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ABSTRACT. Rickets, a disease of vitamin D deficiency, is rarely confronted by the practicing pediatrician in the United States today. At the turn of the 20th century, rickets was rampant among the poor children living in the industrialized and polluted northern cities of the United States. With the discovery of vitamin D and the delineation of the anti-rachitic properties of cod-liver oil by the 1930s, it became possible to not only treat but also eradicate rickets in the United States. Rickets was a common disease in 17th century England. Frances Glisson's treatise on rickets published in 1650, a glorious contribution to English medicine, described the clinical and anatomic features of rickets in great detail. The exact etiology of rickets had been elusive until the 1920s. During the Glissonian era, rickets was a mysterious disease. By the late 19th and early 20th century, faulty diet or faulty environment (poor hygiene, lack of fresh air and sunshine) or lack of exercise was implicated in its etiology. Animal experiments, appreciation of folklore advocating the benefits of cod-liver oil, and the geographical association of rickets to lack of sunshine were all relevant factors in the advancement of knowledge in the conquest of this malady. In this article, the history of rickets pertaining to the discovery of vitamin D, cod-liver oil, and sunlight is reviewed. *Pediatrics* 2003;112:e132–e135. URL: http://www.pediatrics.org/cgi/content/full/112/2/e132; *rickets, vitamin D, cod-liver oil, sunlight, history of medicine.*

Rickets, a disease of vitamin D deficiency, although rare, is still diagnosed in the United States. Infants who are recent immigrants or adopted from orphanages abroad are at risk for rickets. Vitamin D status is determined by diet and degree of exposure to sunlight. Individuals with dark skin pigmentation who reside in northern latitudes or those with poor sun exposure are most at risk for seasonal hypovitaminosis D.[1] Breast milk is a poor source of vitamin D.[2,3] Dark-skinned infants are at risk for rickets if they are exclusively breastfed beyond 6 months without vitamin D supplementation. The Georgia Department of Human Resources and the Center for Disease Control and Prevention reported 6 cases of nutritional rickets among all hospital admissions for children between 6 months and 5 years of age from January 1997 to July 1999.[4] The affected children were 8 to 21 months of age and were breastfed for 8 to 20 months without vitamin D supplementation. Kreiter et al[5] reported 30 cases of nutritional rickets in North Carolina from 1990 to 1999. All the affected infants were black and had been exclusively breastfed without supplemental vitamin D. The mean duration of breast-feeding was 12.5 months. Age at diagnosis ranged from 5 to 25 months and the median age was 15.5 months. These reports reinforce that nutritional rickets is still around in the United States and is relevant for the practicing pediatrician, and awareness of such a fact will help in its early identification, treatment, and prevention. In that context, the history of rickets and the roles of vitamin D, cod-liver oil, and sunlight are reviewed.

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EARLY HISTORY OF RICKETS

Conditions with bony deformities have been described in ancient medical writings from the 1st and 2nd centuries.[6] Soranus, a Roman physician in the 1st and 2nd century AD, had noted bony deformities more frequently among infants residing in Rome than Greece, and attributed such a variation to lack of nurture and hygiene by Roman mothers.[7] Galen, also of the same era, had described the classic bony deformities noted in rickets.[6] Although such descriptions can be interpreted as evidence for existence of rickets, it was not until mid-17th century that clear description of rickets emerged.[6–8] In the mid-17th century England, rickets was endemic in the Southwest counties of Dorset and Somerset.[6–8]

Daniel Whistler, an English physician, is credited with the earliest description of rickets.[6,8] In 1645, while a medical student at Leyden, Whistler published a monograph titled "Inaugural medical disputation on the disease of English children which is popularly termed the rickets."[6] Whistler provided a succinct description of the signs and symptoms of rickets in his thesis and used an alternate term called "Paedosteocaces" to describe the clinical symptoms of rickets.[8] Medical historians have questioned the originality of Whistler's report.[8] It's probable that Whistler's report is based on hearsay rather than personal experience, as he was a medical student and only 26 years of age at the time of its publication.

In 1650, Francis Glisson, a Cambridge physician published in Latin a treatise on rickets titled "De Rachitide."[7,8] Glisson's work remains a classic among medical texts. Unlike Whistler, Glisson's sound and elegant observation of rickets is based on clinical and postmortem experience. Glisson's writing reflects the transitional phase in medical thinking.[6] Glisson's treatise addresses the clinical features

of rickets in a scientific tone, but lapses into medieval mysticism while discussing the etiology of rickets. Glisson ascribed the etiology of rickets to "cold distemper, that is moist and consisting of penury or paucity of and stupefaction of sprits."[6] Despite his affirmation of mysticism in the cause of rickets, Glisson was convinced that rickets was neither contagious nor heritable.[9] His conclusions regarding the relationship of age to onset of rickets has stood the test of times: "We affirm therefore, that this disease doth rarely invade children presently at birth, or before they are six months old; (yea, perhaps before the ninth moneth) but after that time it beginneth by little and little daily to rage more and more to the period of eighteen moneths, then it attaineth its pitch and exaltation, and as it were resteth in it, till the child be two years and six month old: so that the time of the thickest invasion is that whole year, which bears date from the eighteenth month, two years and half being expired, the disease falleth into its declination, and seldom invadeth the child, for the reasons already alledged."[7,9]

Glisson's suggested treatments for rickets included: cautery, incisions to draw out bad humors, blistering, and ligature of soft wool around the limb to retard the return of blood.[7] For correction of bony deformities, Glisson proposed splinting and artificial suspension of the affected infant: "The artificial suspension of the body is performed by the help of an instrument cunningly made with swathing bands, first crossing the brest and coming under the armpits, then about the head and under the chin, then receiving the hands by two handles, so that it is a pleasure to see the child hanging pendulous in the air, and moved to and fro by the spectators. This kind of exercise is thought to be many waies conducible in this affect, for it helpeth to restore the crooked bones, to erect the bended joynts, and to lengthen the short stature of the body."[7]

There were no new advances in the study of rickets for nearly 2 centuries after the Glissonian era. At the turn of the 20th century, rickets was rampant among the underprivileged infants residing in industrialized cities of North in the United States and several polluted cities in Europe. In 1909, among infants 18 months or less who had died, Schmorl found histopathological evidence of rickets in 96% (214 of 221) at autopsy, highlighting the pervasive nature of rickets during that era.[10] Despite its common occurrence, the exact etiology of rickets remained elusive. Deficient diet, faulty environment (poor hygiene, lack of fresh air and sunshine), and lack of exercise were all implicated in its etiology. Dietary animal experiments, appreciation of folklore advocating the anti-rachitic properties of cod-liver oil, and epidemiologic understanding of the geographical association of rickets to lack of sunshine were all relevant in resolving the "rickets" puzzle. The late 19th century and early 20th century witnessed a phenomenal expansion in the knowledge of rickets. Understanding the histopathology of rickets, advances in biochemical and radiologic testing, clarification of the anti-rachitic features of cod-liver oil and ultraviolet light were all responsible for the conquest of rickets as a malady.[6] Alfred Hess referred to this era as "the second great chapter" and the "renaissance" in the history of rickets.[3]

EXPERIMENTAL RICKETS

In 1889, Bland-Sutton observed florid rickets among lion cubs at the London Zoo.[11] Affected cubs were subsisting on an exclusive diet of boneless lean meat. Addition of cod-liver oil and crushed bones to their diet helped the cubs recover fully. Bland-Sutton hypothesized that rickets was caused by deficiency of dietary fat.[11] It was 30 more years before further progress was made in clarifying the role of diet in rickets.

In 1919, Edward Mellanby, an English physician, conducted the earliest definitive experimental study exploring the role of diet in the etiology and treatment of rickets.[11,12] Puppies between 5 and 8 weeks of age were exposed to 1 of 4 natural diets. All 4 diets were rachitogenic after a variable period of exposure. Rickets was severe and developed easily in dogs that grew well on the rachitic diets. Neither yeast (anti-neuritic vitamin) nor orange juice (anti-scorbutic vitamin) hindered the development of rickets. Various foods were added to the rachitic diets and their effect on development of rickets was studied. Foods rich in fat-soluble vitamin A (cod-liver oil, butter, and whole milk) were able to prevent rickets. Mellanby postulated, "It therefore seems probable that the cause of rickets is a diminished intake of an antirachitic factor which is either fat-soluble A, or has a somewhat similar distribution to fat-soluble A."[12] Mellanby had presumed that calcium and phosphorus were adequate in all of his rachitic diets but it was soon established that all of his diets were relatively deficient in calcium and lacked favorable calcium phosphorus ratios.[11] Mellanby's work clearly established the role of diet in the cause of rickets. Discerning the exact nature of the dietary "antirachitic" factor was the next important milestone in the history of rickets. That effort can be credited to Elmer McCollum.

In 1907, on completion of Doctorate in chemistry, Elmer McCollum began his career as a nutritional biochemist at Wisconsin College of Agriculture in Madison, Wisconsin.[13] Over the next decade, McCollum perfected the art of "biological method of analysis" of nutritive value of foods using rats as an animal model.[13] His methodology was elegant. Rats fed restricted diets of single cereal grains or mixtures of several grains ceased to grow reflecting the nutritional inadequacy of the corresponding diets. The physiologic response of such animals to single and multiple purified nutritional supplements helped clarify their nutritional requirements. Eventually it was the perfection of this technique of "biological analysis of foods," which helped McCollum discover vitamin D.

In 1917, McCollum moved to Johns Hopkins University to head the department of chemical hygiene and to further pursue his nutritional research career.[13] McCollum was able to induce various states of malnutrition in experimental animals by modifying the restricted diets. Being a basic scientist, McCollum

lacked the clinical knowledge to explain the symptoms and clinical pathology of the various states of malnutrition he had induced in his experimental animals.[13] By sheer coincidence McCollum found the collaborators he was seeking. In 1918, Dr John Howland, Professor of Pediatrics at Johns Hopkins University, asked McCollum if rickets had ever been experimentally induced in an animal.[13] Hesitantly, McCollum showed 2 of his rats with bony deformities of the thorax and beading of the ribs as possible cases of experimental rickets. McCollum was also able to show other rats on similar rachitogenic diets modified by supplements that were free of rickets. Convinced that the rats were suffering from severe rickets, Howland agreed to collaborate with McCollum. Dr Edward Park and Dr Paul Shipley, experts in bone histopathology immediately joined McCollum and with their arrival McCollum was able to advance further in his quest to unravel the mystery of rickets.

McCollum and his coworkers tested various cereal-based diets characteristically deficient in fat-soluble vitamin A and calcium on young rats and were able to induce skeletal changes consistent with clinical and histologic rickets similar to those seen in rachitic infants.[14] Cautiously, they speculated that "the cause of these diseases might lie in a deficiency of fat soluble A or calcium in the food, or a disturbance in the metabolism of these factors. At present it is only possible to say that the etiologic factor is to be found in an improper dietetic regimen."[14] The effect of cod-liver oil on rats rendered rachitic were studied.[15] Feeding cod-liver oil for 2 to 7 days induced a uniform pattern of healing. Calcium was deposited between the provisional zone of cartilage in a uniform linear pattern, and the width of calcification correlated with the duration of treatment. This work led to the development of the Johns Hopkins "line test" for quantitative assessment of vitamin D in foods.[16,17]

McCollum was now confronted with same question faced by Mellanby, whether fat-soluble A was anti-rachitic by itself or if there was another substance with specific anti-rachitic function with similar distribution as fat-soluble A. McCollum and Mellanby were aware of F. G. Hopkins' report that oxidation destroyed fat-soluble A.[11] Mellanby found oxidized butter fat had lost its anti-rachitic effect, but similarly treated cod-liver oil still retained its protective action against the development of rickets. Mellanby stated "this difference can be explained by the fact that cod-liver oil contains greater quantity of antirachitic vitamin than butter, or that the destructive change takes longer time, or whether some other explanation must be sought."[11] McCollum and his coworkers were soon able to explain the preservation of anti-rachitic function in oxidized cod-liver oil. Unlike Mellanby, they chose to explore the anti-xerophthalmic and anti-rachitic functions of oxidized butter fat and oxidized cod-liver oil. They chose "diet 3143," which was adequately restricted with regard to fat-soluble A to cause severe rickets but still able to prevent the onset of xerophthalmia, to induce rickets in rats.[18] Using the "line test," the anti-rachitic potency of several fish liver oils, vegetable oils, and butter fat were tested. Oxidized cod-liver oil had lost its anti-xerophthalmic function, but still retained its calcium-depositing properties. Untreated coconut oil had no anti-xerophthalmic property, but had minimal anti-rachitic function. McCollum and his coworkers concluded that the anti-rachitic substance found in certain fats was distinct from fat-soluble vitamin A and its "specific property was to regulate the metabolism of the bones."[18] In the sequence of discovery of vitamins, the newly discovered anti-rachitic substance was the fourth; hence it was called vitamin D.[11,16]

COD-LIVER OIL, SUNLIGHT, AND RICKETS

Among people living in coastal areas, folklore has had a long-standing appreciation of the medical benefit of cod-liver oil.[19] The earliest recorded medical use of cod-liver oil dates to 1789, and is credited to Dr Darbey of Manchester Infirmary.[19] He used it for treating rheumatism. The recognition of cod-liver oil as a specific remedy against rickets was noted as early as 1824 in the German medical literature.[19] In 1861, Trousseau of France ventured to state that rickets was caused by lack of sun exposure and a faulty diet, and cod-liver oil could effectively cure it.[19–21] In 1890, addressing the etiology of rickets, Palm studied the relationship between incidence of rickets and its geographical distribution, and concluded that rickets was caused by lack of exposure to sunlight.[22] Palm was able to point out that, despite a superior diet and relatively better sanitary condition, infants residing in Britain were more at risk for rickets than infants living in the tropics. Exposure to plenty of sunshine, which was the norm for infants residing in the tropics, was responsible for their protection against rickets. Palm recommended "systematic use of sun-baths as a preventive and therapeutic measure in rickets."[22] In 1919, Huldchinsky was able to cure rickets in infants with heliotherpy using mercury vapor lamp.[11,20]

CONCLUSIONS

The fact that both sunlight exposure and ingestion of cod-liver oil could cure or prevent rickets was perplexing. The link between cod-liver oil and radiant energy in treatment and prevention of rickets had to be explained. By carefully controlled clinical studies performed in Vienna between 1919 and 1922, Dr Harriette Chick and her coworkers were able to confirm the preventive and therapeutic value of cod-liver oil and sunlight against rickets in young infants.[23] The seasonal variation in the incidence of rickets, the role of skin pigmentation in exacerbation of rickets during the winter months, the role of diet and appreciation of the fact that breast milk per se was not an adequate source of vitamin D were understood.[6] The bridging of the knowledge that photosynthesized vitamin D and vitamin D in cod-liver oil were similar was responsible for the eventual conquest of rickets. By the 1930s, the use of cod-liver oil in the treatment and prevention of rickets became common place.[24] The eventual public health prevention initiative of fortification of milk with vitamin D led to eradication of rickets in the United States.

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