The Decade of Ideas Leading to a Cure for Rickets

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At various intervals in human history, a great leap forward transpires, with novel concepts emerging in a relatively short period. An example is Greece in the 5th century BCE, when the disciplines of philosophy, mathematics, and drama expanded exponentially. In a 50-year period, the Renaissance burst forth in Tuscany. In a generation, the Greek concept of democracy became a reality in America and France.[1] Between 1850 and 1920, the discipline of child health specialists, or pediatricians, emerged in Europe and North America. These physicians were engaged in scientific inquiry concerning the major disorders of the era, including infantile diarrhea and acidosis, tuberculosis, malnutrition, contagious diseases, and rickets.[2] The latter was found in 60%-90% of children aged <4 years in northern urban environments in both Europe and North America.[3]

In this commentary, I posit that a group of events occurred and concepts emerged over the 13-year period from 1883 to 1896 that led to an understanding of the etiology, pathogenesis, improved diagnosis, treatment, and prevention of rickets. All of these components taken together led to the discovery of vitamin D as a distinct compound in 1922,[4] and the subsequent identification of its role in the prevention and cure of rickets.

In August 1883, a volcano on the Indonesian island of Krakatoa erupted and then exploded, releasing a plume of ash and magma a distance of 80 km into the stratosphere and causing a blast heard 6600 km away. The explosion resulted in a deadly tsunami and led to a dimming of light in the sky that lasted until 1889.[5] During the day a so-called "Bishop's ring" was visible. This brown, blue, or purple halo appearing around the sun after volcanic eruptions due to aerosolized sulfur compounds, was named for the Reverend Sereno Bishop from Honolulu, who first described the phenomenon after the explosion of Krakatoa.[6] High levels of sulfur dioxide were released into the stratosphere, which enhanced cloud reflectivity (ie, albedo), limiting the amount of the sun's rays that struck the earth. Compounded with the smoke and smog arising from the massive consumption of coal and coke as fuels[7] in urban industrialized regions and the diminished hours of sunshine in late fall to spring in northern latitudes, many children received scant sunlight exposure. Observations later in the decade pertain to this atmospheric haze.

In 1883, the Imperial Japanese Navy physician Takaki Kanehiro grew concerned about the extremely high prevalence of beriberi in the crews of Japanese warships. Western navies did not experience the disorder, nor did the Japanese officers who consumed a diet of meat and vegetables. The crew essentially ate only white rice, however, and in an 1883 training voyage of 9 months, 169 of 336 crewmembers sustained beriberi, resulting in 25 deaths. Takaki petitioned the Emperor to allow the crew to receive a more complete diet of bread, milk, meat, and vegetables. On a similar voyage in 1884, only 16 of 333 crewmembers suffered the disorder. Consequently, the Japanese Imperial Navy improved the diet of seamen, and the disorder disappeared.[8]

A decade later, in 1894, Christiaan Eijkman in Batavia, Indonesia examined workers (prisoners, actually) fed unpolished versus polished rice and reported beriberi only in the latter group. Eijkman, a Dutch-trained physician, was a keen observer of nature and learned about the milling process, which removed the peripaceum or "silver skin" from brown rice. Eijkman's studies were based on a natural experiment in chickens in which the birds became ill on a diet of polished rice and were "cured" when another keeper fed them uncooked, unpolished rice. This is a real example of serendipity.[9]

The foregoing clinical studies in Japan and Indonesia led to the hypothesis that beriberi was due to a missing dietary factor, later found to be vitamin B_1.[9] The concept that emerged was that some diets were limited in a nutrient needed for life—in this instance, a water-soluble factor later termed thiamine.

The influence of season on the incidence of rickets was first noted by Max Kassowitz in 1884,[10,11] who found that the frequency of tetany and rickets was greatest during the winter months and declined in summer and fall. Kassowitz argued that because the highest incidence of tetany coincided with that of rickets, the 2 conditions were linked. Kassowitz was born in Bratislava, Slovakia in 1842, but was educated in Vienna, where he remained. He was the director of the First Children's Public Health Institute and became an expert on syphilis and rickets. Approximately 20 000 children were afflicted with rickets in Vienna. He understood that phosphate deficiency caused the undermineralized bone characteristic of rickets. He found that the best source of ingested phosphate was oil of phosphate and that, interestingly, the best results were obtained when cod liver oil was used to aid the ingestion of phosphate. This was called Kassowitz medicine. Two concepts arose from the studies of Kassowitz in the 1880s: (1) rickets is more common in winter; and (2) the phosphate cure was best when suspended in cod liver oil. From today's vantage point, we understand that the winter sun emits only limited ultraviolet B rays, and that cod liver oil contains 400 IU (10 mg) per teaspoonful of vitamin D.

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In an 1888 letter published in the *British Medical Journal*, Dr Theobald Palm related his observation that while serving as a medical missionary in Niigata, Japan, he saw poverty, improper sanitation, and limited food, but no rickets, whereas in his practice near Liverpool, England, he encountered many cases of rickets.[12] In 1889, an Investigation Committee of the British Medical Association conducted a United Kingdom–wide topographical survey of various conditions, including rickets. They found the highest prevalence in 5 regions of England and Wales and in the Glasgow-Edinburgh-Aberdeen region of Scotland.[13] Armed with this map, Palm contacted many of his fellow medical missionaries in the Far East and Morocco and enquired whether they had encountered rickets. The missionaries replied that rickets was very rare, even though these children were from impoverished backgrounds and had the same infectious complications as rachitic children, including tuberculosis, scrofula, and dysentery. Palm also noted fewer cases of rickets in British children from rural areas and small towns compared with those from urban areas.[14] Palm could only reconcile these findings with exposure to sunlight. Children in the tropics were often naked until 4-5 years of age and essentially lived outdoors. Rural children, even those in the far north of Scotland, received more sunshine than urban children. Palm suggested relocating rachitic children to rural settings and investigating the "chemistry of sunshine." He further suggested that sunshine had antirachitic properties, a novel concept at the time.

In 1889, John Bland-Sutton, a later-reknowned London surgeon, was consulted about fatal rickets in lion cubs in the Zoological Gardens in Regents' Park.[15,16] The dam had lactation failure, and the cubs were fed horsemeat and hard horse bones. Bland-Sutton suggested milk, goat meat, goat bones (softer than horse bones), and a cone slathered with cod liver oil for the cubs to lick. The rickets was reversed, the cubs survived, and subsequent litters of cubs thrived. Later, other students of nutrition, including Sir Edward Mellanby, added calcium, phosphate, and fat (especially cod liver oil) to the diet of their animal models of rickets.[17] The concept of an antirachitic factor present in cod liver oil that could cure an animal model (the lion cubs) was a key discovery.

Niels Ryberg Finsen, MD, a native of the Faroe Islands, while a student at Copenhagen University, conceived of ultraviolet phototherapy for several conditions, including lupus vulgaris. His studies in practical phototherapy led to the 1903 Nobel Prize.[18] The concept that phototherapy could replace sunshine was based on his work from 1894 to 1896.

In 1895, Wilhelm Conrad Röntgen found that "X-rays" could reveal the status of the bones.[19] Physicians could now diagnose rickets at an early stage, before major bowing occurred. Serial X-ray studies could reveal whether UVB rays or cod liver oil was curative. The power of this technique in assessing cure or prevention was robust.

The work in the 1890s led to 3 Nobel Prizes, awarded to Röntgen, Eijkman, and Finsen. Takaki Kanehiro went on to found a renowned medical school in Tokyo, the Jikei University School of Medicine.[20] Kassowitz was the head of the institute when he appointed a young Dr Sigmund Freud as head of the Department of Neurology at the First Public Institute for Sick Children in Vienna, where he served from 1886 to 1896. Palm's ideas concerning sunlight were fully exploited during World War I, when food for nonmilitary personnel was scarce.[16] Bland-Sutton was knighted for his pioneering studies in surgery and performed the first parathyroidectomy.[21]

In conclusion, some important concepts related to rickets emerged between 1883 and 1896, including that sunlight exposure was needed to overcome the lack of light in smoke-filled cities in northern latitudes, the sun was even more important after a massive volcanic eruption, and a nutrient was missing in certain diets that led to a deficiency disorder. The concept of the seasonality of rickets and of the use of cod liver oil as therapy was developed during this decade. The antirachitic factor was in fats and oils, especially cod liver oil. The clinical course of rickets could be followed by the use of X-rays. The notion that vitamin D could come from the diet or from UVB rays lay in the future. Although not fully developed for another quarter of a century, the basic concepts had been expressed between 1883 and 1896. Moreover, the idea of a missing factor was conceivable. Finally, light rays at various segments of the spectrum proved important. The ideas of that decade still resonate due to the reemergence of rickets today. ■

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