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The Saga of Vitamin D Discovery

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Abstract

While rickets is known as a pediatric bone disease since the 17th century, its etiology remained obscure until the 20th century. During the first decades of the last century evidence from several sources suggested that rickets could be prevented or cured with either cod liver oil or exposure to ultraviolet light. In 1922 a compound present in cod liver oil, distinct from the already known vitamin A, was identified as a steroid, although its precise chemical structure still remained uncertain for several years. The newly identified antirachitic compound was named vitamin D. The findings leading to its discovery are briefly reviewed.

Keywords: Vitamin D; Rickets; Osteomalacia; Secosteroids; Armand Trousseau; Alfred Hess; Harriette Chick; Elmer McCollum; Otto Rosenheim; Adolf Windaus

Abbreviations: CLO: Cod Liver Oil; UVL: Ultraviolet Light

Introduction

The year 2022 is acknowledged as the first centenary of the discovery of vitamin D. Since then, many foods are supplemented with vitamin D and it is also often prescribed by physicians. The importance of vitamin D discovery is mainly related to its ability to prevent and treat two closely related diseases characterized by poor bone mineralization, namely rickets in children and osteomalacia in adults. Rickets was clinically described in the 17th century [1]. However, its etiology remained controversial for almost three centuries, and therefore there was no consensus about its prevention and treatment.

Discussion

In Scandinavian countries, cod liver oil (CLO) had been regarded as a valuable folk medicine for a number of conditions. In the early 19th century, it was often prescribed for rheumatic diseases. John Hughes Bennett (1812-1875), a prominent English physician, published in 1848 a remarkable treatise on the therapeutic use of CLO, which included a full chapter on the treatment of rickets [2]. The outstanding French clinician, Professor Armand Trousseau (1801-1867), who correctly recognized the relationship between rickets and osteomalacia, stated in his influential textbook of internal medicine that both conditions were mostly related to a nutritional deficiency and could be successfully treated with CLO [3].

Unfortunately, the therapeutic use of CLO fell into disrepute for two reasons. The first was that the oil was often adulterated. The second was a growing discomfort among physicians with what was pejoratively known as Dreckapotheke or "dirty pharmacy", meaning the use of filthy or disgusting remedies [4]. In the meantime, the cause of rickets remained unknown. In the late 19th century, Theobald Adrian Palm published an epidemiological paper currently regarded as a landmark, but which did not receive the deserved attention on its day. By comparing data on the prevalence of rickets from England, the rest of Europe, Morocco and Southeast Asia, Palm concluded that lack of exposure to sunlight was an important cause of rickets [5].

Thus, at the dawn of the 20th century the two main hypotheses about the cause of rickets were a lack of a specific, yet unknown, nutrient and an insufficient exposure to sunlight. As it became clear some years later, both hypotheses were correct, since vitamin D may be either obtained from foods or synthesized in the skin exposed to an ultraviolet light (UVL) source, including sunlight [6]. Starting in 1903, the Swiss physician Auguste Rollier (1874-1954) advanced evidence of the efficacy of sunlight treatment for tuberculosis and rickets [7]. In 1919, in Germany, Kurt Huldschinsky (1883-1940) exposed children with severe rickets to a mercury vapor lamp, an artificial source of UVL, and found improvement in bone mineralization after four weeks and

virtually complete healing after two months. He also showed that the effect of UVL was systemic, since irradiation of one arm improved equally the mineralization of the non-irradiated arm [8].

At about the same time in England, Edward Mellanby (1884-1955) showed that CLO was the best supplement for preventing rickets in weaned puppies kept indoors [9]. By that time, it had already became clear that certain specific organic substances, other than proteins, lipids and carbohydrates, were required for a sound nutrition and a normal physiology. These compounds were called "vitamins" by Casimir Funk [10].

In the United States, Alfred Fabian Hess (1875-1933) found that rickets could be prevented with both CLO [11] and sunlight exposure [12]. After World War I, in response to a request by Professor Charles Piquet, Director of the Children's Hospital of the University of Vienna, a group of experts in nutrition led by Dr. Harriette Chick (1875-1977) was sent by the Lister Institute of Preventive Medicine and the British Committee for Medical Research (later British Medical Research Council). Dr. Chick and her team convincingly demonstrated that both CLO and exposure to sunlight were effective preventive and curative treatments for rickets [13]. Their final report was published in 1922 [14].

In the same year Elmer V. McCollum (1879-1967) and his coworkers unequivocally demonstrated the presence of a heat-resistant antirachitic factor in CLO [15], which was called vitamin D. Therefore, 1922 is generally recognized as the year of the discovery of vitamin D. Alfred Hess, already mentioned by his clinical studies, was aware that vitamin D was a compound related to cholesterol. Although it later became clear that the precursor was not cholesterol but a related compound, his remarkable insight deserves to be quoted: "It would seem quite possible that the cholesterol in the skin is normally activated by ultra-violet irradiation and rendered antirachitic (…) This point of view regards the superficial skin as an organ which reacts to particular light waves (the epidermal organ) rather than as a mere protective covering." [16].

A fruitful collaboration ensued between Hess in America, Adolf Windaus (1876-1959) in Germany and Otto Rosenheim (1871-1955) in England. Although only Windaus was awarded the 1928 Nobel Prize in Chemistry for "services rendered through his research on the constitution of sterols and their connection with vitamins" [17], actually Rosenheim had a major role in the research effort. He showed that the vitamin D precursors were contaminants of cholesterol in animal samples and of sitosterol in samples of vegetal origin and identified the latter as ergosterol [18]. By then it was clear that the antirachitic substances were secosteroids, that is, steroid compounds in which one of the rings is open, in this case ring B.

In 1937, Windaus succeeded in isolating and identifying the vitamin precursor compound 7 dehydrocholesterol in pig skin [19]. Thus, by 1937 the two main forms of vitamin D were known, one of vegetal origin (D2) and one of animal origin (D3). It became clear that cholecalciferol is the natural form of vitamin D in animals. Since then, thousands of analogues have been synthesized, of which more than a dozen are available [20]. In a sense, this is the end of the history of the discovery of vitamin D. However, in another sense all the previous findings were but a prelude to a wide research effort that keeps going until this day.

By the 1960s the precise role of cholecalciferol in preventing rickets was still unclear. The investigations of the research groups led by Ego Kodicek in England [21] and Anthony W. Norman [22] and Héctor F. DeLuca [23] in the United States demonstrated that cholecalciferol was actually a precursor that has to undergo two consecutive hydroxylations in the liver and the kidney to yield the steroid hormone, 1,25-dihydroxycholecalciferol. Further work shed light on the multiple roles of 1,25-dihydroxycholecalciferol on bone mineralization and additionally, on a wide variety of physiological functions [24-26].

Conclusion

Despite its generally accepted name, vitamin D should not be properly considered a vitamin, but a prohormone that can be synthesized physiologically in the skin in a reaction catalyzed by UVL, and also be incorporated with the diet. Ironically, this uncommon dual source of vitamin D, dietary and endogenous, was probably a main reason for the delay on its identification and characterization.

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