

REVIEW

Rickets before the discovery of vitamin D

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The story of rickets leading to the discovery of vitamin D is an extraordinary tale, spread over many centuries and involving some remarkable characters with much speculation and a few mysteries, before reaching an exciting climax. It would be wrong to credit a single person as discovering rickets or being the first to describe its features, for reasons that will be set out here. Yet the emergence of the term ‘rickets’ is as important as the discovery of vitamin D itself and the possible causes of its deficiency. It permitted identification of a hitherto ill-defined disease entity, typically occurring in infants and children. It also provided a way for deciding if features of diseases that had been described earlier in the history of medicine could be seen as the symptoms and signs of related conditions.

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Sorano of Ephesus is often credited as being the first to mention some of the features of rickets. Suggestions¹ that there were references to this in earlier Chinese manuscripts, for example in Confucius, 200 years earlier are not convincing. Sorano worked in Alexandria and then in Rome where he practiced during 110–130 AD. One of his classic works is entitled ‘Gynecology’ in which he wrote (in Book II, 48[112]), ‘When the infant attempts to sit and to stand, one should help in its movements. For if it is eager to sit up too early and for too long a period it becomes hunchbacked (the spine bending because the little body has as yet no strength). If, moreover, it is too prone to stand up and desirous of walking, the legs may become distorted in the regions of the thighs’. Temkin² who translated the whole of the ‘Gynecology’ into English referred to this as the ‘classic allusion’ to rickets in his introduction, but he also cited the comments of Ruhrah³ who pointed out that Sorano was writing on the care of infants, not their diseases. Much later, in about 1554, Theodosius of Bologna described⁴ a pale child ‘that could not move or sit, indeed hardly hold its head erect and which showed in the lower dorsal region both a gibbus and a marked lateral curvature’. Whether the child actually had rickets is not clear. Later, it is said that Bartholomaeus Reusner described in 1582 ‘a disease common among the inhabitants of Holland and Switzerland, characterized by bending of bones and cachexia of infants and an insatiable hunger’. Sprengel⁵ who reported this, gave the reference as ‘Dissertatio de tabe infantum, Basel’. Unfortunately, no one has been able to find this article anywhere despite intensive searching over many years. A recent search of current electronic data bases were not helpful either. So it is not possible to confirm either its date or its contents or even its existence. It seems that later texts, from Holland in 1614, might be referring to rickets under the titles of ‘Ailment of Saint Willibrod’ in which children had knobs on their ribs and ‘Ailment

of Saint Machutus’ in which children had deformed legs. The two ailments apparently could exist in the same child.

The word ‘rickets’ can be seen in the hand-written ‘Receipt Books’ of the Fairfax Family. The entry for 25 February 1632 has five remedies for ‘rickets in children’. The word ‘rickets’ first appeared in print in 1634 when it figured in the Annual Bill of Mortality of the City of London for that year. The Bills of Mortality were records of the numbers and causes of death in the area around the Tower of London and St Paul’s Cathedral, which is now the financial area, but which used to be a residential part, within or close to the walls of the City of London. The population covered by these bills was ~200 000. Many of the original records still exist, going back to the late sixteenth century. The annual statistics were based on the weekly records that were kept. A major change in the form of the records was introduced in 1629, although it is not clear who ordered that to be done. Previously, they had only listed the numbers dying in each of the 122 parishes in the city. In 1629, the Bills included, for the first time, an account of the causes of death, divided into ~80 conditions. Rickets was not among those listed that year, or in the subsequent 4 years. It is recorded for 1634, that of a total of 10 900 deaths, rickets was given as the cause of death in 14 of them (**Figure 1**). The frequency of this cause of death apparently rose progressively so that 25 years later, in 1659, there were 441 recorded entries for rickets in the year. The Bills of Mortality were compiled by the ‘searchers’ and were analyzed⁶ in great detail by John Graunt in 1662. Graunt may be considered along with Petty as one of the fathers of the studies of community medicine. Graunt wrote ‘the searchers who are elderly matrons, sworn to their office, repair to the place where the dead corpse lies...’. It has to be said that the accuracy of the causes of death in the lists must have been suspect. On the basis of indirect arguments, Graunt suggested that what was

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A general Bill for this present yeere,
 ending the 18. of *December* 1634. according to
 the report made to the Kings most excellent Ma^{ty}
 By the Company of Parish Clerks of London, &c.
 

The Diseases and Casualties this yeere.

A Bortive and Stilborne— 475	Falling Sicknesse — 5	Plague — 1
Aged — 612	Feaver — 1279	Plannet — 4
Ague — 11	Fistula — 11	Plurisie and Spleene — 21
Appoplexianl Meagrome — 35	Flocks and small Pox — 1354	Poyfoned — 2
Bit with a mad dogge — 1	French Pox — 17	Purples and spotted Feaver — 125
Bleeding — 3	Gangrene — 10	Quinsie — 4
Bloody flux scowring & flux — 512	Goute — 5	Rickets — 14
Burnt and scalded — 3	Greene sicknes — 2	Rising of the lights and Mother — 84
Cancer and Canker — 9	Griefe — 15	Rupture — 3
Childbed — 143	Hanged themselves — 3	Scurvey, Swine Pox and Bleach — 9
Chriofanes and Infants — 2315	laundies and Yellowes — 45	Sores, broken and bruifed Limbes — 19
Cold and Cough — 54	lawfalne — 10	Suddenly — 63
Collicke Stone & Strangury — 49	Impostume — 62	Surfet — 114
Consumption — 1955	Kild by severall accidents, — 41	Teeth — 454
Convulsion and Crampe — 386	Kings Evill — 20	Thrush and Sore mouth — 31
Cut of the Stone — 5	Livergrowne — 77	Timpany — 17
Dead in the streete & fields, and starved — 8	Lunatique — 2	Tiffike — 15
Dropfie and Swelling — 233	Measles — 33	Vomiting — 5
Drowned — 32	Murtherd — 6	Wormes — 28
Executed — 13	Over-laid & starved at nurse — 14	
	Palfie — 21	
	Piles — 1	

Chriftened } Males — 5035	Buried } Males — 5676	Whereof, of the Plague — 1
} Females — 4820	} Females — 5224	
} In all — 9855	} In all — 10900	

Increased in the Burials in the 122 Parishes & at the Pesthouse this yeere. — 2508
 Increased of the Plague in the 122 Parishes and at the Pesthouse this yeere. — 1.

Figure 1 A copy of the Bill of Mortality for 1634. The middle part of this, listing the number of deaths for each of the 122 parishes of the City of London, has been omitted for clarity. The causes of death are listed alphabetically and rickets is included among those on the right side. Reproduced with permission of The Guildhall Library of The City of London, London, UK.

subsequently classified as rickets might have been misclassified in 1629 as 'Livergrown', although that is speculative and the features of that condition were not described. Whether that speculation is correct or not, the fact that rickets was recognized in London 11 years before the first clear clinical description of its features cannot be questioned. Moreover, its incidence seemed to be increasing, as discussed in Graunt's analysis written in 1662. In part that increase might have been the greater awareness of the disease.

In 1640, the apothecary and King's herbalist, John Parkinson,⁷ published a massive, beautifully illustrated 'Botanicum', a section of which is devoted to thistles, and about one of these, a common thistle, he wrote 'Galen saith that the roote and leaves hereof are of an healing quality and good for such persons that have their 'bodies drawn together by some spasm or convulsion or by some other infirmity, which disease is truly to be called the rickets which happening sometimes to children doeth so bind them in their nerves, ligaments and whole structure of their body that it suffereth not to grow or prosper eyther in height, strength or alacrity'. Nothing is known about the contents of extracts of thistle that would justify its empirical use. However, it is clear from the writing of Parkinson that, in 1640, again before the condition had been fully described in the medical literature, there was concern as to how to treat rickets. Evidence for other possible references to rickets prior to 1650 is discussed by Foote.⁸

The first clear descriptions of rickets were published between 1645 and 1668, successively by Whistler, Boot, Glisson and Mayow (Figure 2). It can be argued that they were characterizing what was a matter of public concern and discussion at the time. The first of this quartet, Daniel Whistler, submitted a thesis for the degree of Doctor of Medicine in Leiden. The original records of the University of Leiden still exist and show that he registered for the degree in July 1645. He submitted his dissertation on 18 October 1645 and was examined on it the next day and was awarded the degree.⁹⁻¹¹ The thesis was reprinted in 1684. Whistler went on in later years to be a founding fellow of the Royal Society and President of the College of Physicians of London. The second description, by Arnold Boot, was published in 1649, possibly having been written in 1646. Boot was born in Holland but practiced in Dublin. His description¹² was Chapter 12 in his book on a variety of conditions. The word 'rickets' is used on page 3 of the original Latin text. That work is the least well known of the quartet, perhaps because it did not contain the word rickets in the title of the book or of the chapter in which it was described. It was reprinted in 1664 and 1676. However, the longest and most detailed account of this disease by far was the book published by Glisson in 1650. He was assisted by Bate and Regemorter. Much of their text was concerned with an interpretation of the disease in the light of medical philosophy of the day, but it also



Figure 2 Copies of the title pages of the four publications that appeared in Latin, over a 33-year period. The first three were reproduced from originals in the British Library, London, UK. The fourth is reproduced from the original with permission of the library of The Royal College of Physicians, London, UK. (a) The thesis of Daniel Whistler, 1645, entitled 'Inaugural Medical Disputation, on the Children's Diseases of the English, Which the Inhabitants Idiomatically Call The Rickets'. (b) Arnold Boot's book published in 1649 entitled 'Medical Observations on Neglected Ailments', in which chapter 12, entitled 'Tabes pectoris' described rickets and used that word in the text. (c) Francis Glisson's book, published in 1650 with Bate and Regemorter, entitled 'A Treatise of the Rickets: Being a Disease Common to Children. Wherein (among many other things) is shewed 1 The Essence. 2 The Causes. 3 The Signs. 4 The Remedies of the Disease'. (d) John Mayow's tract, published in 1668, entitled 'Concerning Rickets'.

attempted to explain the cause of deformity in rickets, which is a curvature of the limbs and spine. Later, in 1668, Mayow wrote about rickets and said that the only earlier publication on the subject was by Glisson; so he was not aware of the other two.

He quoted extensively from Glisson but gave an alternative explanation for the cause of deformity. All four of these accounts were written in Latin. A translation¹¹ of Whistler's eight-page thesis into English was only published in the middle of the

twentieth century. No English version of the Boot’s chapter has been published, but it has been analyzed in some detail by Van Andel.¹² Glisson’s book was quickly translated into English and that version was published a year after the Latin version. The translation, published in 1927, of the work of Mayow¹³ is perhaps the one that is most easily understood by a modern reader.

Whistler, Boot and Glisson all used the English word rickets, and each suggested an alternative either in Latin or Greek, but those suggestions never found favor. Whistler and Glisson both discussed the origin of the word rickets without being able to say how it had been derived. Among the suggestions considered was that it was named after an apothecary called Rickets who had successfully treated the disease. The family name ‘Rickets’ was not uncommon and still exists, but there was no evidence to support that theory. Another possibility is that the word was derived from ‘rachitis’, indicating inflammation of the vertebral column. They tried, again unsuccessfully, to derive the word from Greek but they had to conclude that the origin was not known and that the colloquial term ‘rickets’ was already the accepted name at the time.

Glisson and Boot had done dissections (postmortem examinations) of patients that had died with rickets. Both Whistler and Glisson believed that rickets was a ‘new’ disease, which had only appeared ~20 years before they wrote. They both suggested that the earliest cases had been seen in southern England (in the county of Dorset) and in the West Country (in the county of Somerset). All three of these authors described the disease as occurring in London, but Boot said he had seen it in both Ireland and in Paris. The occurrence of rickets in Paris had been mentioned by Guillemeau in 1609, in a brief note.¹⁴ Thus though Whistler referred to Rickets as an ‘Englsh Disease’, it was clearly not confined to England. Although they thought it was a new disease, they could not explain why it had appeared. Glisson thought it was related to the damp climate in England without being able to say why that should be the case. Recently, rickets has been reported¹⁵ in the skeletons of the Medici children buried in a family vault in Florence, 1547–1602.

Whistler had written ‘The disease is most frequent in the ranks of the highest citizens, next amongst the dregs of the populace, least amongst those of moderate means. The cause in the first group I take to be the intemperance of the parents and the fact that the infants are entrusted to the care of hired wet nurses’. A variety of explanations were offered for the development of rickets in children in the other two groups, who presumably were not fed by wet nurses. Later, Glisson also observed that ‘this disease doth more frequently invade the cradles of the rich than afflict poor men’s children’. Thacher *et al.*¹⁶ have stressed the significance of the use of wet nurses, pointing out that the concentration of calcium in breast milk falls as the duration of feeding is extended, and feeding cereal porridges in weaning, with high phytate content, might have added to the calcium deficiency.

Suggestions about treatment were along the lines of all therapies at the time for all diseases. Venesection seemed popular, especially from a particular vein on the lobe of the ear. In 1674 a letter was written concerning ‘Some observations made upon Russia Seed, shewing its admirable virtues in healing rickets’. This was written by a doctor of physic in the country, possibly a Dr Peachi or a Dr Skinner and sent to ‘Esq

Boyle’, who was possibly Robert Boyle, secretary of the recently formed Royal Society. It is not possible now to say what was meant by the name ‘Russia Seed’. An interesting comment was made by Sir Thomas Browne in a letter¹⁷ written around 1664 describing birds in Norfolk. About rooks (crows) he recorded that ‘the young ones commonly eaten, sometimes sold in Norwich markets, and many killed for their livers in order to cure rickets’. Both Whistler and Glisson had included the use of rook liver, and Glisson added frog’s liver as a possible treatment. In hindsight, it is possible to wonder if that provided a source of vitamin D, although that seems unlikely. It was also suggested that patients should have their abdomen exposed to sunlight as a source of heat, and that too might have provided a source of vitamin D.

A clue as to another cause of rickets in the seventeenth century is to be found¹⁸ in Claire Tomlin’s prize winning biography, ‘Samuel Pepys, The Unequalled Self’. In that, she said ‘Londoners spat black’, referring to the periodic effect of smog, which even as recently as 1955, led to the presence of black particles in sputum and nasal droplets. She cites the diary of Robert Hooke¹⁹ On 28 September 1676, he described a cloud covering the city of London and being visible miles away to the south from Banstead Downs. Earlier, in 1661, John Evelyn had published,²⁰ at his Majesty’s command, his ‘Fumfugium’ or ‘The Inconvenience of the Air and Smoak of London Dissipated’. In that classic work, he described the pollution and named its cause as the burning of sea coal. This coal was brought by sea from Newcastle in the north of England. He described how laundry put out to dry in the open air was soiled again by the dirty air and how gardens grew better when there was a shortage of coal in 1644, when Newcastle was blockaded in the Civil War. Evelyn said that the trouble came particularly from the ‘fournaces’ of the ‘brewers, diers, sope and salt boylers and lime burners and the like’. He suggested that a cure for the problem was to move these factories away from the center of the city and preferably downwind. There had been attempts as far back as 1272 to legislate against the use of sea coal, but none of the laws were enforced, and Evelyn’s attempts to get new laws enacted likewise came to nothing. In a little noticed recent work, Brimblecombe,²¹ in his book on ‘The Big Smoke, a History of Air Pollution in London Since Mediaeval Times’, pointed out the significance of the smoky atmosphere in reducing production of vitamin D by UV irradiation of the skin. In offering this explanation for rickets in London at that time, it should be remembered that cases were reported initially in the country, in Dorset and further west, and presumably there was less smoke in those parts.

It is clear that it is reasonable now to suggest that vitamin D deficiency was a major cause of the rickets described in the middle of the seventeenth century. It is not possible to say whether anything had changed that led to what seemed to be new disease in either part of the century. England at that time was a place of great inequalities, great riches setting alongside desperate poverty. Within the walled City of London it was very crowded, and there were many very narrow streets (limiting access to sunlight). With the civil wars there may have been serious food shortages, but that cannot be proved, and rickets seemed to affect both the poor and the upper class. It has been suggested²² that as a child, Charles Duke of Albany (later King Charles I of England) had rickets from 1600 to 1612. Accounts of the diet prescribed in his treatment at that time indicate that the

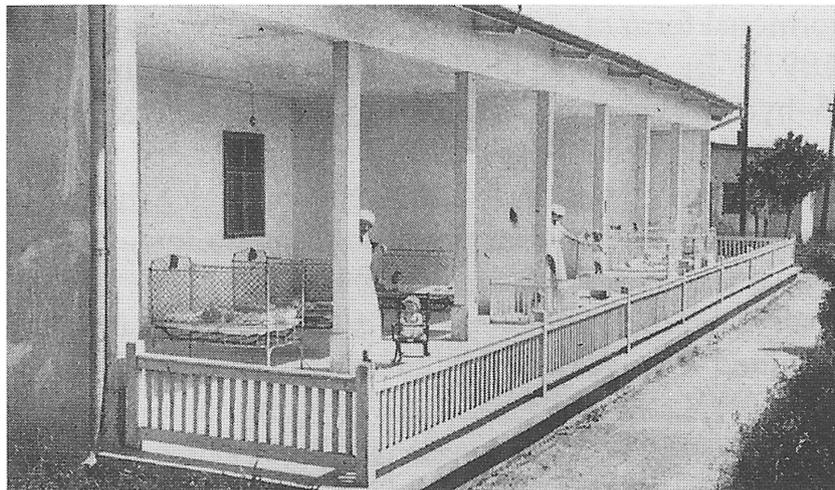


Figure 3 The veranda of the Meidling Hospital in Vienna with infants ‘receiving outdoor treatment in sun and shade respectively’ (MRC 1923: reproduced with permission).

bland diet itself may have contributed to the progress of the disease and aggravated it. His daughter, Princess Elizabeth, also died²³ with rickets, so perhaps the cause in this family was different from most cases at that time. Whereas we may think of vitamin D deficiency as initially being the product of the Industrial Revolution and the resulting smoke in the atmosphere, at the end of the nineteenth and early twentieth centuries, these may, in fact, have been serious problems 300 years earlier.

Little progress was made over the next two centuries though there were reports from the Royal Infirmary in Manchester that cod liver oil could heal rickets. In 1728, Moore²⁴ wrote on the effectiveness of shark liver ointment in the treatment of rickets. In 1724–1926 Schenk²⁵ and Schutte²⁶ wrote that cod liver oil by mouth for 5 weeks could cure rickets. In 1822, Sniadeki²⁷ from Poland wrote ‘the sun, the direct action of which on our bodies must be regarded as one of which on our bodies, must be regarded as the most efficient methods for the prevention and cure of this disease’. Later Trousseau,²⁸ in 1868 described, very elegantly, how he came to treat rickets with cod liver oil.

Then a series of papers was presented by John Bland-Sutton (initially Lecturer on Comparative Anatomy and later Surgeon at the Middlesex Hospital in London) in The Proceedings of the Zoological Society ‘On the diseases of the monkeys in the Society’s gardens’. Writing of rickets, he recorded ‘this disease is extremely frequent in monkeys living in captivity in London. Nearly half the total number of monkeys introduced into the Zoological Society’s garden die rickety, provided they live a few months after reaching London. The changes in the skeleton develop so rapidly that a capuchin monkey, apparently in good health and thriving well, when introduced into the cages died horribly deformed by rickety changes in four months’. There was debate as to whether what was being described was in fact rickets, since it would appear that the picture is rather different in the monkeys from what is seen in humans and other animals, and the changes in the vertebral column and compression of the spinal cord seemed to be features seen in monkeys. In the last of these papers, Bland Sutton²⁹ in 1889 wrote ‘that the bulk of the material has come under observation during my attendance at the prosector’s room of the Zoological Society, London during

the last seven year’. That paper included observations on lion cubs and contained the remarkable statement ‘it may be mentioned that some rickety cubs, which early manifested signs of rickets, were promptly fed bone dust and cod liver oil, made a good recovery and were alive and active, presenting no signs of paralysis two years afterward’. Those observations^{30,31} were, of course, made before vitamin D had been discovered and it is interesting to note that though the Monkey House was light and airy, it was enclosed by glass that would not have let through UV. Shortly after that Palm³² in 1890 looked at the geographical distribution of rickets and noted it was more common where there was less sunlight and he promoted the use of sunbaths to prevent rickets. The importance of sunshine was reinforced by the findings of Schmorl that at postmortem evidence of rickets was more common in winter/spring than in summer/autumn.

Progress in studies of the causes and treatment of rickets suddenly moved much faster, in the period 1917–1922. At the beginning of that time, Huldshinski³³ advocated ultraviolet light treatment for rickets. At the same time, Hess³⁴ showed that cod liver oil could prevent and cure rickets in Afro-American children in New York. In 1918, Mellanby showed that he could prevent experimental rickets in puppies with cod liver oil and discussed the role of an ‘accessory factor’ in the production of rickets.³⁵ That was at the end of The First World War. At that time it was found that rickets was a major problem in Vienna but its cause was not known. A group from the British Medical Research Council led by Harriet Chick went to Vienna to study the problem. The possibility that rickets might be caused by something in the water or a feature of the diet, or something in the air, or possibly an infection, were all considered. The children with rickets at the Kinderklinik in Vienna were divided^{36,37} into four groups. Two of these groups were kept in the ward and the other two groups were kept out on the balcony which must have been very cold in the Viennese winter. In the ward, one group was given the normal diet only while the other group was also given supplementary cod liver oil. The rickets in the latter group of children was healed as demonstrated radiologically, while the first group remained sick. On the veranda (**Figure 3**) one group was kept well covered while the

other group of children, wearing remarkably little clothing, was exposed to sunlight. This second group got better. Thus it was shown that cod liver oil and exposure to sunlight both healed rickets. However, it was not clear at that time whether the effectiveness of cod liver oil was due to vitamin D or to vitamin A, both of which had been discovered by then. In 1921, Hess and Unger³⁸ showed the importance of sunlight in curing rickets.

McCollum *et al.*³⁹ gave the title ‘Vitamin D’ to Mellanby’s ‘Accessory factor’ in 1922, in a paper suggesting the existence of ‘a vitamin which promotes calcium deposition’. Then in papers published in 1924 Hess and Weinstock⁴⁰ and Steenbock and Black⁴¹ described the effects of the ultraviolet irradiation of food. Thus the scene was set for the remarkable progress that followed the discovery of vitamin D. The events leading up to this have shown the sound basis on which that progress was based, and has been well described by Tausk,⁴² by Ebstein,⁴³ and by Fourman and Royer⁴⁴ in their historical reviews, which describe the scene leading up to the discovery of vitamin D and all that followed.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgements

Figures 1 and 2 are reproduced from O’Riordan.⁴⁵ Figure 3 is reproduced from O’Riordan.⁴⁶ We are grateful for the help of Russell W Chesney (rchesney@uthsc.edu) in locating precisely the relevant text in Bland Sutton.²⁹

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