmune diseases are not fully understood we do know that vitamin D plays an important role in cellular immunity.<sup>135</sup> Inactivated T- and B-lymphocytes are unable to respond to 1,25(OH)<sub>2</sub>D because they lack a VDR. However when they become activated they express a VDR and are now responsive to the immunomodulatory activity of 1,25(OH)<sub>2</sub>D (Fig. 60).<sup>22,63,150</sup>

In B-cells 1,25(OH)<sub>2</sub>D down-regulates immunoglobulin synthesis<sup>151</sup> and B-cell memory. Thus by doing so it may reduce production of autoantibodies responsible for causing autoimmune diseases.<sup>152</sup> 1,25(OH)<sub>2</sub>D also has a multitude of functions in activated T cells.<sup>153-158</sup> This hormone decreases T cell proliferation<sup>154</sup> as well as the number of Th<sub>1</sub>-Th<sub>17</sub> lymphocytes while

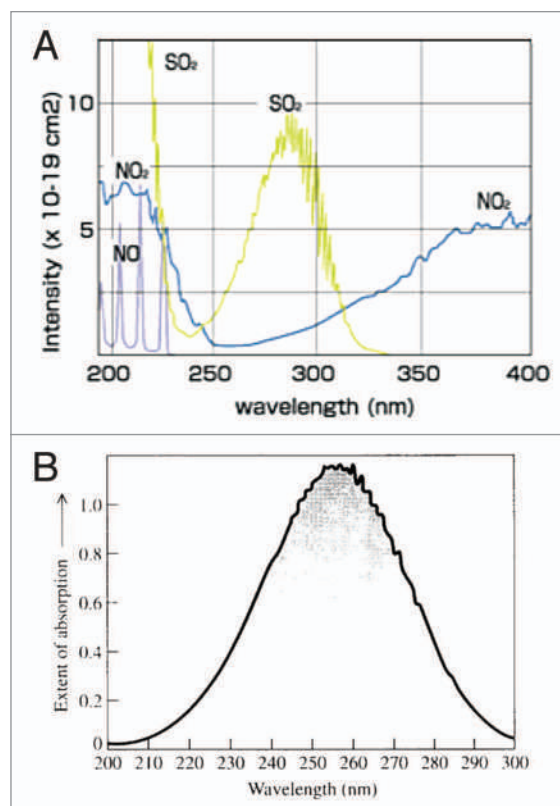


increasing T-regulatory lymphocytes<sup>155</sup> by increasing the production of Th<sub>2</sub>-Th<sub>3</sub> lymphocytes.<sup>156</sup> 1,25(OH)<sub>2</sub>D also directly influences the expression and synthesis of several immunomodulatory cytokines. Bouillon et al.<sup>151</sup> summarized that 1,25(OH)<sub>2</sub>D downregulates pro-inflammatory cytokines and interleukins (IL) such as IL-2, IL-4, IL-8, IL-12, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$  and upregulates anti-inflammatory interleukins such as IL-10.

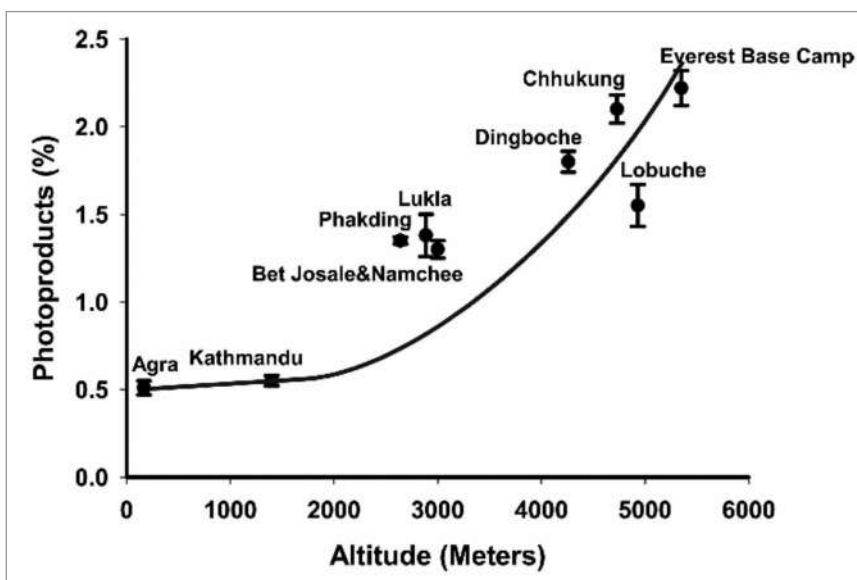
### Sunlight and Vitamin D: Cardiovascular Health

In 1997 Rostand et al.<sup>159</sup> reported that there was an inverse association with latitude and blood pressure (Fig. 66) and the prevalence of hypertension. This was followed by the observation of Krause et al.<sup>160</sup> who reported that exposure to UVB radiation in a clinical setting not only improved circulating concentrations of 25(OH)D by more than 160% but also significantly reduced both systolic and diastolic blood pressure in patients with hypertension. A control group was exposed to the same UV lamps that were covered by an acrylic shield absorbing all UVB radiation and thus was exposed to UVA radiation only. The control group's subjects demonstrated no significant change in their circulating concentrations of 25(OH)D as well as no change in their hypertension (Fig. 67). These data suggested that vitamin D may somehow be involved in cardiovascular health. One of the first insights as to how vitamin D could influence cardiovascular health was the observation that 1,25(OH)<sub>2</sub>D<sub>3</sub> suppressed the production of renin.<sup>161</sup> This observation was also supported by the report that VDR knockout mice have a dysregulation of the renin-angiotensin-aldosterone axis.<sup>162</sup>

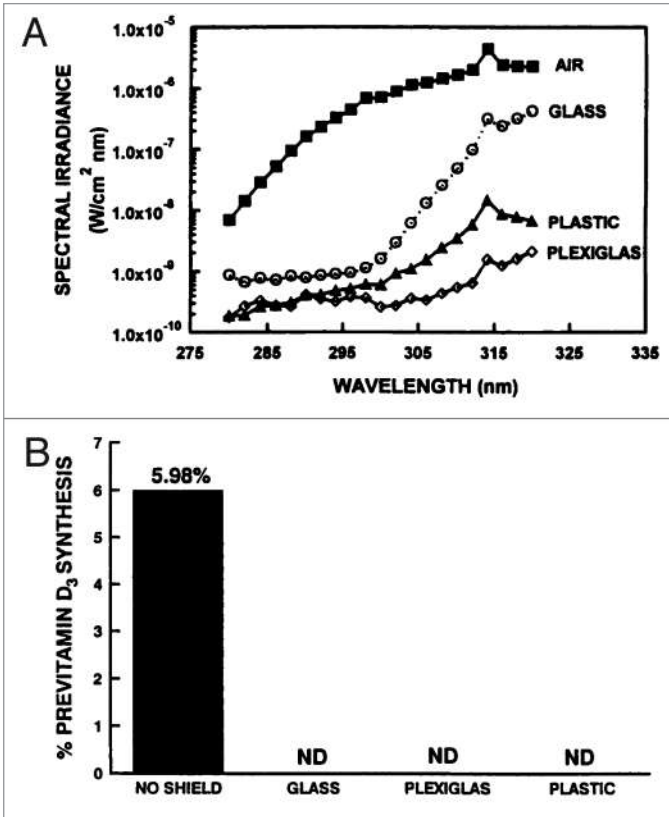
There have been a multitude of association studies suggesting that vitamin D deficiency not only increases risk for a myocardial infarction by as much as 50% but also was associated with more than one 100% increased risk of mortality from the heart attack.<sup>73,106,163-168</sup> In the US an estimated 50 million teenagers are vitamin D deficient or insufficient and this was associated with a 2.4 fold increased risk for high blood pressure.<sup>167,169</sup> Dong et al.<sup>168</sup> conducted a 16-week randomized, blinded, clinical trial in 49 normotensive black boys and girls aged  $16.3 \pm 1.4$  y to evaluate the effect of enhancing vitamin D intake from 400 IUs or 2000 IU vitamin D<sub>3</sub> daily on arterial wall stiffness, determined by measuring carotid-femoral pulse wave velocity. The teenagers who received 400 IUs of vitamin D daily increased their circulating concentrations of 25(OH)D from 14 to 24 ng/mL and had an increase in the carotid-femoral pulse wave velocity ( $5.38 \pm 0.53$  m/sec to  $5.71 \pm 0.75$  m/sec;  $p = 0.016$ ). By contrast teenagers who received 2000 IUs of vitamin D daily for 4 mo not only increased their blood level of 25(OH)D from 13 to 34 ng/mL but also showed a significant decrease



**Figure 27.** (A) Absorption spectra for NO, NO<sub>2</sub>, and SO<sub>2</sub>. The absorption spectra show that SO<sub>2</sub> and NO<sub>2</sub> absorb UVB radiation (280–315 nm) required for cutaneous production of vitamin D. (B) Absorption spectrum of ozone which also absorbs UVB radiation. Holick copyright 2005. Reproduced with permission.



**Figure 28.** Ampoules containing 7-dehydrocholesterol in ethanol were exposed for 1 h between 11:30 a.m. and 12:30 p.m. at 27° North in India at various altitudes. The conversion of 7-dehydrocholesterol to previtamin D<sub>3</sub> and its photoproducts was determined by HPLC. Reproduced with permission from ref. 46.



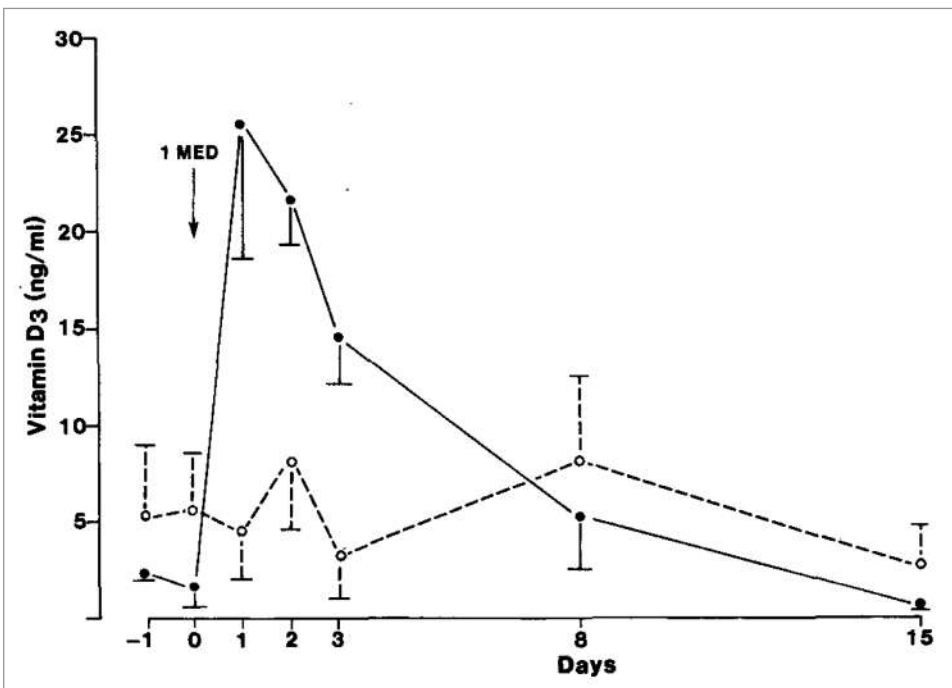
**Figure 29.** (A) Transmission of UV radiation through air, glass, plastic, and Plexiglas (Dupont Chemical Company, Memphis TN). Holick, copyright 2003. (B) Prevention of previtamin D<sub>3</sub> formation as a result of glass, plastic, or plexiglass (Dupont Chemical Company, Memphis, TN) placed between the simulated-sunlight source and the provitamin D<sub>3</sub> (7-DHC). Reproduced with permission from ref. 31.

in carotid-femoral pulse wave velocity ( $5.41 \pm 0.73$  m/sec to  $5.33 \pm 0.79$  m/sec;  $p = 0.031$ ).

Two major contributing factors for cardiovascular disease are type 2 diabetes and obesity.<sup>170</sup> It is well known both in children and adults that there is an inverse association between serum concentrations of 25(OH)D and body mass index (BMI) due to a sequestration and volumetric dilution of the lipophilic vitamin D in the fat tissue.<sup>73,171-174</sup> Furthermore there is also an association with vitamin D deficiency and increased risk for type 2 diabetes.<sup>175,176</sup> A similar observation was made in the Nurses' Health Study where a combined daily intake of > 1200 mg calcium and > 800 IU vitamin D was associated with a 33% lower risk of type 2 diabetes.<sup>177</sup> An inverse association between vitamin D status and diabetes was also shown in a study by Scragg et al.<sup>178</sup> The odds ratio for diabetes in non-Hispanic whites and Mexican Americans who had 25(OH)D levels in the highest quartile compared with the lowest was reduced by up to 83%.<sup>178</sup> However, this inverse association was not observed in non-Hispanic blacks.<sup>178</sup>

Several epidemiologic studies and prospective studies have reported a highly significant association with vitamin D deficiency with not only type 2 diabetes but also hypertension, hyperlipidemia and peripheral vascular disease

all causative factors for coronary artery disease, myocardial infarction, heart failure and stroke.<sup>166,175,179</sup> The prospective Intermountain Heart Collaborative Study revealed that in more than 40,000 participants a circulating concentration of 25(OH)D < 15 ng/mL compared with a concentration of > 30 ng/mL significantly increased all of these risk factors.<sup>175</sup> A meta-analysis examining the association between vitamin D status or vitamin D supplementation revealed that adults with the highest circulating concentration of 25(OH)D had a 43% lower risk of developing cardiometabolic disorders compared with adults with low levels of 25(OH)D.<sup>180</sup> Furthermore a prospective study following up with more than 2000 adults showed that the risk of progression from pretype 2 diabetes to type 2 diabetes was reduced by 48% in adults who had the highest circulating concentrations of 25(OH)D compared with those with the lowest.<sup>181</sup>



**Figure 30.** Mean ( $\pm$  SEM) serum vitamin D<sub>3</sub> concentrations in eight normal subjects. Four subjects (○) applied PABA (para-aminobenzoic acid) with a SPF of 8 and four applied vehicle (●) to the entire skin before exposure to UVB. On day 0, all subjects underwent total body exposure to 1 MED (minimal erythema dose) UVR (UV radiation). To convert nanograms of vitamin D per mL to nanomoles per L, multiply by 2.599. Reproduced with permission from ref. 47.

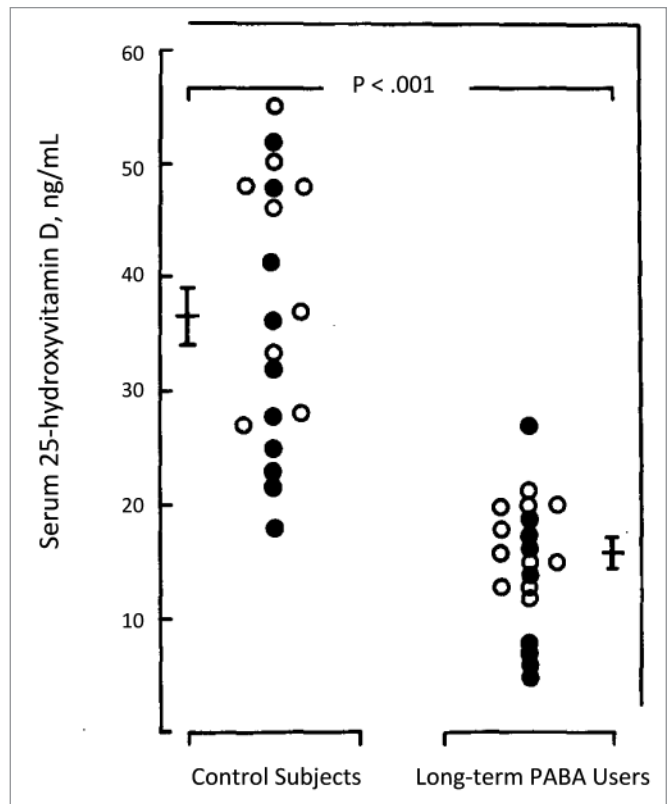
Beta islet cells in the pancreas have a VDR and  $1,25(\text{OH})_2\text{D}_3$  is a potent stimulator of insulin production.<sup>182</sup> Improvement in vitamin D status has also been associated with improvement in insulin sensitivity<sup>183</sup> mediated by upregulation of insulin receptors.<sup>184</sup> There is evidence that vascular smooth muscle and cardiomyocytes have a VDR<sup>73,166,171</sup> and that  $1,25(\text{OH})_2\text{D}_3$  causes vascular relaxation by suppressing the renin-angiotensin-aldosterone system<sup>73,163,185,186</sup> and improves cardiomyocyte contractility.<sup>171</sup> In addition  $1,25(\text{OH})_2\text{D}_3$  inhibits macrophage cholesterol uptake and foam cell formation thereby reducing risk for atherosclerotic plaque formation (Fig. 68).<sup>73,166,187</sup> Vitamin D deficiency negatively affects numerous physiological processes that are important in the pathogenesis of cardiovascular disease. This could explain why vitamin D deficiency is associated with an increased overall and cardiovascular mortality in patients with metabolic syndrome.<sup>188</sup>

### Sunlight, Vitamin D and Mental Health

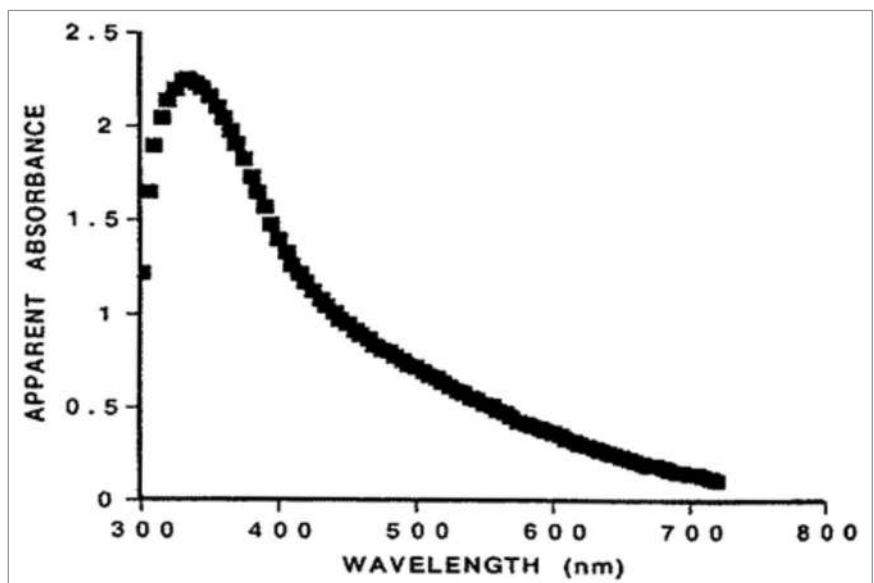
Schizophrenia has been associated with inadequate sun exposure and vitamin D deficiency (Fig. 69).<sup>189</sup> Schizophrenia is more common in the Scandinavian countries.<sup>189,190</sup> Winter births have been associated with an increased risk for developing schizophrenia later in life even in Australia.<sup>191,192</sup> In British immigrants, incidence in schizophrenia is higher in children of immigrants from the Caribbean who moved to cities in countries farther North.<sup>193</sup> Finnish male infants who received 2000 IUs of vitamin D daily during their first year of life reduced their risk of developing schizophrenia by 77% compared with infants who received less than 2000 IUs of vitamin D daily.<sup>194</sup>

Vitamin D could play an indirect role in the pathogenesis of schizophrenia. Several studies suggest that a prenatal influenza exposure increases the risk for schizophrenia later in life.<sup>195-197</sup> The vitamin D status seems to influence the risk for an influenza infection respectively vitamin D supplementation has proven to decrease the risk for influenza infection.<sup>2-4,118,119,121</sup>

There are a variety of association studies relating vitamin D deficiency with increased risk for depression,<sup>198,199</sup> Alzheimer disease,<sup>200</sup> epilepsy,<sup>201</sup> and neurocognitive decline.<sup>202,203</sup> The brain not only has a VDR but also a 1-OHase.<sup>204</sup> Evidence suggests that  $1,25(\text{OH})_2\text{D}_3$  could increase calcium binding protein expression,<sup>205</sup> although this could not be shown in all studies.<sup>206</sup>  $1,25(\text{OH})_2\text{D}_3$  could also act by increasing serotonin levels in the brain.<sup>207,208</sup> Furthermore  $1,25(\text{OH})_2\text{D}_3$  has also been demonstrated to stimulate amyloid- $\beta$  phagocytosis and clearance by macrophages in Alzheimer patients.<sup>209</sup> This may help explain the association between neurocognitive decline,<sup>202,203</sup> dementia,<sup>210</sup> depression,<sup>198,199</sup> and Alzheimer disease<sup>200</sup> with a high prevalence of vitamin D deficiency.<sup>211</sup> In a community setting depressed adults had

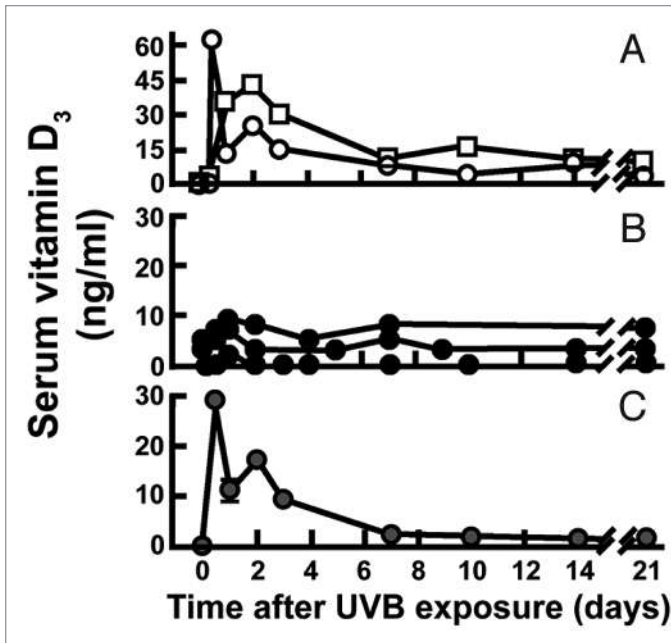


**Figure 31.** Serum concentration of 25-hydroxyvitamin D in longterm sunscreen users and in age- and sex-matched controls from same geographical area. Blood samples were obtained simultaneously from patients and controls. Mean serum 25-hydroxyvitamin D level was significantly lower in long-term sunscreen users ( $p < 0.001$ ). Two long-term sunscreen users had absolute vitamin D deficiency, 25-hydroxyvitamin D level below 20 nmol/L. PABA indicates p-aminobenzoic acid; open circles, subjects from Philadelphia; closed circles, subjects from Springfield, Ill. Reproduced with permission from ref. 48.



**Figure 32.** Absorption spectrum of melanin. Holick copyright 2005. Reproduced with permission.





**Figure 33.** In two lightly pigmented Caucasian (A) and three heavily pigmented Afroamerican subjects (B) after total body exposure to 0.054 J/cm<sup>2</sup> of UVR. (C) Serial change in circulating vitamin D after re-exposure of an Afroamerican subject (● in panel B) to a 0.32 J/cm<sup>2</sup> dose of UVR. Reproduced with permission from ref. 50.

significantly lower serum concentrations of 25(OH)D than those without depression.<sup>212</sup>

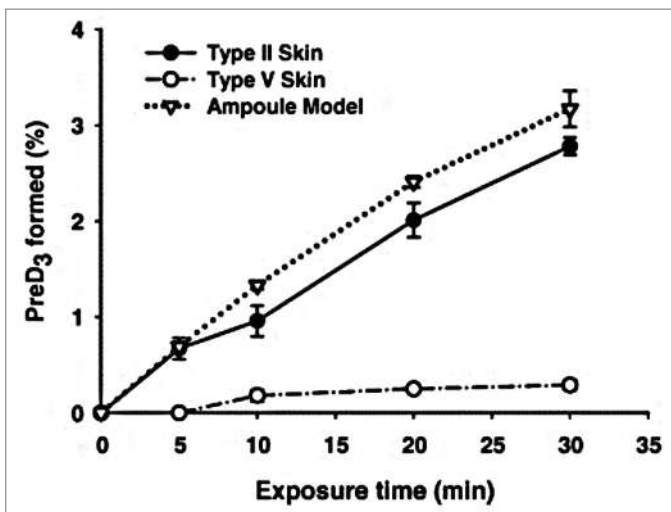
### Approaches for Preventing and Treating Vitamin D Deficiency

The Institute of Medicine using a population model defined vitamin D deficiency for bone health as a circulating concentration of 25(OH)D < 20 ng/mL. They recommended that to satisfy 97.5% of the United States population's needs for vitamin D that children 0–1 y, and adults 1–70 y and 70+ years require 400, 600 and 800 IUs of vitamin D daily respectively (Fig. 70).<sup>213</sup> The Endocrine Society used a medical model to make recommendations for the prevention and treatment of vitamin D deficiency [25(OH)D < 20 ng/mL] and vitamin D insufficiency [25(OH)D of 21–29 ng/mL] and concluded that a range rather than an absolute amount of vitamin D could be recommended for children 0–1 y, children 1–18 y and all adults of 400–1000 IUs, 600–1000 IUs and 1500–2000 IUs of vitamin D daily respectively (Fig. 70).<sup>24</sup>

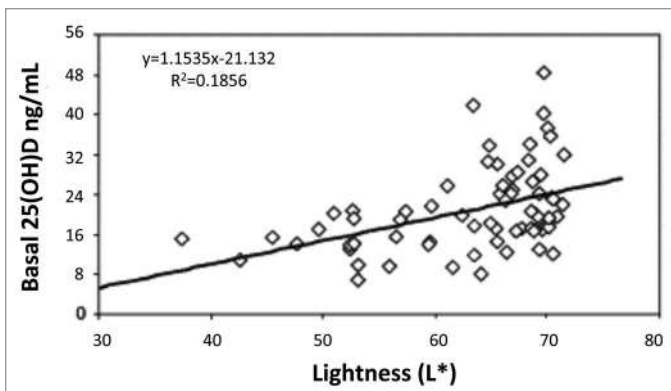
Both the IOM<sup>213</sup> and The Endocrine Society<sup>24</sup> concluded that a circulating concentration of 25(OH)D up to 100 ng/mL was safe. They also found that most but not all of the literature supports the concept that vitamin D<sub>2</sub> is as effective as vitamin D<sub>3</sub> in maintaining circulating concentrations of 25(OH)D.<sup>24,73,213–221</sup>

For almost 100 y a variety of strategies have been used to treat and prevent vitamin D deficiency especially in children.<sup>5,68,73,114</sup> From 1930 through 1950s parents purchased a lamp at their local pharmacy that emitted vitamin D<sub>3</sub> producing UVB radiation (Fig. 71).<sup>70,222,223</sup> Children wearing eye protection had their arms, abdomen and legs were routinely exposed to a UV emitting lamp several times a week (Fig. 6).<sup>12,13</sup> In Russia children in school in wintertime were routinely exposed to a mercury arc lamp placed in the center of the school room that emitted UVB radiation to prevent vitamin D deficiency rickets (Fig. 72).<sup>224</sup>

The Sperti lamp which originally was designed with a single mercury arc lamp<sup>225,226</sup> was commonly used in the United States in the 1940s and 1950s to prevent rickets and children (Fig. 71).<sup>8,70,114</sup> This lamp was also effective in improving the circulating concentrations of 25(OH)D in individuals who had cystic fibrosis and who were unable to absorb vitamin D from dietary and supplemental sources (Fig. 73A and B).<sup>227,228</sup> Because the lamp produced a lot of heat the Sperti lamp was redesigned and the mercury arc lamp was replaced with 4 fluorescent lamps (Fig. 74) that emitted UVB radiation and produced previtamin D<sub>3</sub> (Fig. 75).<sup>229</sup> This lamp was effective in raising circulating



**Figure 34.** The conversion of 7-dehydrocholesterol to previtamin D<sub>3</sub> in an ampoule model, Type II and Type V skin after exposing to noon sunlight in June at Boston (42°N), Massachusetts. The data represent the means ± SEM of duplicate determinations. Reproduced with permission from ref. 51.

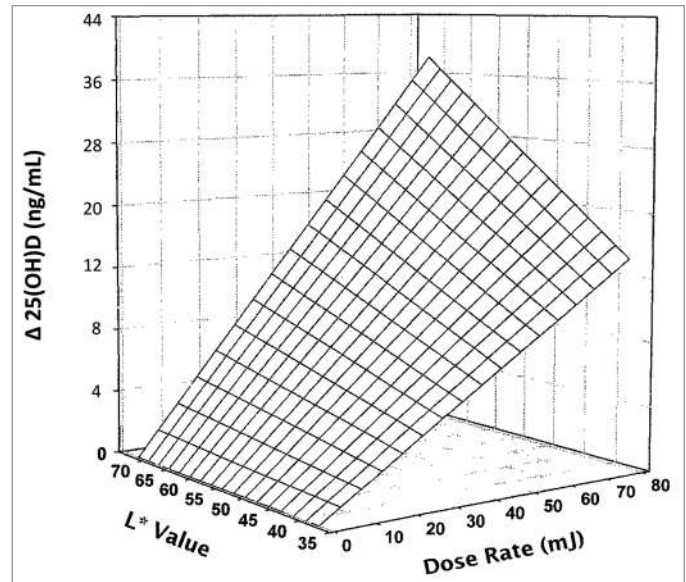


**Figure 35.** Scatter plot of baseline serum 25-hydroxyvitamin D (25-OH-D) on skin lightness (L\*) score for unexposed skin, showing significant positive correlation of serum 25-OH-D and L\* (r<sup>2</sup> = 0.1856). Heaney, copyright 2006. Reproduced with permission.

concentrations of 25(OH)D in healthy adults with skin types 2 and 3 (Fig. 76).<sup>227,228</sup>

Tanning beds which emit UVB radiation (estimated about 95% of tanning beds in the United States) can be a good source of vitamin D especially for patients with malabsorption syndromes.<sup>227,228</sup> A patient with Crohn's disease and only 2 feet of her small intestine remaining had severe debilitating osteomalacic bone discomfort. Supplementing 400 IU dietary vitamin D from a multivitamin and 200 IU vitamin D from total parenteral nutrition couldn't correct her severe vitamin D deficiency. Exposure to a tanning bed emitting UVB radiation was effective in improving her circulating concentration of 25(OH)D and as a result markedly improved her bone discomfort (Fig. 77).<sup>230</sup> Tanners in Boston who frequented a tanning salon at least once a week had robust healthy circulating concentrations of 25(OH)D on average 46 ng/mL compared with age and sex matched controls whose blood level on average was 24 ng/mL (Fig. 78). Furthermore an evaluation of their bone mineral density revealed that the tanners had a significantly higher bone mineral density in their hip compared with the control group.<sup>231</sup>

Sensible sun exposure can also be an excellent source of vitamin D for both children and adults.<sup>232,233</sup> Sensible means never to be exposed to an amount of sunlight that would cause a sunburn since this is the major cause for both melanoma and non-melanoma skin cancer.<sup>234-237</sup> Studies conducted worldwide using the in vitro ampule model<sup>39</sup> and measuring 25(OH)D levels after quantitative UVB exposure in a tanning bed have been used to develop guidelines for sensible sun exposure based on latitude, season, time of day, altitude, and skin sensitivity, i.e., degree of skin pigmentation.<sup>22,46,51,66,231-233,237-239</sup> The rule of thumb is to be exposed to an amount of sunlight that is about 50% of what it would take to cause a mild sunburn i.e., slight pinkness to the skin 24 h later (minimal erythema dose) followed by good sun protection i.e., clothing, hat and or sunscreen.<sup>22,239</sup> The "rule of nines" helps to estimate the percentage of skin exposed to sunlight or UVB radiation and can be used to calculate the amount of vitamin D<sub>3</sub> being produced. The face accounts for 9% of the body surface, each arm for 9%, each leg for 18%, and the abdomen and the back for 18% each.<sup>240</sup> Exposure of the whole body in a bathing suit to 0.5 MED of UVB radiation is approximately equivalent to ingesting about 7000–10,000 IUs of vitamin D<sub>2</sub>.<sup>22,25,31</sup> Therefore exposing 20% of the body surface to an amount of sunlight equal to 0.5 MED is equivalent to ingesting approximately 1400–2000 IUs of vitamin D<sub>3</sub>. This is effective for all skin types and the increase in serum 25(OH)D attained from exposure to UVB radiation is often more effective



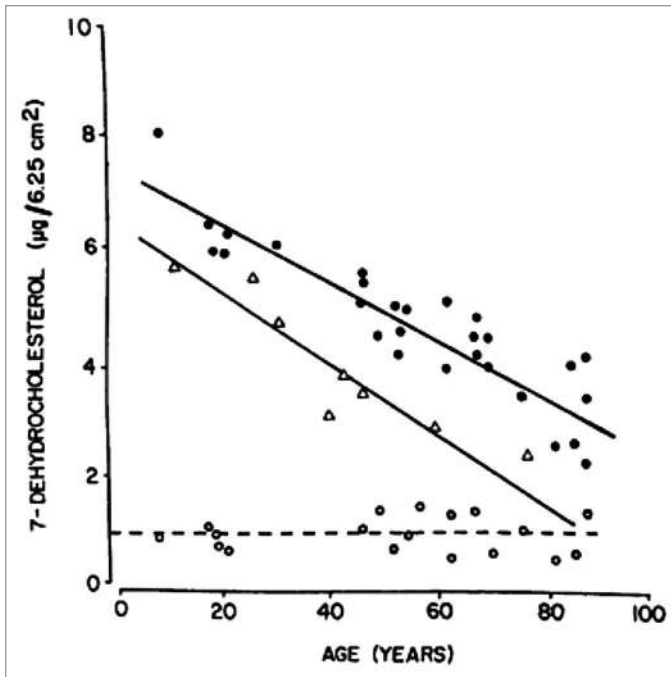
**Figure 36.** Three-dimensional scatter plot of 4-week serum 25-hydroxyvitamin D response change above baseline expressed as function both of basic skin lightness (L\*) and UV-B dose rate. Surface is a hyperboloid, plotting equation and was fitted to data by least squares regression methods. Heaney, copyright 2006. Reproduced with permission.

than ingesting 1000 IU vitamin D<sub>2</sub> or vitamin D<sub>3</sub> daily (Fig. 79).<sup>241</sup> Always protect the face with a hat or sunscreen since it provides very little vitamin D<sub>3</sub> and is most sun exposed and more prone to skin damage and skin cancer from sun exposure.<sup>242-244</sup>

Because foods contain very little vitamin D it is difficult to obtain enough vitamin D from dietary sources even when consuming foods fortified with vitamin D.<sup>22,51,246</sup> The exception is indigenous populations including Inuits who consumed

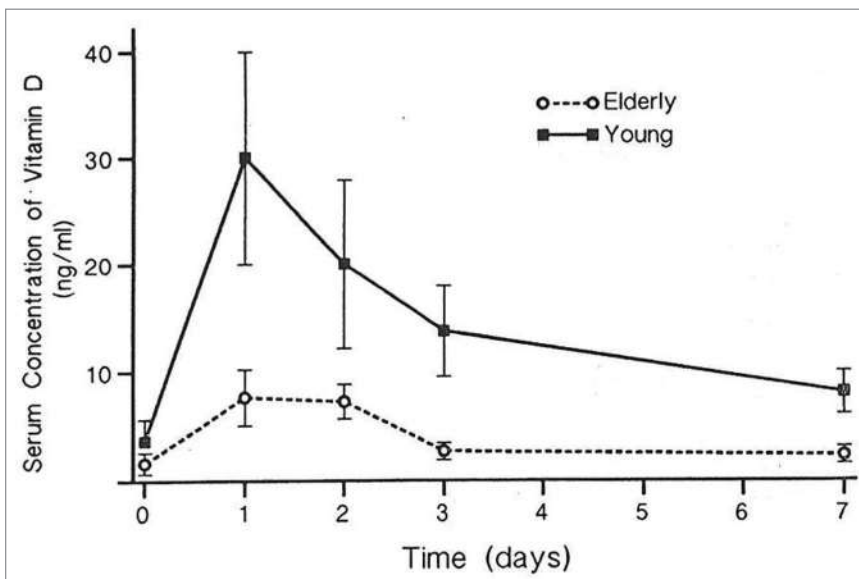


**Figure 37.** Maasai men demonstrate their muscle strength who have been reported to have 25(OH)D ~46 ng/mL. Holick, copyright 2013, reproduced with permission.



**Figure 38.** Concentrations of 7-dehydrocholesterol (provitamin D<sub>3</sub>) per unit area of human epidermis (●), stratum basale (△) and dermis (○) obtained from surgical specimens from donors of various ages. A linear regression analysis revealed slopes of  $-0.05$ ,  $-0.06$ , and  $-0.0005$  for the epidermis ( $r = -0.89$ ), stratum basale ( $r = -0.92$ ), and dermis ( $r = -0.04$ ), respectively. The slopes of the epidermis and stratum basale are significantly different from the slope of the dermis ( $p < 0.001$ ). Reproduced with permission from ref. 58.

foods with high content of vitamin D such as oily fish, seal and whale blubber and polar bear liver.<sup>246,247</sup> Therefore it is necessary without adequate sun exposure to improve childrens' and



**Figure 39.** Circulating concentrations of vitamin D in healthy young and elderly volunteers exposed to UV radiation. Reproduced with permission from ref. 59.

adults' vitamin D status by encouraging them to take a vitamin D supplement (Fig. 70).<sup>22,24,213</sup>

Infants should receive 400 IUs of vitamin D soon after they are born. This has been endorsed by the American Academy of Pediatrics, the Endocrine Society and the Institute of Medicine.<sup>24,213,248</sup> However infants who are vitamin D deficient should be aggressively treated with pharmacologic doses of vitamin D in order to build up the body stores and quickly correct the vitamin D deficiency. The best method to treat and cure rickets is to give a total dose of 5–15 mg (200,000–600,000 IUs) of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> orally with adequate dietary calcium.<sup>8,249</sup> These doses can be given safely either as a single-day therapy or as daily doses of 2000–4000 IUs/day (50–100 µg/d) for 3–6 mo.<sup>8</sup>

Children one year and older should receive at least 600 IUs of vitamin D daily. The Endocrine Society recommends at least 600 IUs and up to 1000 IUs daily is safe and effective to prevent vitamin D deficiency and insufficiency.<sup>24</sup> Infants and toddlers who received 50,000 IUs of vitamin D<sub>2</sub> once a week or 2000 IUs of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> daily for 6 weeks corrected their vitamin D deficiency without any untoward side effects.<sup>8,24,217</sup> A study done in the young Lebanese girls who received 14,000 IUs of vitamin D weekly for one year were able to maintain their blood level of 25(OH)D in what is considered to be a healthy physiologic range above 30 ng/mL.<sup>250</sup>

The Endocrine Society recommends that all adults receive 1500–2000 IUs of vitamin D daily.<sup>15</sup> A study in healthy adults in Boston who had a baseline serum concentration of 25(OH)D ~18 ng/mL in the winter revealed that ingesting 1000 IUs of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> was ineffective in raising and maintaining blood levels 25(OH)D above 30 ng/mL (Fig. 80).<sup>215</sup> This is not at all unexpected since it is documented that for every 100 IUs of vitamin D ingested the circulating concentration of 25(OH)D increases by approximately 0.6–1.0 ng/mL.<sup>215,251</sup>

Because vitamin D is fat soluble upon its ingestion or production in the skin vitamin D<sub>3</sub> gets incorporated into the body fat and is also transported to the liver to be converted to 25(OH)D.<sup>22,73,171-174</sup> As a result to treat vitamin D deficiency and prevent recurrence, vitamin D can be given daily, weekly and even monthly with the same outcome i.e., improvement in circulating concentrations of 25(OH)D.<sup>24</sup> One strategy that is effective to quickly fill up the empty vitamin D tank is to give 50,000 IUs of vitamin D<sub>2</sub> or 50,000 IUs of vitamin D<sub>3</sub> once a week for 8 weeks.<sup>252</sup> This is equivalent to ingesting approximately 6600 IUs of vitamin D daily.<sup>253</sup> To prevent recurrence of vitamin D deficiency patients have been instructed to take 50,000 IUs of vitamin D<sub>2</sub> (equivalent to 3300 IUs of vitamin D daily) once every 2 weeks forever. This strategy has been effective in maintaining blood levels of 25(OH)D in the range of 40–60 ng/mL for up to 6 y without any toxicity

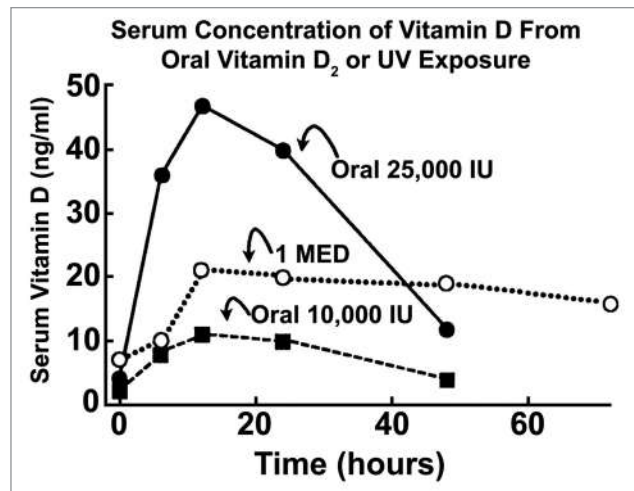


(Fig. 81).<sup>253</sup> Other strategies that have been equally effective have been to take 50,000 IUs of vitamin D daily for several days followed by maintenance therapy. Patients who have a BMI > 30 often need 3–5 times as much vitamin D to both treat and prevent recurrence of vitamin D deficiency.<sup>24</sup> Patients with malabsorption syndromes or who have had gastric bypass surgery may require 50,000 IUs of vitamin D at least up to 7 times a week.<sup>22</sup> Monitoring serum levels of 25(OH)D is important to prevent toxicity. Patients on glucocorticoids, anti-seizure medications and AIDS medications may also need more vitamin D to both treat and prevent vitamin D deficiency.<sup>22</sup> Patients however with granulomatous disorders such as sarcoidosis have a hypersensitivity to vitamin D because of the uncontrolled conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D by activated macrophages within the granulomas. This can also occur in patients with some lymphomas.<sup>22,24</sup>

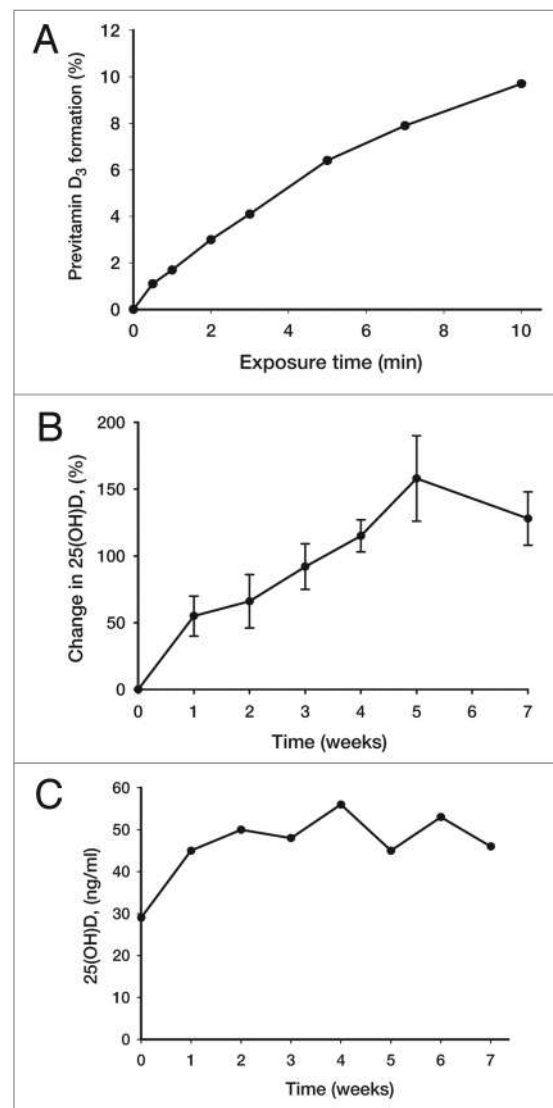
### Concern about Vitamin D Intoxication

Vitamin D intoxication is one of the rarest medical conditions and is often caused by inadvertent or intentional ingestion of extremely high doses of vitamin D for prolonged periods of time. Vitamin D intoxication is associated with hypercalcemia, hyperphosphatemia, suppression of PTH that can lead to nephrocalcinosis and soft tissue calcification especially of blood vessels. Usually vitamin D intoxication is not observed until a 25(OH)D > 200 ng/mL.<sup>254-256</sup>

No matter how much sun exposure a person has this will never cause vitamin D intoxication because sunlight itself destroys any excess vitamin D and previtamin D.<sup>256</sup> However there are several reports in adults that ingesting up to 1 million IUs of vitamin D<sub>3</sub> daily for several months can raise blood levels of 25(OH)D > 500 ng/mL which was associated with hypercalcemia in the range of 15 mg/dL. Often simply removing all sources of vitamin D along with hydration can result in the serum calcium returning to normal within a relatively short period of time and with no sequelae.<sup>254-257</sup> A recent report of a 3 mo old inadvertently receiving 14,000 IUs of vitamin D<sub>3</sub> daily for 20 d (i.e., total of 280,000 IUs of vitamin D<sub>3</sub>) and achieving a circulating concentration of 25(OH)D of 425 ng/mL with suppression of PTH demonstrated no significant change in either the infant's serum calcium or phosphorus level and no change in kidney function demonstrates that short-term high doses of vitamin D resulting in very high serum concentrations of 25(OH)D > 400 ng/mL was well tolerated even in infants.<sup>258</sup> Even pregnant women who received



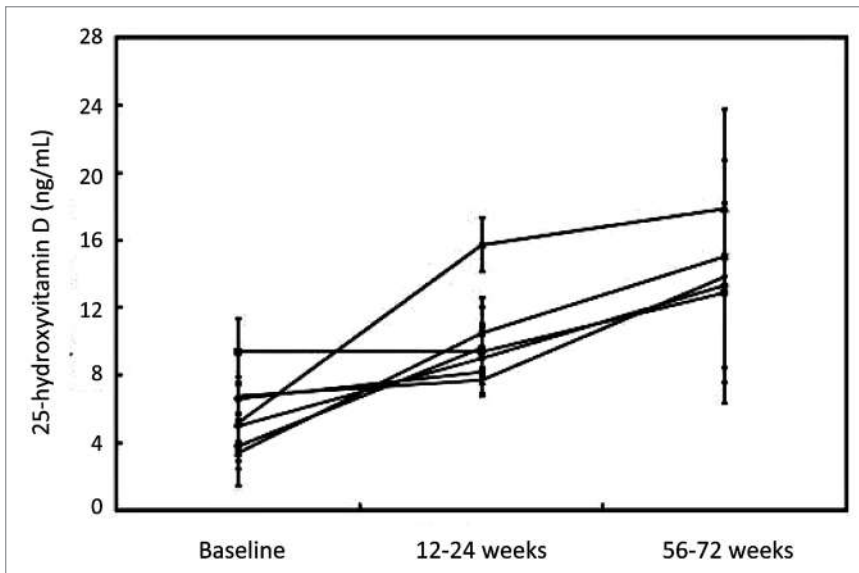
**Figure 40.** Comparison of serum vitamin D<sub>3</sub> levels after a whole-body exposure (in a bathing suit; bikini for women) to 1 MED (minimal erythemal dose) of simulated sunlight compared with a single oral dose of either 10,000 or 25,000 IU of vitamin D<sub>2</sub>. Holick, copyright 2004. Reproduced with permission.



**Figure 41.** Production of previtamin D<sub>3</sub> and serum level of 25(OH)D after the exposure of 7-DHC solution in ampoules and human volunteers to a tanning bed lamp. **(A)** Ampoules containing 7-DHC were placed and exposed to a tanning bed lamp. At various times, an ampoule was removed and the conversion of 7-DHC to previtamin D<sub>3</sub> was measured by HPLC. **(B)** Healthy young adults were exposed to 0.75 MED in a tanning bed three times a week for 7 weeks. Circulating concentrations of 25(OH)D were determined at baseline and once a week thereafter. **(C)** A healthy 76-y-old man was exposed to tanning bed radiation equivalent to 0.75 MED three times a week for 7 weeks. His circulating concentrations of 25(OH)D were obtained at weekly intervals. Holick copyright 2007, reproduced with permission.



**Figure 42.** The UVB lamps and residents in a day room of a nursing home. Reproduced with permission from ref. 60.



**Figure 43.** Mean ( $\pm 1$  sd) 25(OH) vitamin D values pre-irradiation, 12–24 weeks and 56–72 weeks after irradiation in 7 subjects with abnormal baseline values ( $< 25$  nmol/l). Reproduced with permission from ref. 60.

It is prolonged intake of extremely high doses of vitamin D for at least several months that not only markedly increases the circulating concentrations of 25(OH)D  $> 200$  ng/mL but also results in hypercalcemia, hyperphosphatemia and if untreated can lead to kidney failure, soft tissue calcification and ultimately death.<sup>22,260</sup>

### Conclusion and Perspective

Our ancestors routinely worshiped the sun for its life giving properties (Fig. 82).<sup>261,262</sup> It is curious that some of the earliest photosynthetic life forms for more than 500 million years have been producing vitamin D and that throughout evolution most vertebrates including humans have depended on sun exposure for their skeletal health.<sup>263</sup> The driver for the evolution of hypopigmented humans i.e., Caucasians is likely due to the need to have more vitamin D producing solar UVB radiation to penetrate into the skin to produce vitamin D<sub>3</sub>. Females born with vitamin D deficiency and suffering from infantile rickets resulted in them having a flat pelvis and a small pelvic outlet. These

4000 IU vitamin D/day through their pregnancy showed no change in either serum calcium or urinary calcium secretion.<sup>259</sup>

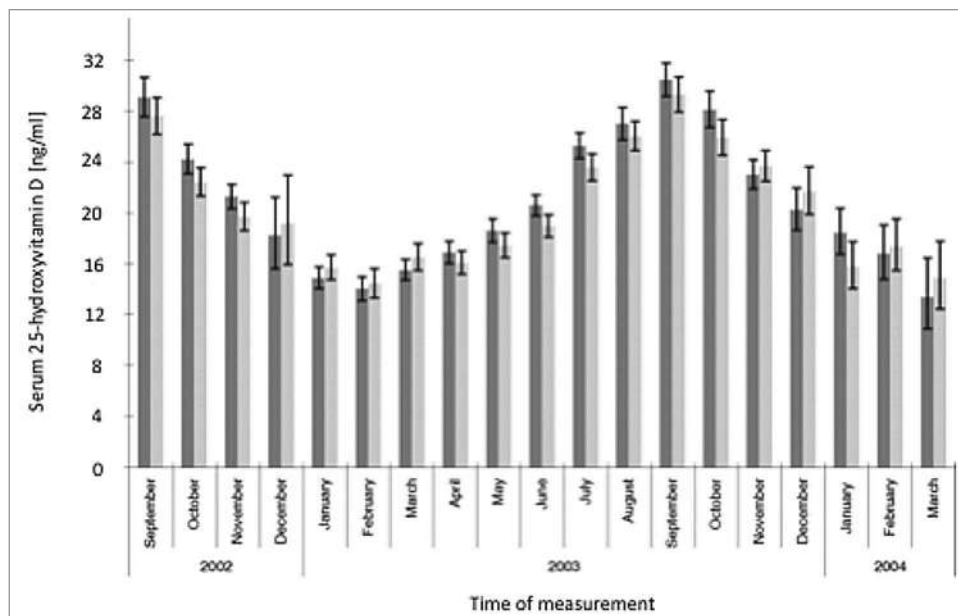
min D deficiency and suffering from infantile rickets resulted in them having a flat pelvis and a small pelvic outlet. These

females although fertile would have had a difficult time, if not impossible, to give vaginal birth resulting in both maternal and fetal death.<sup>54,55</sup> Indeed it was because of the vitamin D deficiency pandemic in late 1800s that Cesarean sectioning became common practice for the delivery of healthy children of mothers who had suffered from vitamin D deficiency in utero and during their first few years of life.<sup>8,54,55</sup> Vitamin D deficiency in pregnant women today is still associated with a 400% increase in the predicted probability for a Cesarean section (Fig. 83).<sup>54</sup>

It is remarkable that for more than 100 y investigators have been reporting an inverse association with latitude and many chronic illnesses including common cancers,<sup>85</sup> several autoimmune diseases including type 1 diabetes and multiple sclerosis<sup>73,134-139</sup> as well as hypertension.<sup>159</sup> In addition the revelation that exposure to sunlight or UV radiation could cure and prevent rickets<sup>12,13</sup> led to the widespread recommendation by health regulators and government agencies to encourage sensible sun exposure, i.e., amount of sun that would be beneficial for producing vitamin D and reducing risk for rickets while preventing sunburning (Fig. 8).

The global appreciation of the beneficial effects of vitamin D for health lead to widespread vitamin D fortification throughout Europe and the United States in the 1930s-1940s. Not only milk but hot dogs, soda, custard, bread, cereals and even beer was fortified with vitamin D (Fig. 9). Schlitz even promoted their vitamin D fortified beer in the winter with the slogan “if you want to keep sunny energy all winter long drink vitamin D fortified Schlitz beer” (Fig. 84). They may have been correct now with the revelation that vitamin D deficiency was associated with depression, seasonal affective disorder and neurocognitive dysfunction.<sup>198-200,202,203,210</sup>

Unfortunately in the early 1950s the outbreak of hypercalcemia in British infants, who also had birth defects which included altered facial features, mental retardation, and heart problems, was incorrectly attributed to be over fortification of milk with vitamin D since it was believed that these were signs of vitamin D intoxication.<sup>20,22</sup> The more likely explanation is that these children had a syndrome which is associated with a hypersensitivity to vitamin D causing hypercalcemia and also with an elfin appearance and heart problems.<sup>20</sup> However because this “outbreak” was associated with infants who had birth defects and mental retardation laws were quickly passed forbidding the fortification of not only foods but any consumer product including skin cream with vitamin D. This legislation was quickly adopted in most European countries and was used as a reason by other countries not to fortify milk with vitamin D.



**Figure 44.** Geometric mean (95% CI) monthly variation in serum 25-hydroxyvitamin D [25(OH)D] concentrations in men (■; n = 3725) and women (□; n = 3712) in the 1958 British birth cohort at age 45 y. The interaction between sex and month was significant [p = 0.02, linear regression analyses on log 25(OH)D]. n per sex and month ranged from 17 to 340: 98 in December 2003 for women and < 100 for both sexes in December 2002 (n = 40 M, 37 F), January 2004 (n = 95 M, 75 F), February 2004 (n = 58 M, 70 F), and March 2004 (n = 22 M, 17 F). Reproduced with permission from ref. 61.

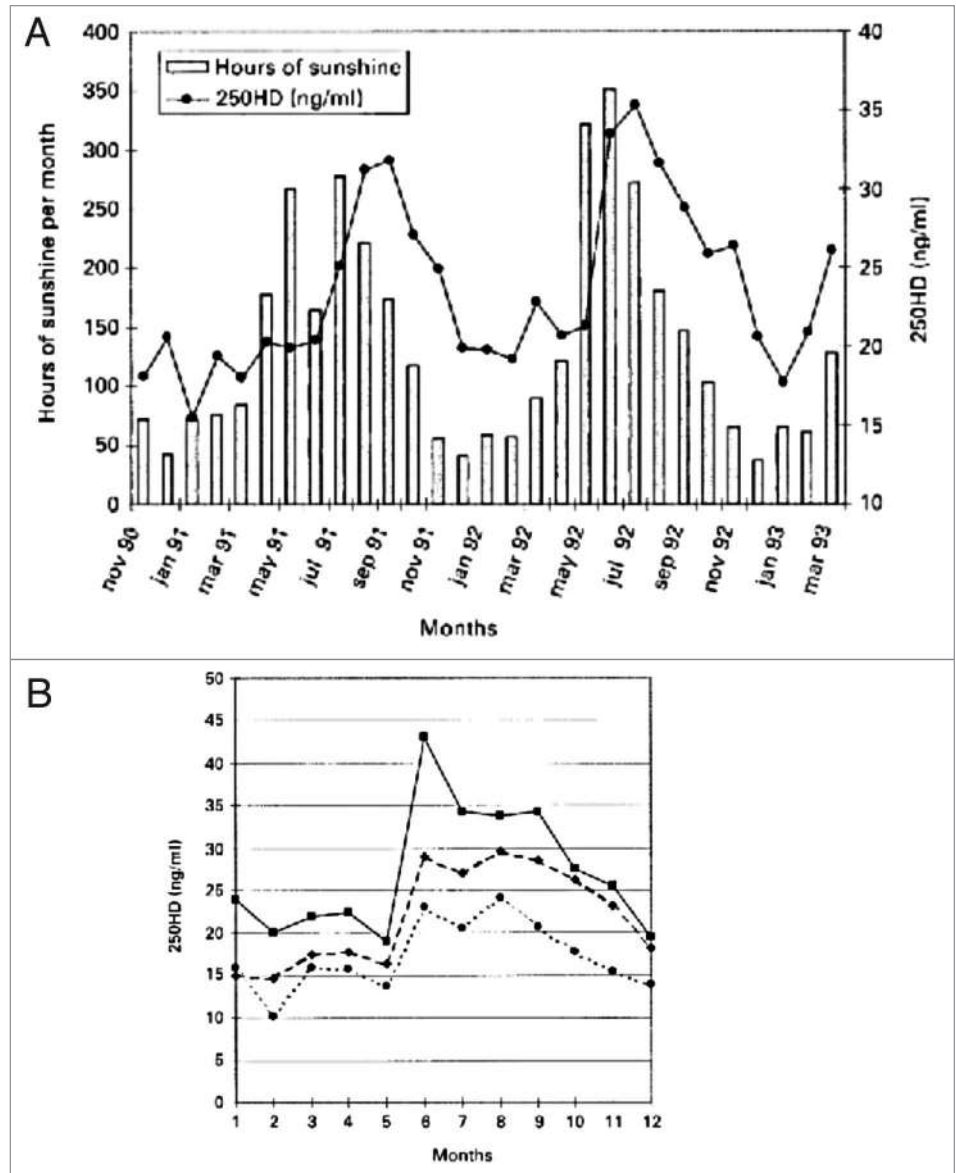
Clearly the paranoia about food fortification with vitamin D causing toxicity needs to be reconsidered in light of observations that infants who consumed 2000 IU vitamin D per day during their first year of life not only did not have any evidence of toxicity but for the ensuing 31 y markedly decreased their risk for type 1 diabetes.<sup>145</sup>

In the 1970s sunscreens were first introduced as a way to prevent sunburning. The sunscreens contained UVB absorbing chemicals such as paraaminobenzoic acid because it was believed that only UVB radiation damaged the skin and caused skin cancer. It is now realized that UVA radiation not only alters the immune system making it more immunotolerant but also increases risk for non-melanoma and melanoma skin cancers. Over the past four decades with very little thought as to its consequences, several national and international health organizations have condemned any direct sun exposure. The American Academy of Dermatology has taken the extreme position of recommending that no one should ever be exposed to direct sunlight without sun protection. This radical view of sunlight and UVB radiation has led to its designation as a carcinogen. To suggest that one should never be exposed to sunlight because excessive exposure to sunlight is linked to an increased risk for non-melanoma skin cancer is like suggesting that because breathing 100% oxygen can cause lung damage and death, that no one should breath an atmosphere that contains 20% oxygen.

The lack of appreciation of the importance of sensible sun exposure for providing children and adults with their vitamin D requirement has led to a worldwide vitamin D deficiency pandemic.<sup>22,173</sup> In the United States the Center for Disease



**Figure 45.** (A) Seasonal fluctuation of serum 25(OH)D in healthy perimenopausal Danish women and relationship between hours of sunshine and serum 25(OH)D. (B) Seasonal fluctuation of serum 25(OH)D according to frequency of sun exposure. ■, regular sun exposure; ◆, occasional sun exposure; ●, avoiding direct sun exposure. Reproduced with permission from ref. 173.



Control and Prevention (CDC) reported that 32% of children and adults have a circulating concentration of 25(OH)D < 20 ng/mL. Reports from Mexico, South America, Europe, Asia, India and even Africa suggest that more than 50% of the world population is at risk for vitamin D deficiency.<sup>22,265,266</sup> Even in Australia, the skin cancer capital of the world, it is now recognized that the slip, slap, slop message has led to more than 40% of the population being vitamin D deficient.<sup>265-268</sup> Even the Australian Dermatology Society now recommends sensible sun exposure as a source of vitamin D. A study of Australian dermatologists at the end of the summer revealed that 87% had a 25(OH)D < 20 ng/mL.<sup>269</sup>

More than 90% of the healthcare professionals in India were found to be vitamin D deficient.

The CDC concluded that vitamin D deficiency is becoming more prevalent in the US because of obesity, decrease in the consumption of vitamin D fortified milk and increased sun protection.<sup>269</sup> Thus a three-part strategy should be employed worldwide to prevent vitamin D deficiency and its many negative health consequences (Fig. 89). Sensible sun exposure which is free, eating foods that naturally contain vitamin D or are fortified with vitamin D as well as taking a vitamin D supplement should guarantee vitamin D sufficiency.<sup>22,66</sup> A global strategy to reduce the risk of vitamin D deficiency should be

to consider not only increasing programs for food fortification not only of dairy products but also juice products, flour, and other commonly used food sources. There is no downside to increasing vitamin D intake and there could be a substantial upside, i.e., improvement not only of musculoskeletal health but overall health and welfare. It has been estimated that as much as 25% of health care dollars could be saved just by improving the world's vitamin D status.<sup>79</sup>

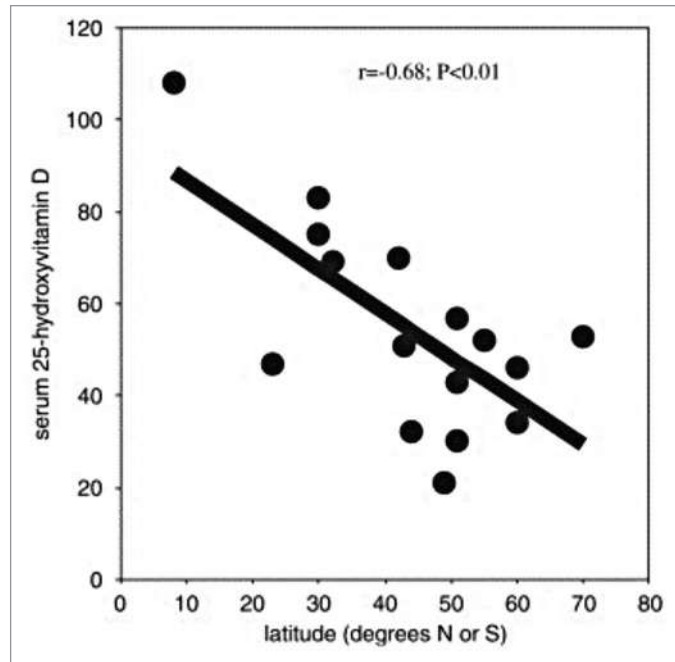
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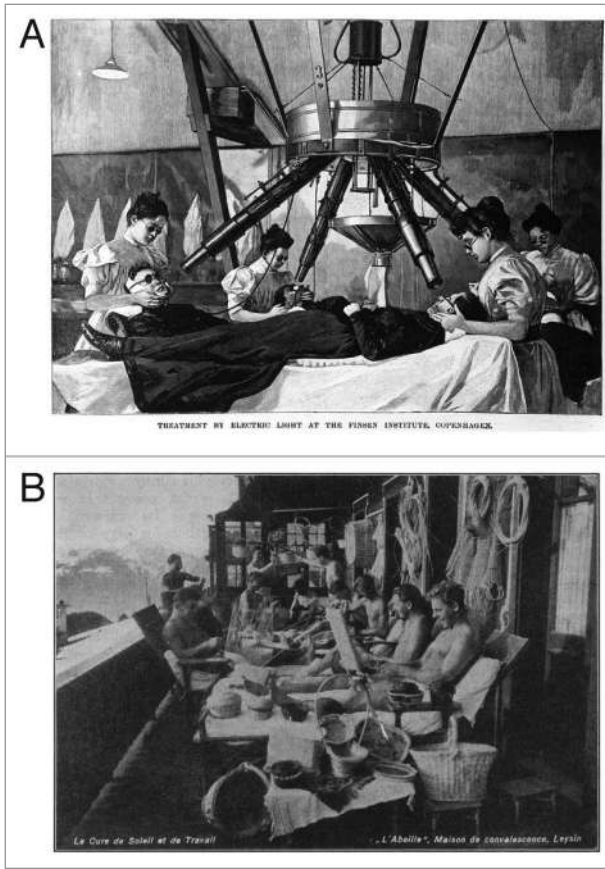
**Figure 46.** Mean circulating 25-hydroxyvitamin D levels in children, adolescents, and adults according to geographic latitude. Reproduced with permission from ref. 64.

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**Figure 47.** Niels Ryberg Finsen, \* December 15, 1860, Thorshavn, Faroe Islands; + 24 September 1904; Nobel Prize was awarded "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science."

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**Figure 48. (A)** 1901 Illustration from Scientific American showing phototherapy with the Finsen carbon-arc UV lamp in 1901. **(B)** Sunbathing individuals at sanatorium Leysin in Switzerland.

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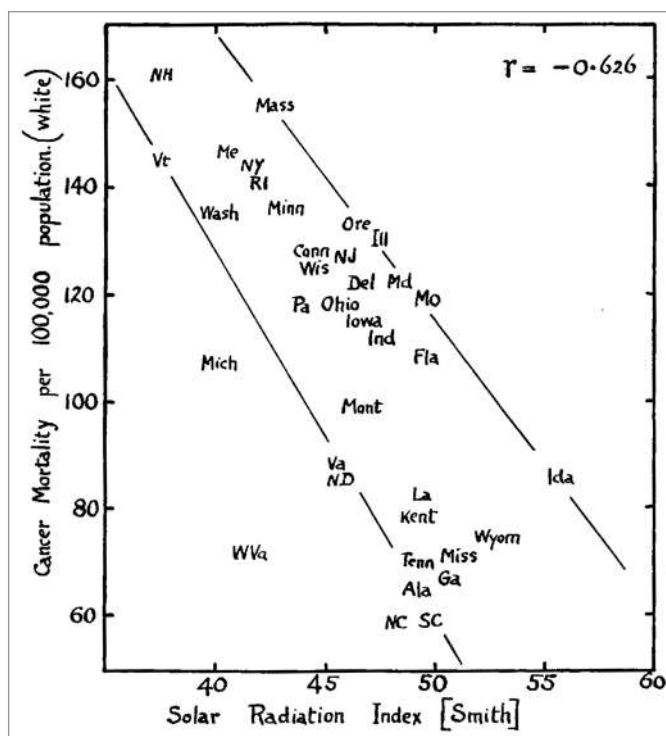


**Mortality from Cancer in Cities, according to Latitude  
Eastern and Western Hemispheres, 1908-1912**

EASTERN HEMISPHERE				WESTERN HEMISPHERE		
Degree of Latitude	No. of Cities	Rate per 100,000 Population	Index Number	No. of Cities	Rate per 100,000 Population	Index Number
60 N. -50 N.	35	105.7	98	..	..	..
50 N. -40 N.	22	108.4	100	26	77.3	100
40 N. -30 N.	6	66.9	62	18	85.5	111
30 N. -10 N.	3	13.6	13	4	77.2	100
10 N. -10 S.	1	11.6	11	3	82.7	107
10 S. -30 S.	1	34.4	32	6	38.2	49
30 S. -40 S.	1	90.1	83	4	89.8	116
<b>Total.....</b>	<b>69</b>	<b>98.3</b>		<b>61</b>	<b>78.0</b>	

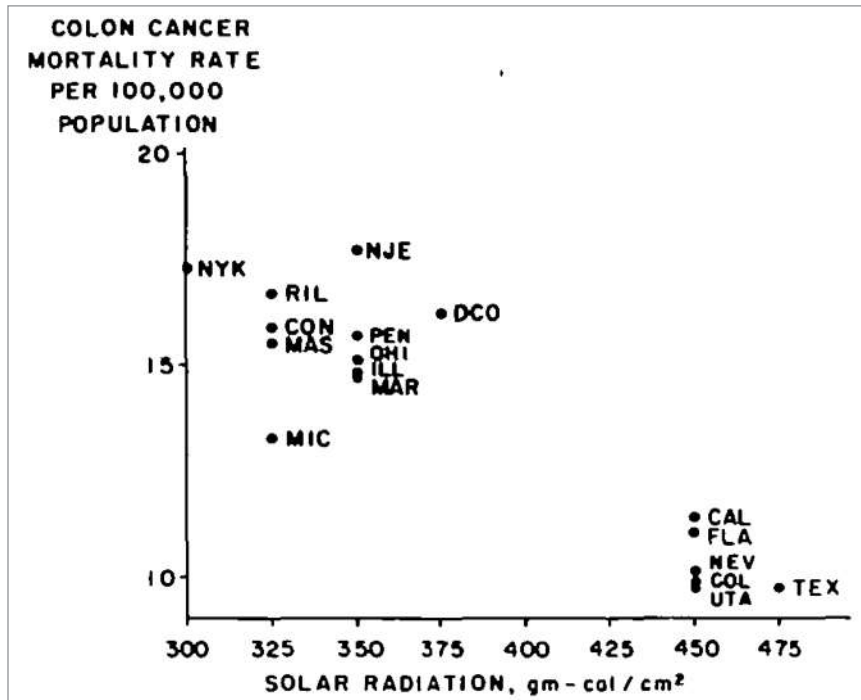
**Figure 49.** Mortality from cancer in cities according to latitude, 1908–1912.

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**Figure 50.** Showing the relation of total cancer mortality rates to Smith's Solar Radiation Index in the American states, (white population only).

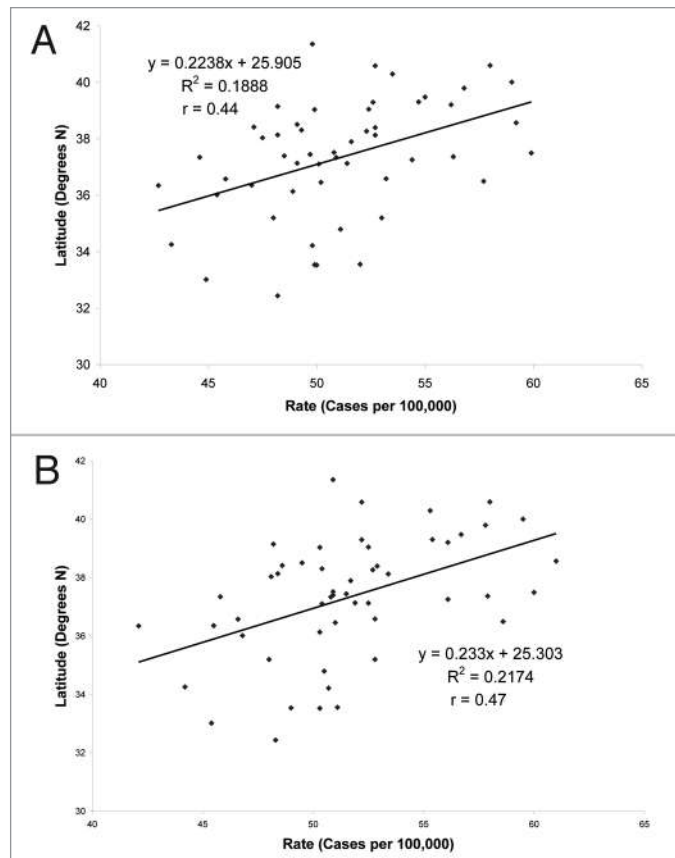
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**Figure 51.** Annual mean daily solar radiation (gm-cal/cm<sup>2</sup>) and annual age-adjusted colon cancer death rates per 100,000 population, white males, 17 metropolitan states, United States, 1959–61. Reproduced with permission from ref. 77.

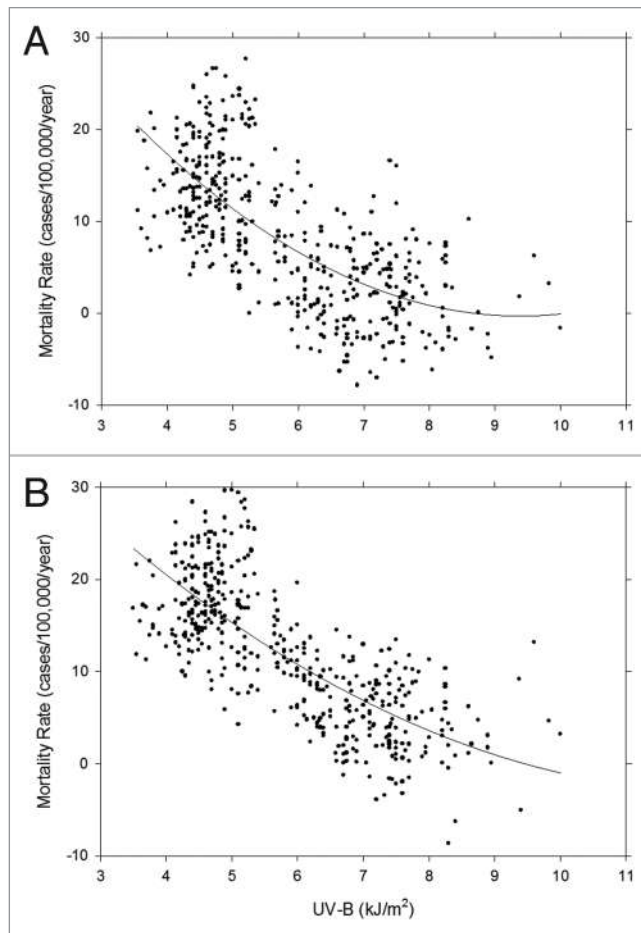
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**Figure 52.** (A) Latitude vs. number of individuals diagnosed with colon cancer in California, independent of race. (B) Latitude vs. the number of Caucasian individuals diagnosed with colon cancer in the state of California. Holick copyright 2005. Reproduced with permission.





**Figure 53. (A)** Premature mortality due to cancer with insufficient UVB in white males, US, 1970–1994, vs. July 1992 DNA-weighted UVB radiation. **(B)** Premature mortality due to cancer, white females, vs. TOMS July 1992 DNA-weighted UVB. Reproduced with permission from ref. 79.

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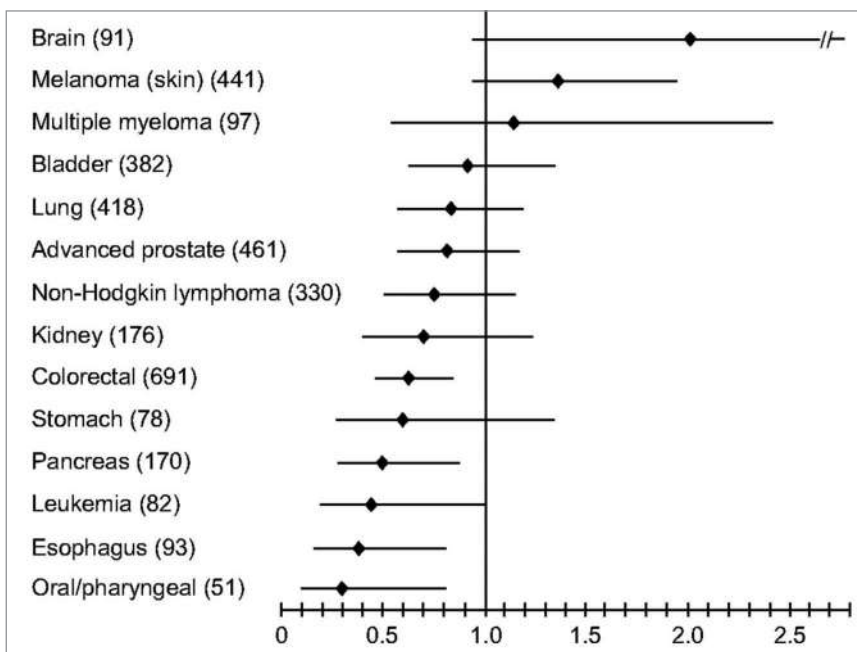
Cancer site	Incidence		Mortality	
	Males	Females	Males	Females
Esophagus (males)	1.27 (1.21–1.34)		1.36 (1.31–1.41)	
Stomach	1.42 (1.35–1.49)	1.27 (1.19–1.36)	1.31 (1.26–1.36)	1.26 (1.21–1.32)
Colon	1.11 (1.08–1.13)	1.14 (1.11–1.16)	1.27 (1.24–1.30)	1.24 (1.22–1.27)
Rectum	1.27 (1.23–1.32)	1.14 (1.09–1.18)	1.53 (1.45–1.60)	1.37 (1.30–1.44)
Gallbladder (females)		1.86 (1.66–2.09)		1.98 (1.82–2.16)
Other biliary	1.20 (1.07–1.35)	1.21 (1.07–1.36)	1.56 (1.40–1.75)	1.58 (1.43–1.76)
Uterus		1.49 (1.45–1.53)		1.52 (1.46–1.58)
Vulva		1.18 (1.09–1.29)		1.93 (1.72–2.17)
Prostate	1.20 (1.19–1.22)		1.17 (1.15–1.19)	
Bladder	1.13 (1.10–1.16)	1.15 (1.11–1.20)	1.24 (1.20–1.28)	1.21 (1.15–1.27)
Hodgkin lymphoma	1.16 (1.04–1.29)	1.19 (1.05–1.34)	1.14 (1.00–1.30)	1.25 (1.09–1.43)
Myeloma	1.19 (1.12–1.27)	1.22 (1.14–1.31)	1.16 (1.11–1.22)	1.16 (1.11–1.21)

<sup>a</sup>Adjusted for the variables listed in Table 1 and excluding high-migration counties. Incidence includes states and counties shown in Figure 1 for the period 1998–2002 ; mortality includes entire United States except Alaska and Hawaii for the period 1993–2002.

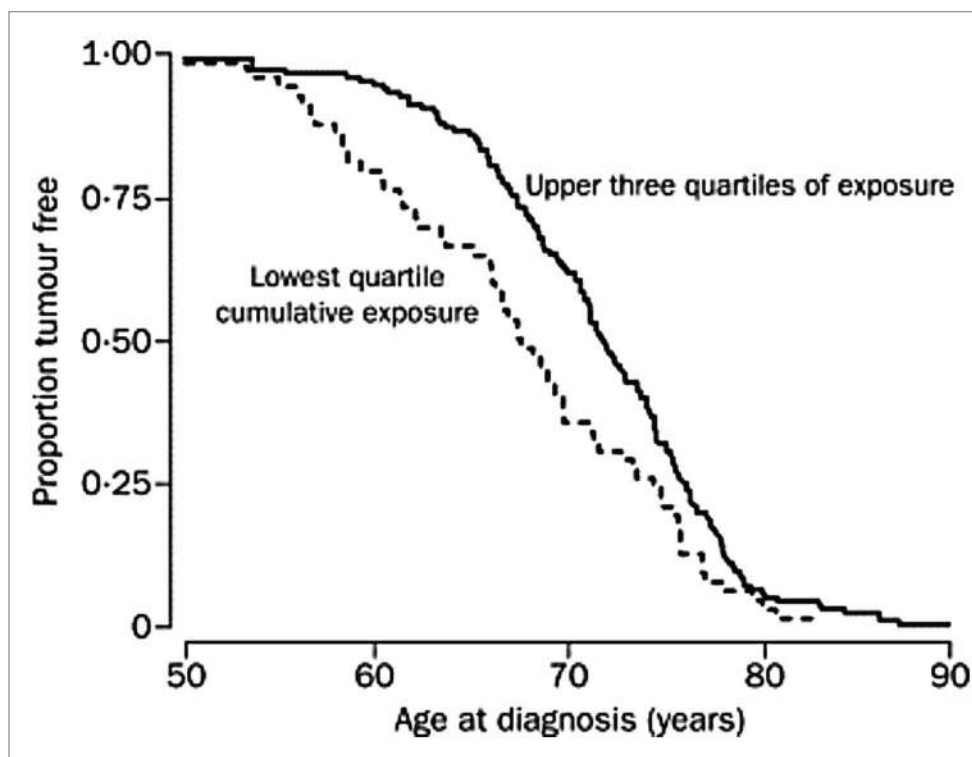
<sup>b</sup>Relative risk of receiving annual average of 650 kJ/m<sup>2</sup> of erythemally-weighted ultraviolet exposure (a value typical of northern Maine, Minnesota or Washington) versus annual average of 1540 kJ/m<sup>2</sup> (a value typical of southern Florida, Texas, or Arizona).

**Figure 54.** Relative risk of cancer incidence and mortality related to solar UV-B exposure, northern vs. southern United States boundary, non-Hispanic whites (95% CI in parentheses); Cancer sites with strongest evidence of an inverse association with solar UV-B exposure. Reproduced with permission from ref. 86.

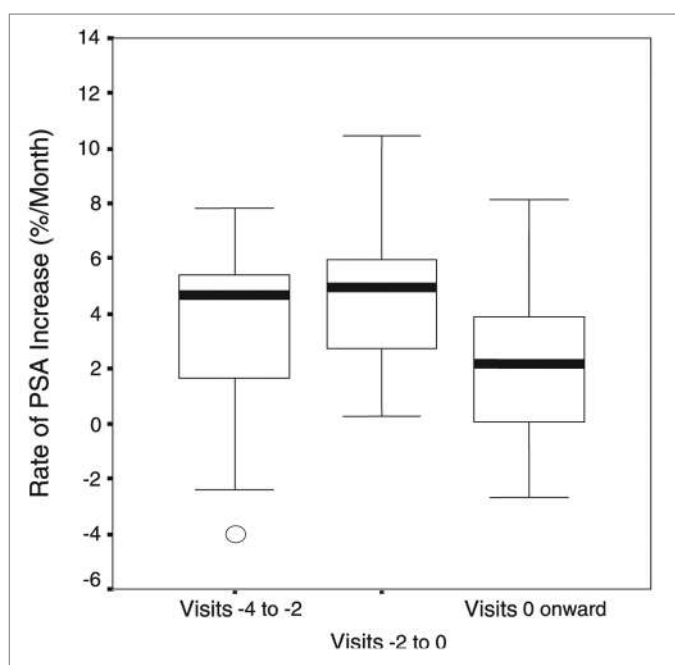
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**Figure 55.** Multivariable relative risks and 95% confidence intervals for an increment of 25 nmol/L in predicted plasma 25-hydroxy-vitamin D level for individual cancers in the Health Professionals Follow-up Study (1986–2000). Number in parentheses = number of cases. Covariables included in the Cox proportional hazards model: age, height, smoking history, and intakes of total calories, alcohol, red meat, calcium, retinol, and total fruits and vegetables. Reproduced with permission from ref. 87.



**Figure 56.** Kaplan-Meier plot showing association of UVR exposure and age at diagnosis with prostate cancer. Reproduced with permission from ref. 88.



**Figure 57.** Effect of cholecalciferol on rate of rise of PSA. Median and quartiles of rate of PSA increase prior to starting cholecalciferol (visits -4 to -2 and visits -2 to 0) and after starting cholecalciferol (visits 0 onward). Reproduced with permission from ref. 105.

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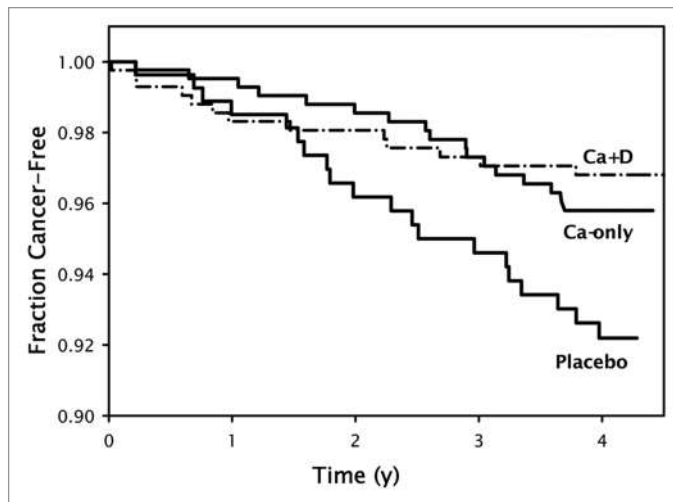
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**Figure 58.** Kaplan-Meier survival curves (i.e., free of cancer) for the 3 treatment groups randomly assigned in the entire cohort of 1179 women. Sample sizes are 288 for the placebo group, 445 for the calcium-only (Ca-only) group, and 446 for the calcium plus vitamin D (Ca + D) group. The survival at the end of study for the Ca + D group is significantly higher than that for placebo, by logistic regression. Copyright Robert P. Heaney, 2006. Reproduced with permission.

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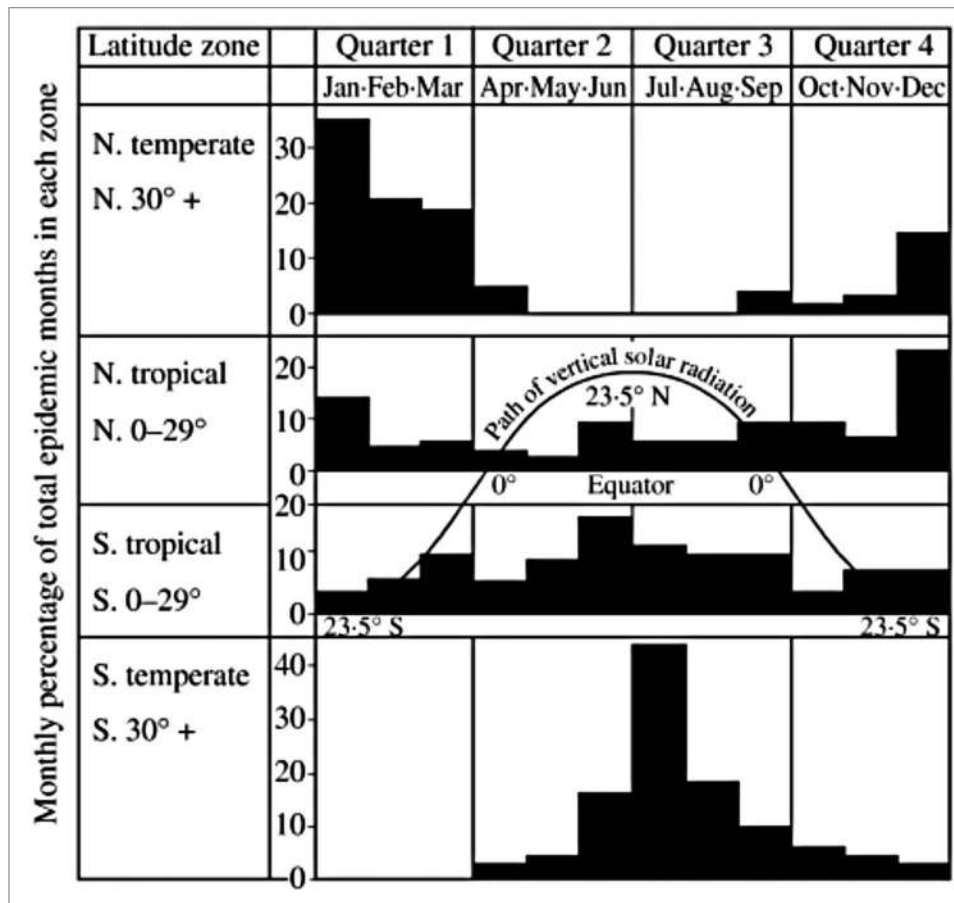
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**Figure 59.** The seasonal and latitudinal distribution of outbreaks of type A influenza in the world, 1964–1975, summarized from the Weekly Epidemiological Record of the World Health Organization into major zones. The diagrams show for each calendar month the percentage of each zone’s total outbreaks. In both north and south temperate zones the epidemics are distributed around the local midwinter, whereas the tropical zones show a transition, each approximating toward the distribution of its own temperate zone. The curve indicates the ‘midsummer’ path taken annually by vertical solar radiation. The ‘epidemic path’ seems to parallel it, but to lag 6 mo behind it.

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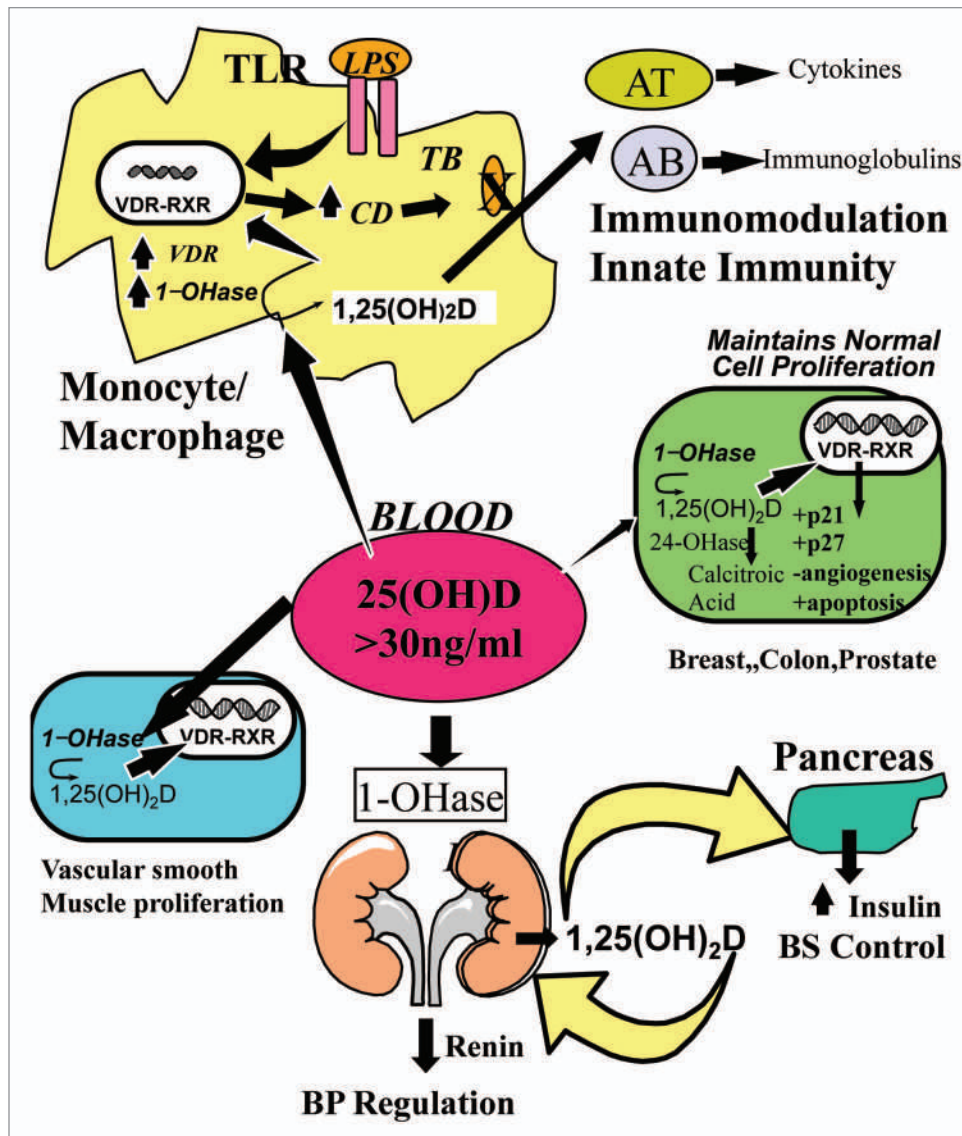
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**Figure 60.** Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] for non-skeletal functions. When a monocyte/macrophage is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infective agent such as Mycobacterium tuberculosis (TB), or its lipopolysaccharide (LPS) the signal upregulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase). 25(OH)D levels > 30 ng/mL provides adequate substrate for the 1-OHase to convert it to 1,25(OH)<sub>2</sub>D. 1,25(OH)<sub>2</sub>D returns to the nucleus where it increases the expression of cathelicidin which is a peptide capable of promoting innate immunity and inducing the destruction of infective agents such as TB. It is also likely that the 1,25(OH)<sub>2</sub>D produced in the monocytes/macrophage is released to act locally on activated T (AT) and activated B (AB) lymphocytes which regulate cytokine and immunoglobulin synthesis respectively. When 25(OH)D levels are ~30 ng/mL, it reduces risk of many common cancers.<sup>22-32</sup> It is believed that the local production of 1,25(OH)<sub>2</sub>D in the breast, colon, prostate, and other cells regulates a variety of genes that control proliferation. Once 1,25(OH)<sub>2</sub>D completes the task of maintaining normal cellular proliferation and differentiation, it induces the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). The 24-OHase enhances the metabolism of 1,25(OH)<sub>2</sub>D to calcitroic acid which is biologically inert. Thus, the local production of 1,25(OH)<sub>2</sub>D does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity and the local production of 1,25(OH)<sub>2</sub>D inhibits the expression and synthesis of PTH. The production of 1,25(OH)<sub>2</sub>D in the kidney enters the circulation and is able to downregulate renin production in the kidney and to stimulate insulin secretion in the β-islet cells of the pancreas. Holick, copyright 2007. Reproduced with permission.

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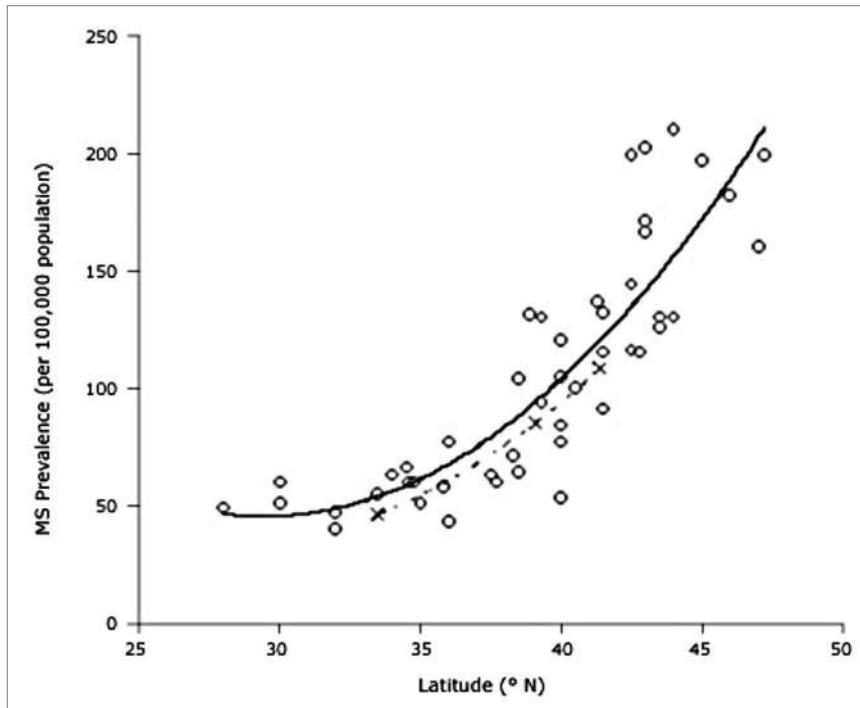
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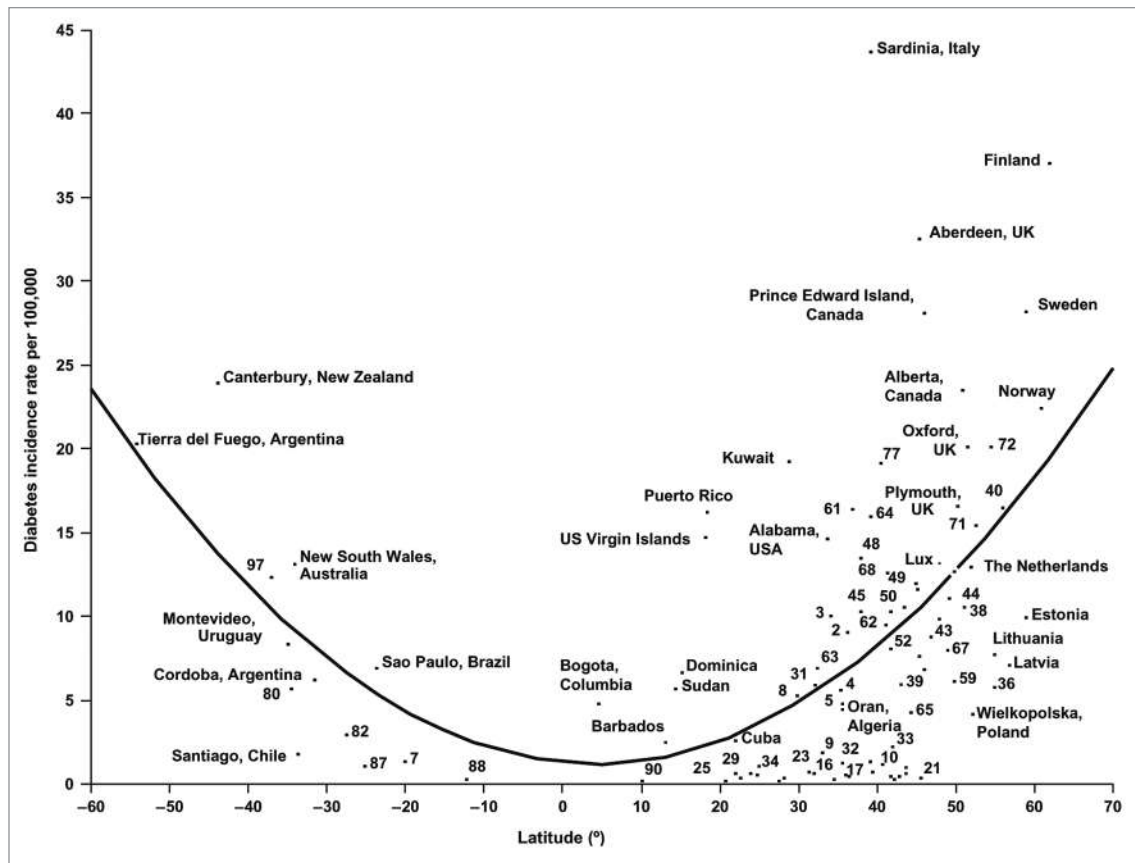
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**Figure 61.** Prevalence of multiple sclerosis (MS) by latitude in the United States according to data from Noonan et al.<sup>140</sup> (x) and Wallin et al.<sup>141</sup> (o). The dashed line is a quadratic fit to the data from Noonan et al.,<sup>140</sup> and the solid line is a fit to the data from Wallin et al.<sup>141</sup> Reproduced with permission from ref. 134.

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**Figure 62.** Age-standardized incidence rates of type 1 diabetes per 100,000 boys <14 years of age, by latitude, in 51 regions worldwide, 2002. Data points are shown by dots; names shown adjacent to the dots denote location, where space allows. Where space was limited, numerical codes (below) designate location. Source: data from WHO DiaMond [3]. Lux., Luxembourg. Numerical codes for areas: 2. Beja, Tunisia; 3. Gafsa, Tunisia; 4. Kairoan, Tunisia; 5. Monastir, Tunisia; 7. Mauritius; 8. Wuhan, China; 9. Sichuan, China; 10. Huhehot, China; 16. Nanjing, China; 17. Jinan, China; 21. Harbin, China; 23. Changsha, China; 25. Hainan, China; 29. Hong Kong, China; 31. Israel; 32. Chiba, Japan; 33. Hokkaido, Japan; 34. Okinawa, Japan; 36. Novosibirsk, Russia; 38. Antwerp, Belgium; 39. Varna, Bulgaria; 40. Denmark; 43. France; 44. Baden, Germany; 45. Attica, Greece; 48. Sicily, Italy; 49. Pavia, Italy; 50. Marche, Italy; 52. Lazio, Italy; 59. Krakow, Poland; 61. Algarve, Portugal; 62. Coimbra, Portugal; 63. Madeira Island, Portugal; 64. Portalegre, Portugal; 65. Bucharest, Romania; 67. Slovakia; 68. Catalonia, Spain; 71. Leicestershire, UK; 72. Northern Ireland, UK; 77. Allegheny, PA, USA; 80. Avellaneda, Argentina; 82. Corrientes, Argentina; 87. Paraguay; 88. Lima, Peru; 90. Caracas, Venezuela; 97. Auckland, New Zealand. Data points not labelled because of space constraints (latitude in degrees, rate per 100,000): 11. Dalian, China (39, 1.1); 12. Guilin, China (24, 0.6); 13. Beijing, China (40, 0.7); 14. Shanghai, China (32, 0.7); 15. Chang Chun, China (44, 0.6); 18. Jilin, China (43, 0.4); 19. Shenyang, China (42, 0.4); 20. Lanzhou, China (36, 0.5); 22. Nanning, China (23, 0.3); 24. Zhengzhou, China (35, 0.2); 26. Tie Ling, China (42, 0.2); 27. Zunyi, China (28, 0.1); 28. Wulumuqi, China (44, 0.9); 35. Karachi, Pakistan (25, 0.5); 37. Austria (48, 9.8); 46. Hungary (47, 8.7); 51. Turin, Italy (45, 11.9); 53. Lombardia, Italy (46, 7.6); 66. Slovenia (46, 6.8); 79. Chicago, IL, USA (42, 10.2).  $R^2 = 0.25$ ,  $p < 0.001$ .

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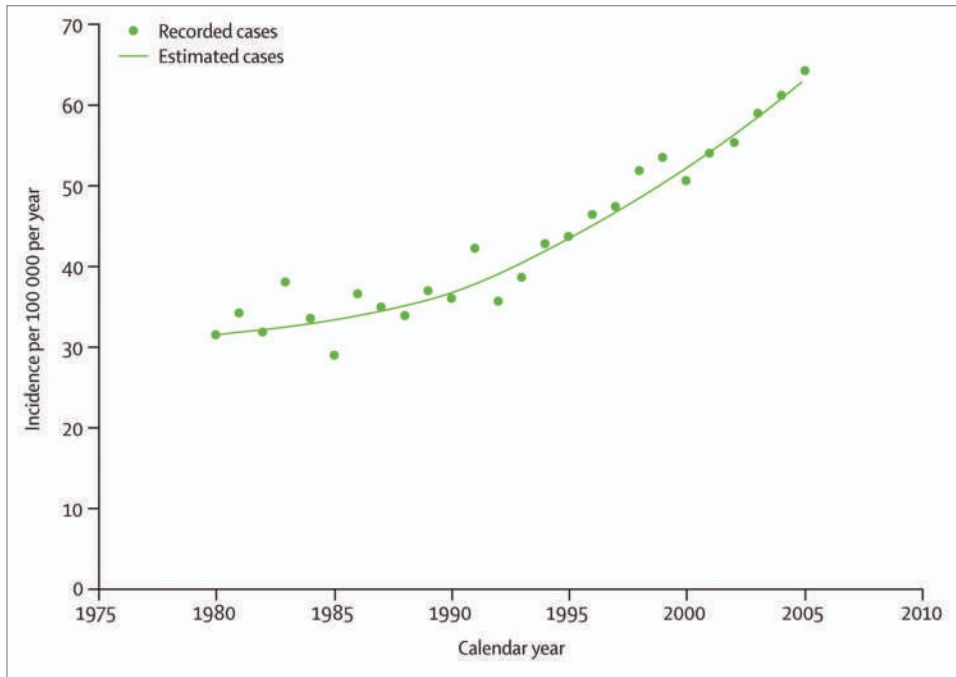
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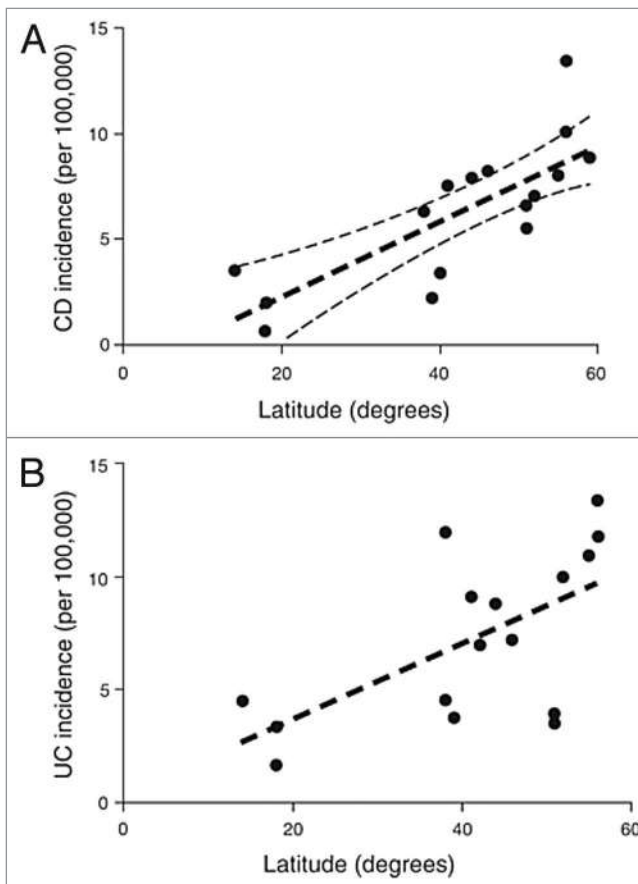
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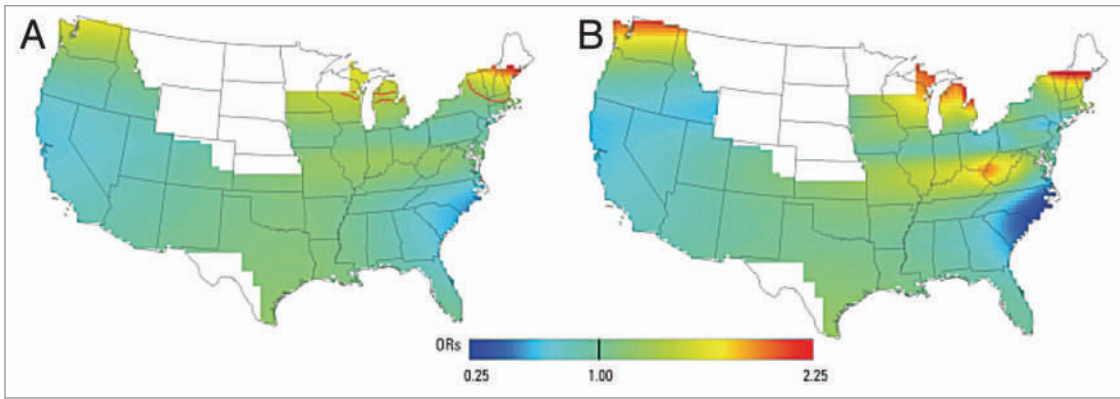
**Figure 63.** Incidence rate of type 1 diabetes diagnosed at or before 14 y of age in Finland. Reproduced with permission from ref. 271.



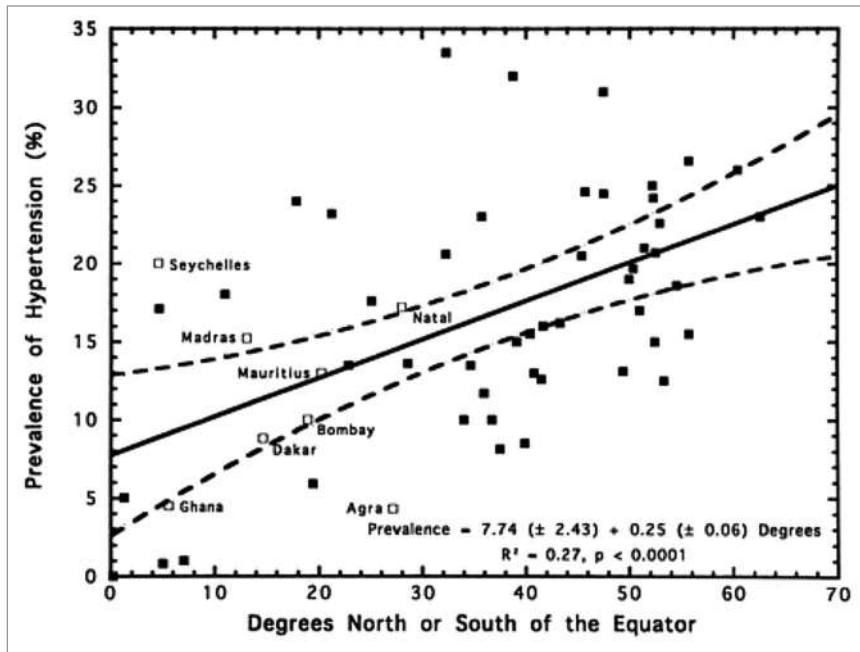
**Figure 64.** Variation in inflammatory bowel disease incidence rates with degrees latitude from the equator. **(A)** Variation in Crohn's disease incidence rates.  $R^2 = 0.62$ ,  $p = 0.0002$ . **(B)** Variation in ulcerative colitis incidence rates.  $R^2 = 0.38$ ,  $p = 0.011$ . Reproduced with permission from ref. 138.

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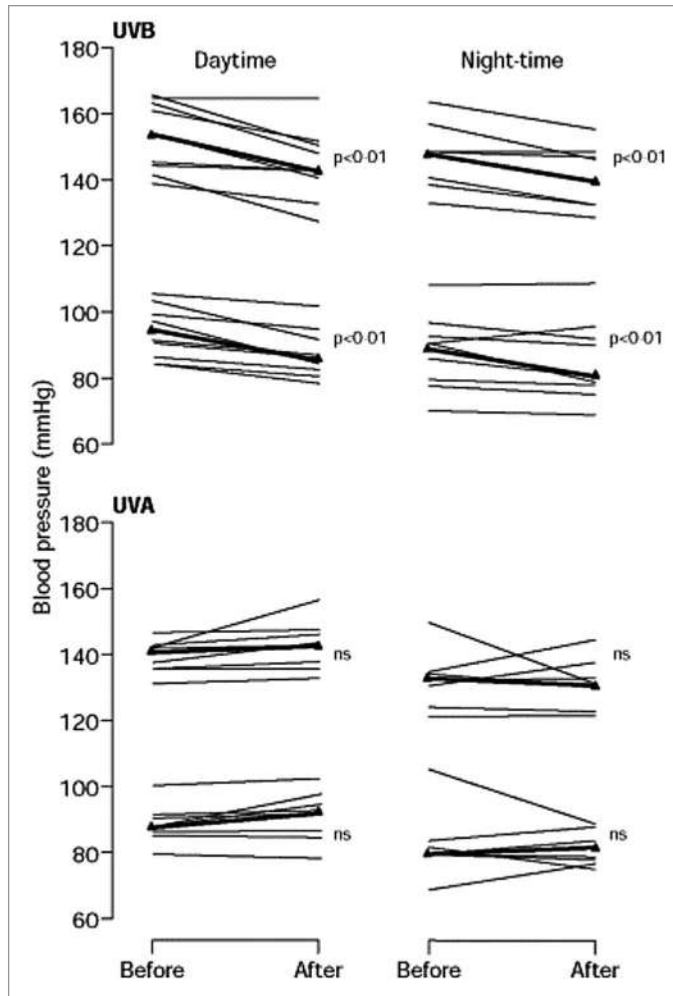




**Figure 65.** This figure illustrates the geographic variation in rheumatoid arthritis risk and shows a clear North-South gradient. Odds ratios are relative to the whole study area. **(A)** Adjusted, optimal span of 0.55 (global  $p = 0.034$ ); contour lines denote areas of significantly increased (red) and decreased (blue) risk at the 0.05 level. **(B)** Adjusted, span of 0.20. Small span size results in more spatial variation in risk. Results for addresses at time of censoring.

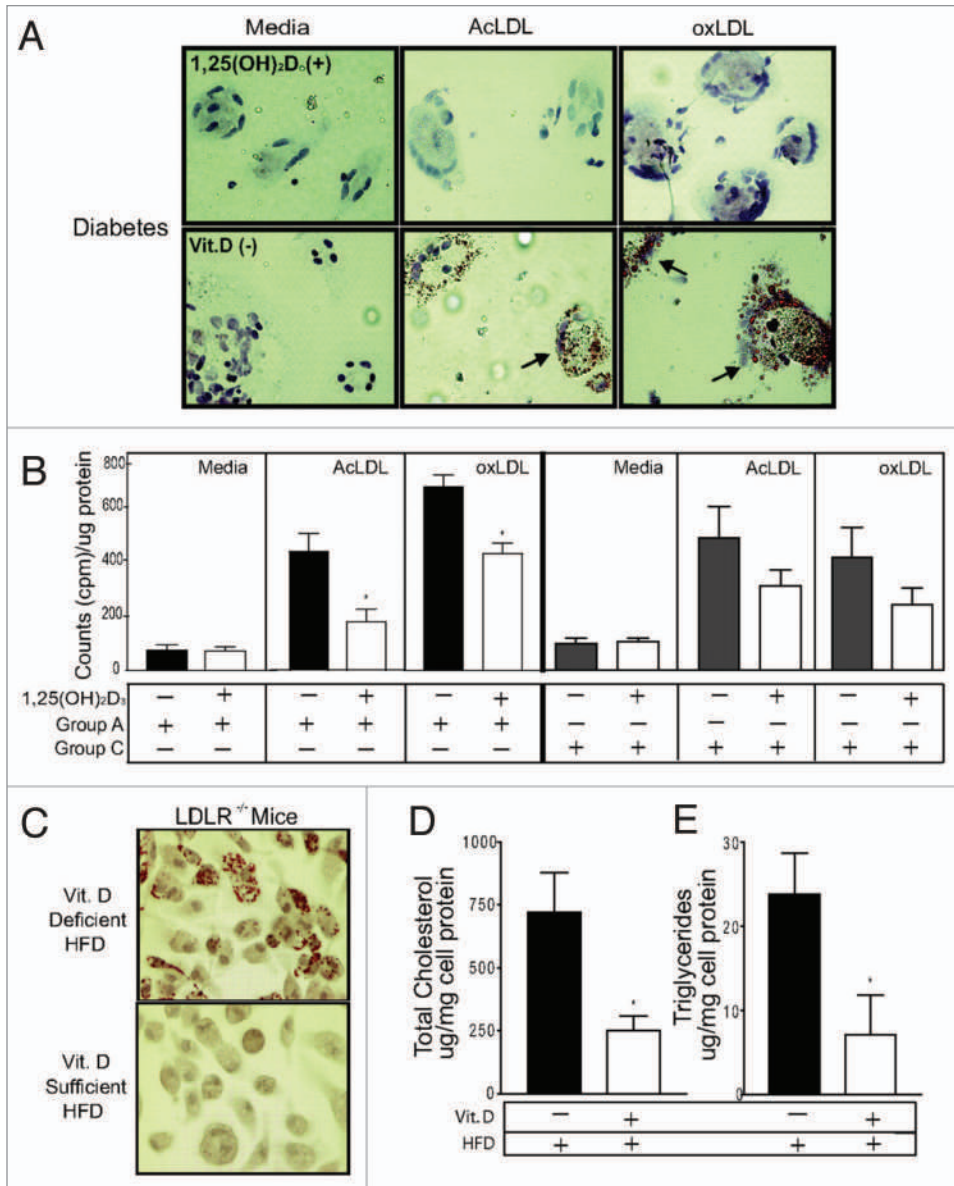


**Figure 66.** Relationship of prevalence of hypertension to distance north or south of the equator. Labeled open boxes represent non-INTERSALT centers; solid boxes are INTERSALT centers. Broken lines represent 95% confidence limits. Regression line and confidence limits are derived from INTERSALT centers only.

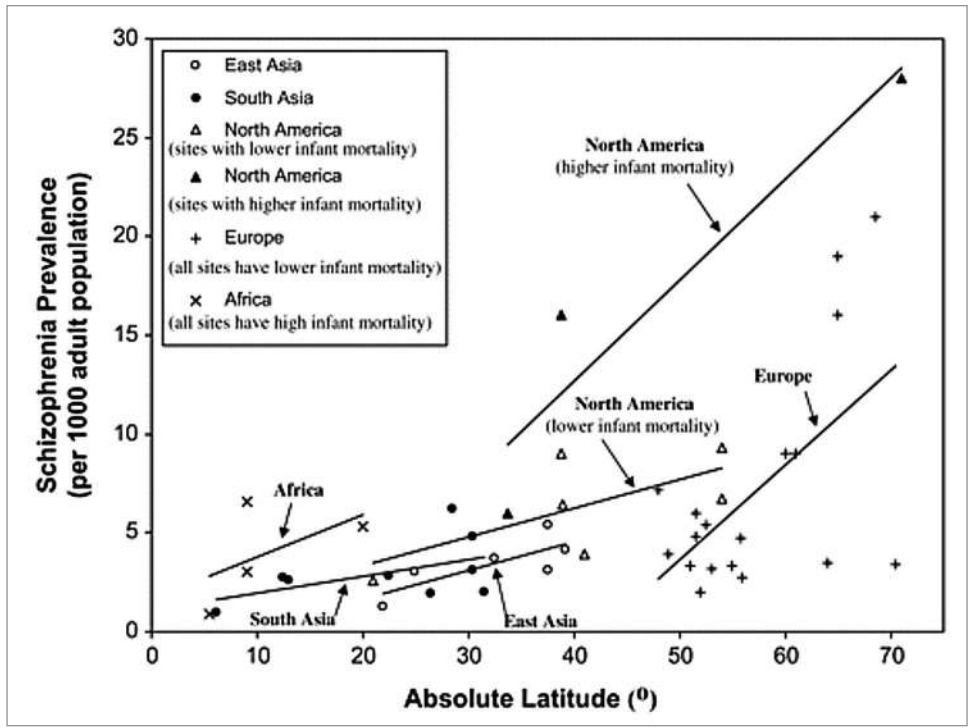


**Figure 67.** Effect of UV irradiation on ambulatory daytime and night-time blood pressures was non-significant. Thick line represents the mean. Reproduced with permission from ref. 160.





**Figure 68.** 1,25(OH)<sub>2</sub>D<sub>3</sub> prevents foam cell formation. Macrophages stained with Oil Red O. **(A)** Diabetic subjects (group A). Top, 1,25(OH)<sub>2</sub>D<sub>3</sub>-treated cells; bottom, vitamin D-deficient cells. Arrowheads indicate foam cells. **(B)** Cholesteryl ester formation in macrophages from diabetics (group A) incubated in vitamin D-deficient (black bars) or 1,25(OH)<sub>2</sub>D<sub>3</sub>-supplemented (white bars) media or in macrophages from nondiabetic, vitamin D-deficient nondiabetic controls (group C) (n = 8 per group) incubated in vitamin D-deficient (gray bars) or 1,25(OH)<sub>2</sub>D<sub>3</sub>-supplemented (white bars) media (\*p < 0.01 vs. vitamin D deficient). **(C)** Oil Red O stain. **(D)** Cholesterol. **(E)** Triglycerides from peritoneal macrophages from LDLR<sup>-/-</sup> mice fed vitamin D-deficient or -sufficient high-fat diet (n = 5 per group) (\*p < 0.05 vs. vitamin D deficient). Reproduced with permission from ref. 187.



**Figure 69.** Association between latitude and schizophrenia prevalence on several continents. Reproduced with permission from ref. 189.

Life Stage Group	IOM Recommendations				Endocrine Society's Recommendations	
	AI	EAR	RDA	UL	Daily Allowance (IU/day)	UL (IU)
<i>Infants</i>						
0 to 6 months	400 IU (10 µg)			1000 IU (25 µg)	400–1000	2000
6 to 12 months	400 IU (10 µg)			1500 IU (38 µg)	400–1000	2000
<i>Children</i>						
1–3 years		400 IU (10 µg)	600 IU (15 µg)	2500 IU (63 µg)	600–1000	4000
4–8 years		400 IU (10 µg)	600 IU (15 µg)	3000 IU (75 µg)	600–1000	4000
<i>Males</i>						
9–13 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
14–18 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
19–30 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
31–50 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
51–70 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
>70 years		400 IU (10 µg)	800 IU (20 µg)	4000 IU (100 µg)	1500–2000	10,000
<i>Females</i>						
9–13 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
14–18 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
19–30 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
31–50 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
51–70 years		400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
>70 years		400 IU (10 µg)	800 IU (20 µg)	4000 IU (100 µg)	1500–2000	10,000
<i>Pregnancy</i>						
14–18 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
19–30 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
31–50 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
<i>Lactation*</i>						
14–18 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	600–1000	4000
19–30 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000
31–50 years	---	400 IU (10 µg)	600 IU (15 µg)	4000 IU (100 µg)	1500–2000	10,000

\* Mother's requirement 4000–6000 (mother's intake for infant's requirement if infant is not receiving 400 IU/day);  
 AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

**Figure 70.** Recommendations of the Institute of Medicine and the Endocrine Society Practice Guidelines for daily vitamin D supplementation to prevent vitamin D deficiency. Reproduced with permission from ref. 24.

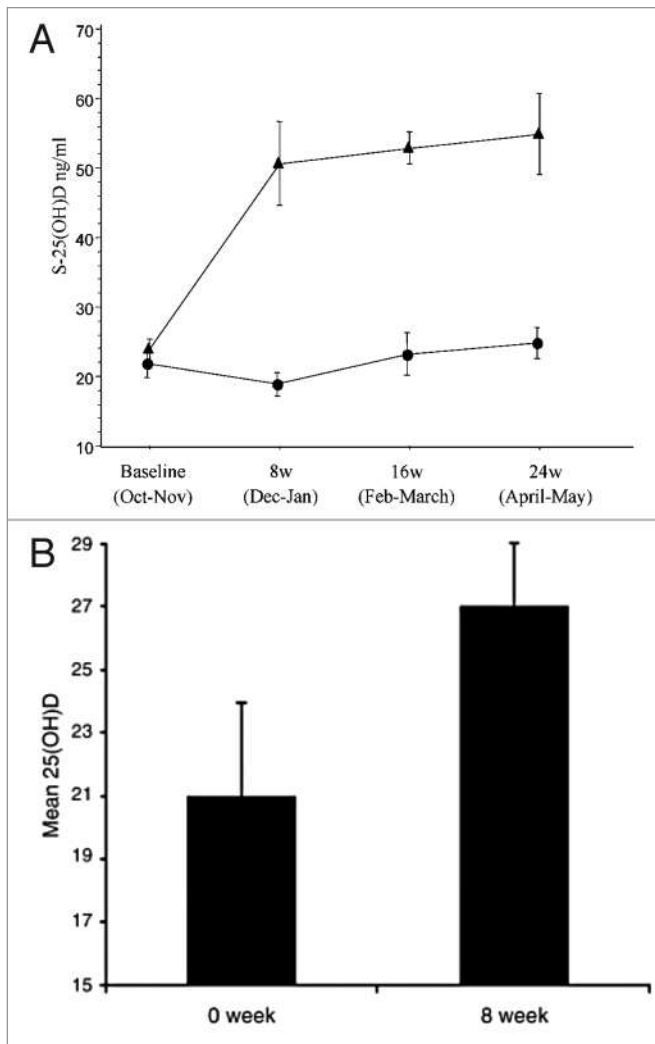




**Figure 71.** Various UVB lamps including Sperti and Sun Kraft used for vitamin D production and rickets prevention. Holick, copyright 2013. Reproduced with permission.



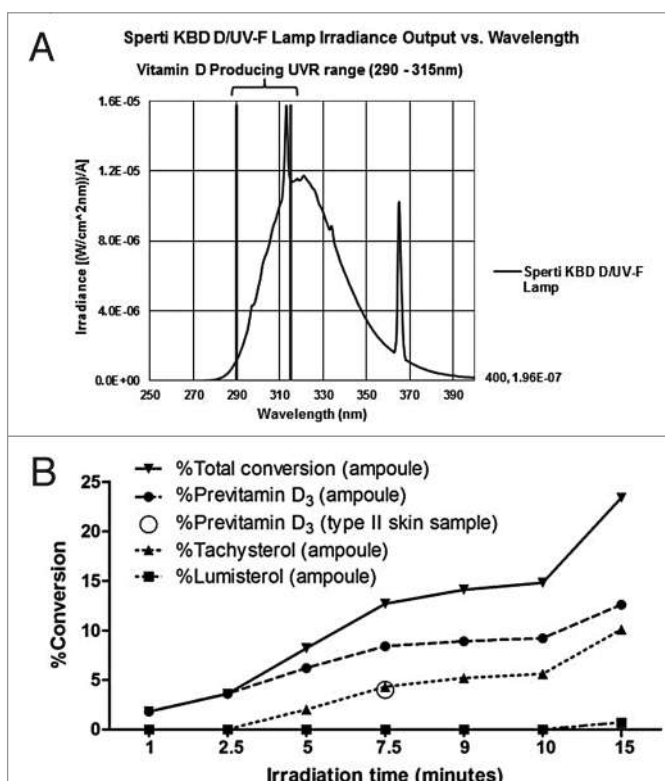
**Figure 72.** Russian children who are being exposed to UVB radiation.



**Figure 73. (A)** Mean (SEM) serum levels of 25(OH)vitamin D in patients with cystic fibrosis, treated with UVB (▲) (n = 9), and non-treated CF patients as controls (●) (n = 14) at baseline and after 8, 16 and 24 weeks. There were significant differences between the groups at all time points except at baseline (ANOVA,  $p < 0.0001$ ). **(B)** Mean ( $\pm$  SEM) serum 25-hydroxyvitamin D concentration (ng/mL) before and after 8 weeks of UV light to cystic fibrosis (CF) subjects. Serum 25-hydroxyvitamin D [25(OH)D] levels in the five CF subjects at baseline were  $21 \pm 3$  ng/ml, which increased to  $27 \pm 4$  ng/ml at the end of 8 weeks ( $p = 0.05$ ). Reproduced with permission from ref. 227.

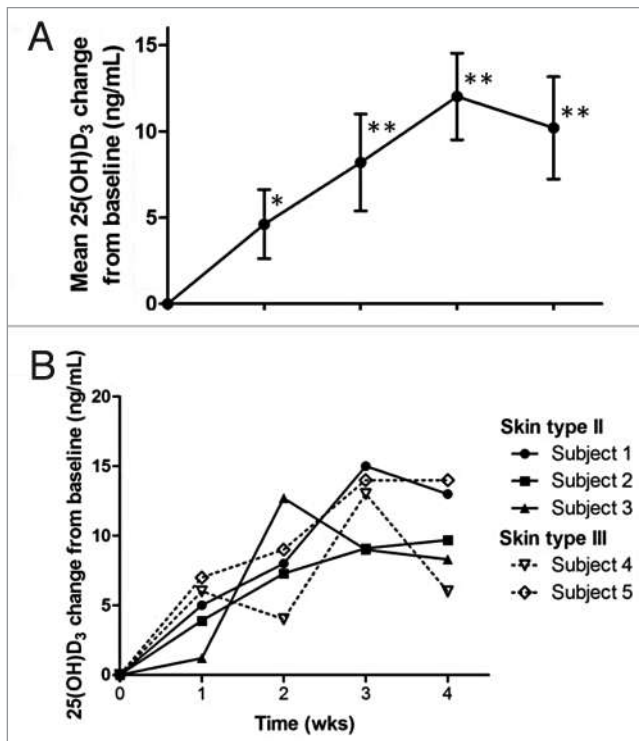


**Figure 74.** Photograph of a current version of the Sperti lamp with four fluorescent lamps. Holick, copyright 2013. Reproduced with permission.

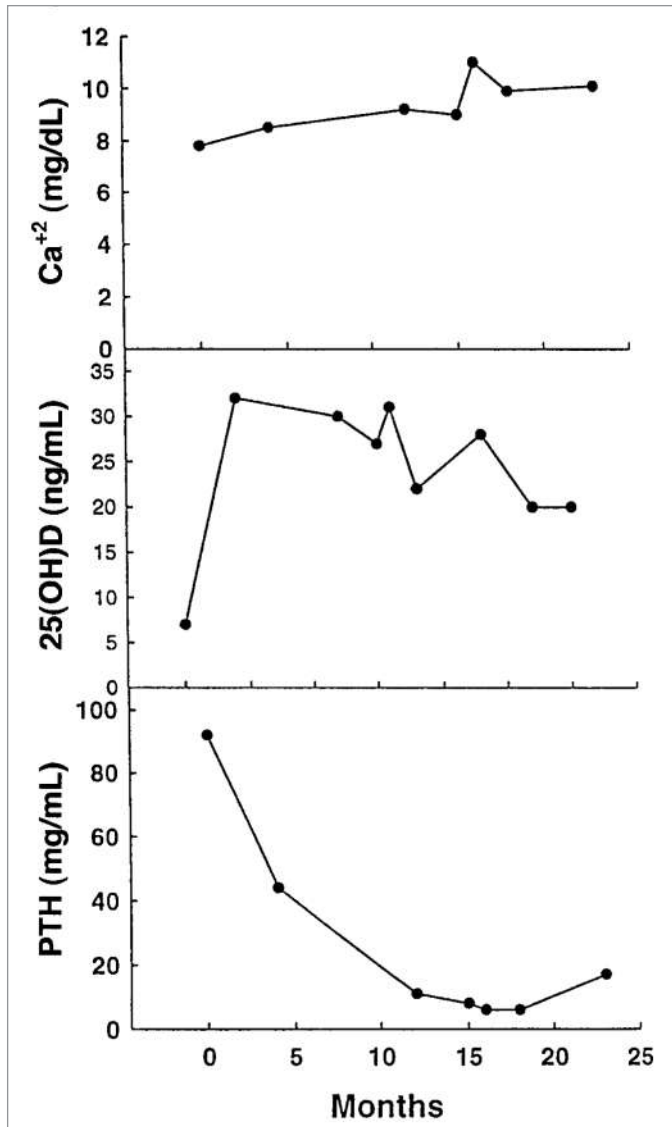


**Figure 75. (A)** The Sperti KBD D/UV-F lamp irradiance output overlaps with UV wavelengths necessary for cutaneous vitamin D<sub>3</sub> production (290–315 nm). **(B)** Relationship between UV irradiation time and conversion of 7-DHC to previtamin D<sub>3</sub>, lumisterol, and tachysterol in borosilicate glass ampoules containing 7-DHC. Conversion of 7-DHC to previtamin D<sub>3</sub> in a type II human skin sample is represented by the open circle. Reproduced with permission from ref. 229.

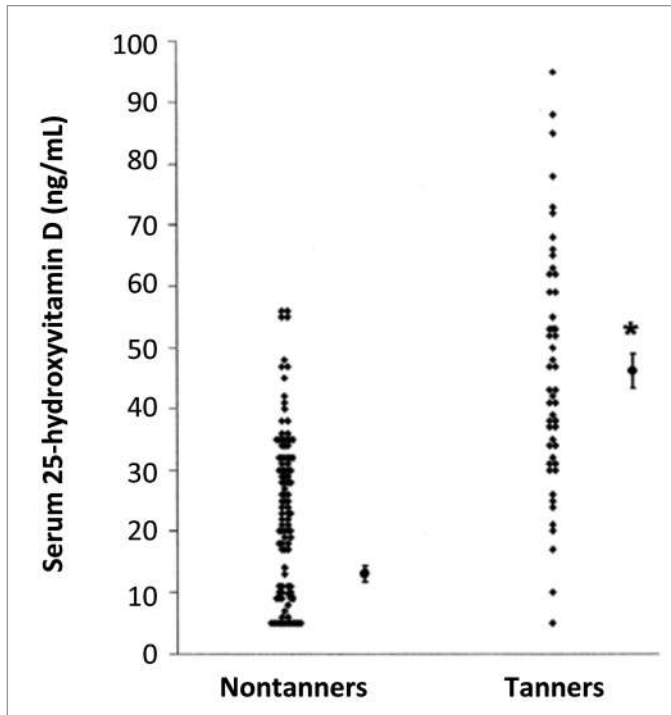




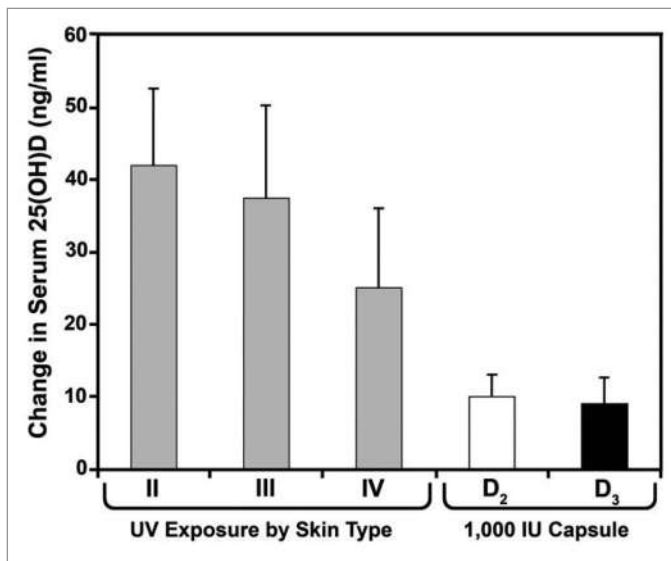
**Figure 76.** (A) Mean change in serum 25(OH)D<sub>3</sub> levels (ng/mL) compared with baseline among the five subjects during the study, error bars represent standard deviation. (\*) denotes  $p < 0.01$  and (\*\*) denotes  $p < 0.005$  compared with baseline serum 25(OH)D<sub>3</sub>. (B) Changes in serum 25(OH)D<sub>3</sub> (ng/mL) in each individual subject compared with baseline. Reproduced with permission from ref. 229.



**Figure 77.** Serum 25(OH)D, PTH and calcium levels in a patient with Crohn's disease who had whole-body UVB exposure for 10 min 3 times a week for 6 mo. Reproduced with permission from ref. 230.

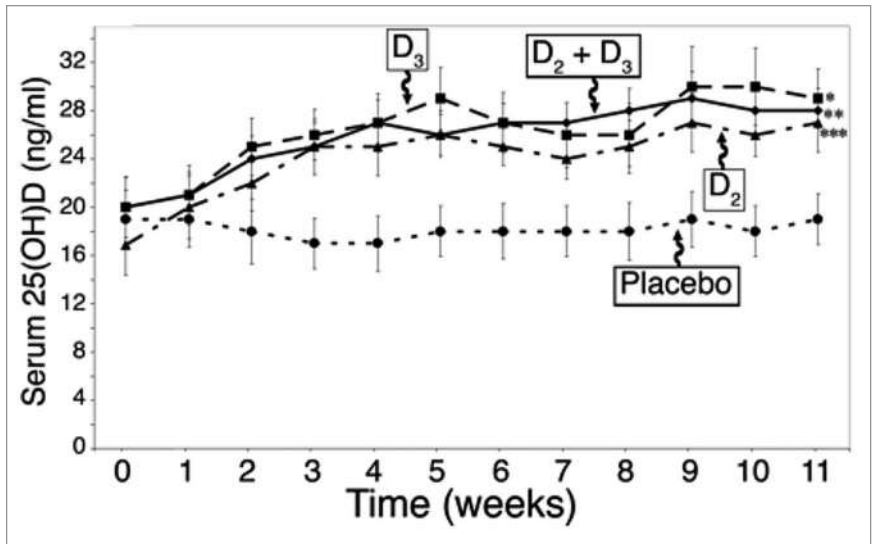


**Figure 78.** Mean ( $\pm$  SEM) serum 25-hydroxyvitamin D concentrations in tanners and nontanners. Single points for each category are means  $\pm$  SEMs. \*Significantly different from nontanners,  $p < 0.001$ . Reproduced with permission from ref. 231.

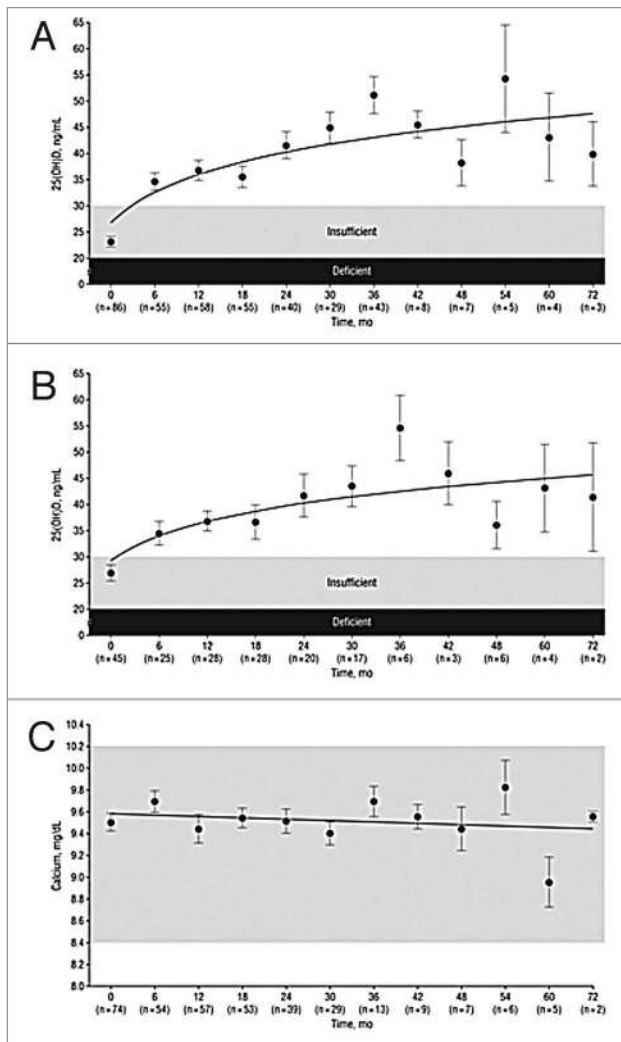


**Figure 79.** Comparison of the percentage increase in serum 25(OH)D levels of healthy adults who were in a bathing suit and exposed to suberythemal doses (0.5 MED) of UV B radiation once a week for 3 mo with healthy adults who received either 1000 IU of vitamin D<sub>2</sub> or 1000 IU of vitamin D<sub>3</sub> daily during the winter and early spring for a period of 11 weeks. Fifty percent increase represented approximately 10 ng/ml from baseline  $18 \pm 3$  to  $28 \pm 4$  ng/ml. Skin type is based on the Fitzpatrick scale: Type II always burns, sometimes tans; type III always burns, always tans; type IV sometimes burns, always tans; type V never burns, always tans. Data are means  $\pm$  SEM. Holick, copyright 2008. Reproduced with permission.

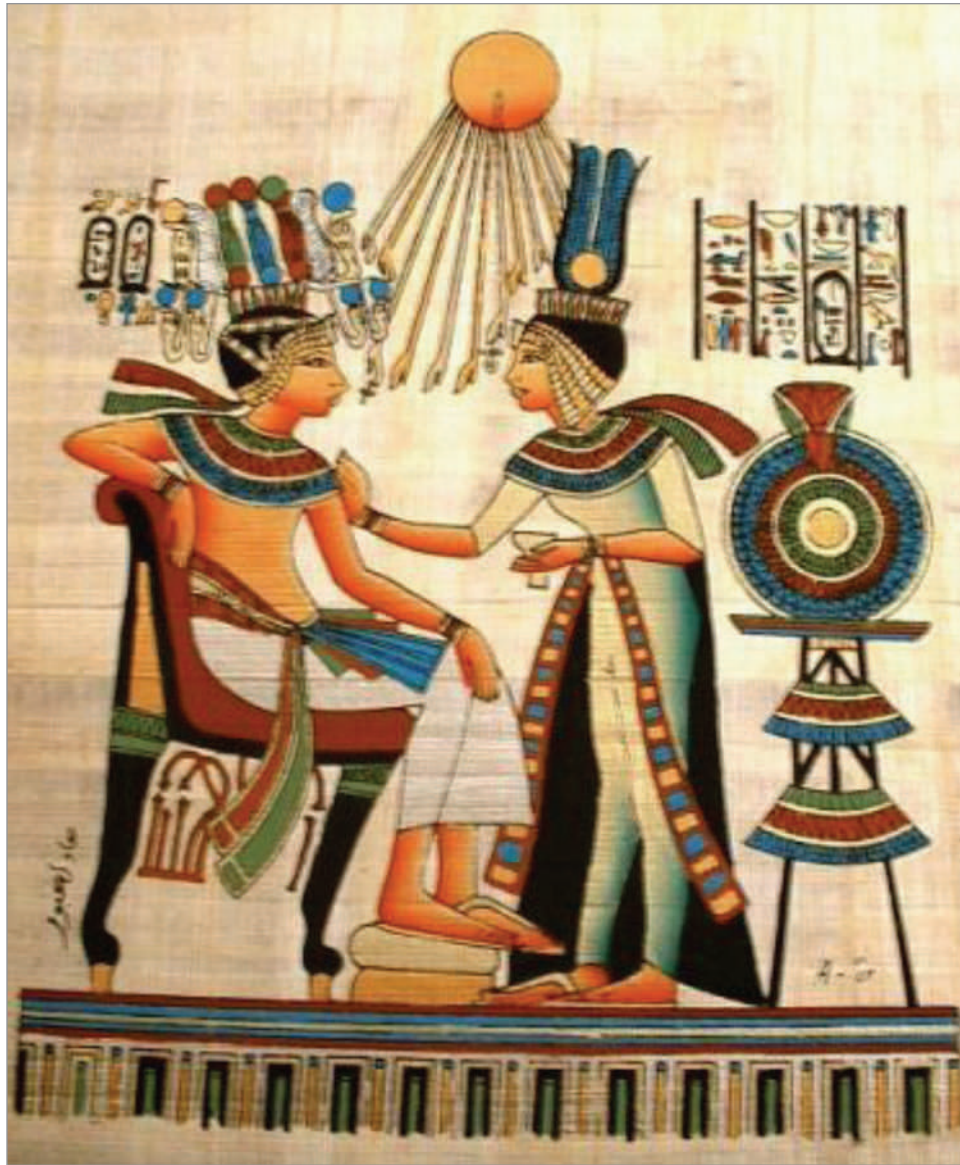




**Figure 80.** Mean ( $\pm$  SEM) serum 25(OH)D levels after oral administration of vitamin D<sub>2</sub> and/or vitamin D<sub>3</sub>. Healthy adults recruited at the end of the winter received placebo (●; n = 14), 1000 IU vitamin D<sub>3</sub> (D<sub>3</sub>; ■; n = 20), 1000 IU vitamin D<sub>2</sub> (D<sub>2</sub>; ▲; n = 16), or 500 IU vitamin D<sub>2</sub> and 500 IU vitamin D<sub>3</sub> [D<sub>2</sub> and D<sub>3</sub>; ◆; n = 18] daily for 11 weeks. The total 25(OH)D levels are demonstrated over time. \*, p = 0.027 comparing 25(OH)D over time between vitamin D<sub>3</sub> and placebo; \*\*, p = 0.041 comparing 25(OH)D over time between 500 IU vitamin D<sub>3</sub> plus 500 IU vitamin D<sub>2</sub> and placebo; \*\*\*, p = 0.023 comparing 25(OH)D over time between vitamin D<sub>2</sub> and placebo. Reproduced with permission from ref. 215.

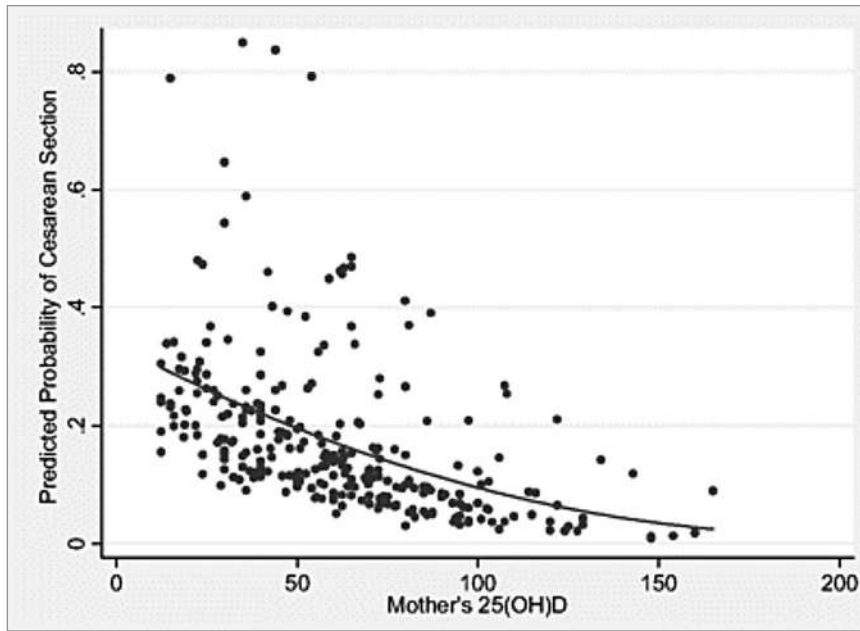


**Figure 81.** Mean serum 25-hydroxyvitamin D (25[OH]D) and calcium levels. Results are given as mean (SEM) values averaged over 6-mo intervals. Time 0 is initiation of treatment. **(A)** Mean 25(OH)D levels in all patients treated with 50,000 IU of ergocalciferol (vitamin D<sub>2</sub>) every 2 weeks (maintenance therapy, n = 86). Forty-one of the patients were vitamin D insufficient or deficient and first received 50,000-IU ergocalciferol weekly for 8 weeks before being placed on maintenance therapy of 50,000 IU of ergocalciferol every 2 weeks. The mean 25(OH)D level of each 6-mo interval was compared with initial mean 25(OH)D level and showed a significant difference of  $p < 0.001$  for all time points. To convert 25(OH)D to nanomoles per liter, multiply by 2.496. **(B)** Mean serum 25(OH)D levels in patients receiving maintenance therapy only. There were 38 patients who were vitamin D insufficient (25[OH]D levels < 21–29 ng/mL and 7 patients who were vitamin D sufficient (25[OH]D levels  $\geq 30$  ng/mL) who were treated only with maintenance therapy of 50,000 IU of ergocalciferol (vitamin D<sub>2</sub>) every 2 weeks. The mean 25(OH)D levels in each 6-mo interval were compared with mean initial 25(OH)D levels and showed a significant difference of  $p < 0.001$  for all time points up to 48 mo. The data for interval months 60 and 72 were pooled, and there was a significant difference of  $p < 0.01$  compared with the baseline value. **(C)** Serum calcium levels. Results for all 86 patients who were treated with 50,000 IU of ergocalciferol (vitamin D<sub>2</sub>). The reference range for serum calcium level is 8.5 to 10.2 mg/dL (to convert to millimoles per liter, multiply by 0.25). Reproduced with permission from ref. 252.

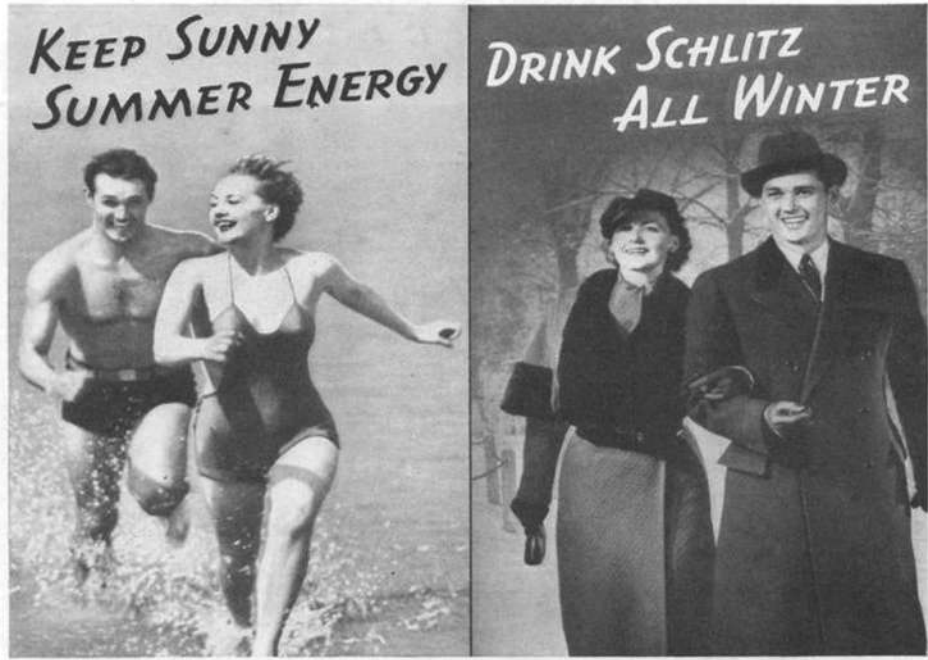


**Figure 82.** Egyptian painting showing the pharao and the queen being exposed to sunshine.





**Figure 83.** This graph shows the association between mother's increasing 25(OH)D level in nmol/L, and decreasing predicted probability of having a Cesarean section vs. vaginal delivery, with a quadratically fit line. The predicted probabilities of Cesarean section are derived from a multivariate logistic regression model controlling for mother's age, education, insurance status, and race. Additionally, the model controls for reporting ever drinking alcohol during pregnancy, as this was statistically significant in univariate analysis and remained statistically significant at the  $p < 0.05$  level in multivariate analysis. Reproduced with permission from ref. 54.



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SUMMER ENERGY**

**DRINK SCHLITZ  
ALL WINTER**

**T**O help retain the peak of sunny summer energy—to help maintain rugged resistance all through Fall and Winter—drink SCHLITZ, with SUNSHINE VITAMIN D.

As the summer sun heads south; as days grow shorter and stormier—we get less and less of sunshine's benefits. Likewise, our ordinary foods are lacking in Sunshine Vitamin D, so essential to robust vitality.

SCHLITZ, with SUNSHINE VITAMIN D\*, gives you the sunny source of energy you need the

whole year around. Beer is good for you—but SCHLITZ, with SUNSHINE VITAMIN D, is extra good for you. It has all the old-time SCHLITZ FLAVOR AND BOUQUET brewed to mellow ripe perfection under PRECISE ENZYME CONTROL, with new health benefits . . . and at no increase in price.

Drink SCHLITZ regularly—every day—for enjoyment—for energy. Jos. Schlitz Brewing Company, Milwaukee, Wisconsin.

\*Each 12-ounce bottle or can of SCHLITZ contains 100 U.S.P. XI Units of Sunshine Vitamin D. SCHLITZ brewer's yeast contains pro-vitamin D which is activated directly by the ultra-violet rays of the sun to form Vitamin D. (Protected by U.S. Letters Patent.)

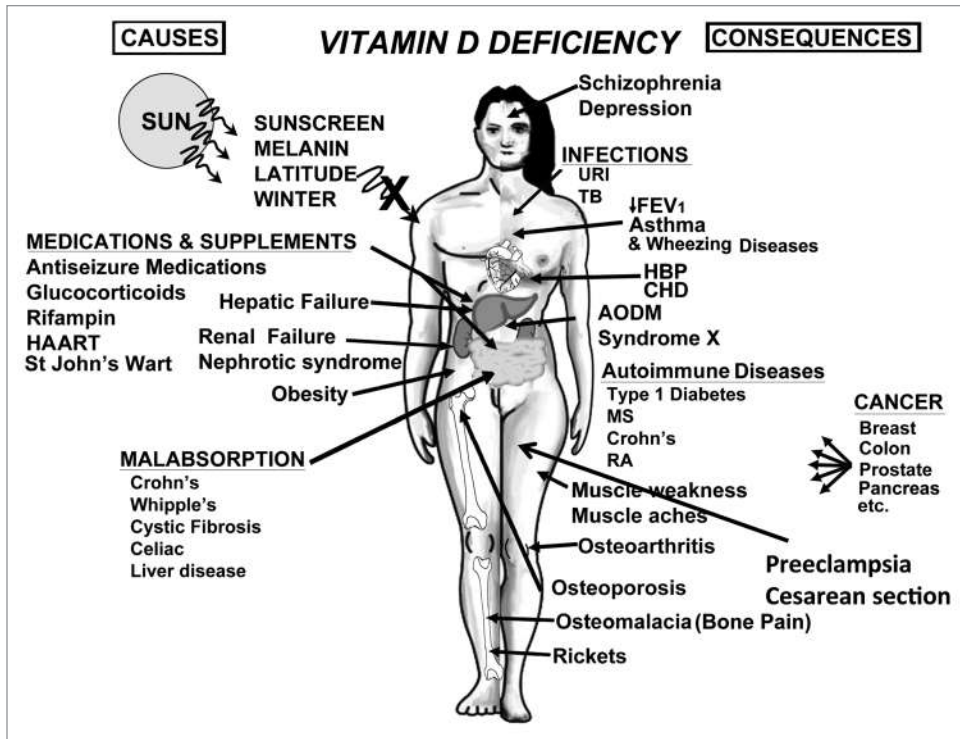
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WITH SUNSHINE VITAMIN-D



**The Beer That Made Milwaukee Famous**

**Figure 84.** Schlitz Beer advertisement with the slogan “keep sunny energy all winter long drink vitamin D fortified Schlitz beer” from 1936.



**Figure 85.** A Schematic representation of the major causes for vitamin D deficiency and potential health consequences. Holick, copyright 2007. Reproduced with permission.