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 D₃ which in turn isomerizes into vitamin D₃. Preitamin D₂ and vitamin D₃ also absorb UV B 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 D₃ (Fig. 1). 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 D₃. Once formed this thermodynamically unstable isomer is transformed into vitamin D₂. Similarly yeast and fungi also contain high amounts of ergosterol and when exposed to sunlight produce vitamin D₃.

Although the functions of ergosterol and vitamin D₃ 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). After absorbing UVB radiation previtamin D₃ 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 photodamage (Fig. 2). When previtamin D₃ is exposed to UVB radiation it is converted to tachysterol, 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). 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 D₃, 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.

The amount of previtamin D₃ 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.

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 D₃ 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.
including calcium. This could be the connection for why vertebrates including humans have depended on sun exposure for the maintenance of their calcium metabolism.\(^2,5,7\)

**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).\(^8,9\)

The first insight into the possible relationship between the industrialization of Northern Europe and rickets was made by Sniadecki\(^10\) (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\(^11\) 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 Huldschinsky\(^12,13\) (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).\(^12,13\)

Finally in 1921 Hess and Unger\(^8,14\) (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.\(^8\) Steenbock and Black\(^15\) (Fig. 5D) and Hess and Weinstock\(^16\) 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\(_2\) to the milk (Fig. 7).\(^4\)

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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.

**Figure 2.** UV absorption spectra for (A) previtamin D\(_3\), (B) tachysterol, (C) provitamin D\(_3\) (7-dehydrocholesterol), (D) lumisterol, (E) DNA, and (F) albumin. Holick, copyright 2007. Reproduced with permission.
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). Within a few years these interventions essentially eradicated rickets.

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. 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).

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. Legislation quickly followed banning the fortification of any food or personal use products with vitamin D in Great Britain. 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. 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. Sweden and Finland now permit milk to be fortified with vitamin D. 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 years juice products including orange juice have been fortified in the United States with 100 IU vitamin D/8 oz without any reports of toxicity.

Photochemistry of Provitamin D₃

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. Most of this UVB radiation is absorbed in the epidermis and as a result when exposed to sunlight most of the vitamin D₃ 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 D₃ 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
for previtamin D₃ that was produced in the skin to convert to vitamin D₃. Studies of lizard skin exposed to simulated sunlight revealed that the conversion of previtamin D₃ to vitamin D₃ was 10 times faster when compared with previtamin D₃ in an isotropic organic solution (Fig. 12).⁶ A similar observation was made in human skin (Fig. 13).⁷ This suggested that the skin had some property that accelerated the conversion of previtamin D₃ to vitamin D₃. One possible explanation was that an enzyme existed that catalytically converted previtamin D₃ to vitamin D₃. Skin homogenates incubated with previtamin D₃ did not result in an enhancement in its conversion to vitamin D₃. 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 D₃ upon exposure to solar UVB radiation (Fig. 11).⁶,7,26-28

From a physiologic perspective it made little sense for it to take several days for previtamin D₃ to convert to vitamin D₃ 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 D₃ to convert in the skin to vitamin D₃. Studies of lizard skin exposed to simulated sunlight revealed that the conversion of previtamin D₃ to vitamin D₃ was 10 times faster when compared with previtamin D₃ in an isotropic organic solution (Fig. 12).⁶ A similar observation was made in human skin (Fig. 13).⁷ This suggested that the skin had some property that accelerated the conversion of previtamin D₃ to vitamin D₃. One possible explanation was that an enzyme existed that catalytically converted previtamin D₃ to vitamin D₃. Skin homogenates incubated with previtamin D₃ did not result in an enhancement in its conversion to vitamin D₃. 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 D₃ upon exposure to solar UVB radiation (Fig. 11).⁶,7,26-28

Once formed, this unstable conformer rapidly converted to vitamin D₃.⁶,7,26-28 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 D₃ to vitamin D₃ (Fig. 15).²⁷

Because vitamin D₃ 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...
Therefore sensible sun exposure to produce previtamin D₃, vitamin D₃ and its photoproducts may have some additional benefits above and beyond simply taking a vitamin D₃ supplement or ingesting vitamin D₃ from dietary sources.

Factors that Influence Cutaneous Vitamin D₃ 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. 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. 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. This is the explanation for why during the winter when living above and below approximately 33° latitude very little if any vitamin D₃ can be produced in the skin from sun exposure. People who live farther North and South often cannot make any vitamin D₃ in their skin for up to 6 mo of the year. For example in Boston at 42° North essentially no vitamin D₃ can be produced in the skin from November through February. Inhabitants living in Edmonton Canada at 52° North, Bergen Norway at 60° North,
or Ushuaia Argentina at 55° South are unable to produce any significant vitamin D₃ for about 6 mo of the year (Figs. 23 and 24).²,³⁹,⁴¹

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 D₃.⁴²,⁴³

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 D₃ can be produced in the skin before 10 a.m. and after 3 p.m. even in the summer time (Figs. 23 and 25).⁴⁴

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 D₃ in the skin (Fig. 27).¹⁰,⁴⁵ The amount of UVB radiation available for cutaneous vitamin D₃ 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.⁴⁵

Figure 8. Brochure of the US Department of Labor promoting sensible sun exposure in children in 1931.
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 D₃. 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 D₃ synthesis in vitro was conducted at higher altitudes at the same latitude during the same month. In November in Agra very little previtamin D₃ was produced during exposure to the sun. It was observed that there was a direct correlation with increased previtamin D₃ production with increased altitude. At Mt Everest base camp (5300 M) there was almost a 5-fold increase in previtamin D₃ production compared with what was observed in Agra (Fig. 28). 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 D₃ in the skin (Fig. 29). Sunscreens were designed to absorb solar UVB radiation. 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 D₃ by the same amount i.e., 95–98%. This was confirmed with the report that the application of sunscreen with a SPF of only 8 dramatically reduced the blood level of vitamin D₃ after exposure to simulated sunlight in a tanning bed (Fig. 30). 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).

b) Skin pigment. Humans evolved at the equator. They were constantly exposed to sunlight and developed an efficient natural sunscreen melanin, which has an absorption spectrum of 290–700 nm and thus can effectively absorb solar UVB radiation (Fig. 32). 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 D₃. 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 D₃ more than 30 fold the black adults demonstrated no significant increase in their blood levels of vitamin D₃. However when the black adults were exposed to 5 times more UVB radiation, they increased their blood level by about 15-fold (Fig. 33). 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 D₃ in the white skin sample whereas only about 0.3% of 7-dehydrocholesterol was converted to previtamin D₃ in the black skin (Fig. 34). These findings could explain the positive association between skin lightness and
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.53

Although there have been several explanations for why skin pigment devolved 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 D₃ 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 D₃.49 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 D₃ 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.22,54 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 D₃.54,55 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.56,57 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. 35). The associations between skin lightness, UVB dose and 25(OH)D are documented in Figure 36.
in a tanning bed. The increase in the blood level of vitamin D₃ 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 D₃ (Fig. 39). With this marked age-related decrease in the cutaneous production of vitamin D₃ could the elderly benefit from being exposed to sunlight or UVB radiation? The skin has a large capacity to produce vitamin D₃. 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 IU's of vitamin D₃ (Fig. 40). 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 D₃ (Fig. 41A). 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). A study in elderly in a bathing suit in a tanning bed was also effective in raising and maintaining 25(OH)D levels in these residents (Fig. 43).

Influence of Latitude and Season on Vitamin D Status

It is well documented that seasonal differences in cutaneous vitamin D₃ production have a dramatic influence on both children's and adults' vitamin D status (D represents vitamin D₂ or vitamin D₃). 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 (~30 ng/mL) and the nadir was observed in February (~14 ng/mL) (Fig. 44). 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).
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. In the early 1900s Finsen observed that exposure to sunlight 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. 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. The rise in the use of pharmaceuticals to treat acute and chronic diseases led to the demise of heliotherapy especially in United States.

**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, 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. In 1937 Peller and Stephenson 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. Four years later, Apperly 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. 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 nonmelanoma 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.

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 literature.

Latitude also has a dramatic influence on the cutaneous production of vitamin D and therefore on a person’s vitamin D status. 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. However another study reported that those living at the highest latitudes in Europe had higher circulating concentrations of 25(OH)D.

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 in their skin for more than half of the year adapted by eating foods rich in vitamin D including oily fish while others did not.
connection with the association with latitude and cancer mortality could be linked to an inverse relationship with cancer mortality and vitamin D status. Even in California where there is a large difference in latitude there was a positive association with colorectal cancer prevalence with latitude (Fig. 52).

A multitude of epidemiologic studies followed these initial observations not only in the United States and Canada but worldwide. Grant 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
associations with exposure to solar UVB radiation and cancer risk and mortality were reported for ovarian and breast cancer, and prostate cancer. A meta-analysis of studies reporting cancer incidence rates for numerous malignancies was strongly related to solar UVB exposure in 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. Boscoe and Schymura found 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. Boscoe and Schymura found 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. Boscoe and Schymura reported men who worked outdoors had a 3-y hiatus before developing prostate cancer compared with indoor workers (Fig. 54). Giovannucci et al. 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. 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. Knight et al. 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 synthesis as the beneficial factor responsible for these observations. It is known that exposure to sunlight also has other physiologic effects on the skin including altering the immune system, increasing production of β endorphin and nitric oxide. 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. Woo et al. 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 per day had a statistically significant decrease in the rate of PSA rise (Fig. 57).

Lappe et al. 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 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 daily for up to 8 y had no reduced risk for colorectal cancer. 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 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. 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 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. 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. 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.

**Sunlight and Vitamin D: Innate Immune Health**

Cod liver oil was used in the mid-1800s to treat tuberculosis. In the early 1900s heliotherapy was promoted for treating both...
likely to die of them.8,14,115,116 Therefore sun exposure and vitamin D were used in the early 1900s to treat and prevent tuberculosis113,114,117 and upper respiratory tract infections.72

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.8,14,115,116 Therefore sun exposure and vitamin D were used in the early 1900s to treat and prevent tuberculosis113,114,117 and upper respiratory tract infections.72
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.\(^1\)\(^2\)

Macrophages play an important role in fighting infectious diseases by ingesting and then destroying them.\(^1\)\(^3\) When a macrophage ingests an infectious agent like tuberculosis toll-like receptors are activated to initiate an innate immune response.\(^1\)\(^4\) 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)\(_2\)D. 1,25(OH)\(_2\)D interacts with the VDR and increases the expression of cathelicidin\(^1\)\(^5\) which is a member of the defensin proteins and rapidly permealizes 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.\(^1\)\(^5\) 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.\(^1\)\(^6\) 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)\(_2\)D\(_3\) from 25(OH)D\(_3\) 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.\(^1\)\(^7\)\(^-\)\(^1\)\(^0\) 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.\(^1\)\(^1\) Calcium and vitamin D supplementation...
was associated with a lower risk of tooth loss in elderly men and women, respectively and with better periodontal health.\textsuperscript{132,133}

**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.\textsuperscript{73,134-139} Being born and living for the first 10 y at a latitude of \(-40°\) North compared with \(-33°\) North increases a person’s risk of developing multiple sclerosis by 100\% (Fig. 61).\textsuperscript{134,140,141} Munger et al.\textsuperscript{142} 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\%.\textsuperscript{143}

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).\textsuperscript{144}

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\%.\textsuperscript{145} 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
there is an impressive increase in the incidence of type 1 diabetes occurring in Finland over the past 3 decades (Fig. 63).\textsuperscript{145}

A pronounced North-South gradient has also been reported for inflammatory bowel disease, in particular Crohn’s disease (Fig. 64).\textsuperscript{138} 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.\textsuperscript{139} 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.\textsuperscript{146}

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).\textsuperscript{147} These latitude-dependent differences in the prevalence of rheumatoid arthritis could be explained by differences in the vitamin D status. Merlino et al.\textsuperscript{148} 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%.\textsuperscript{73} However, other investigators did not find such an association when reviewing the data from this study.\textsuperscript{149}

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.\textsuperscript{135} Inactivated T- and B-lymphocytes are unable to respond to 1,25(OH)\textsubscript{2}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)\textsubscript{2}D (Fig. 60).\textsuperscript{22,63,150}

In B-cells 1,25(OH)\textsubscript{2}D downregulates immunoglobulin synthesis and B-cell memory. Thus by doing so it may reduce production of autoantibodies responsible for causing autoimmune diseases.\textsuperscript{152} 1,25(OH)\textsubscript{2}D also has a multitude of functions in activated T cells.\textsuperscript{153,154} This hormone decreases T cell proliferation as well as the number of Th\textsubscript{1}-Th\textsubscript{17} lymphocytes while...
increasing T-regulatory lymphocytes\(^{155}\) by increasing the production of Th\(_2\)-Th\(_3\) lymphocytes.\(^{156}\) 1,25(OH)\(_2\)D also directly influences the expression and synthesis of several immunomodulatory cytokines. Bouillon et al.\(^{151}\) summarized that 1,25(OH)\(_2\)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.\(^{159}\) 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.\(^{160}\) 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)\(_2\)D suppressed the production of renin.\(^{161}\) This observation was also supported by the report that VDR knockout mice have a dysregulation of the renin-angiotensin-aldosterone axis.\(^{162}\)

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.\(^{73,106,163-168}\) 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.\(^{167,169}\) Dong et al.\(^{168}\) conducted a 16-week randomized, blinded, clinical trial in 49 normotensive black boys and girls aged 16.3 ± 1.4 y to evaluate the effect of enhancing vitamin D intake from 400 IUs or 2000 IU vitamin D\(_3\) 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 ± 0.53 m/sec to 5.71 ± 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.
Two major contributing factors for cardiovascular disease are type 2 diabetes and obesity. 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. Furthermore there is also an association with vitamin D deficiency and increased risk for type 2 diabetes. 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. An inverse association between vitamin D status and diabetes was also shown in a study by Scragg et al. 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%. However, this inverse association was not observed in non-Hispanic blacks.

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. 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. 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. 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.
Beta islet cells in the pancreas have a VDR and 1,25(OH)\textsubscript{2}D\textsubscript{3} is a potent stimulator of insulin production\textsuperscript{182}. Improvement in vitamin D status has also been associated with improvement in insulin sensitivity\textsuperscript{183} mediated by upregulation of insulin receptors.\textsuperscript{184} There is evidence that vascular smooth muscle and cardiomyocytes have a VDR\textsuperscript{3,166,171} and that 1,25(OH)\textsubscript{2}D\textsubscript{3} causes vascular relaxation by suppressing the renin-angiotensin-aldosterone system\textsuperscript{73,163,185,186} and improves cardiomyocyte contractility\textsuperscript{171}. In addition, 1,25(OH)\textsubscript{2}D\textsubscript{3} inhibits macrophage cholesterol uptake and foam cell formation thereby reducing risk for atherosclerotic plaque formation (Fig. 68)\textsuperscript{73,166,187}. 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.\textsuperscript{188}

**Sunlight, Vitamin D and Mental Health**

Schizophrenia has been associated with inadequate sun exposure and vitamin D deficiency (Fig. 69)\textsuperscript{189}. Schizophrenia is more common in the Scandinavian countries\textsuperscript{189,190}. Winter births have been associated with an increased risk for developing schizophrenia later in life even in Australia.\textsuperscript{191,192} In British immigrants, incidence in schizophrenia is higher in children of immigrants from the Caribbean who moved to cities in countries farther North.\textsuperscript{193} Finnish male infants who received 2000 IU\textsubscript{s} 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 IU\textsubscript{s} of vitamin D daily.\textsuperscript{194}

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.\textsuperscript{195-197} 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.\textsuperscript{2-4,118,119,121}

There are a variety of association studies relating vitamin D deficiency with increased risk for depression,\textsuperscript{198,199} Alzheimer disease,\textsuperscript{200} epilepsy,\textsuperscript{201} and neurocognitive decline.\textsuperscript{202,203} The brain not only has a VDR but also a 1-OHase.\textsuperscript{204} Evidence suggests that 1,25(OH)\textsubscript{2}D\textsubscript{3} could increase calcium binding protein expression,\textsuperscript{205} although this could not be shown in all studies.\textsuperscript{206} 1,25(OH)\textsubscript{2}D\textsubscript{3} could also act by increasing serotonin levels in the brain.\textsuperscript{207,208} Furthermore, 1,25(OH)\textsubscript{2}D\textsubscript{3} has also been demonstrated to stimulate amyloid-\textbeta~phagocytosis and clearance by macrophages in Alzheimer patients.\textsuperscript{209} This may help explain the association between neurocognitive decline,\textsuperscript{202,203} dementia,\textsuperscript{210} depression,\textsuperscript{198,199} and Alzheimer disease\textsuperscript{200} with a high prevalence of vitamin D deficiency.\textsuperscript{211} In a community setting depressed adults had
significantly lower serum concentrations of 25(OH)D than those without depression.  

**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). They found that most but not all of the literature supports the concept that vitamin D3 is as effective as vitamin D2 in maintaining circulating concentrations of 25(OH)D. For almost 100 y a variety of strategies have been used to treat and prevent vitamin D deficiency especially in children. From 1930 through 1950s parents purchased a lamp at their local pharmacy that emitted vitamin D3 producing UVB radiation (Fig. 71). Children wearing eye protection had their arms, abdomen and legs were routinely exposed to a UV emitting lamp several times a week (Fig. 6). 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). The Sperti lamp which originally was designed with a single mercury arc lamp was commonly used in the United States in the 1940s and 1950s to prevent rickets and children (Fig. 71). This lamp was also effective in raising circulating levels of vitamin D in individuals who had cystic fibrosis and who were unable to absorb vitamin D from dietary and supplemental sources (Fig. 73A and B). Because the lamp produced a lot of heat the Sperti lamp was redesigned and the mercury arc lamp was replaced with 4 fluorescent lamps that emitted UVB radiation and produced previtamin D3 (Fig. 74). This lamp was effective in raising circulating levels of vitamin D.
concentrations of 25(OH)D in healthy adults with skin types 2 and 3 (Fig. 76).227,228

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.227,228 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).250 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.231

Sensible sun exposure can also be an excellent source of vitamin D for both children and adults.232,233 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.234-237 Studies conducted worldwide using the in vitro ampule model19 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.22,46,51,66,231-233,237-239 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 erythemal dose) followed by good sun protection i.e., clothing, hat and or sunscreen.22,239 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 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.240 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 D3.22,25,31 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 D3. 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 than ingesting 1000 IU vitamin D3 or vitamin D2 daily (Fig. 79).241 Always protect the face with a hat or sunscreen since it provides very little vitamin D3 and is most sun exposed and more prone to skin damage and skin cancer from sun exposure.242-244

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.22,51,246 The exception is indigenous populations including Inuits who consumed...
foods with high content of vitamin D such as oily fish, seal and whale blubber and polar bear liver. Therefore it is necessary without adequate sun exposure to improve children’s and adults’ vitamin D status by encouraging them to take a vitamin D supplement (Fig. 70).22,24,213

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.24,213,248 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 D3 or vitamin D2 orally with adequate dietary calcium.8,249 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.8

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.24 Infants and toddlers who received 50,000 IUs of vitamin D3 once a week or 2000 IUs of vitamin D3 or vitamin D2 daily for 6 weeks corrected their vitamin D deficiency without any untoward side effects.8,24,217 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.250

The Endocrine Society recommends that all adults receive 1500–2000 IUs of vitamin D daily.15 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 D2 or vitamin D3 was ineffective in raising and maintaining blood levels 25(OH)D above 30 ng/mL (Fig. 80).215 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.215,251

Because vitamin D is fat soluble upon its ingestion or production in the skin vitamin D3 gets incorporated into the body fat and is also transported to the liver to be converted to 25(OH)D.22,73,171-174 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.24 One strategy that is effective to quickly fill up the empty vitamin D tank is to give 50,000 IUs of vitamin D3 or 50,000 IUs of vitamin D2 once a week for 8 weeks.252 This is equivalent to ingesting approximately 6600 IUs of vitamin D daily.253 To prevent recurrence of vitamin D deficiency patients have been instructed to take 50,000 IUs of vitamin D3 (equivalent to 3500 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.
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. 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. 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. 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)2D by activated macrophages within the granulomas. This can also occur in patients with some lymphomas.

**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.

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. However there are several reports in adults that ingesting up to 1 million IUs of vitamin D3 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. A recent report of a 3 mo old inadvertently receiving 14,000 IUs of vitamin D3 daily for 20 d (i.e., total of 280,000 IUs of vitamin D3) 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. Even pregnant women who received

![Figure 40. Comparison of serum vitamin D3 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 D3. Holick, copyright 2004. Reproduced with permission.](image)

![Figure 41. Production of previtamin D3 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 D3 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.](image)
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.22,260

Conclusion and Perspective

Our ancestors routinely worshiped the sun for its life giving properties (Fig. 82).261,262 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.263 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$_3$. Females born with vitamin D deficiency and suffering from infantile rickets resulted in them having a flat pelvis and a small pelvic outlet. These

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

Figure 43. Mean (± 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.

4000 IU vitamin D/day through their pregnancy showed no change in either serum calcium or urinary calcium secretion.259
females although fertile would have had a difficult time, if not impossible, to give vaginal birth resulting in both maternal and fetal death.\textsuperscript{54,55} 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.\textsuperscript{8,54,55} Vitamin D deficiency in pregnant women today is still associated with a 400\% increase in the predicted probability for a Cesarean section (Fig. 83).\textsuperscript{74}

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,\textsuperscript{85} several autoimmune diseases including type 1 diabetes and multiple sclerosis\textsuperscript{73,134-139} as well as hypertension.\textsuperscript{159} In addition the revelation that exposure to sunlight or UV radiation could cure and prevent rickets\textsuperscript{12,13} 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.\textsuperscript{198-200,202,203,210}

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.\textsuperscript{20,22} 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.\textsuperscript{20} 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.

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.\textsuperscript{145}

In the 1970s sunscreens were first introduced as a way to prevent sunburning. The sunscreens contained UVB absorbing chemicals such as paraaminobezoic 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 lead to a worldwide vitamin D deficiency pandemic.\textsuperscript{22,173} In the United States the Center for Disease
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.269 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.22,66 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.79

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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.

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

**Figure 50.** Showing the relation of total cancer mortality rates to Smith’s Solar Radiation Index in the American states, (white population only).
Figure 51. Annual mean daily solar radiation (gm-cal/cm²) 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-weighed UVB radiation. (B) Premature mortality due to cancer, white females, vs. TOMS July 1992 DNA-weighed UVB. Reproduced with permission from ref. 79.
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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.

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.
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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.
Figure 60. Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25-dihydroxyvitamin D 1,25(OH)\(_2\)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)\(_2\)D. 1,25(OH)\(_2\)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)\(_2\)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.\(^{22-32}\) It is believed that the local production of 1,25(OH)\(_2\)D in the breast, colon, prostate, and other cells regulates a variety of genes that control proliferation. Once 1,25(OH)\(_2\)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)\(_2\)D to calcitroic acid which is biologically inert. Thus, the local production of 1,25(OH)\(_2\)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)\(_2\)D inhibits the expression and synthesis of PTH. The production of 1,25(OH)\(_2\)D in the kidney enters the circulation and is able to downregulate renin production in the kidney and to stimulate insulin secretion in the \(\beta\)-islet cells of the pancreas. Holick, copyright 2007. Reproduced with permission.

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Figure 61. Prevalence of multiple sclerosis (MS) by latitude in the United States according to data from Noonan et al.188 (x) and Wallin et al.228 (O). The dashed line is a quadratic fit to the data from Noonan et al.228 and the solid line is a fit to the data from Wallin et al.228 Reproduced with permission from ref. 134.
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. Motherwell, United Kingdom; 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. Tunis, Tunisia; 32. Chiba, Japan; 33. Hokkaido, Japan; 34. Okinawa, Japan; 38. Antwerp, Belgium; 39. Varna, Bulgaria; 43. France; 44. Baden, Germany; 45. Attica, Greece; 46. Bucharest, Romania; 47. Edinburgh, UK; 48. Sicily, Italy; 49. Pavia, Italy; 50. Marche, Italy; 52. Lazio, Italy; 53. Krakow, Poland; 61. Algarve, Portugal; 62. Madeira Island, Portugal; 64. Portalegre, Portugal; 65. Russian Federation; 66. Slovenia; 68. Catalonia, Spain; 71. Leicestershire, UK; 72. Northern Ireland, UK; 77. Allegheny, PA, USA; 80. Avellaned, Argentina; 82. Corrientes, Argentina; 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, 0.2); 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, 9.3); 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). R² = 0.25, p < 0.001.

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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. R² = 0.62, p = 0.0002. (B) Variation in ulcerative colitis incidence rates. R² = 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)2D3 prevents foam cell formation. Macrophages stained with Oil Red O. (A) Diabetic subjects (group A). Top, 1,25(OH)2D3-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)2D3-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)2D3-supplemented (white bars) media (*p < 0.01 vs. vitamin D deficient). (C) Oil Red O stain. (D) Cholesterol. (E) Triglycerides from peritoneal macrophages from LDR−/− 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) |
| Infants 0 to 6 months | 400 IU (10 µg) | 600 IU (15 µg) | 1000 IU (25 µg) | 400 IU (10 µg) | 400–1000 | 2000 |
| 6 to 12 months | 400 IU (10 µg) | 600 IU (15 µg) | 1500 IU (38 µg) | 400 IU (10 µg) | 400–1000 | 2000 |
| Children 1–3 years | 400 IU (10 µg) | 600 IU (15 µg) | 2500 IU (63 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 4–8 years | 400 IU (10 µg) | 600 IU (15 µg) | 3000 IU (75 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| Males 9–13 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 14–18 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 19–30 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 31–50 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 51–70 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| >70 years | 400 IU (10 µg) | 800 IU (20 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| Females 9–13 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 14–18 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 19–30 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 31–50 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 51–70 years | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| >70 years | 400 IU (10 µg) | 800 IU (20 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |

Pregnancy

| Life Stage Group | IOM Recommendations | Endocrine Society’s Recommendations |
|------------------|---------------------|------------------------------------|
|                  | AI      | EAR      | RDA      | UL      | Daily Allowance (IU/day) | UL (IU) |
| 14–18 years | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 19–30 years | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 31–50 years | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| Lactation * | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 600–1000 | 4000 |
| 14–18 years | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 µg) | 1500–2000 | 10,000 |
| 19–30 years | --- | 400 IU (10 µg) | 600 IU (15 µg) | 4000 IU (100 µg) | 400 IU (10 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 (± 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 ± 3 ng/ml, which increased to 27 ± 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 D₃ production (290–315 nm). (B) Relationship between UV irradiation time and conversion of 7-DHC to previtamin D₃, lumisterol, and tachysterol in borosilicate glass ampoules containing 7-DHC. Conversion of 7-DHC to previtamin D₃ 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$_3$ 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$_3$. (B) Changes in serum 25(OH)D$_3$ (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 (± SEM) serum 25-hydroxyvitamin D concentrations in tanners and nontanners. Single points for each category are means ± 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$_3$ or 1000 IU of vitamin D$_2$ daily during the winter and early spring for a period of 11 weeks. Fifty percent increase represented approximately 10 ng/ml from baseline 18 ± 3 to 28 ± 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 ± SEM. Holick, copyright 2008. Reproduced with permission.
Figure 80. Mean (± SEM) serum 25(OH)D levels after oral administration of vitamin D$_3$ and/or vitamin D$_2$. Healthy adults recruited at the end of the winter received placebo (●; n = 14), 1000 IU vitamin D$_3$ (D$_3$, ■; n = 20), 1000 IU vitamin D$_2$ (D$_2$, ▲; n = 16), or 500 IU vitamin D$_3$ and 500 IU vitamin D$_2$ (D$_2$ and D$_3$, ◆; 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$_3$ and placebo; **, p = 0.041 comparing 25(OH)D over time between 500 IU vitamin D$_3$ plus 500 IU vitamin D$_2$ and placebo; ***, p = 0.023 comparing 25(OH)D over time between vitamin D$_2$ 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) 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 ≥ 30 ng/mL) who were treated only with maintenance therapy of 50,000 IU of ergocalciferol (vitamin D) 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). 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 pharaoh 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.
**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.