Elizabeth Trenkwalder

Chemistry and the Needs of Society:

Rickets and Vitamin D

Bowed limbs and soft, curved bones characterize the disease that became known as "the English disease" after Daniel Whistler published his doctoral thesis (1): "Concerning a Disease of English Children Which is Popularly Called the Rickets" in 1645. Rickets became increasingly common in children in the 18th century and research into this disease led to the identification of vitamin D in 1937. Were it not for society's need for a cure to this disease, vitamin D might not have been discovered. In this and other cases, epidemiology has historically influenced and propagated the discovery of vitamins.

The epidemiological history of rickets played a very important role in the discovery of vitamin D. Here, we first outline a history of rickets, and then move on to the historical context wherein vitamin D was discovered. Next, we look into the chemical properties of vitamin D and its role in the human body. Finally, we consider how the discovery of vitamin D led to the prevention of rickets and the contemporary importance of this essential vitamin.

I. History of Rickets

Daniel Whistler's publication outlined the symptoms of rickets. Following Whistler's publication, there was an outbreak of rickets diagnoses that led to the formation of a committee of physicians in London (1) to research the disease. In 1650, the committee published a book on symptoms and possible causes and cures of the disease that suddenly struck many children in Europe. Although their book proposed dietary deficiencies as the source of the disease, later research found that this was not the case (2).

In Northern Europe, the early Industrial Age of the 18th century brought many more cases of rickets. Physicians were surprised to note the curiously lower incidence of rickets in rural areas (1) where poverty was more prevalent and diets more meager. Because rickets affected wealthier, urban children, scientists realized that rickets was not simply a dietary deficiency as previously thought. Many postulated that poor air circulation and perhaps lack of sunlight exposure (2) were factors that contributed to rickets.

We now know that the outbreak of rickets was directly linked to the Industrial Revolution. Due to burning coal, air pollution was high, and thus the amount of ultraviolet radiation that reached people in urban areas was much lower (1) than that in rural areas. Lower exposure to the sun prevented children from receiving the necessary amount of vitamin D from the sun to stay healthy. Despite acknowledging that the disease arose from something in addition to or separate from dietary deficiency, it was not until the 20th century (3) that scientists finally began to understand the science behind this disease.

II. Discovery of Vitamin D

In 1906 (4), Frederick Hopkins proposed that there were certain substances, or 'factors', necessary for preventing dietary-deficiency diseases. The first factor discovered was deemed 'fat-soluble factor A,' which later came to be known as 'Vitamin A'. Vitamin A was a key dietary factor (3) in what was then used to prevent and cure rickets – cod-liver oil. Around 1920, Edward Mellanby discovered that cod-liver oil retained its anti-rachitic property (ability to cure rickets) when heated and exposed to oxygen (5), while other fats lost their anti-rachitic property when exposed to heat. Because fat-soluble vitamin A was destroyed by excessive heat or

oxidation, Mellanby hypothesized (5) that there existed a specific anti-rachitic substance or vitamin, distinct from vitamin A.

Experimenting to test Mellanby's hypothesis, E.V. McCollum, Nina Simmonds, J. E. Becker, and P.G. Shipley demonstrated the existence of a "vitamin whose specific property … is to regulate the metabolism of bones" (6). The deficiency of this fourth vitamin[1], vitamin D, is the cause of rickets. However, dietary deficiency was not the only reason many people were affected by rickets.

Around the same time vitamin D was discovered, scientists recognized that ultraviolet light irradiation also prevented and helped to cure rickets. Kurt Huldschinsky (2), a Berlin pediatrician, used UV light to irradiate just one arm of a child with rickets and noted the improvement of rickets throughout the child's body. This experiment allowed him to deduce (2) that irradiation of the skin releases an anti-rachitic chemical into the bloodstream.

Initially, scientists believed that UV irradiation was independent (3) of any relation to vitamin D. It was only when three separate experiments linked vitamin D and UV irradiation, that scientists realized that these were not two independent cures to the same disease. All three experiments (3) produced activation of the anti-rachitic compound vitamin D in foods through UV irradiation.

After the discovery that UV irradiation activates vitamin D, scientists sought the precursor to this vitamin, and turned to German steroid chemist Alfred Windaus. The first hypothesis postulated that cholesterol is the vitamin D precursor. However, after recrystallizing the dibromide of cholesterol, followed by a reaction with sodium amalgam (NaHg), Windaus and his partners A.F. Hess and O. Rosenheim (3), realized that cholesterol contained an impurity that

[1] Vitamins B and C had been previously discovered.

had the anti-rachitic property. Although in small quantity (7), the impurity was either the same or very similar to the precursor to vitamin D (provitamin D).

Upon comparing the chemical properties and the absorption spectrum of the impurity in cholesterol to those of a variety of steroid preparations (3), Windaus, Hess, Rosenheim, and Webster determined that ergosterol was the provitamin D. They named the irradiation (3) product of ergosterol 'Vitamin D-2' or 'calciferol'. In 1937, Windaus identified 7-dehydrocholesterol as the chemical present in human skin that becomes the anti-rachitic substance, Vitamin D-3 (3), after exposure to UV radiation.

III. The Chemistry of Vitamin D-3

7-Dehydrocholesterol, shown on the left in **Fig. 1,** is converted to cholecalciferol (an isomer of Vitamin D-3) when sunlight activates it in the skin by the mechanism shown in Fig. 1. The mechanism of this synthesis is a 6-electron electrocyclic reaction. The net result of the electrocyclic reaction is the conversion of one π-bond into one σ-bond (8). Electrocyclic reactions are photoinduced, explaining why UV radiation promotes this reaction (8). As the name indicates, electrocyclic reactions either open or close rings. In the synthesis of cholecalciferol, this reaction opens the ring (8).

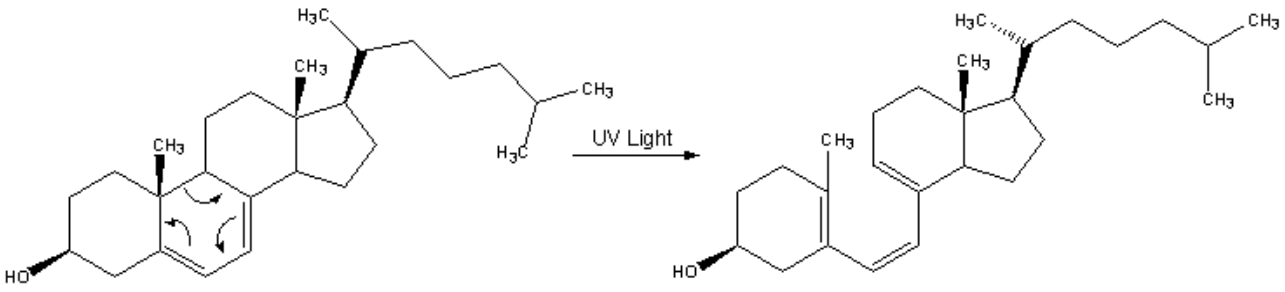

Fig. 1. The electrocyclic reaction of 7-dehydrocholesterol, irradiated by UV light, to form cholecalciferol.

Cholecalciferol, shown in **Fig. 2**, creates the isomer that is Vitamin D-3 by a hydride [1,7] sigmatropic shift (9). In a sigmatropic shift, the net result is that one σ-bond converts into another σ-bond.

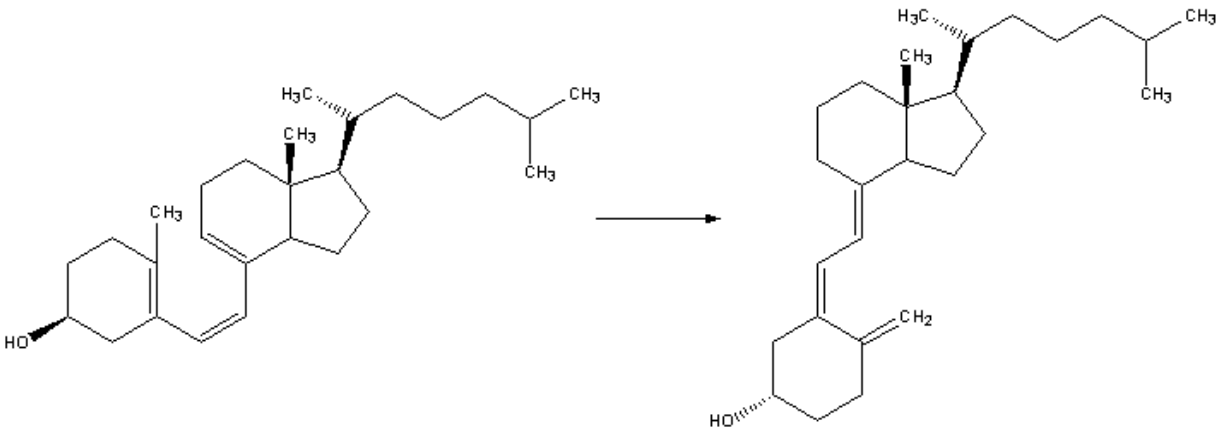

Fig. 2. Sigmatropic shift of cholecalciferol to form its isomer – vitamin D-3.

Once vitamin D-3 is created in the skin, it undergoes hydroxylation in the liver by the enzyme 25-hydroxylase to form 25-hydroxycholecalciferol, as shown in **Fig. 3**(10). Vitamin D-3 is then converted into its biologically active form, 1,25-dihydroxycholecalciferol in the kidneys (11).

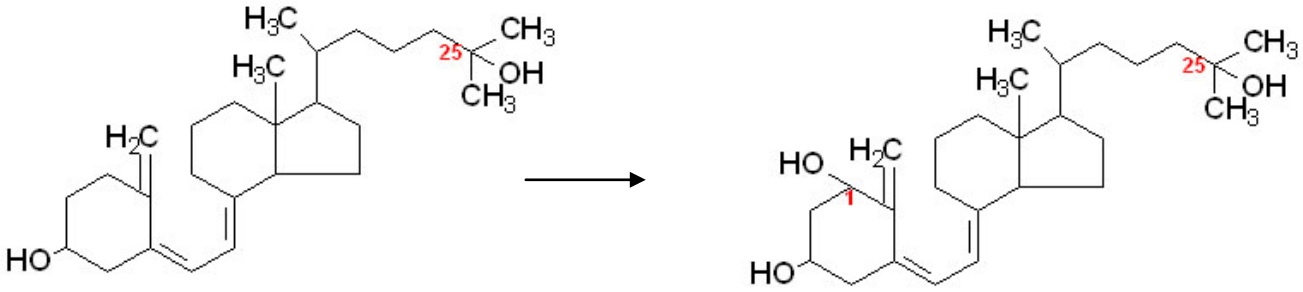

Fig. 3. Conversion of 25-hydroxycholecalciferol to the activated form: 1,25-dihydroxycholecalciferol

IV. Rickets Today

Paved by Windaus, understanding the chemistry of vitamin D has been important in combating rickets in children. Because we now understand the synthesis of vitamin D, we fortify foods to help prevent rickets. The current low incidence of vitamin D-deficiency diseases in the U.S. is due to vitamin D fortification of foods. However, rickets is not an extinct disease; it persists as a public-health problem in many less developed countries (12).

Rickets adversely affects public health and the economy. In areas like China and Mongolia, rickets affects about one in ten children (13). Because rickets depletes the strength of bones, it can often leave its victims crippled for life.

The historic epidemiology of rickets represents a situation where society demanded a solution. Under the pressures of societal necessity, researchers found that solution by identifying the cause of rickets. However, were it not for social pressures and the need for a result, researchers would not have investigated the substance they discovered to be vitamin D. Upon discovering vitamin D, chemists were able to improve public health. We have here a striking example that indicates how chemistry and society exist in a mutual symbiosis, where each challenges the other and promotes the success of the other.

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