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REVIEW ARTICLE

Economic and Social Factors in the Etiology of Childhood Rickets over the Past Four Centuries

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Abstract: *Economic and social factors can determine the prevalence and severity of a health condition, as well as enhance co-morbidities. This article reviews forces that have influenced the appearance and persistence of nutritional rickets over the past 400 years. Childhood rickets first appeared from 1600 to 1640 as an epidemic disorder in the south and west of England when the woolen trade developed as a home labor industry. Later, with the coal-fueled factory system, agrarian laborers migrated to cities, creating a wage earner class. Their children were raised in smog-ridden and crowded conditions and were victims of an urban-based form of rickets lasting from the 1640s to the 1930s.*

With the discovery of vitamin D, arising from both dietary sources and from photocutaneous biosynthesis by exposure to ultraviolet B wavelengths from the sun, and recognition of its use as a therapeutic agent, epidemic rickets largely disappeared. The pro-sunshine era was ushered in between 1930 and 1965. Since, rising rates of skin cancer have greatly tempered enthusiasm for sun exposure and led to recommendations for sun protection strategies.

Beginning in the 1960s, examples of nutritional rickets have been seen in dark-skinned immigrants moving to northern latitudes. Often rickets occurred in association with vitamin D-deficient mothers who exclusively breast-fed their offspring. Also, vitamin D deficiency is more evident in young children, adolescents, pregnant mothers and the elderly, many of who remain indoors and do not use vitamin supplements.

These factors - child labor, the almost universal use of coal as a fuel, dietary deprivations during wars, migration of dark-skinned populations to regions where sunshine is scarce, and cancer-associated fear of sun exposure - have resulted in the persistence of nutritional rickets despite the knowledge of medical practitioners, nutritionists, and even parents. This manuscript reviews these factors and their impact on the health of children.

Keywords: *rickets, vitamin D, history, etiology*

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Introduction

Children have been harmed by economic and social pressures throughout recorded history. Used as laborers and farm workers and perceived as chattel by their parents, landlords and foremen, children were exposed to traumatic injury, toxic agents, fire, frigid conditions and inadequate nutrients [1]. Children were and are forced to be street vendors, work long hours (precluding sleep), and even function as miners. Children as young as four years of age were employed in factories, and it was only in the late 19th century that laws in the United Kingdom made illegal a more than 12-hour work day for children under the age of 12 [2]. Children were frequent employees of factories, of mines (in part because the shafts were so narrow) and famously functioned in the traditional role of the chimney sweep.

Young women also joined the labor force, particularly in the large mill cities of the United Kingdom and such American locales as Lowell and Lawrence, Massachusetts. Their infants, frequently born out of wedlock, were often rachitic [3]. These mothers, who worked up to 12 hours daily, six days per week, were likely to be vitamin D-

deficient themselves, which further affected their offspring.

The concept that rickets occurred as a consequence of social and economic factors has been articulated in the past [4]. However, the variety of forms of nutritional rickets needs to be expanded. Moreover, C. E. Dent was critical of Dick's analysis [5] because Dick ignored the discoveries of Mellanby concerning the nutritional cause of experimental rickets in beagles [6]. Dick mainly focused on known disorders of bone, and even advocated massage and skin friction as a treatment for rickets [4]. The current article examines a cascade of factors that have ultimately led to nutritional rickets for more than 400 years, with a special emphasis on social factors (Table). We further posit that rachitogenic conditions have frequently been the consequences of economic forces, but also, at times, children have developed this disorder as an unintended outcome of well-meant actions.

Table. Historical social and economic factors affecting childhood rickets

Type	Years	Social or Economic Factors Affecting Children
Glissonian rickets	1610 - 1650	Home weaving trade
Industrial revolution rickets	1640 - 1930	Factories, urbanization, coal fuel, smog, child labor
Wartime rickets	1870 - 1871 1914 - 1920 1939 - 1947	Children suffered dietary deprivation, were uprooted and orphaned, stayed indoors
Sunshine era	1925 - 1965 1965 - present	Exposure to sunshine, tanning encouraged Rising incidence of skin cancers results in recommendation for dietary source of vitamin D
Immigrant rickets	1965 - present	Migration of dark-skinned immigrants to northern areas of Europe and North America; the wearing of heavy, skin-concealing clothing; infants exclusively fed breast milk from vitamin D-deficient mothers
Human milk-fed infants	1980 - present	Mothers who may be vitamin D-deficient themselves avoid sunshine, fail to provide dietary vitamin D supplementation to infants

Glissonian rickets

Skeletal remains with findings consistent with rickets have been noted since antiquity, predating the initial classical description of the condition [7, 8]. However, it was from 1610 to 1640 that a raging epidemic of rickets was seen, with twisted limbs and swollen wrists, knees and ankles in sufferers of the disease. Initially termed "The English Disease," the medical school thesis of an English physician named Daniel Whistler at the University of Lyden, related a clear description [9]. More importantly, the masterful report of Francis Glisson published in 1650 (an English translation was published in 1651) is recognized as the definitive description of rickets [10, 11]. They remarked that children in the south and west of England, but rarely in the north, manifested this new condition, and they essentially described all the features that we recognize today to define rickets [12]. Medical historians have emphasized that rickets emerged at the time of the industrial revolution [9, 13]. but it was the opinion of Kellett [14] that the original Glisson report defined a different population of children, rather than those affected by the industrial revolution. To wit, at the end of the Tudor era, the English population had expanded and the main non-agrarian work force in the south and west of England was engaged in weaving and textiles. The system of the master clothier, with the spinning jenny and looms in the home, utilized the labor of many children, who hence remained indoors. This home labor system employed approximately one million people (of a population of five million in the United Kingdom), and resulted in the rise of a wage-earning class. Wool from sheep raised and shorn in England, which had formerly

been exported to Flanders, was now spun at home. The consequence of this family-based industry was to markedly limit time that children spent outdoors, particularly in comparison to children living and working on farms. In a wage earning system, all family members contribute to the household income and longer hours resulted in greater wages. There was little time for childhood play outdoors, and these families did not raise food. Confinement indoors greatly limited exposure to UVB wavelength rays, and inadequate photocutaneous synthesis of vitamin D contributed to the resultant rickets [14]. These childhood victims of Glissonian rickets were not the same population as those who were deprived of adequate sunlight as the burning of coal became widespread.

Industrial revolution rickets

The next phase in the history of nutritional rickets occurred as urbanization and the use of coal as a fuel developed circa 1650 [13-15]. Relative to home weaving, large-scale factories in which cloth was mass-produced were more efficient. This system of factory work became a norm for industrialized nations and, ironically, underpinned the socioeconomic conditions contributing to rickets until the early 20th century. The factory system brought a major exodus of rural families from farmlands into cities, causing overcrowding and a housing shortage. Two post-1650 cataclysmic events in England – the English Civil War (1645 to 1652) and the Great Fire of London (1666) – also contributed to the emergence of an epidemic of urban rickets. The Civil War ushered in a time of economic uncertainty and stoppages in the wool trade [14, 16-19], and poverty increased. After the Great Fire of London, a frenzy of rebuilding occurred simultaneously with a four-fold expansion of the population of London [20]. Pressures on the supply of timber soon exceeded the capacity of nearby forests and a new source of fuel was required: coal [21]. Initially, sea coal was harvested from beaches, where eroded cliffs deposited it. The demand for coal led to the mining industry, and by 1700 England produced over 80 percent of the world's coal [21, 22]. Coal was employed both to fuel industries and to heat dwellings. Urban centers other than London then emerged, especially in the north of England and Scotland near coal mining regions. Factories were erected in Manchester, Lancashire, Newcastle and the Clyde-Firth region of Glasgow and Edinburgh, all sites of coal deposits that became centers of mining.

The need for labor in these factories, initially textile plants in the 17th and 18th centuries, and later iron- and steel-based industries (including ship building, rail engines and bridges) in the 19th century, was to change the nature of British society. Migration to urban areas further increased, and these rural workers brought their families. While wages had been stable in the 17th century, the shift away from farms led to an inflation in the price of food (particularly wheat) and led to the agrarian revolt, which required "more food for more people"[23]. The apex of food prices occurred between 1640 and 1660 [24-26]. Workers had to move into tenements, often four to five stories high and slotted right next to one another. In these urban environments, the skies were filled with a haze from coal soot and smoke, a pea soup-like smog. Children reared in these environments, many of who toiled in factories or workhouses, were almost never exposed to solar UVB rays, particularly because coal soot particles absorb these wavelengths. In addition, the latitude of these industrial revolution cities, in Britain and in northern Europe and North America, was such that scant UVB rays penetrated into the earth from late fall to late spring anyway [13, 15, 27]. Moreover, the urban working class had limited wages and lacked the family income to afford a quality diet. They ate potatoes and other starches with little meat, fish or vegetables.

Not only was rickets prevalent in these crowded cities, (sometimes up to 60 to 80 percent of the child population) [28, 29], but infectious diseases – dysentery, measles, pneumonia and tuberculosis – were rampant [30, 31]. These infections were serious, and some felt they were components of rickets. Until the 1880s, contagion was felt to be due to miasma, which led many Europeans to wear heavy clothes, full-length sleeves, and, at the extreme, gloves and masks [30]. This personal drapery also limited sun exposure. The economic impact of an industrial society with the rise of an owner/manager class and a large laboring underclass contributed to a social and economic climate in which childhood nutritional rickets was rampant. The necessity of factory work with urban population density, haze enmeshed skies, and the dietary inadequacies for a substantial segment of the population resulted in the 1650 to 1930 (180 year long) epidemic of childhood rickets [29, 32-35]. Epidemic rickets only subsided when the role of cod-liver oil, sunshine exposure and other sources of vitamin D were understood and employed in the prevention and treatment of rickets.

Sunshine era

The sun has been deified since ancient antiquity. Symbols of a sun god have been found in temples as old as 11,600 years [36]. Egyptian, Mesopotamian, Greek and Roman

mythology contain stories of figures that we recognize as solar deities [37]. Pagan myths and Midsummer's Day are key components of many cultures, including the Druids and Scandinavians [38]. Numerous South American and Mexican cultures erected temples dedicated to solar events. All ancient and medieval cultures recognized the life-giving qualities of the sun [39]. Recognition that the sun provided curative rays that could treat or prevent rickets came about in the late 1800s and early 1900s [40, 41]. We now know that UVB wavelength rays can cause the cutaneous photoisomerization of 7-dehydrocholesterol to pre-vitamin D_3 and then a thermal conversion to vitamin D_3, [27] and that this is a biologic mechanism to produce vitamin D in man.

Because of the prevalence of rickets, a plethora of theories as to its cause were circulating from the late 18th to the early 20th centuries [8, 13, 42]. Great emphasis was placed on an infectious origin of the condition [43]. However, in 1822 Snaidecki had noted that among children in western Poland, rickets were less frequent if they were exposed to sunlight and resided in rural areas rather than in towns or cities [40]. Two noteworthy 19th century advocates of solar exposure were Florence Nightingale and Hugh Owen Thomas. In 1878, Thomas urged exposure to sunshine and clean, open air for treatment of crippling conditions of childhood [44, 45]. However, these recommendations were made for children with spinal deformities, usually arising from tuberculosis.

A critical observation was made in 1890 by Theobald A Palm, MD [41] concerning the relationship between sunlight and rickets, but the significance of the observation was not widely appreciated for many years. Palm was a medical missionary, who while in Japan for 10 years, rarely encountered rickets, albeit many of these children were raised in poverty and unclean living conditions. He wrote to other medical missionaries to inquire about their own experiences with the condition. Rickets was indeed rare in the tropics and common in the United Kingdom, especially in urban areas. In his treatise, Palm pointed to the powers of the sun and felt strongly that the sun itself held curative powers. He also indicated that demographic surveys indicated that rickets was more prevalent in northern Europe than in southern Europe. Gradually, over the 40 years from 1890 to 1930, the observations of Palm influenced pediatric scholars in the study of rickets. Max Kassowitz had noted that he encountered rickets in his Vienna clinic more frequently in the winter than in summer [46]. He followed up on these observations into the 20th century. Neils Ryberg Finsen, a Danish scientist, actually used phototherapy to treat lupus vulgaris, a cutaneous form of tuberculosis, and his technique was emulated by others [47]. Raczynski used phototherapy in 1908 and claimed to have found a cure for rickets [48]. Huldschinsky in 1920 demonstrated that light from quartz crystal mercury vapor lamps could be used to either cure or prevent rickets [49].

Alfred F. Hess, a New York pediatrician, noted remarkable rates of rickets in African-American and either Italian-American or other immigrant children living in the Columbian Heights section of Manhattan. He advocated either sunshine or phototherapy as a cure [50, 51]. Other accounts of severe rickets in Italian immigrant children were found in Chicago, Illinois [52] and New Haven, Connecticut [53], and in each locale sunshine therapy was encouraged. Hess in New York [51] and Steenbock [54] in Wisconsin showed that irradiation of skin and food produced an antirachitic substance that could cure rickets in animal models or children. Eliot also proved the value of UV irradiation in children in New Haven [55] and later, when she led the Children's Bureau in Washington D.C., she stressed the value of exposure to sunshine.

Advocates of sunshine investigated which of the sun's rays had curative powers and showed that UVB wavelengths were critical [56, 57].

The "sunshine era" began in the late 1920s and persisted until the mid-1960s. When vitamin D was identified [58, 59] it became known as "the sunshine vitamin." During this 40-year period after 1928 the concept was that to be tan was to be healthy, and that exercising outdoors under the sun was conducive to good health. The extreme of this view was the Aryan ideal of blond-haired, blue-eyed, golden tanned athletes depicted in Nazi propaganda posters. Parents were encouraged to see that their children were sunbathed until their skin was bronzed, and it was even recommended that infants obtain "an early coat of tan" [60].

Beginning in the 1960s and '70s it was becoming clear that excessive sun exposure resulted in an increased incidence of skin cancer [61]. The three major types of skin cancer – basal cell and squamous cell carcinoma, and melanoma – are caused by UVA and UVB rays that damage DNA in the skin and can lead to signature mutations found in non-melanoma cancer (UVB rays) and metastatic melanomas (UVA rays) [62]. Children growing up in the period between 1920 and 1960, who were encouraged to acquire a healthy tan, are now the late middle-aged to elderly adults in whom the rising rates of skin cancer are evident [63]. With the intent to assure vitamin D adequacy from sunshine exposure, children and families were given

advice that paradoxically contributed to cancer and cancer deaths. These good intentions of a generation of sunshine advocates have resulted in a situation in which more than minimal sun exposure, such as traveling from a car to a building, cannot be recommended for pale-skinned individuals and infants [61].

Wartime rickets

Children suffer greatly in times of war, especially in the combatant nations. Among the deprivations of wartime are severe dietary restrictions, such as those leading to the outbreaks of rickets seen in Parisian children during the Franco-Prussian War.

The siege of Paris from September 19, 1870 to January 28, 1871 resulted in severe starvation, and, as a consequence, rats, cats, dogs, horses and even zoo animals were eaten. Rominger reviewed information concerning Parisian children after the peace treaty, and reported in the Zeitschrift fur Kinderheilkun that a majority of children were afflicted with rickets (as reviewed in the Journal of the American Medical Association in 1915) [64]. The theme of dietary deprivation is common in wartime. Extreme cases of rickets in Berlin and Vienna were described during and after World War I [65-67] and in children placed in concentration camps during the Holocaust in World War II [68]. It has been estimated that these children suffered a daily caloric reduction of approximately 25 percent less than normal [68].

The situation in the 1914-1918 war was that Britain and France imposed a strict embargo on shipping to Germany, Austria and Turkey. Shortages of meat, oil, fish and other sources of protein were universal. The rickets developing in German and Austrian children was especially marked and was even found in older children and adolescents, ages at which rickets is not usually encountered [13, 65]. One of the extraordinary features of the embargo was that it continued after the Armistice and until the Peace Conference in 1920. It was the severity of the rickets encountered that led to the experiments of Huldschinsky, who used irradiation with quartz crystal mercury vapor lamps to treat the condition [49, 69] and opened the field of phototherapy of rickets. Harriette Chick, an esteemed nutritional biochemist and physician, was dispatched from London to Vienna to deal with the problem of rickets due to wartime. She experimented with phototherapy, cod-liver oil and various dietary supplements. These trials have been recognized as models of nutritional research [65, 70].

Although Clausewitz famously remarked, "War is not merely a political act, but also a real political instrument, a continuation of political commerce, a carrying out of the same by other means," [71] the effect of this political act on children is devastating. Children have no voice in this commerce and are not combatants, but suffer the consequences.

The adequacy of human breast milk

Breastfeeding of infants has had a varied impact on the prevalence of rickets. From the 19th century until now, infants who were born to mothers with lactation failure or whose time period of breastfeeding was limited suffered from higher mortality rates, malnutrition and much higher rates of rickets [52]. Breast milk has been and still is the main nutrient of children until they can eat solids. This milk also contains the calcium and phosphate necessary to mineralize growing bones [72, 73]. If inadequate dairy or human milk is available, infants demonstrate bone hypomineralization. The risk factors for rickets include infants being fed other foods much before six months of age (especially those which are devoid of calcium, phosphate and vitamin D), a lack adequate sun exposure, and the constant and real occurrence of serious infectious diseases. The mortality rate of these infants is extremely high [14], with the result that rickets was listed on the Death Bills in London [10, 11, 14]. Even today in developing countries such as Ethiopia, Kenya and India, these dying children also suffer from lower respiratory tract infections, tuberculosis and measles [74-77]. The duration of breastfeeding as a deterrent to the development of rickets is an epidemiologic association. However, the association between potentially fatal infection and rickets has been noted since the mid 19th century [8, 13-15].

Why should vitamin D deficiency be associated with infection? It was in the late 20th century that an appreciation of the immune, anti-autoimmune, anti-cancer and innate immune properties of vitamin D emerged [78]. For example, synthesis of an anti-microbial peptide, cathelicidin, is dependent upon the active vitamin D metabolite 1,25-$(OH)_2$ vitamin D [79-81]. Currently, prospective studies are sorting out which of the non-osseous properties of the vitamin are causal in preventing infection and which are mainly epidemiologic associations [82].

The risk of breast milk as an exclusive source of nutrients, relative to rickets, was perceived following the migration of dark-skinned individuals to northern latitudes or forced immigration, such as Indians forced out of Uganda. Both Palm and Loomis stressed the absence of rickets in tropical regions [41, 83, 84]. Loomis noted that the nearer to the equator an individual lived, the more melanin their skin

contained. This observation has been reconfirmed on numerous occasions [27, 61]. Cutaneous melanin, not unlike atmospheric soot and ash particles, absorbs UVB wavelengths and results in greatly diminished photocutaneous synthesis of the vitamin.

The rickets experienced by Asians moving to the United Kingdom occurred first in the 1970s [85]. Many of these families of Indian subcontinent extraction had been expelled from Uganda by Idi Amin [86]. Holding British passports, they flocked to the cities and maintained their traditional ethnic heritage customs. Among these were the wearing of saris or other body-covering robes and headdresses, a vegetarian diet, exclusive breastfeeding, and very limited exposure to the outdoors. Florid rickets occurred in their offspring and the mothers themselves were often vitamin D-deficient [87]. A similar form of rickets was described in the United States among families who had migrated from southern states to urban centers in the north. Some of the women wore heavy robes and head coverings because of the doctrines of their spiritual leaders An example is the Reverend Major Jealous Divine (Father Divine) and other similar cult leaders [88]. These mothers were also vegetarians who were possibly vitamin D-deficient and who exclusively breastfed their infants. Another similarity between these two ethnic groups is their ingestion of phosphate-binding foods such as chapatti [89] or cornstarch.

Other dark-skinned immigrants have been reported as having rachitic offspring, especially Turkish and Middle Eastern immigrants moving to Germany or Sweden [90, 91]. These families had departed from more tropical zones and moved into temperate areas. People already living in temperate locales (such as Caucasians and Northern Asians) had, through a process of natural selection, developed mutations in the melanin synthetic pathways in their keratinocytes that limited melanin synthesis, because they had adapted with pale skin to the scant UVB ray exposure of the latitude in which they lived [62]. Dark-skinned families who migrated from South Asian and African origins to northern latitudes for higher wages and improved living conditions thus entered an environment that put them at risk for rickets. It is these immigrant mothers for whom breastfeeding, without assuring their own vitamin D adequacy, may put their infants at risk. There is an obvious analogy between the migration of these immigrants to northern latitudes and the migration of rural mothers of the 1600s and 1700s to a region of smoggy skies. At the center of the issue of vitamin D sufficiency of human milk is the notion that human milk is the best nutrient for infants. Literally thousands of studies and reports have indicated the advantage of human milk over other nutrients [92]. Infant formula manufacturers are always striving to create a formula that is most similar to human milk. Nonetheless, it has long been recognized that human milk does not contain a sufficient concentration of vitamin D to preclude the development of rickets in certain populations of infants who are exclusively breast-fed [93]. For this reason the American Academy of Pediatrics has recommended that all exclusively breast-fed infants receive vitamin D supplementation [94, 95].

A controversy arose in the late 1970s when it was reported that human milk contained adequate vitamin D content, albeit in the sulfated form [96]. The advantage of a sulfated form of vitamin D would be that it could be present in the aqueous phase of milk. This finding could not be confirmed and it was reaffirmed that human milk-fed infants required vitamin D supplementation [93]. Some strong advocates of breastfeeding still embraced the vitamin D sulfate story and urged that no supplements be added to the diet of breast-fed infants. However, because of case reports of human milk-fed infants developing rickets, the American Academy of Pediatrics recommended that all breast-fed infants receive vitamin D; first at 200 IU daily [93] and later at 400 IU/day [97].

Medical research clearly supports the nutritional advantage of human milk relative to cow milk-based formulas [98]. Only when high doses of vitamin D (e.g., up to 6400 IU/day) are provided to the nursing mother will human milk reach vitamin D values comparable to supplemented milk [99]. A double-blind, randomized clinical trial of the safety and efficacy of 4000 IU vitamin D supplementation during pregnancy showed that this level of supplementation resulted in infants with normal 25(OH)D values of 80 nmol/L at age one month [100].

The rickets evident in exclusively breast-fed infants represents, in part, a lack of appreciation of the inadequate values of vitamin D in the blood of vitamin D-deficient or -insufficient mothers. Not only are the circulating concentrations of 25(OH)D reduced but breast milk values are reduced as well [100]. Some advocates of breastfeeding could not countenance any supplementation to the diet of breast-fed infants and, inadvertently, recommended a course of action that could lead to rickets.

By contrast, there has emerged new information that supports prolonged breastfeeding as an anti-rachitic measure among poor families in developing countries. Rickets is common in larger families, particularly in children born later in a family. A case control trial found that most cases of rickets were in children breastfed for

shorter intervals, and concluded that prolonged breastfeeding is protective [76, 77]. This observation has been made in Ethiopia, Israel, Iran, and even in the United States [101]. At the same time, many of these rachitic children have had limited exposure to sunlight and/or are heavily clothed.

Finally, the most likely scenario for nutritional rickets, even in tropical latitudes and in adolescents, is a combination of belonging to populations with low 25(OH)D concentrations, avoidance of the sun, less exercise, and limited intake of dairy products [101-105]. Federal committees, such as the Institute of Medicine (IOM), when giving advice on the recommended daily allowance of vitamin D for infants, children and pregnant women, may not have fully accounted for these societal changes and historically had recommended 200 IU/day of vitamin D, until the 2010 IOM Report recommended 400 IU/day in infants and 600 IU/day in older children [82].

Social and political pressures often precluded the universal addition of irradiated ergosterol or cholecalciferol to the milk supply. Two remarkable examples of this are the Canadian Province of Quebec and the Deutsche Demskratische Republic (DDR) of East Germany, both at northern latitudes. Children in Quebec suffered severely from rickets, and because of the known influence of vitamin D deficiency on enamel formation, dental caries were extraordinarily common [106]. East German children underwent UV light therapy in lieu of vitamin D supplementation until 1955 [107]. Quebec supplemented milk by law after 1968 [108]. In both instances, the power of the state, through irrational theories, blocked laws that would support supplementation, the consequences being high rates of rickets.

The situation in the DDR was far more complex. The DDR had a national health care plan that guaranteed medical care to all citizens [109]. In the late 1940s the prevalence of rickets was especially high in the Soviet-occupied east zone of Germany [107]. The large German pharmaceutical firms were all in the western zones. Jenapharm was founded in 1950 in Jena to produce steroids, beginning with hog bile as the base for synthesis [110]. The company produced a wide range of steroids including corticosteroids, anabolic steroids, estrogens and vitamin D. Their method for the synthesis of vitamin D_2 could produce 10 kg/year. This allowed for oral supplementation of children. Thus, for the first few years of the DDR, UVB phototherapy was employed. However, after 1955, all infants were supplemented with high dose intramuscular vitamin D, or stoss therapy. At the age of 3 months, each infant received 600,000 IU of vitamin D_2, which was repeated every 3 months until age 18 months [107]. The DDR publicly stated that no vitamin D toxicity was encountered, but with serum 25(OH)D levels of 200 nmol/L, one would suspect toxicity. Because of idiopathic hypercalcemia of infancy experienced in Britain in the 1950s, the daily dose of vitamin D was dropped [107, 111]. It has been stated that these high doses of vitamin D_2 were given to children in Germany and the United Kingdom because so many children had suffered nutritional inadequacies during World War II [112]. In a recent follow-up to this practice, several families in which a mutation in the 24 α-hydroxylase gene (part of a vitamin D degradative pathway) had occurred were identified [113]. They were among those receiving stoss therapy in the DDR, and the children were found to have ideopathic hypercalcemia [114]. Several of these families who became hypercalcemic after stoss therapy were finally described in the 1980s [115, 116]. While stoss therapy would certainly prevent rickets, this era provided another example of how children may be harmed because of good intentions and public health policy.

Nutrition scientists have forced an ongoing discussion of the adequate daily intake of vitamin D to prevent deficiency- or insufficiency-related diseases [100, 111, 117]. Based upon sequential NHANES (2004, 2007) reports, the proportion of subjects with a serum 25(OH)D concentration of < 20 ng/ml has risen, especially in infants, children, adolescents and the elderly [101]. This rising tide of vitamin D deficiency is multifactorial, including such things as children spending more time indoors, increasing obesity (adipose tissue stores vitamin D), the eschewing of milk ingestion by adolescent females, and the general failure of segments of the population to follow USDA or other national nutrition guidelines. At the same time, a number of observations concerning a non-osseous role for the vitamin in cardiovascular, autoimmune, immune and oncologic disorders have been made. Vitamin D scholars have called for daily doses much higher than the 200 to 400 IU/day recommended by the IOM report of 1999 [111], and there have been proclamations of the safety of 2000 to 10,000 IU daily of vitamin D [103, 111, 118]. The most recent IOM report, published in late 2010, recommended a dose of 400 IU daily in infants and 600 IU/day in older children, but felt that the evidence for many of the claims of the role of the vitamin in multiple sclerosis, various cancers, diabetes and cardiovascular disorders were not supported by prospective, placebo-controlled clinical trials [82]. Only by conducting these trials will these claims of a non-osseous influence be

clarified. Despite this well balanced report, the popular press has embraced the theme of a population of youngsters remaining indoors, playing computer games and risking rickets or osteomalacia, and have urged that more and more vitamin D intake is justified.

Critiques of health policy concerning vitamin D intake

The debate on appropriate doses of vitamin D has been aimed at several national health policies. In the current era, with an appreciation of the non-osseous properties of vitamin D and the association of higher serum 25(OH)D values with reduced cardiovascular disease, multiple sclerosis and certain cancers, there are strong critics of the health policies that recommend limited vitamin D intake and sunshine exposure [117, 119-121]. The crux of the debate is that large segments of not just American, but also Canadian, British and German populations are shown to be vitamin D-deficient or -insufficient in large national surveys [121, 122]. The precise value for deficiency, 50 nmol/L, or 20 ng/ml, as set by the 2010 IOM report, is debated, and the concept of insufficiency (< 30 ng/ml to 20 ng/ml) is also controversial. In addition, sun exposure recommendations that limit exposure from 10:00 AM to 3:00 PM in these four countries (northern United States, Canada, Britain and Germany) would effectively obviate adequate UVB exposure for much of the year in people living above the latitude of 40° N. Gillie makes the point that British sun exposure policy is set based upon Australian and United States standards even through the latitude of Britain is from 40° - 55° N [119]. The oral dosage form of vitamin D in Germany is limited to 2.5 μg/day (100 IU) without a prescription [121]. Zitterman even makes the suggestion that tanning lamps be employed to assure adequate serum 25 (OH)D values of > 100 nmol/L rather than for acquiring a tan. Recently the Endocrine Society issued guidelines that state that levels less than 50 nmol/L are deficient, and those between 50 and 72.5 nmol/L are insufficient. They recommend an "ideal" level of 100 to 150 nmol/L for non-osseous effects, which would require 1500 to 2000 IU/day [123]. As stated, because IOM reports are based upon evidence from randomized clinical trials, the resolution of differences in viewpoints concerning National Health policies will depend on future trials.

Conclusions

As in the Glissonian era, children have developed rickets because of economic trends, warfare, migration to more northern latitudes, recommendations for breastfeeding when mothers are vitamin D-deficient themselves, and possibly overzealous sun protection. Rickets, as the expression of vitamin D deficiency in the growing child, was also a consequence of the Industrial Revolution and the extensive use of child labor. In conclusion, rickets is a condition in which social, environmental and economic factors can play a critical role. It is also a reminder of how we must continue to strive to do no harm when considering the health of children.

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