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Vitamin D: part I; from plankton and calcified skeletons (500 million years ago) to rickets

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Abstract
The vitamin D history started early in the evolution of life (billion years ago) as a photochemical reaction producing an inert molecule. During the early evolution of vertebrates, this molecule became essential for calcium and bone homeostasis of terrestrial animals and arrived to the status of hormone. Phytoplankton, zooplankton, and most plants and animals that are exposed to sunlight have the capacity to make vitamin D. Vitamin D is critically important for the development, growth, and maintenance of a healthy skeleton from birth until death. The major function of vitamin D is to maintain calcium homeostasis. It accomplishes this by increasing the efficiency of the intestine to absorb dietary calcium. When there is inadequate calcium in the diet to satisfy the body's calcium requirement, vitamin D communicates to the osteoblasts that signal osteoclast precursors to mature and dissolve the calcium stored in the bone. The typical "vitamin D-deficiency" disorder was observed for growing children in the west and south of England in the early 1600s. This disease was described by Glisson and named "rickets" (known also as "the English disease") and was observed with epidemic proportions in northern Europe and North America. The corrections of deformities of rickets were at the origin of the name "orthopedia" and of the technique of osteotomies.

Keywords Vitamin D history · Calcium history · Glisson · Rickets · Rachitis · Osteotomy history

The vitamin D molecule (Fig. 1) originated as photochemical reaction producing first an inert molecule before the apparition of life. Vitamin D without a subscript refers to either D_2 or D_3 or both. These are known collectively as calciferol. The only structural difference between vitamin D2 and D3 is in their side chains; the side chain for vitamin D2 contains a double bond between carbons (C) 22 and C-23 and a methyl group on C-24. The vitamin D3 molecule originated early in the evolution of life as the end product of the photochemical conversion of 7-dehydrocholesterol by ultraviolet light B (UVB). The cholesterol synthesis starts from squalene, present in rocks preceding the presence of life [1, 2], spontaneously rearrange to form lanosterol, starting point of biochemical steroid synthesis into cholesterol. This synthetic pathway [3] is found in all eukaryotes, and vitamin D might have acquire a function early in the evolution of unicellular eukaryocytes. Vitamin D was highly efficient for protection of life in early marine organisms (plankton) against DNA damage induced by UVB a few billion years ago due to absence of ozone layers in the atmosphere. Of course, these organisms needed access to sunlight for their photosynthesis, and vitamin D was made by plant plankton 500–750 million years ago probably to protect DNA from UVB.

Historical background of vitamin D during early evolution of life

Origin of vitamin D

Vitamin D was therefore regularly found in phytoplankton (Fig. 2) as well as in zooplankton [4, 5]. It is transferred along the food chain into the seafood, where it is stored and concentrated. The physiologic function of vitamin D in the early organisms is unknown, since it was many years before animals with calcified eggs and skeleton. Recent work has demonstrated a causal link between vitamin D and the normal innate immune response with as result antimicrobial peptide (AMP)-generating, autophagy-stimulating, and inflammation-activating genes to combat infection [6]. This might be one of

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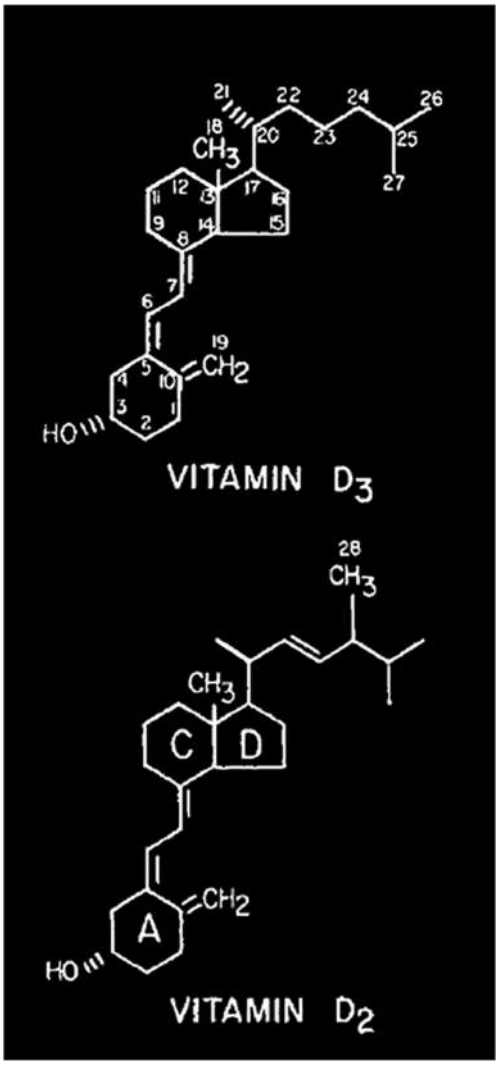


Fig. 1 Structure of vitamin D3 and D2, 7-dehydrocholesterol, and ergosterol

the principal functions of vitamin D before the apparition of calcified eggs and skeleton and this function will be discussed for periprosthetic infection [7] in the part II of this historical perspective.

Relation between plankton and cod liver oil in fish

Bills [8, 9] in 1924 suggested that vitamin D found in oily fish and in fish liver oils in cod liver oil was probably due to the dietary intake of vitamin D from phytoplankton, vitamin D made by sunlight falling on the green plankton in waters of the North Atlantic. In support of this hypothesis, Copping in 1934 [10] collected copepods in the North Atlantic and the dried copepods were found to have antirachitic activity. To better define whether phytoplankton could photosynthesize vitamin D, Holick [4, 5] grew 100 L of *Emiliania huxlei* (an organism that has existed unchanged in the Sargasso Sea for at least 750 million years). The amount of ergosterol in *E. huxlei* was 1.0 μg of ergosterol/g wet weight. Every 24 h, a single fish consumes 1.2% of its body weight as phytoplankton. Thus, it is not surprising that if phytoplankton photosynthesizes only a very small amount of vitamin D, through the concentrating power of the food chain [11], fish can obtain a large amount of vitamin D (Fig. 2) ultimately stored in body fat. To conquer earth, fish amphibians and tetrapods used this vitamin to move towards a milieu poor in calcium and rather rich in phosphate.

Origin and evolution of regulation of bone mineralization by vitamin D

Life originated in sea water about 3.5 billion years ago [12, 13]. The calcium concentration of sea water is about 10 mM whereas it is about 2.5 mM in extracellular fluids of fish, and the intracellular calcium concentration is 100- to 1000-fold lower; this gradient is vital for cell function; this role is for nerve and muscular function (including cardiomyocytes), coagulation, and tooth and bone formation. The phosphate concentration (also vital for cellular functions) is much lower in seawater than in body fluids. Therefore, during the evolution of life in seawater, calcium was available in excess whereas phosphate supply was limited.

When conquering earth, amphibians and tetrapods were confronted [14, 15] with a milieu poor in calcium and rather rich in phosphate. This required intestinal calcium absorption and an internal reservoir of calcium to cope with variable dietary calcium supply. As these terrestrial animals had to deal with a six fold higher gravity (Fig. 2) in comparison with marine animals living in a low gravity water milieu, bone structure was necessary to support of muscles for mobility and was also used to stock calcium. Skeleton growth and normal serum calcium homeostasis [16] needed to be regulated by turnover of bone. Vitamin D is one of the hormones necessary for this regulation. Moving from the sea to earth, the photochemical reaction leading to the production of vitamin D was transferred to the skin of the animals during the evolution.

Skin and vitamin D in the evolution

Vitamin D probably had a major role in human evolution out of Africa; decreasing access to UVB was probably responsible of gene selection for skin depigmentation [17, 18]. The dark skin of early humans in Africa avoided excess production of vitamin D and protected them against UV destruction of folic acid. In terms of human evolution, the original African population required minimal storage of vitamin D in the tropical environment; at reverse in the ice-age environment, white skin was better adapted to vitamin D production. Regarding the amount of vitamin D production in human skin, it depends therefore on several variables including geographic latitude (Fig. 3), weather conditions (cloudiness), amount of air pollution, and environmental factors such as clothes which can all interfere with the amount of UVB radiation reaching the skin.

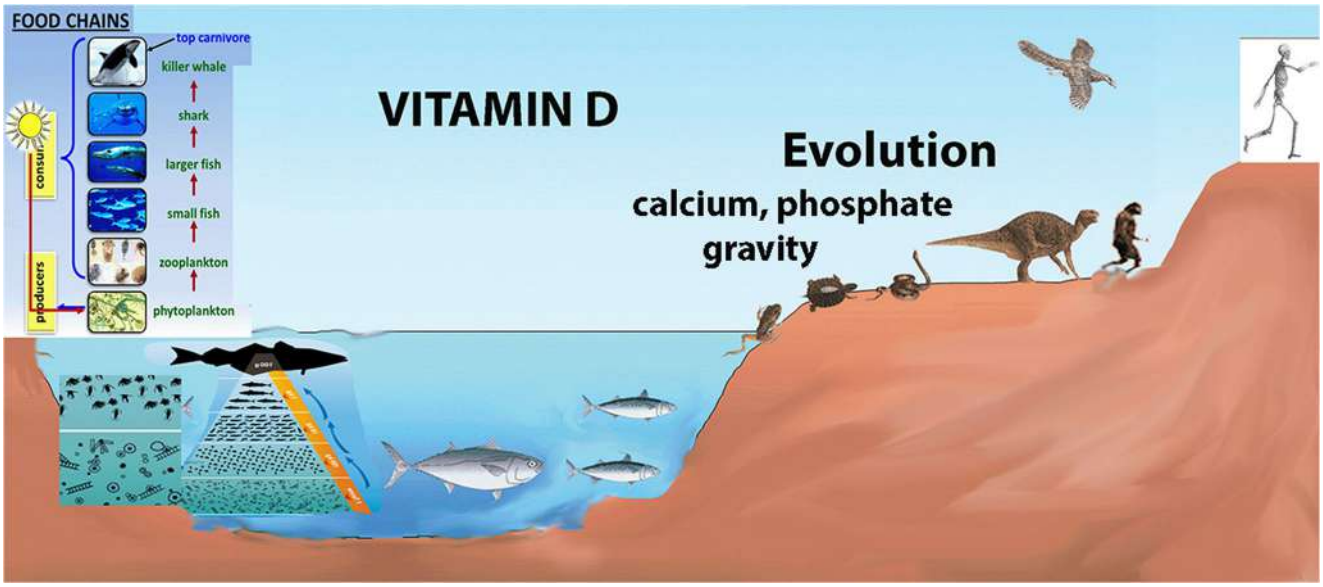


Fig. 2 Vitamin D3 was already found early as products of the photochemical reaction of 7-dehydrocholestol with ultraviolet light B. The vitamin D story then started as molecule in plankton but gained an essential role for calcium and bone homeostasis in terrestrial animals to cope with the challenge of higher gravity and calcium-poor environment

Human history of vitamin D deficiency before Glisson

First reference to the physiological effect of sunlight deficiency and bone weakness

In terms of human history of vitamin D deficiency, the *first reference to the physiological effect of sunlight on vitamin D* was illustrated by the Greek historian Herodotus [19]. Herodotus was a Greek historian who was born in Halicarnassus in the Persian Empire (modern-day Bodrum, Turkey) and lived in the fifth century BC (c. 484–c. 425 BC), a contemporary of Thucydides, Socrates, and Euripides. He is often referred to as "The Father of History", a title first conferred by Cicero. Herodotus (485–426 BC) visited the battlefield where Cambyses (525 BC) overcame the Egyptians and inspected the skulls of slain Persians and Egyptians. He observed that Persian warriors had much softer skulls than Egyptian warriors and attributed it to the turbans worn by Persians. He noted that the Persian skulls were so fragile that they broke even when struck with a pebble, whereas those of the Egyptians were strong and could

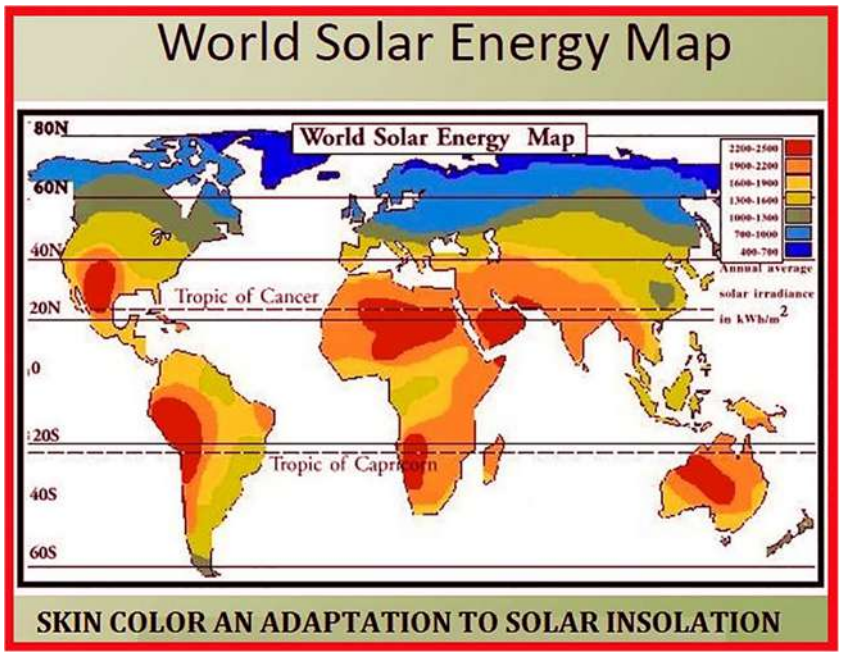


Fig. 3 Correlation between skin depigmentation evolution out of Africa and access to UVB

scarcely be broken even when struck with a stone. The relationship between bone weakness and sun might be very old since the Egyptians' explanation to Herodotus was that they went bareheaded from childhood exposing their heads to sunlight (Fig. 4), whereas Persians covered their heads with turbans shading them from the sun resulting in skull bone weakness. Two millennium were necessary to rediscovery and remember the observation of Egyptians reported by Herodotus: only in 1890, addressing the etiology of rickets, Palm [20] studied the relationship between incidence of rickets and its geographical distribution, and concluded that rickets was caused by lack of exposure to sunlight. Palm was able again 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.

First description of rickets

Soranus of Ephesus (98–138 AD) in "A Treatise on the Diseases of Women" is often credited as being the first to mention some of the features of rickets [21]. Sorano (Fig. 5) worked in Alexandria and then in Rome. One of his classic works is entitled "Gynecology" in which he wrote (Book II), "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."

Marcus Valerius Martialis (known in English as Martial) was a Roman poet [22] from Hispania (modern Spain) best known for his 12 books of Epigrams, published in Rome between AD 86 and 103, during the reigns of the emperors Domitian, Nerva, and Trajan. One of the epigram probably corresponds to rachitism (Fig. 6): "Cum sunt crura tibi simulent quae corbuae lunae in rhytis poteras, Phoebe, lavare pedes" (Since, Phoebe, your legs are bent like half-moons, you might wash your feet in a drinking-horn.). Claudius Galenus of Pergamon (Mysia, Anatolia, now Bergama, Turkey), another Greek physician of the Roman Empire, wrote of a disease suggesting the appearance of rickets in De Morborum Causis. However, he attributed the chest deformities of the affected infants and toddlers to the pressure of swaddling clothes [23]. Diseases, as rickets, were also known in ancient China. Needham (1900–1995) was a British historian and sinologist, who traveled multiple times into Eastern countries and who reported the disease in China [24].

Rickets in the Middle Age

Indeed, iconography of the cities of Italy, Germany, and Holland, at least 200 years before Whistler's description, definitely support the thesis that rickets existed to some extent at all times and periods of the world's history [25]. Families (poor or powerful) were not able to prevent their children from suffering from rickets during the Renaissance. Rickets was present in Italy in the sixteenth century based on the description of several members of the Medici family (one of the most powerful families) who suffered from vitamin D deficiency-related bone changes during the Italian Renaissance (16th and 17th centuries), as shown by examination of their skeletons [39–42]. Bone collagen analysis of their skeleton could identify a number of pathological lesions, including porosity shown in the skull, orbits, costochondral regions, and growth

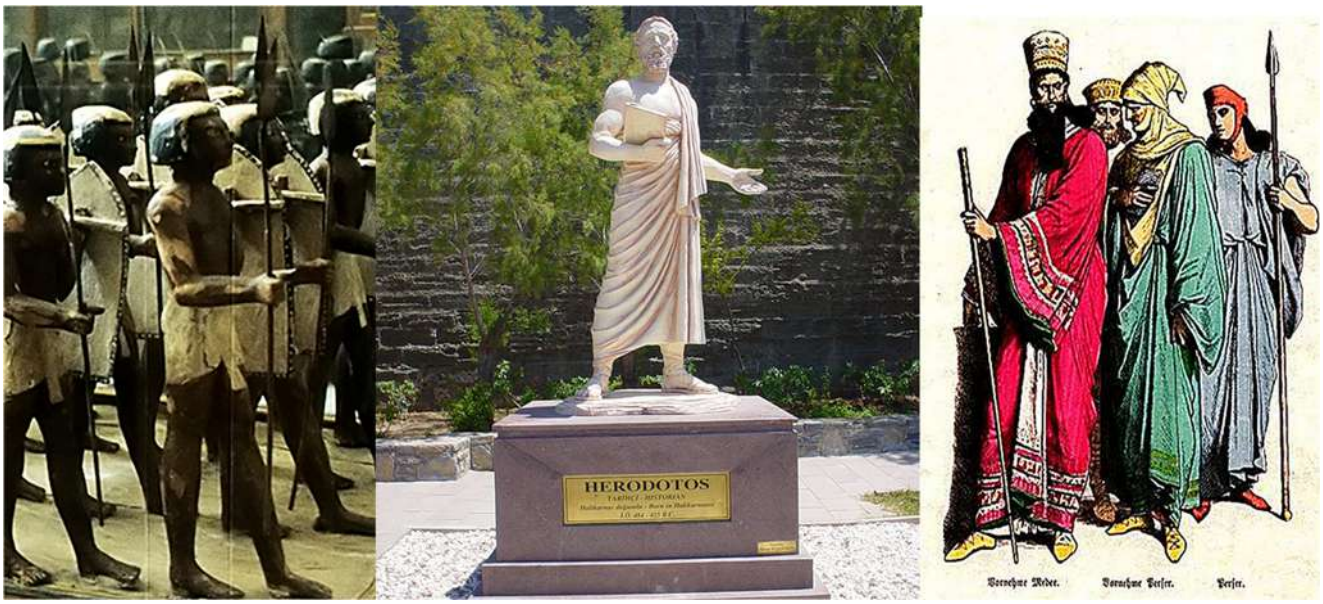


Fig. 4 The statue of Herodotus in his hometown of Halicarnassus, modern Bodrum, Turkey. On the left of Herodotus costume of Persian warrior; on the right costume of Egyptian warrior

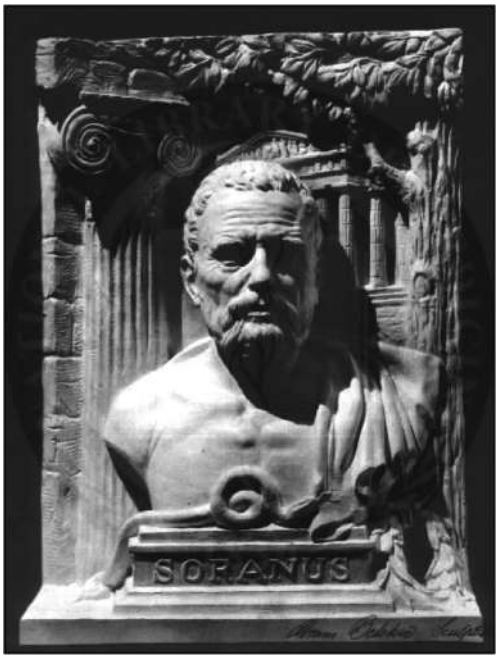


Fig. 5 Portrait of Soranus de Ephesus

plates of long bones in addition to the enlargement of rib ends and bending of long bones [26]. Another remarkable pre-Glisson rickets case (Fig. 7) may have been represented in Caravaggio's Amore dormiente [27].

Much later, in about 1554, Theodosius of Bologna described a pale child that could not move or sit, indeed hardly hold it 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.

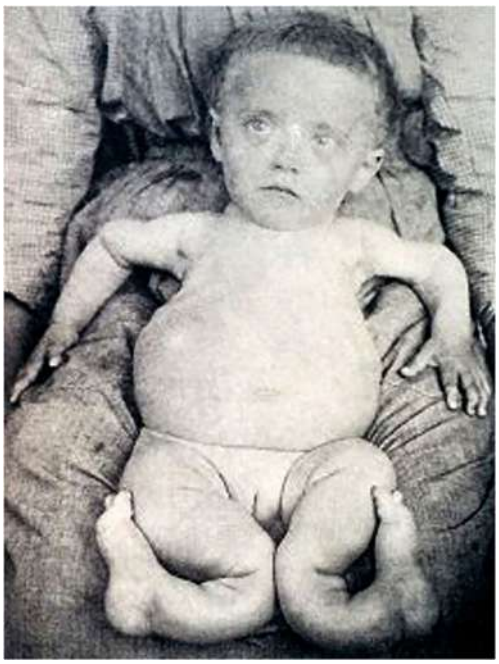


Fig. 6 Photography of ricket with legs bent like half-moons as described by Martial

Glisson and the name ricket

Glisson

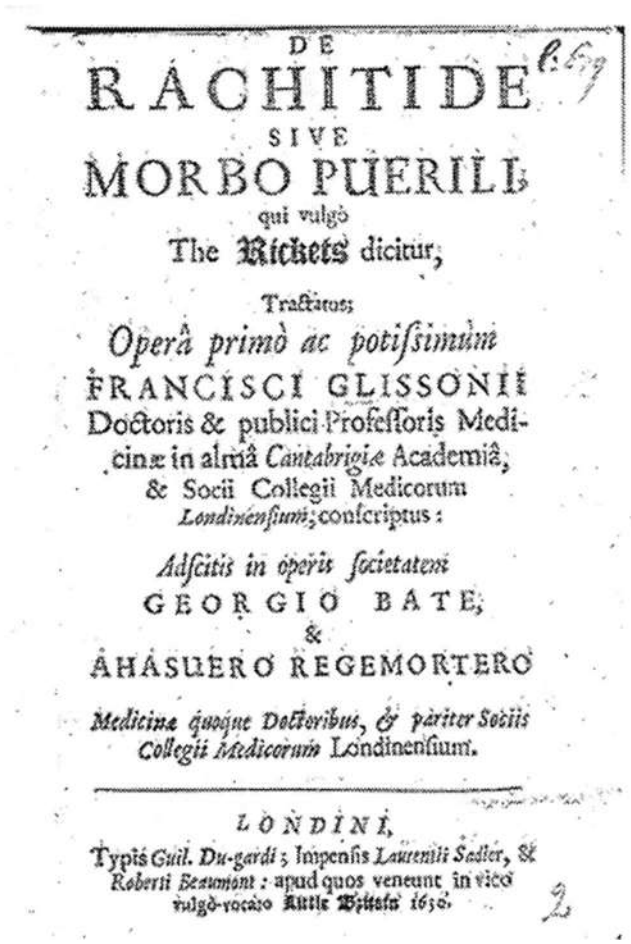
Francis Glisson (1597–1677) (Fig. 8) was born in Dorsetshire and attended both Cambridge and Oxford Universities before receiving his medical degree in 1634. The following year, he became a member of the Royal College of Physicians and was made Regius Professor of Physic at Cambridge, a position he held until his death. Glisson played an important role in the medical and scientific affairs of his time. He was one of the founders and first members of the Royal Society. He was particularly famous as an anatomist and is remembered for his description of what came to be known as *Glisson's capsule*, which is the membrane surrounding the liver [28]. During the Civil War, he moved to loyalist Colchester, where he practised medicine with great reputation and was present during the siege by parliamentary forces in 1648. Shortly afterwards, he went to live in London and became very active in the affairs of the College of Physicians, holding, successively, the posts of censor, councilor, and president (1667–9). Soon after arriving in London, Glisson joined a small group of distinguished doctors and scientists who met weekly to discuss natural and experimental philosophy. This group, with additional members, became the Royal Society after the Restoration.

Around 1645, a group of fellows of the Caius College in Cambridge began to exchange notes on rickets, thought to have been recently spread in England. They were Glisson, Sheaf, Bate, Regemorter, Pagett, Goddard, and Trench. Bate and Regemorter were assigned to publish a book on the subject. The investigation of the essential nature of the disease fell to Glisson [29], who impressed his co-workers so much that they entrusted him with drafting the whole book (Fig. 9), into which their own observations and possibly those of authors like Daniel Whistler were incorporated [30]. "Tractatus de Rachitide Sive Morbo Puerilii" appeared in 1650 with Glisson as the author [29], Bate and Regemorter as his associates, and with five, additional contributors. In the preface to his book on rickets, Glisson and two of his colleagues point out that the material in the book was collected by a committee consisting of Glisson and collaborators, making this

Fig. 7 Sleeping Cupid is a painting by the Italian master Caravaggio

gathering one of the earliest instances of collaborative research carried out in England. Glisson stated that he had been studying rickets for 5 years and that it was an "...absolutely new disease, and never described by any ancient or modern writers in their practical books which are extant at this day of the diseases of children". Of course, the disease was ancestral but the description was new. As early as 1668, he realized that this was a disease of children with devastating consequences in young women with deformed pelvis, resulting in maternal

Fig. 8 Portrait of Francis Glisson (1597–1677)



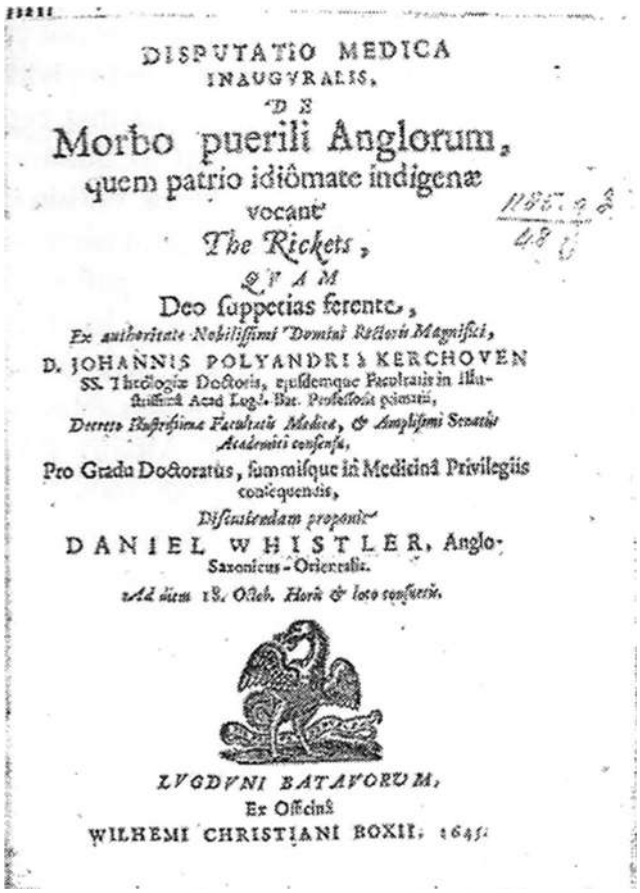
DE
RACHITIDE
SIVE
MORBO PUERILI,
qui vulgò
The Rickets dicitur,
Tractatus;
Operâ primò ac potissimùm
FRANCISCI GLISSONII
Doctoris & publici Professoris Medicinæ in almâ *Cantabrigiæ* Academiâ,
& Socii Collegii Medicorum
Londinensium; conscriptus:
Adscitis in operis societatem
GEORGIO BATE;
&
AHASUERO REGEMORTERO
Medicinæ quoque Doctoribus, & pariter Sociis
Collegii Medicorum Londinensium.
LONDINI,
Typis *Guil. Du-gardi*; Impensis *Laurentii Sadler*, &
Roberti Beaumont: apud quos veneunt in vico
vulgò vocato Little Britain 1650.

Fig. 9 Francis Glisson's book, published in 1650 with Bate and Regemorter, entitled "A Treatise of the Rickets: Being a Disease Common to Children"

mortality. It was then known as *the English disease*, *morbus anglicus*, *morbus anglorum*, and *rachitic*.

Whistler

In fact, Glisson's text had been pre-empted by a slim thesis (Fig. 10) on rickets for the degree of MD in Leyden, delivered by Daniel Whistler in 1645 [30, 31]; therefore, the year 1645 is commonly recognized as the opening year for the scientific literature on rickets. That year is mostly famous for several events linked to the English Civil War and to the battle of Jankau of the Thirty Years' War. In the same year, two public health events happened, i.e., Black Death (plague) causing many town or city councils, such as Edinburgh, to prohibit all gatherings except for weddings or funerals; and Jeanne Mance founding the Hôtel-Dieu de Montréal, the first hospital in North America [33]. In 1645, David Whistler (1619–1684) defended his M.D. thesis at the University of Leiden, the Netherlands, with the title "De morbo puerile anglorum, quem patrio idiomate indigenae vocant the Rickets" (concerning the disease of English children, which in English it is called "Rickets"). Dr. Whistler named the rickets "Paedosplanchosteocaces" [34], a rational, but probably awkward name, which was not favoured by the scientific community and future generations.



DISPUTATIO MEDICA
INAUGVRALIS,
DE
Morbo puerili Anglorum,
quem patrio idiômate indigenæ
vocant
The Rickets,
QVAM
Deo suppetias ferente,
Ex authoritate Nobilissimi Domini Rectoris Magnifici,
D. JOHANNIS POLYANDRI à KERCHOVEN
SS. Theologiæ Doctoris, ejusdemque Facultatis in Illustrissima Acad. Lugd.-Bat. Professoris primarii,
Decreto Clarissimæ Facultatis Medicæ, & Amplissimi Senatûs Academici consensu,
Pro Gradu Doctoratûs, summisque in Medicinâ Privilegiis consequendis,
Discutiendam proponit
DANIEL WHISTLER, Anglo-Saxonicus-Orientalis.
Ad diem 18. Octob. Horis & loco consuetis.
LVGDVNI BATAVORUM,
Ex Officinâ
WILHEMI CHRISTIANI BOXII. 1645.

Fig. 10 The thesis of Daniel Whistler, 1645, entitled "Inaugural Medical Disputation, on the Children's Disease of the English, Which the Inhabitants Ideomatically Call the Rickets

Whistler (Fig. 11) had been born in Walthamstow in 1619 and had studied at Merton College, Oxford. He gave a clinical description of the disease that was excellent, mentioning the enlargement of the head, the epiphyses, and the abdomen, the rickety rosary: "the whole bony system ... flexible like wax that is rather liquid, so that the flabby and toneless legs scarcely sustain the weight of the superimposed body, so that the tibiae yield to the weight of the fabric pressing down on them from above and become bent". After acquiring the diploma of medical doctor at Leyden and incorporated at Oxford, Whistler was appointed professor of geometry at Gresham College, London in 1648. He was a successful physician who shone in society and was elected a fellow of the Royal Society in 1663. He also became a fellow of the London College of Physicians in 1649. In 1684, Dr. Whistler was appointed as President of the College of Physicians in England, but he died the same year when his thesis was republished in Latin. In reality, the English translation [31] of Whistler's eight-page thesis was only published in the middle of the twentieth century. In reverse, Glisson's book was quickly translated into English [32] and that version was published only a year after the Latin version [29] which explains that the description of ricket was attributed to Glisson.

The term ricket

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

Fig. 11 Daniel Whistler, 1619–84. Portrait in the Royal College of Physicians, London

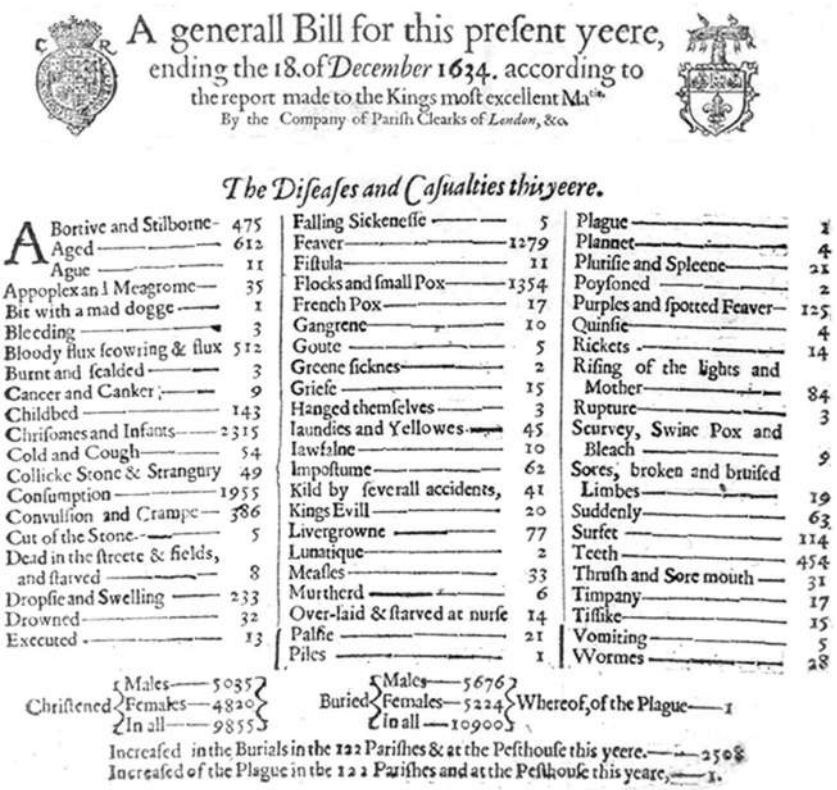
Bill of Mortality of the City of London for that year (Fig. 12). The Bills of Mortality were records of the numbers and causes of death in the area around the Tower of London and St Paul's Cathedral, which is now the financial area, but which used to be a residential part, within or close to the walls of the City of London. 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. The condition described by Glisson was called *rickets* by the local population, and while Glisson labored to find its root in Greek, it probably stemmed from the Anglo-Saxon or Old English *wrick* or *wrikken*, that is, to twist, or to *wrick*, one's ankle.

The etymologic puzzle as to where the English derived their common expression has never been solved. In old French word, *riquet*, signifying a hunchback. It was also suggested that French and English terms might have a common origin in the German *Riicken*, the back or spine. 'Rack' did mean the backbone in Old English and a 'rackbone' is a vertebra. It has also been suggested that there is no problem at all, that around 1620 a Newbury doctor had acquired a reputation for treating the disease, that his name was Rickets, and that the disease came to be called by his name. There is, however, only one source for this belief—John Aubrey, the dilettante author of *Brief Lives*: "I will whilst tis in my mind insert this Remarque, viz. - about 1620 one Ricketts of Newberye, a practitioner in Physick, was excellent at the Curing Children with swoln heads and small legges: and the Disease being new, and without a name, he being famous for the cure of it, they called the Disease the Ricketts: as the Kings Evill from the King's curing of it with his touch: and now tis good sport to see how they vex their Lexicons and fetch it from the Greek rachis, the backbone.!"

The English disease (morbus anglicus, morbus angloram)

Because the disease was originally described in England, it became known as the English disease (*morbus anglicus*, *morbus angloram*), as well as rachitis and rickets. It is recorded for 1634, that of a total of 10,900 deaths in London, rickets was given as the cause of death in 14 of them (Fig. 12). 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 analyzed 6 in great detail by John Graunt in 1662. Graunt [35] may be considered along with Petty as one of the fathers of medical epidemiology.

Glisson also noted correctly that the disease (Fig. 13) did not occur in children younger than six months old and occurred most frequently in children of the well-to-do rather than in those of the poorer classes: "About the joynts, especially in the wrists and ankles certain swellings are conspicuous, which



A generall Bill for this prefent yeere, ending the 18. of *December* 1634. according to the report made to the Kings moſt excellent Ma^tie^
By the Company of Pariſh Clearks of *London*, &c.

The Diſeaſes and Caſualties this yeere.

Abortive and Stilborne	475	Falling Sickeneſſe	5	Plague	1
Aged	612	Feaver	1279	Plannet	4
Ague	11	Fiſtula	11	Pluriſie and Spleene	21
Appoplex an I Meagrome	35	Flocks and ſmall Pox	1354	Poyſoned	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 ſickneſs	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
Chriſomes and Infants	2315	Iaundies and Yellowes	45	Sores, broken and bruiſed Limbes	19
Cold and Cough	54	Iawfalne	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	Tiſſike	15
Dropſie and Swelling	233	Meaſles	33	Vomiting	5
Drowned	32	Murthered	6	Wormes	28
Executed	13	Over-laid & ſtarved at nurſe	14		
		Palſie	21		
		Piles	1		

Chriſtened: Males 5035, Females 4820, In all 9855
Buried: Males 5676, Females 5224, In all 10900
Whereof, of the Plague 1

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 yeare, 1.

Fig. 12 A copy of the Bill of Mortality for 1634. The middle part of this, listing the number of deaths in 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 these on the right side

Fig. 13 Skeleton of ricket corresponding to the description of Glisson and Whistler

if they are opened, not in the fleshy or membranous parts, but in the very ends of the bones, you may perceive them to be rooted in their appendances; and if you will file away those prominencies of the bones, you will easily perceive them to be of the same similarly substance with the other parts of the bones.. .. The top of the ribs to which the stern is conjoyned with gristles, are knotty, like unto the joynts of the Wrists and Ankles, as we have already said [the rickety rosary]…the joynt in the Knee must needs stand outwardly bent; and on the contrary, if the inward part be lifted up, and the outward depressed, the same Joynt must needs stand inwardly bent."

He also noted that scurvy was sometimes seen in patients with rickets. He described the use of swathing and splints for the extremities and the use of suspension and local pressure to prevent the progress of spinal deformities. At the beginning of the seventeenth century, rickets probably was a *disease of the rich* instead of the poor. The rich preferred to keep their children inside the house and feed them with meat and bread only, which made them very vulnerable to vitamin D deficiency. It is argued though that in these days, rickets was not caused only by vitamin D deficiency, but also by a lack of calcium. The disease was not only new but was becoming commoner as pointed out by, John Graunt, in his observations on the Bills of Mortality, of 1676.

There is much evidence that the disease suddenly became prevalent in England during the first 20 years of the seventeenth century. Much has been written about the sudden increase in prevalence of rickets and the causes of this rise. One of the factors in seventeenth and eighteenth century Britain is the large amount of coal used, causing the large cities to be covered in smog, sunlight being unable to penetrate the cloud. With the onset of the industrial revolution in the eighteenth century and the migration of farmers to the cities, where they lived in crowded and dark houses in narrow alleys, rickets became a disease highly prevalent in the large cities. As early as 1773, it was said that 20,000 children in London were affected by rickets. But it was also the case in all the north of Europe [36]. Probably somewhere in the eighteenth century, rickets turned *from a disease of the rich into a disease of the poor*, but the exact moment of this change is unclear.

It was not until the works of Julius O. Moller [37] and Thomas Barlow [38, 39] that a clear distinction between *rickets and infantile scurvy* was made clinically. Julius O. Moller (1819–1887) was born and educated in Konigsberg, East Prussia, where he also practiced medicine. In 1859, he published a paper dealing with what he called *acute rickets*, which described infantile scurvy. This paper preceded the publication of Thomas Barlow's paper, "On Cases Described as 'Acute Rickets'," which appeared 24 years later. These two papers are the basis for referring to infantile scurvy as Moller-Barlow's disease. Thomas Barlow (1845–1945) was born in Lancastershire and, after a preliminary education in Manchester, studied medicine at University College in London. He became a physician on the staff of Charing Cross Hospital and the Hospital for Sick Children. He was the physician to Queen Victoria during her last illness and was also physician to Kings Edward VII and George V. He was president of the Royal College of Physicians from 1910 through 1914. His longevity was rewarded by the opportunity to see the causes of rickets and scurvy discovered [40], two diseases in which he had a special interest, and to see effective prophylaxis and treatment become available.

Rickets' disease was the beginning of orthopedic, osteoclasis, and osteotomies

Nicolas Andry coined the term "Orthopedia"

Most of the orthopaedic literature dealing with the subject has tended to follow the example of Nicolas Andry [41], who discussed rickets in one section of his book *Orthopaedia*, and the treatment of deformities of the extremities, almost all of which were caused by rickets, in another section. While he had nothing important to offer in the section on rickets, it was in the section on treatment of deformities in the leg that he discussed the value of splinting, using the famous crooked tree as an example. He also inveighed against early weight bearing in small children if there was a tendency to deformity.

Fig. 14 Levacher de la Feutrie book

Levacher de la Feutrie coined the term "rakitis"

Levacher de la Feutrie (1738–1790) wrote the first book designated on treatment of rickets [36]. The text begins with a history of rickets, followed by sections on the nature of the disease, the parts of the body affected, those most at risk, a refutation of other opinions on the disease, the foundations of theories on rickets, description of the disease and its diagnosis, the various causes, warning signs of the disease, a short explanation of the curving and swelling of the bones associated with rickets, a general prognosis for victims, treatments and remedies, and, finally, some observations on therapeutic treatments for rickets. At the end of the text, he depicts orthopaedic devices developed specifically for the treatment of rickets-deformed bones, including leg braces, corsets, and instruments to realign the spine (Fig. 14).

Osteoclasis for rickets

The intentional fracture of a bone in order to correct a deformity could be carried out manually or by means of instruments called *osteoclasts* (Fig. 15). The manual method had its advocates, but was not popular. A. H. Tubby [42] criticized the method because the fractures produced could be oblique, comminuted, or in the wrong place and the collateral ligaments of die knee or the epiphyses could be damaged. An osteoclast of his own design was used by Francesco Rizzoli (1809–1880) of Bologna [43] in 1869 as a method of equalizing leg length. Even with an osteoclast, it was difficult to fracture the diaphysis of the bone close to the joint. However, osteoclasts remained in the armamentarium of orthopaedic surgeons well into the first quarter of the twentieth century.

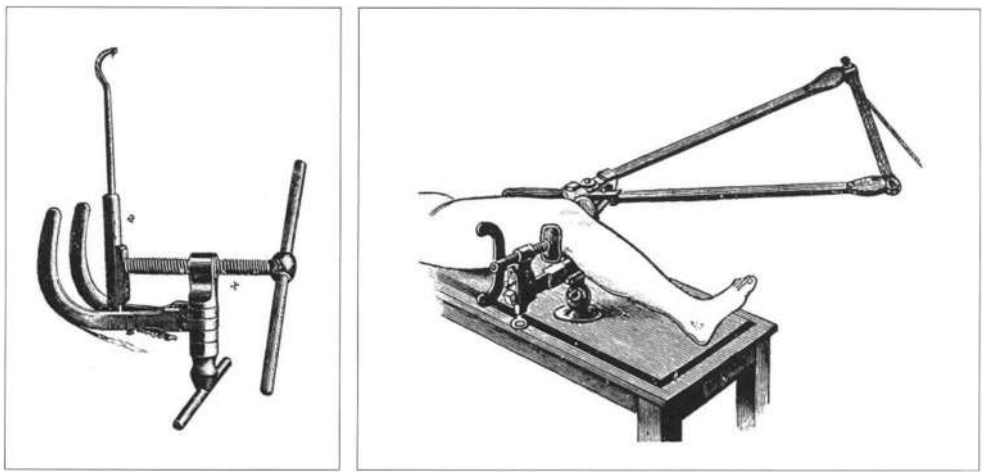


Fig. 15 Left to right: Grattan's osteoclast and Colin's osteoclast. From A. H. Tubby [42]

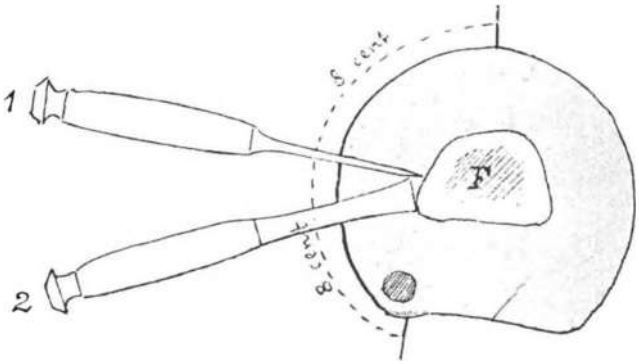


Fig. 16 The method of using the osteotome for subcutaneous osteotomy of the femur: (1) The blade inserted down to the bone parallel to the muscle fibres; (2) the blade turned 90 degrees to transversely divide the bone. AS we can remark, mini-invasive surgery is not an invention of the 20th century

Osteotomies for rickets

Because of the high risk of infection and its complications, surgeons developed methods similar to the subcutaneous osteotomy (a very small incision through which a very narrow instrument was inserted) in the hopes of alleviating the risk of infection. Bernhard Langenbeck (1810–1887) in Berlin [44] used a saw with a point an eighth-of-an-inch wide and four inches long, which was introduced through a very small incision to divide the femur almost completely, the remainder of the femur being fractured as the deformity was corrected. But until the introduction of antiseptic and aseptic surgical techniques, the risk of such operations was substantial. In 1875, Richard Volkmann (1830–1889) of Halle [45], a close friend and admirer of Joseph Lister (1827–1912), described two cases of osteotomy carried out using the antiseptic system [46]. In both cases, the wounds healed without infection.

Immediately following this, William Macewen (1848–1924) in Glasgow began his work on osteotomy in rickets. William Macewen was born on the island of Bute off the west coast of Scotland, where his father ran a small shipping business. When he was 12 years old, his father retired and moved his family to Glasgow, where William continued his education [47]. As a medical student on die wards of the Royal Infirmary, he came under the spell of Joseph Lister. As his surgical training progressed, Macewen became a firm believer in Lister's ideas regarding the antiseptic treatment of wounds. After graduating in 1869, he continued his surgical training at the Royal Infirmary and joined the hospital staff as a surgeon following experience as a general practitioner. He had a long and illustrious career. His studies of bone growth, bone grafting, and osteotomy were major contributions to orthopedic surgery. Prior to Macewen, surgeons divided the bone with chisels and saws. He discarded the saw as inappropriate for the task and used the chisel only for paring, shaving, or cutting wedges out of the bone. For dividing or making incisions into the bone, he designed a new instrument that he called an *osteotome.* The osteotome was quite similar to a chisel except that at the cutting edge, it was beveled on both sides to resemble a very slender wedge. His osteotomes were made with a calibration in inches marked on the shaft so that it could be determined how far the instrument had been advanced through the skin. He was very particular about the material and temper of his chisels and osteotomes and how they were to be used. "It is advisable that one wishing to use them should practice on the dead subject, or on the bones of animals, so as to familiarize the hand and acquire the necessary dexterity. A carpenter would not permit a fine piece of work to pass into the hands of one not thoroughly conversant with the use of his tools."

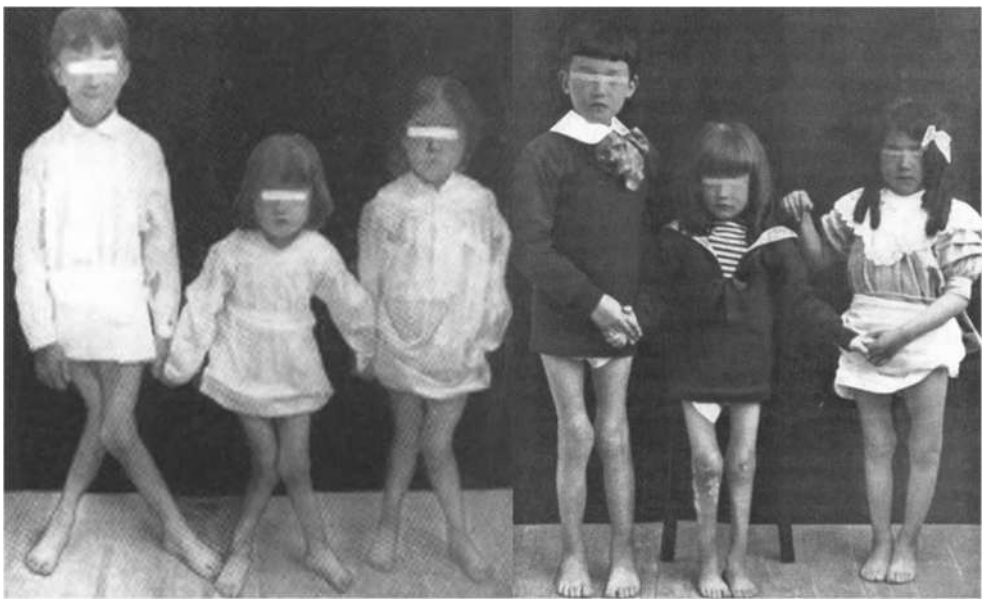


Fig. 17 Three children with deformities due to rickets, and the same children following recovery from corrective osteotomy. From Calot [49]

The osteotome became the classic instrument for use in bone surgery and still maintains a prominent place in the orthopaedic armamentarium. The operation of subcutaneous osteotomy was performed with the limb supported on a sand bag (Fig. 16). Operations were carried out under anesthesia and a tourniquet was used. The incision was made parallel to the muscle fibers and the osteotome inserted down to the bone. It was then turned 90 degrees and the bone divided. The deformity was corrected and the leg was placed in a splint. In the five years between the first performance of the operation and the publication of his book [48], Macewen operated upon 557 limbs in 330 patients, with generally satisfactory results.

In France, Francois Calot (1861–1944) in his role as head of the Hopital Rothschild, the Hopital Cazin, the Hopital du Departement de L'Oise, and the Institut Orthopedique de Berck, all institutions for the treatment of bone diseases located on the north coast of France, had the opportunity to gather an enormous clinical experience with osteotomies and rickets (Fig. 17). Through his publications, which were numerous [49], he influenced the treatment of patients throughout the world.

Conclusion

The routine use of X-rays, and particularly the use of intraoperative X-rays, continued to improve the results of the correction of deformities by means of osteotomies until supplementation by oral vitamin D was possible. Two centuries [4, 5] were necessary to realize that rickets was a lack of an antirachitic nutrient obtained in the diet or by skin exposure to ultraviolet radiation. While not needed as frequently for the treatment of rachitic deformities, osteotomies continue to be used to correct a wide variety of other deformities. Of all the many folk remedies used for the treatment of rickets, osteotomy became recognized as being of real benefit and continue to be used in the twenty-first century in other indications.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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