THE METABOLISM, PHYSIOLOGY, AND FUNCTION OF VITAMIN D

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HISTORICAL BACKGROUND

Although it is difficult to document, there is evidence that the disease rickets, a well-known deficiency disease of vitamin D, was first recognized in antiquity (1). However, the first scientific description of this disease appeared in 1645 at the hands of Glisson or Whistler (1). With the development of the Industrial Revolution and its consequent urbanization of society, especially in geographical areas of low-incident sunlight and the appearance of pollutants in the air, the disease rickets appeared in epidemic proportions, especially in Northern Europe and the United States (1). This debilitating disease remained an unsolved medical problem until approximately 1930.

Through the work of many brilliant scientists, the concept of accessory food substances made its appearance. For example, Eickman had learned that polished rice produced the disease beri-beri in prisoners of the Dutch-West Indies and that it could be corrected by the administration of the rice hulls (2). His countryman, Grijns (3), deduced that this was the result of an accessory food substance found in the rice hulls. This substance later became known as vitamin B₁. Holst and Frolich (4) had learned that fresh vegetables administered to sea-faring sailors cured the disease scurvy. Funk (5) had proposed the term, vital amines, to describe substances in food required for health and development. However, it was the work of McCollum, et al. (6,7) that clearly established the existence of both fat- and water-soluble substances that prevent deficiency diseases. His work and that of Osborne and Mendel (8) established the existence of vitamins A and B. The two substances were used, therefore, to correct the dietary deficiency diseases of xerophthalmia, night blindness, and neurological disorders such as neuritis and beri-beri. These discoveries, undoubtedly inspired Sir Edward Mellanby (9) of Great Britain to study the question of whether rickets might be a dietary
deficiency disease. He succeeded in producing the disease experimentally in dogs by feeding them a diet of oat meal and maintaining them in the absence of sunlight. He cured the disease with cod liver oil, a substance known to contain the fat-soluble vitamin A described by McCollum. Sir Edward Mellanby concluded that this antirachitic activity was another property of the fat-soluble vitamin A. With stability tests, however, McCollum, et al. (10) clearly demonstrated that the vitamin A activity could be destroyed leaving behind the antirachitic activity. They correctly concluded that the antirachitic activity was the result of another accessory food substance which he termed vitamin D.

Following several isolated reports, Huldshinsky (11) and independently Chick (12) in Vienna demonstrated that rickets in children could be cured by exposing them to ultraviolet light from artificial or natural sources. It appeared curious, therefore, that ultraviolet light could prevent the same disease that could be prevented by cod liver oil. Steenbock and Hart (13) had been working with lactating goats and learned that ultraviolet light could put them into positive calcium balance. Goldblatt and Soames (14) healed rickets in rats by feeding livers taken from other rachitic rats that had been irradiated with ultraviolet light. It was Steenbock and Black (15), however, who clearly demonstrated that ultraviolet light induced the antirachitic vitamin in the fat-soluble portion of foods and skin thereby ending the confusion. This work, that was confirmed by Hess and Weinstock (16), was to provide the basic biological information required for the isolation and elucidation of the structure of vitamin D₂ completed in 1931 by Askew, et al. (17) and somewhat later by Windaus and his colleagues (18). The work of Steenbock and his collaborators also provided a convenient means of introducing vitamin D activity into such foods as butter and milk. This approach was then used to prevent and eliminate the disease rickets as a major medical problem.

Windaus and his collaborators (19) continued working on the chemistry of the vitamin D compound producing 7-dehydrocholesterol synthetically and demonstrating its conversion to another antirachitic vitamin, vitamin D₃. This form was later to be established as the natural form of vitamin D produced in skin (20). While the elegant work on the chemistry of the vitamin D compounds was progressing, other work had been initiated on understanding the mechanism of action of the antirachitic substance. Howland and Kramer (21), studying in vitro calcification of rachitic