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# The History of the Discovery of Vitamin D and Its Daughter Steroid Hormone

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**Key Words**
Vitamin D · Rickets · 1,25$(OH)_2D_3$ · UV irradiation

**Abstract**
It is largely through historical accident in the interval of 1920–1940 that vitamin $D_3$ became classified as a vitamin rather than as a steroid hormone. The formal definition of a vitamin is that it is a trace dietary constituent required to produce the normal function of a physiological process or processes. The emphasis here is on trace and the fact that the vitamin must be supplied regularly in the diet; this implies that the body is unable to metabolically synthesize the vitamin in question. However, the ultraviolet exposure of 7-dehydrocholesterol present in the skin results in the photochemical production of vitamin $D_3$. Thus, vitamin $D_3$ becomes a true vitamin only when the animal or human does not have regular access to sunlight or ultraviolet light. Under normal physiological circumstances, all mammals, including humans, can generate, via ultraviolet exposure of 7-dehydrocholesterol present in the skin, adequate quantities of vitamin $D_3$ to meet their nutritionally defined requirements. There is a vibrant historical record beginning in 1650 and culminating in 1963 concerned with the determination of the chemical structures of vitamin $D_3$ and vitamin $D_2$. A surprising aspect concerning vitamin $D_3$ is that it is itself biologically inert. There are no known essential biological actions or contributions that rely specifically on the molecule vitamin $D_3$. While chemists had certainly appreciated the strong structural similarity between the vitamins D and other steroids, this correlation was never widely acknowledged in the biological, clinical, or nutritional sciences until 1965–1970. The biological role of vitamin $D_3$ is to serve as a substrate for the liver 25-hydroxylase which produces 25-hydroxyvitamin $D_3$ [25$(OH)D_3$]. 25$(OH)D_3$ in turn serves as the substrate for the kidney proximal tubule 25$(OH)D_3$-1α-hydroxylase enzyme which produces the steroid hormone 1α,25$(OH)_2$-vitamin $D_3$ [1α,25$(OH)_2D_3$].



## Introduction

It is largely through historical accident that vitamin $D_3$ has been classified as a vitamin rather than as a steroid hormone. The formal definition of a vitamin is that it is a trace dietary constituent required to participate in the normal function of a specific physiological process or processes. The emphasis here is on trace and the fact that the vitamin must be supplied regularly in the diet; this implies that the body is unable to metabolically synthesize the vitamin in question. However, the ultraviolet exposure of 7-dehydrocholesterol present in the skin (fig. 1) results in the photochemical production of vitamin $D_3$. Thus, vitamin $D_3$ becomes a true vitamin only when the animal or human does not have regular access to sunlight or ultraviolet light. Under normal physiological circumstances, all mammals, including humans, can generate,

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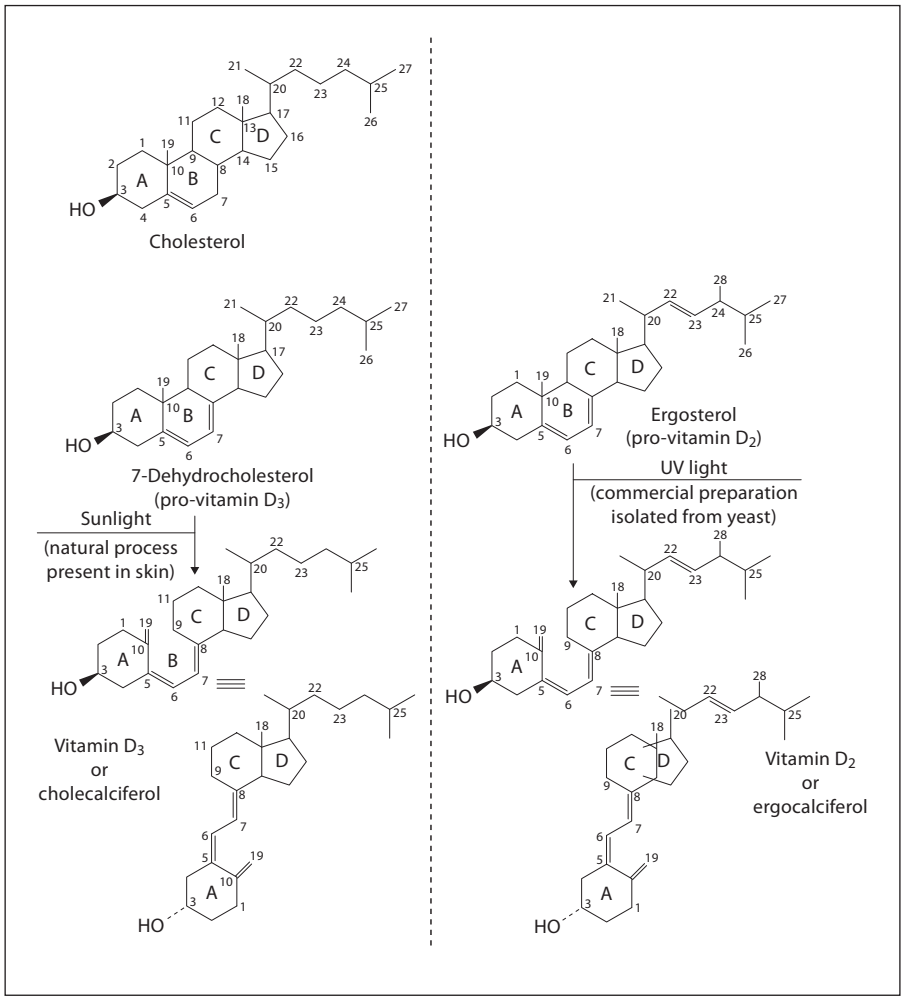



**Fig. 1.** Structural relationship of vitamin $D_3$ (cholecalciferol) and vitamin $D_2$ (ergocalciferol) with their respective provitamins, 7-dehydrocholesterol and ergosterol. The two structural representations presented at the bottom for both vitamin $D_3$ and vitamin $D_2$ are equivalent. Both secosteroids have 360 degree rotation (millions of times per second) around the carbon 6-carbon 7 single bond. Thus, both vitamin D secosteroids are highly conformationally flexible and present to their local environment a plethora of three-dimensional shapes. The only structural difference between vitamin $D_3$ and vitamin $D_2$ is the side chain. Vitamin $D_3$ has the side chain of cholesterol (shown separately), while vitamin $D_2$ has the side chain of ergosterol. Also vitamin $D_2$ has a C22=C23 double bond and an additional methyl group on C24. It is to be emphasized that vitamin $D_3$ is the naturally occurring form of the vitamin; it is produced from 7-dehydrocholesterol which is present in the skin by the action of sunlight. Vitamin $D_2$ is produced commercially by the irradiation of the plant sterol ergosterol with ultraviolet light. According to R.P. Heaney, vitamin $D_2$ has only ~30% of the biological activity of vitamin $D_3$ in humans and only 10% in birds [48, 49].

via ultraviolet exposure of 7-dehydrocholesterol present in the skin, significant quantities of vitamin $D_3$ to meet their nutritionally defined requirements.

But a surprising aspect concerning the chemical substance vitamin $D_3$ is that it is biologically inert. There are no known essential biological actions generated specifically by the molecule vitamin $D_3$. While chemists since the 1930s have certainly appreciated the strong structural similarity between the vitamins D and other steroid hormones, this correlation was never widely acknowledged in the biological, clinical, or nutritional sciences until it was discovered in 1965–1971 that the biological role of vitamin $D_3$ is to serve as a substrate for the liver 25-hydroxylase which produces the product 25-hydroxyvitamin $D_3$ [25(OH)$D_3$]. Then, 25(OH)$D_3$ in turn serves as the substrate for the kidney proximal tubule 1α-hydroxylase enzyme which produces the steroid hormone 1α,25$(OH)_2$-vitamin $D_3$ [1α,25$(OH)_2D_3$].

## History from 1645 to 1900

The first scientific description of the classic bone disease rickets was provided in 1645–1660 by Dr. Daniel Whistler (1619–1684) at the University of Leiden, The Netherlands [1], and Prof. Francis Glisson (1597–1677) at the University of Cambridge, UK [2].

The 18th century provided little in the way of specific advances towards the discovery of vitamin D. It can be most properly characterized as a period of recognition and acceptance of the views of Glisson and Whistler, i.e. that there was a distinct bone disease state termed rickets. In 1849, Armand Trousseau (1801–1867) and Charles Lasègue (1816–1883) [3] appreciated that osteomalacia and rickets were different expressions of the same malady, while Gustav Pommer (1851–1935) in 1885 provided a thorough histological and pathological description of the rachitic skeleton [4]. Although cod liver oil had been used

medicinally for some time, it was in 1824 that D. Schütte proposed cod liver oil as a treatment for rickets and osteomalacia [5]. Theobald Palm, in 1890, pioneered a quantitative geographic study of the worldwide distribution of rickets, especially in all European countries, China, Japan, India, West Indies, and the United States [6].

### Discovery of an Antirachitic Factor, 1901–1930

These observations on rickets set the stage for the later brilliant formulation of the vitamin concept in 1906 by Sir Frederick Gowland Hopkins (1861–1947) [7]. Also in 1914, Casimir Funk (1884–1967) wrote in his classic *Die Vitamine*: 'It is very probable that rickets occurs only when certain substances in the diet essential for normal metabolism are lacking or are supplied in insufficient amounts. The substances occur in good breast milk, also in cod-liver oil, but are lacking in sterilized milk and in cereals'; this was translated in 1929 by Alfred F. Hess (1875–1933) [8].

These views were not overlooked by Sir Edward Mellanby (1884–1955). In a landmark series of studies (from 1919 to 1924) involving the feeding of a plethora of scientifically devised diets to more than 400 dogs over a period of 5 years, he unequivocally established that rickets was caused by a deficiency of a trace component present in the diet [9, 10]. In 1921, he wrote: 'The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin' [11]. Furthermore, he established that cod liver oil was an excellent antirachitic agent.

Mellanby was acutely aware of the complicated nature of rickets and understood how the existence of a specific antirachitic substance could have been previously overlooked. He stated: 'It has been shown that many of the food elements exert a potent influence on the operation of bone calcification or growth.' A detailed summary of Mellanby's scientific and medical contributions and accomplishments is in 'Sir Edward Mellanby (1884–1955): The Man, Research Worker, and Statesman' by B.S. Plant in 1956 in the *Annual Reviews of Biochemistry* [12].

Although many would argue that the prime accomplishment of Mellanby was the unequivocal demonstration that a true dietary component was the causative agent of rickets, in retrospect, his accomplishments were much more far-reaching. Of far greater value was his application of the scientific technique to the infant field of nutrition so that it was possible to routinely raise a vitamin D-deficient animal. This great stride forward made it possible for scientists all over the world to use this scientific technique to unravel the mode of action of the elusive 'antirachitic factor'.

As with all phases of rapid development, it is difficult in retrospect to unravel the precise order of discovery of the many facets of the total problem. There were three areas in which progress had to be made: (1) separation of vitamin A and D activities; (2) appreciation that ultraviolet light and cod liver oil could both effect the same cure of rickets, and (3) demonstration that irradiation of food (in the absence of the animal) produces the same effect as irradiation of the animal.

Kurt Huldschinsky (1883–1941) [13] first showed in 1919 that the ultraviolet rays from a mercury vapor lamp were quite effective in increasing the calcification of the epiphysis of rachitic infants.

In their historic paper, Elmer McCollum (1879–1967) et al. [14] demonstrated that the antirachitic activity of cod liver oil could survive both aeration and heating to 100°C for 14 h, whereas the 'anti-xerophthalmic factor', or vitamin A, was inactivated by this process. They stated:

> 'The evidence set forth in this paper demonstrates that the power of certain fats to initiate the healing of rickets depends on the presence of a substance which is distinct from fat-soluble A. these experiments clearly demonstrate the existence of a fourth vitamin whose specific property, as far as we can tell at present, is to regulate the metabolism of the bones.'

Later, the new substance was named vitamin D. Although the correlation between ultraviolet light and cod liver oil in terms of their equivalent efficacy in preventing rickets was appreciated by most of the workers of that period, there was no simple explanation put forth for the observation. Both ultraviolet light and cod liver oil were found to be equivalently effective in reversing the roentgenographic evidence of the ravages of rickets upon the skeleton. However, until the separate work of Harry Goldblatt (1891–1977) and Harry Steenbock (1886–1967) no connection was made between the mysterious curative powers of ultraviolet light on rickets and the presence of an equally effective molecular species in cod liver oil.

In 1923, Goldblatt and Katherine Soames [15, 16] irradiated rat livers that had been excised from rachitic rats with ultraviolet light and found that when the irradiated tissue was ground and fed to other rachitic rats, there was a remission of the D deficiency. In parallel studies, Steenbock and Black [17] and Steenbock et al. [18] found that food which was irradiated and subsequently fed to rachitic rats had acquired the property of being 'antirachitic'. In short, both groups had for the first time produced

in vitro the elusive vitamin D component of the fat-soluble vitamin. Without a doubt, the specific effect of light was no longer mysterious; it simply had produced a permanent chemical change in a component in the rat diet.

Hess and Weinstock [19, 20] in an elegant experiment confirmed the dictum that 'light equals vitamin D'. They excised a small portion of skin from rachitic rats, irradiated it with ultraviolet light, and fed the skin to groups of rachitic rats. The skin that had been irradiated provided an absolute protection against rickets, whereas the non-irradiated skin provided no protection whatsoever.

## Structure Determination of Vitamins $D_3$ and $D_2$, 1930–1963

Beginning in 1930, a description of the evolution of our understanding of vitamin D becomes largely chemical in nature. What was unappreciated initially was that Steenbock et al. [18] had produced vitamin $D_2$ from irradiation of the ergosterol in a yeast component of their rat diet, whereas Hess and Weinstock [19, 20] had generated vitamin $D_3$ via irradiation of the skin. Also, the relation of both of these substances to the antirachitic component of cod liver oil remained to be established. Vitamin $D_3$ and vitamin $D_2$ and their respective provitamins, 7-dehydrocholesterol and ergosterol, have both significant structural similarities and differences (fig. 1). It is important to know that ergosterol and vitamin $D_2$ are not biosynthesized or present in vertebrates. Thus, strictly speaking, both ergosterol and vitamin $D_2$ are structural analogs of the naturally occurring 7-dehydrocholesterol and vitamin $D_3$ and there should be no expectation that they have the same biological effects.

These studies began to culminate in 1932 when Adolf Windaus (1876–1959) et al. [21] and Frederick A. Askew and colleagues [22] separately but simultaneously identified the chemical structure of vitamin $D_2$. The puzzling inability of digitonin to precipitate the 'antirachitic sterol' was now solved; the antirachitic sterol, vitamin D, was actually a secosterol. The implications of this fact were largely unappreciated for another 25–30 years.

Vitamin $D_3$ was not chemically characterized until 1936, when Windaus et al. [23] determined the structure of the antirachitic factor that resulted after ultraviolet irradiation of 7-dehydrocholesterol. Virtually simultaneously, the elusive antirachitic component of cod liver oil was shown to be identical to vitamin $D_3$ by Brockmann [24] in 1936. Brockmann isolated 2 g of crystalline vitamin $D_3$ from 150,000 g of tuna liver oil. At last, all was clear. Natural vitamin D present in cod liver oil is identical to vitamin $D_3$. Thus 7-dehyrocholesterol, not ergosterol, is the true provitamin of the 'natural' vitamin $D_3$.

Of equal importance, it was unmistakably clear that the antirachitic substance, vitamin D, was a steroid, more specifically a secosteroid (fig. 1). Thus, the close of the 'structure determination of vitamins $D_3$ and $D_2$' era of vitamin D was virtually at hand. All that remained was for Dr. Dorothy Crowfoot-Hodgkin (1910–1994) in 1948 to complete her laborious, but elegant, X-ray crystallographic structural analysis of the vitamin $D_3$ molecule [25, 26], which emphasizes the seco nature of vitamin D. Because the 9–10 carbon bond of ring B of the provitamin is broken upon irradiation, the A ring is free to assume a more extended configuration (fig. 1). However, in all other respects, the X-ray image of vitamin $D_3$ is like that of most other steroids. Thus, the official chemical name of vitamin $D_3$ is 9,10-secocholesta-5,7,10(19)-trien-beta-ol.

## Acceptance that Vitamin D Was a Precursor of a Steroid Hormone, 1964–1984

It was clear as of 1964 that the role of vitamin $D_3$ in the general nutrition arena (both human and agricultural) was firmly established. What is surprising, in retrospect, is that almost half a century passed between the specific recognition of the existence of vitamin D in 1921 [11] and the formulation of a theory of the 'mode of action' of vitamin D that was consistent with many if not all of the known facts. This hypothesis states that vitamin D is in reality a steroid and that its mode of action is akin to that of many steroid hormones [27].

In the intestine, there was a major problem facing biochemists who wished to clarify the detailed mechanism of action of the steroid vitamin D: this was the elucidation of the steps of interaction of the putative steroid hormone with its target tissue and an understanding of how the presence of the steroid hormone initiates the classic physiological response of increased intestinal calcium absorption.

The approach pioneered in the laboratories of Anthony Norman, Egon Kodicek, and Hector DeLuca was to administer small physiological doses of radioactive vitamin D and to trace the appearance of the radioactive label in the target tissue. In the course of these studies, it became apparent not only that there was a specific localization of radioactivity within the target intestinal nuclear and chromatin fraction, but also that this radioactivity was not chemically identical to that of the parent vitamin

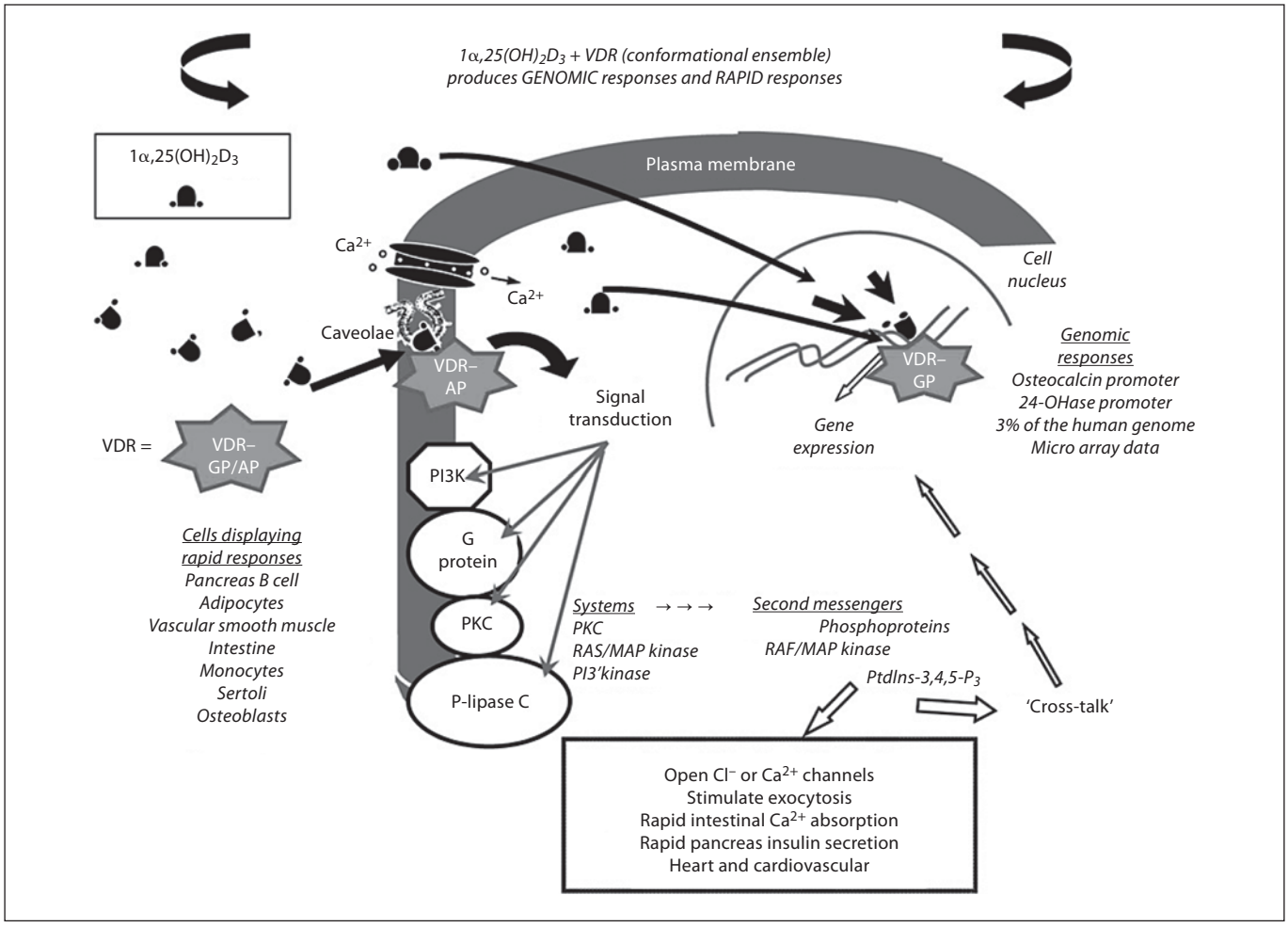
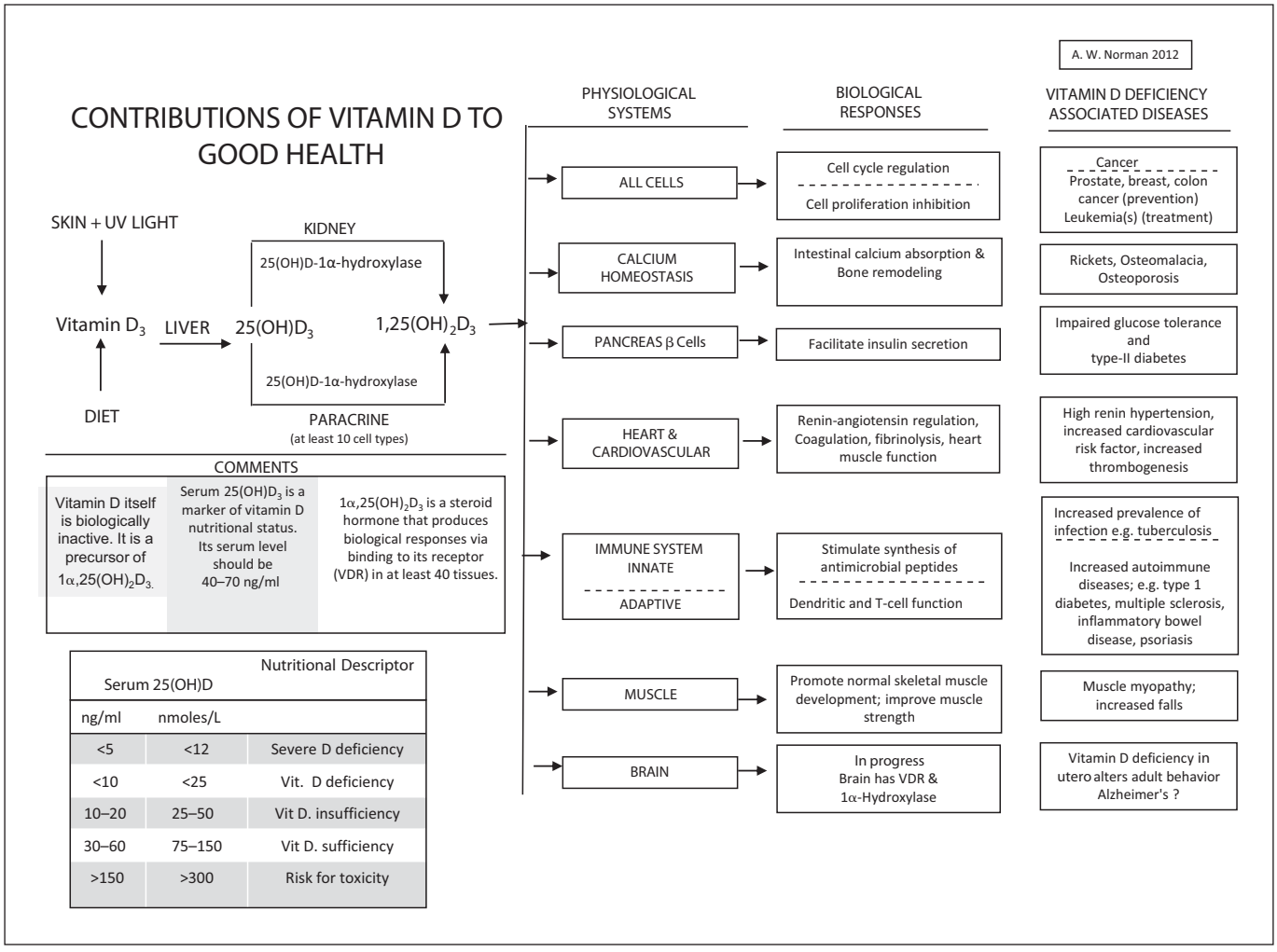



**Fig. 2.** 1,25$(OH)_2D_3$ activation of genomic and non-genomic (rapid response) cellular signaling. This schematic model illustrates how the conformationally flexible 1,25$(OH)_2D_3$ interacts with the VDR in the nucleus to generate genomic responses via regulation of gene transcription, whereas 1α,25$(OH)_2D_3$ also binds to VDR associated with caveolae of the plasma membrane to generate non-genomic responses. In the genomic pathway, occupancy of the nuclear VDR by 1α,25$(OH)_2D_3$ leads to an up- or downregulation of genes subject to hormonal control. The human genome contains about 22,000 genes; of these, approximately 3,000 are regulated by the VDR [41]. Binding of 1α,25$(OH)_2D_3$ to caveolae-associated VDR can result in the activation of one or more second-messenger systems, including G-protein-coupled receptors, phosphatidylinositol-3'-kinase (PI3K), or protein kinase C (PKC). A number of possible outcomes exist, including opening of the voltage-gated chloride channels or calcium channels, or generation of the indicated second messengers.

$D_3$. Further studies from the Norman and Kodicek groups demonstrated that this substance, which selectively localized in the target intestine, and its nuclear fraction was chemically different from both vitamin $D_3$ and the intermediate 25-hydroxyvitamin $D_3$ [28, 29]. With the concomitant demonstration that this polar metabolite was ~400× more potent than vitamin $D_3$ in terms of stimulation of the intestinal transport of calcium [28, 30], the extensive effort necessary to chemically characterize the substance was undertaken. This resulted in simultaneous, yet independent, reports in the first 3 months of 1971 from the three laboratories that the chemical structure of this vitamin $D_3$ metabolite was 1α,25-dihydroxyvitamin $D_3$ [31–33].

Further studies by the Norman laboratory in 1968–1969 of the specific localization of the tritium radioactivity in the crude nuclear fraction of the intestine revealed that it was also present when purified nuclei were prepared [30] or when the subnuclear chromatin fraction was prepared [34, 35]. This permitted the first isolation




| Serum 25(OH)D | | Nutritional Descriptor |
|---|---|---|
| ng/ml | nmoles/L | |
| <5 | <12 | Severe D deficiency |
| <10 | <25 | Vit. D deficiency |
| 10–20 | 25–50 | Vit D. insufficiency |
| 30–60 | 75–150 | Vit D. sufficiency |
| >150 | >300 | Risk for toxicity |

**Fig. 3.** Contribution of vitamin D to good health. The three columns on the right side, respectively, indicate the six physiological systems that the essential nutrient vitamin $D_3$ supports by its metabolism to $25(OH)D_3$ and $1\alpha,25(OH)_2D_3$; offer examples of biological responses generated by $1\alpha,25(OH)_2D_3$ in the six physiological systems, and identify for each system some of the disease states that are associated with an inadequate vitamin D nutritional status. More detail is provided by Norman and Bouillon [40] and Bouillon et al. [41]. The Food and Nutrition Board of the Institute of Medicine in 1997 defined serum 25(OH)D levels as a surrogate marker for describing vitamin D nutritional status. Serum 25(OH)D levels entered in the table in the lower left corner describe the 'total' concentration of 25(OH)D, i.e. the sum of the concentration of $25(OH)D_3$ and $25(OH)D_2$ present in a serum sample. The use of total serum levels of 25(OH)D as a marker for vitamin D nutritional status is justified by the following three points: (1) there is no clinical assay for the parent vitamin D; (2) the metabolism of vitamin $D_3$ into $25(OH)D_3$ by the liver vitamin D-25-hydroxylase is not regulated and thus the serum concentration of $25(OH)D_3$ is believed to be an accurate 'reporter' of both cutaneous ultraviolet-stimulated synthesis and dietary intake of vitamin $D_3$, and (3) the plasma levels of 25(OH)D correlate with many clinical disease states [50, 51].

and characterization of a specific binding protein (receptor) for $1,25(OH)_2D_3$ [36]; this protein is now known as the vitamin D receptor (VDR).

A clinical application of $1,25(OH)_2D_3$ immediately became apparent in 1971 in the field of chronic kidney disease which is characterized by the presence of the bone disease of renal osteodystrophy. The onset of the bone disease is caused by damage to the kidney's proximal tubule which inactivates the 25(OH)D-1α-hydroxylase enzyme which converts $25(OH)D_3$ into the steroid hormone $1,25(OH)_2D_3$. Thus, the patient will become deficient in $1,25(OH)_2D_3$. The first treatment of patients with renal

osteodystrophy was carried out by oral dosing of $1,25(OH)_2D_3$ by the laboratories of Jack Coburn and Anthony Norman [37, 38].

## Expansion of the Vitamin D Endocrine System, 1987–2012

A general mechanism of the steroid hormone action of $1\alpha,25(OH)_2D_3$ in collaboration with its cognate VDR describing both genomic and non-genomic signal transduction responses is presented in figure 2. These more recent developments occurred over the interval of 1987–2012 [39].

VDR, the receptor for the steroid hormone $1\alpha,25(OH)_2D_3$, is now known to be widely distributed in over 40 tissues, applying the endocrine paradigm that if a cell expresses the receptor for a hormonal ligand, then that cell will be empowered to produce ligand VDR-dependent biological responses. Collectively, this suggests that these cells can produce a wide array of biological responses beyond intestinal calcium absorption and the prevention of rickets and osteomalacia [40].

Figure 3 summarizes all the contributions of the parent vitamin $D_3$ to good health after its metabolism to $1,25(OH)_2D_3$ and binding to its widely distributed VDR [40, 41]. Thus, the vitamin D endocrine system extends far beyond the classical calcium homeostasis system. It now is clearly involved in the pancreas cell and secretion of insulin and type 2 diabetes [42], the heart and cardiovascular system [43], the immune system (both the innate and adaptive component) [44], muscle (and muscle strength) [45], and likely the brain. More detailed information is available in Norman and Bouillon [40] and Bouillon et al. [41].

## Vitamin D and Nobel Prizes – Some Near Misses

Nobel Prizes have been awarded to two highly distinguished scientists each of whom made significant contributions in the field of vitamin D research after receiving their prestigious awards.

Prof. Adolf Windaus received the Nobel Prize in Chemistry in 1928 for 'his work on steroids and their relation to vitamins'. In 1919, his laboratory transformed cholesterol into cholanic acid (steroids comprising the bile acids, generally in conjugated form), and in 1926, he proved that the precursor of vitamin D is present in samples of cholesterol and is converted into vitamin D by exposure to sunlight. However, it was only after Windaus received the Nobel Prize that he discovered and synthetically prepared vitamin $D_3$ [22]; it is the naturally occurring form of vitamin D that is most important in preventing the bone disease rickets.

Dorothy Crowfoot Hodgkin was awarded the Nobel Prize in Chemistry in 1964 'for her determinations by X-ray techniques of the structures of important biochemical substances'. She is regarded as one of the pioneer scientists in the field of X-ray crystallography studies of biomolecules. Her Nobel Award cited her most influential discoveries were 'for the x-ray structures of penicillin and vitamin B12'. It is important to note that Dorothy Crowfoot's PhD dissertation used the pioneering technique of small molecule X-ray diffraction to define unequivocally the chemical structure of vitamin $D_3$ [25, 26].

Prof. Robert Koch (1843–1910) received his Nobel Prize in Physiology or Medicine in 1905 for his discovery of *Mycobacterium tuberculosis*, the bacterium that causes tuberculosis. The concept of use of a sanatorium for treatment of patients with tuberculosis was included by Prof. Koch in his 1905 Nobel Lecture [46]. The standard medical therapy for decades to come was based on rest in a sanatorium at a mountain elevation where ultraviolet light was amply prevalent. In 2012, tuberculosis is second only to HIV/AIDS as the greatest killer worldwide due to a single infectious agent. In 2010, 8.8 million people became ill with tuberculosis and 1.4 million died from it. In 2006, new data supported a link between vitamin D deficiency [as determined by the blood levels of 25(OH)D] and tuberculosis and macrophage toll-like receptors stimulated by the VDR + $1\alpha,25(OH)_2D_3$ activation of the innate immunity system [47].

## Acknowledgement

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