ABSTRACT: The exploration of vitamin D metabolism and function has led to the discovery of active forms of vitamin D that find great usefulness in treating patients with bone disease or renal failure and also perhaps in topical application for the treatment of skin disorders, such as psoriasis. It may also be effective in some types of autoimmune disease. This warrants our attention to maintaining an adequate vitamin D level in our blood to assure that the expected functions of vitamin D take place. However, we must not get so overenthusiastic as to expect vitamin D to be effective in treating or preventing many diverse diseases and especially caution is urged in considering that vitamin D compounds might be used to suppress cancerous growth.

Key words: calcium, osteomalacia, phosphorus, rickets, vitamin D

INTRODUCTION

The existence of essential nutrients, known now as vitamins, was clearly shown by the discovery of vitamin A by McCollum and Davis (1913). This was followed by the discovery of vitamin B by McCollum et al. (1916) at the University of Wisconsin and Osborne and Mendel (1917) at Yale University. These discoveries led Sir Edward Mellanby in Great Britain to believe that rickets might also be a dietary deficiency disease (Mellanby, 1919). He was able to produce rickets in dogs by maintaining them indoors and feeding a diet of oatmeal. Mellanby further found that rickets could be prevented or cured by supplementing the oatmeal diet with cod liver oil. Since cod liver oil was a source of vitamin A discovered by McCollum and Davis, Sir Edward Mellanby believed that the healing of rickets was a further property of vitamin A (Mellanby, 1919). However, rickets could also be cured by ultraviolet light either of artificial origin or from sunlight, as demonstrated by Hulshinsky (1919) and Chick et al. (1923). The dichotomy then that cod liver oil equals sunlight in curing this disease was a difficult one to understand. Steenbock at the University of Wisconsin, however, demonstrated very clearly that exposure to UV irradiation of the animals or their food could cure rickets (Steenbock, 1924; Steenbock and Black, 1924). Furthermore, he followed this UV activation to a lipid component in the diet and, further, to a nonsaponifiable fraction of the lipid (Steenbock and Black, 1925). Therefore, sunlight produced what appeared to be a compound similar to what is in cod liver oil that cured rickets. McCollum, who had transferred to Johns Hopkins University from the University of Wisconsin, demonstrated that oxygen destroyed the vitamin A activity in cod liver oil but did not destroy its ability to cure rickets (McCollum et al., 1922). Therefore, he correctly concluded that curing rickets was the property of a separate nutrient, which he termed “vitamin D” (McCollum et al., 1922).

DISCOVERY OF FUNCTIONAL VITAMIN D METABOLISM

The fortification of foods by UV irradiation eliminated rickets as a major medical problem in the 1920s decade (Jenkins, 1991). Ultimately synthetically produced vitamin D replaced the irradiation of foods as a
preventive of rickets although the synthetically produced vitamin D included an irradiation step (Bills, 1954). The idea that irradiation could be used to produce vitamin D led Askew et al. (1930) to isolate and identify vitamin D₂ and Windaus and Schenck (1937) to identify vitamin D₃. Therefore, it was known by that time that vitamin D in some way causes the calcification of the skeleton thereby curing rickets in children and osteomalacia in adults. The structure of vitamin D₃, the natural form of vitamin D produced in skin by UV irradiation of 7-dehydrocholesterol, is provided in Fig. 1 along with the numbering system.

Between 1930 and 1949, the chemical change that occurs to 7-dehydrocholesterol in response to 280 to 315 nm UV light was elucidated by the work of Havinga (1973) and of Velluz et al. (1949). Until 1968, the idea that vitamin D directly acted to heal rickets remained intact (Kodicek, 1956). One of the well-established functions of vitamin D is to increase the ability of the intestine to absorb calcium and phosphorus (Nicolaysen, 1937; Nicolaysen et al., 1953), which are the 2 major components needed to mineralize the skeleton. It became clear from the work of Lamm and Neuman (1958) and in our own laboratory (DeLuca, 1967) that plasma is normally supersaturated with calcium and phosphorus, which is required for catalyzed crystallization, the believed mechanism of mineralization of the collagen fibrils of bone. In vitamin D deficiency, calcium and phosphorus levels in plasma are low, leading to an undersaturated solution that is unable to support the mineralization of the skeleton. Thus, it became clear that vitamin D causes mineralization of the skeleton by facilitating the elevation of plasma calcium and phosphorus to supersaturating levels (Lamm and Neuman, 1958; DeLuca, 1967).

Following the time course of response to vitamin D in vitamin D-deficient rats, a lag of 12 to 16 h was noted between the time of administration of vitamin D and the response of the intestinal calcium transport system (Lund and DeLuca, 1966; DeLuca, 1967; Morii et al., 1967). This prompted the synthesis of radiolabeled vitamin D with high enough specific activity to follow its course before the elevation of calcium absorption in the intestine (Norman and DeLuca, 1963; Neville and DeLuca, 1966). It became clear that vitamin D₃ itself disappeared and the radioactivity appeared in polar metabolites before the response of intestine (Lund and DeLuca, 1966; Morii et al., 1967). When the metabolites of vitamin D were isolated in sufficient quantity and tested for their biopotency, they were more effective and acted more rapidly than vitamin D itself to initiate intestinal calcium absorption (Lund and DeLuca, 1966; Morii et al., 1967). This led to the isolation and chemical identification of the first activated form of vitamin D, namely 25-hydroxyvitamin D (25-OH-D; Blunt et al., 1968a). Its structure was confirmed by synthesis (Blunt and DeLuca, 1969) and its biopotency was shown to be between 1.5 to 2 times that of vitamin D₃ itself (Blunt et al., 1968b). When it was radioactively labeled (Suda et al., 1971), 25-OH-D also disappeared before the response of intestine or bone, which ultimately led to the isolation and identification of the final active form, 1α,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃; DeLuca et al., 1971; Holick et al., 1971; Suda et al., 1971; Semmler et al., 1972). This resulted in our knowledge of the activation of vitamin D in preparation for function (DeLuca, 1974), as shown in Fig. 2. We now know that the liver is the site of the first modification of vitamin D, which is a 25-hydroxylation by a cytochrome P450 (CYP) 2R1 enzyme found in the microsomes of the liver (Cheng et al., 2003). Currently, there is a belief that there is 1 remaining CYP enzyme that also 25-hydroxylates vitamin D but that has yet to be identified (Zhu et al., 2013). This produces the blood form of vitamin D or 25-OH-D, which is currently measured to assess the vitamin D status of patients and animals. This compound is converted primarily, if not exclusively, in the proximal convoluted tubule cells of
the kidney (Fraser and Kodicek, 1970; Gray et al., 1971; Brunette et al., 1978) to a final vitamin D hormone by a CYP27B1 enzyme (Shinko et al., 1997; St.-Arnaud et al., 1997; Takeyama et al., 1997), which is the highly regulated step of vitamin D metabolism (Boyle et al., 1971, 1972a; DeLuca, 1974). It is this compound that acts directly on intestine and bone to facilitate the elevation of calcium and phosphorus that is responsible for the mineralization of the skeleton (Boyle et al., 1972b; Holick et al., 1972). This was the beginning of our understanding of the vitamin D endocrine system that is responsible for the regulation of plasma calcium and phosphorus, as described subsequently.

THE VITAMIN D–BASED ENDOCRINE SYSTEM

Experiments of nature established very clearly that 1α-hydroxylation is the final necessary step in vitamin D activation since vitamin D–dependency rickets Type I (VDDR-I) proved to be a failure in the CYP27B1 system (Shinko et al., 1997; St.-Arnaud et al., 1997; Takeyama et al., 1997), which is the highly regulated step of vitamin D metabolism (Boyle et al., 1971, 1972a; DeLuca, 1974). It is this compound that acts directly on intestine and bone to facilitate the elevation of calcium and phosphorus that is responsible for the mineralization of the skeleton (Boyle et al., 1972b; Holick et al., 1972). This was the beginning of our understanding of the vitamin D endocrine system that is responsible for the regulation of plasma calcium and phosphorus, as described subsequently.

Figure 3. Diagrammatic representation of the regulation of plasma calcium concentration by the intervention of the active form of vitamin D, that is, 1α,25-dihydroxyvitamin D3 (1,25-(OH)2D3) and the parathyroid hormone (PTH). See online version for figure in color.
is well known that calcium is sometimes not found in the diet and, therefore, even if the calcium transport process is turned on in the intestine, it cannot maintain serum calcium at supersaturating levels. To be sure that serum calcium is maintained to prevent hypocalcemic tetany, the body has another mechanism whereby calcium can be pumped from the bone fluid compartment back into the plasma compartment through the osteoclast, causing bone resorption but maintaining the level of plasma calcium (Carlsson, 1952; Bauer et al., 1955; Jones et al., 1998). This process requires 2 hormones: the vitamin D hormone and the parathyroid hormone (PTH). It is clear that vitamin D is required for PTH to mobilize bone and vice versa (Rasmussen et al., 1963; Garabedian et al., 1974). A final mechanism is in the distal renal tubule. The last 1% of the filtered load of calcium comes under control of the vitamin D hormone and the PTH, again acting in concert (Yamamoto et al., 1984). Although 1% appears to be a small figure, because 7 g of calcium are filtered per day, 1% of that figure is a significant contribution to the calcium homeostatic process.

Continued experimentation has led to an understanding of the vitamin D–based endocrine system, which is illustrated in Fig. 4 (DeLuca, 1974; Jones et al., 1998). Serum calcium level is tightly held at 1 mM ionized calcium or 10 mg/dL total calcium. When calcium concentration falls slightly below that level, the parathyroid glands secrete the 84–amino acid peptide hormone PTH that has 2 targets of action. It is bound throughout the nephron of the kidney and it acts through the osteoclast to facilitate osteoclastic bone resorption (Heersche et al., 1994). It also acts together with the vitamin D hormone in the distal renal tubule for reabsorption of calcium (Yamamoto et al., 1984). In the kidney, its primary function is to activate the production of the vitamin D hormone (Boyle et al., 1971; Garabedian et al., 1972; DeLuca, 1974). It is this compound that then goes to intestine, bone, and kidney where it facilitates the active transport of calcium, resorption of bone, and reabsorption of calcium in the kidney, driving calcium up in the plasma, clearing the set point, and shutting off parathyroid secretion. Overshoot is monitored by the parafollicular or “C” cells of the thy-
Vitamin D: Bones and beyond

**Figure 5.** The catalysis of degradation of 1α,25-dihydroxyvitamin D₃ (1,25-(OH)₂D₃) to its final excretion product, calcitroic acid by the enzyme, cytochrome P450 (CYP) 24A1. 2-Methylene-19-nor-(20S)-1,25-dihydroxyvitamin D₃ is clearly a bone anabolic compound. 1,24,25-(OH)₃D₃ = 1α,24,25-trihydroxyvitamin D₃; 24-OXO-1,23,25-(OH)₃D₃ = 24-keto-1α,23,25-dihydroxyvitamin D₃; 24-OXO-1,25-(OH)₂D₃ = 24-keto-1α,25-dihydroxyvitamin D₃.

roid that secrete a 32–amino acid peptide hormone, calcitonin that generally blocks bone resorption to keep serum calcium from becoming too high (Deftos, 1981). It also causes a very low level of production of the vitamin D hormone to be sure that this required hormone is made at least in small amounts even under conditions of high plasma calcium concentration (Shinki et al., 1999).

One of the new findings is that the vitamin D hormone has an important target in the parathyroid gland (Hughes and Haussler, 1978; Stumpf et al., 1979; Demay et al., 1992) where it suppresses parathyroid production and secretion, thus preventing what is called secondary hyperparathyroidism where there is a runaway parathyroid gland that can produce excessive bone resorption (Demay et al., 1992; Silver and Naveh-Many, 2005; Slatopolsky and Dusso, 2005).

1,25-Dihydroxyvitamin D₃ is one of the most potent compounds made in the body. One-half microgram produces a full serum calcium response in an adult man (Gallagher et al., 1982). Its potency is so great that it must be tightly regulated by degradation as well as by synthesis. One of the functions of the vitamin D hormone is to induce a CYP24A1 in all target tissues of vitamin D, and this enzyme carries out a series of degradation steps on the vitamin D hormone (as shown in Fig. 5) that results in the elimination of the inactive product, calcitroic acid, in the bile (Esvelt et al., 1979), thereby eliminating this most potent hormone from continuing to raise serum calcium (Beckman et al., 1996; Omdahl and May, 2005; Schlingmann et al., 2011). Between the regulation of its synthesis and the regulation of its degradation, 1,25-(OH)₂D₃ is under very strict control and is used to maintain normal levels of calcium and phosphorus in the plasma.

**THE VITAMIN D RECEPTOR**

Another important discovery is the idea that vitamin D, being a steroid, works through a nuclear receptor mechanism. Brumbaugh and Haussler (1975) produced the first demonstration of a protein that specifically binds 1,25-(OH)₂D₃. This was very rapidly confirmed (Kream et al., 1976) and led to the immediate identification of another set of vitamin D–resistant rickets cases, called vitamin D–dependency rickets Type II (VDDR-II; Brooks et
al., 1978; Balsan et al., 1983; Malloy et al., 2005). These patients have a defect in the vitamin D receptor (VDR) that can either lead to a dependency on high levels of the vitamin D hormone or a complete failure to respond to this hormone. After birth, these VDDR-II patients exhibit severe rickets, severe hypocalcemia, and hypophosphatemia and are in serious trouble (Brooks et al., 1978). The most severe of these mutations require that these patients receive calcium and phosphorus infusions into the bloodstream to substitute inadequate absorption (Balsan et al., 1983). While the prognosis for these patients is poor, the biology behind their misfortune has added greatly to our knowledge of how vitamin D functions. Since that time, several VDR knockout animals have been produced confirming the essentiality of this protein for the function of vitamin D (Li et al., 1997; Yoshizawa et al., 1997). There have been a number of reports in the literature based on in vitro cellular experiments claiming that vitamin D works by a nongenomic mechanism independent of VDR (Norman, 2005). So far, no convincing evidence has appeared that such a mechanism takes place in vivo. Therefore, these experiments remain interesting but appear to have little or no significance for explaining the in vivo mechanisms at this time.

The VDR has been cloned by 2 research groups (Baker et al., 1988; Burmester et al., 1988), the ligand binding domain has been crystallized (Rochel et al., 2000; Vanhoeke et al., 2004), and a great deal of work is being performed at the molecular level to try and understand how the vitamin D hormone and its receptor act to control the transcription of genes that carry out the functions of vitamin D. In target genes, we now know that there are responsive elements, which are 2 heximer repeats separated by 3 nonspecified base pairs that bind the VDR and the retinoid X receptor (Umesono et al., 1991). In many target genes, several such binding sites have been found (Pike, 2011) and current work is centered on which of these sites are responsible for either the initiation or the inhibition of transcription of particular genes. A discussion of this is beyond the scope of this paper but more details of these mechanisms are available elsewhere (Pike, 2011).

MECHANISM UNDERLYING THE FUNCTION OF VITAMIN D ON INTESTINE AND BONE

The realization that vitamin D works through a VDR has led to a more complete understanding of how the vitamin carries out its functions on intestine and especially bone. It is well known from the work of Wasserman and his colleagues that the vitamin D hormone causes an increase in production of a soluble calcium binding protein in the intestine called calbindin D9k (Kallfelz et al., 1967). Another group has discovered the TRPV6 (transient receptor potential cation channel, subfamily V, member 6), which is a calcium doorway protein found at the brush border membrane that is activated by the vitamin D hormone (Song et al., 2003). There is a belief that the calcium adenosinetriphosphatase (ATPase) at the basal lateral membrane is responsible for pumping calcium out of the cytoplasm into the plasma compartment causing an elevation of plasma calcium that is also stimulated by 1,25-(OH)2D3 (Cai et al., 1993; Kumar, 1995). A similar mechanism can be stated for phosphate where a phosphate transporter appears to be responsible. Unfortunately we cannot write a detailed description of how the response to the vitamin D hormone results in an elevation of plasma calcium. A knockout of calbindin D9k did not impair the response of the intestine to the vitamin D hormone in terms of calcium transport (Akhter et al., 2007). Similarly, a knockout of TRPV6 was unable to inhibit the active transport of calcium in the intestine induced by vitamin D (Kutuzova et al., 2008). Unfortunately, a knockout of the calcium ATPase has not been possible since it appears to be a lethal mutation. Therefore, a full mechanism of how 1,25-(OH)2D3 activates intestinal calcium and phosphate transport is not yet available.

The role of vitamin D in the resorption of calcium from bone is perhaps better understood. There is no doubt that there are no VDR in the osteoclast (Stumpf et al., 1981; Merke et al., 1986; Wang et al., 2012b) that is charged with the responsibility of bone resorption. However, the osteoblast is rich in VDR. The vitamin D hormone appears to induce the appearance of the receptor activator of nuclear factor kappa-B ligand (RANKL), often known as the osteoclast-differentiating factor (Yasuda et al., 2005; Pike, 2011). This factor acts by causing the differentiation and formation of the giant osteoclast. Furthermore, the vitamin D hormone through the RANKL also activates resting osteoclasts to become active (Yasuda et al., 2005; Pike, 2011). It is this latter process that is the rapid response that one sees when a vitamin D–deficient animal is given a dose of 1,25-(OH)2D3. The giant osteoclast then causes bone resorption releasing calcium into the bloodstream, correcting hypocalcemia.

The molecular mechanism whereby the vitamin D hormone activates gene expression is under intensive investigation and will likely not be totally solved in the near future. However, it is currently believed that the vitamin D hormone interacts with the VDR causing a change in the conformation of the receptor (Singarapu et al., 2011). The change in VDR conformation is believed to release co-repressors and allow the binding of VDR to the responsive elements together with the retinoid X receptor. The VDR appears to bind on the proximal side of the 2 heximers while retinoid X receptor binds to the downstream side of the heximer. There is a binding of a number of factors that causes a loosening of the chromatin, but additional factors are bound that
either stimulate transcription or impair transcription, as the case may be. A diagrammatic sketch of the concepts of how 1,25-(OH)₂D₃ acts through its receptor to regulate transcription of target genes is shown in Fig. 6.

**THE PARATHYRIOIDS ARE A PROVEN TARGET OF 1α,25-DIHYDROXYVITAMIN D₃**

Progress in understanding how vitamin D functions to heal rickets, osteomalacia, and vitamin D–resistant diseases has clearly been made. However, we now know that vitamin D has functions far beyond mineralizing the skeleton. One of the primary reasons we know this is because VDR is not only found in the intestinal enteroctye, the osteoblast, and the renal cells, but it is found in the parathyroid glands, keratinocytes, lymphocytes that are activated, and other components of the immune system (Merke et al., 1986; Sandgren et al., 1991; Wang et al., 2012b). It also is found in abundant quantities in the islet cells of the pancreas, in pituitary cells, some ovarian cells, and aortic endothelial cells. Therefore, we can expect that vitamin D has functions beyond bones.

One of the first places that the application of the vitamin D metabolites have been made is the treatment of patients who have lost their kidneys and are unable to produce the circulating 1,25-(OH)₂D₃. These patients suffer severe bone disease and are difficult to manage. The disease is called renal osteodystrophy. This disease is characterized by a loss of kidney mass, which eliminates a major supply of the vitamin D hormone (Silver and Naveh-Many, 2005; Slatopolsky and Dusso, 2005). Furthermore, the kidney is the primary way in which the body gets rid of excess phosphate. With the destruction of renal mass, there is an inability to get rid of dietary phosphorus that is absorbed (Silver and Naveh-Many, 2005; Slatopolsky and Dusso, 2005). As a result, there is a hyperphosphatemia that suppresses ionized calcium and aggravates a hypocalcemic situation. Hypocalcemia causes massive secretion of PTH. With any small amounts of the vitamin D hormone remaining, there is an excessive erosion of bone that causes renal osteodystrophy. In the management of these patients, physicians first control the intake of phosphate to reduce the phosphatemia and then they provide treatment with the active form of vitamin D to increase calcium absorption, but most important is that vitamin D acts to suppress excessive production of the PTH and proliferation of the parathyroid glands (Llach et al., 1998; Slatopolsky et al., 2007). In fact, this is a major way in which the vitamin D hormone and its analogs are used in medicine today. There are at least 4 analogs of 1,25-(OH)₂D₃ that are in current use or being developed for the treatment of secondary hyperparathyroidism of kidney failure. The same active forms of vitamin D are used to treat vitamin D–resistant rickets (young) and osteomalacia (adult).

The primary problem with using 1,25-(OH)₂D₃ to treat renal patients is that this compound has a propensity to elevate plasma calcium. This causes unwanted calcification of soft tissues. Management of these patients with
1,25-(OH)₂D₃ is difficult and requires careful dosing and correction of hyperphosphatemia. A calcium mimetic that desensitizes the parathyroid gland to hypocalcemia is often used in patients who tend to hypercalcemia in response to 1,25-(OH)₂D₃ and its analogs (Brown, 2005).

In our laboratory, we continue to develop analogs that will be better suited for treatment of secondary hyperparathyroidism of renal failure. One that is currently under development is 2-methylene-19-nor-(20S)-1α,25-dihydroxyvitamin D₃ (2MD). To illustrate how effective 2MD is, we have used the 5,6-nephrectomized rat model to test whether it can be used to suppress secondary hyperparathyroidism. It is the most effective compound we have found that does not raise serum calcium at effective doses and is currently in phase 2 trials.

**APPLICATION OF 1α,25-DIHYDROXYVITAMIN D₃ OR ANALOGS TO DISEASES**

Another important application of vitamin D analogs has been the disease psoriasis. The keratinocytes of skin in psoriasis are hyperproliferative and result in the disease. This disease can be treated with topical 1,25-(OH)₂D₃ (Perez et al., 1996) or an analog called Dovonex prepared by Leo Pharmaceuticals (Ballerup, Denmark; Kragballe et al., 1991). Dovonex is quite effective in about 70% of patients (Binderup et al., 1997). Another application of the active forms of vitamin D has been postmenopausal osteoporosis, primarily in countries where there are lower calcium intakes, such as Japan and Australia.

Besides correcting hypocalcemia and hypophosphatemia, 1,25-(OH)₂D₃ has bone anabolic activity, as demonstrated by Goltzman’s group in Canada (Xue et al., 2006). They have shown in mice that do not make 1,25-(OH)₂D₃ (i.e., CYP27B1 null) or secrete PTH (i.e., PTH null) that exogenous 1,25-(OH)₂D₃ will cause increased bone synthesis. Therefore, besides correcting calcium and phosphorus, 1,25-(OH)₂D₃ appears to have anabolic bone activity. We have been testing many of our analogs in primary cultures of human osteoblasts to determine if they have bone anabolic activity. Of all the compounds tested, 2MD has remarkable ability to cause synthesis of bone in culture at doses as low as 10⁻¹² M whereas the native hormone at 10⁻⁸ M shows some bone anabolic activity (Shevde et al., 2002; Fig. 7). Shown in Fig. 8, 2MD has equally potent ability to cause bone resorption. When given to ovarioctomized female rats, 2MD markedly increases bone mass (Ke et al., 2005; Plum et al., 2006). It is known that unlike humans where bone is largely being remodeled, rats are a largely bone modeling animal (Frost, 1966). In postmenopausal women, 2MD administration did not increase bone mass but revealed a marked increase in bone turnover (DeLuca et al., 2011). Likely, 2MD would be effective in reducing the incidence of fracture of osteoporotic women but it is unlikely that this will be available because of the cost (US$1 billion or more) of carrying out a fracture incidence study in postmenopausal women.

Autoimmune diseases, such as multiple sclerosis (MS) and type 1 diabetes, have been studied as possible targets of treatment with 1,25-(OH)₂D₃ and its analogs.
Type 1 diabetes is particularly interesting because the islet cells of the pancreas contain large amounts of the VDR (Wang et al., 2012b). Zella and DeLuca (2003) have shown that, in nonobese diabetic (NOD) mice, vitamin D deficiency results in elevated rates and rapidity of appearance of type 1 diabetes. The administration of vitamin D3 to these mice significantly reduces the incidence of type 1 diabetes and also delays its onset. Most important is that when NOD mice are given 1,25-(OH)₂D₃, it blocks diabetes. Unfortunately, the doses of 1,25-(OH)₂D₃ needed to suppress the diabetes causes unacceptable hypercalcaemia. An analog of 1,25-(OH)₂D₃ (i.e., 2α-methyl-19-nor-(20S)-1α,25-dihydroxyvitamin D₃) can suppress type I diabetes in NOD mice without causing hypercalcaemia (J. Hansen, L. A. Plum, and H. F. DeLuca, Department of Biochemistry, University of Wisconsin-Madison, unpublished data). If this finding can be extended to human type I diabetes, then a vitamin D–based prevention of the diabetic symptoms seems possible.

Another disease that has received a great deal of attention by vitamin D scientists is MS. Multiple sclerosis is a disease that is found in high proportions in the very northern and southern hemispheres but is practically absent at the equator (Goldberg, 1974). This led Goldberg to suggest that vitamin D might be the primary agent that reduces the onset of MS. Scientists have paid very close attention to this and reported that 1,25-(OH)₂D₃ can block experimental autoimmune encephalomyelitis (EAE), a mouse model of human MS (Cantorna et al., 1996). Unfortunately, hypercalcemia accompanies the suppression of EAE by 1,25-(OH)₂D₃. When it is given with a low calcium diet where no hypercalcemia results, there is very little effect of 1,25-(OH)₂D₃ (DeLuca and Plum, 2011). Hypercalcemia itself induced by PTH also blocks EAE independent of vitamin D (Meehan et al., 2005). Furthermore, 2 laboratories have independently found that vitamin D deficiency prevents the development of EAE, providing strong evidence against the idea that vitamin D can suppress EAE and presumably MS (Fernandes de Abreu et al., 2010; Wang et al., 2012a).

By returning to the observation that UV light or sunlight reduces the incidence of MS, we have found that UV light markedly reduces the incidence and severity of EAE (Becklund et al., 2010). However, it is not the production
of vitamin D that is responsible but a narrow band of wavelength at 300 to 315 nm that is responsible and this wavelength does not produce vitamin D$_3$ (Wang et al., 2013). We do not know the basis for this effect but at least we can safely say that this provides evidence that the effect of UV light in suppressing EAE does not involve vitamin D.

There is an abundance of publications that correlate a reduced incidence of colorectal and breast cancer with greater blood levels of 25-OH-D (Institute of Medicine, 2011). There have been several retrospective epidemiological studies in support of this concept (Institute of Medicine, 2011). Abe et al. (1981) made the important observation that 1,25-(OH)$_2$D$_3$ stops the growth of leukemia cells in culture and causes them to differentiate into functional monocytes. This idea has caught fire and many people have been interested in the possibility that vitamin D might be effective in therapy or the prevention of cancerous growth. A word of caution must be exercised however. There have been studies on both sides of this issue, some indicating that there is an effect of vitamin D in reducing the incidence of cancer and others indicating that there is no effect (Institute of Medicine, 2011). In experimental models performed by our group, we have been unable to find any evidence that 1,25-(OH)$_2$D$_3$ is anticarcinogenic, and it does not appear to have a significant effect on the growth of colorectal tumors in vivo (Irving et al., 2011). Although we would like it to be the case, we must say that, at the present time, this remains an area of vitamin D therapy or prevention that is certainly not established.

**SUMMARY AND CONCLUSIONS**

The field of vitamin D metabolism has been reviewed to include recent advances. Furthermore, the application of 1α,25-dihydroxyvitamin D$_3$ and its analogs to the treatment or prevention of a variety of diseases has been discussed, especially including new analogs and possible uses. Included are reviews of possible application where results are lacking.

**LITERATURE CITED**


Xue, Y., A. C. Karaplis, G. N. Hendy, D. Goltzman, and D. Miao. 2006. Exogenous 1,25-dihydroxyvitamin D$_3$ exerts a skeletal anabolic effect and improves mineral ion homeostasis in mice that are homozygous for both the 1α-hydroxylase and parathyroid hormone null alleles. Endocrinology 147:4801–4810.


