Hochberg Z (ed): Vitamin D and Rickets.
Endocr Dev. Basel, Karger, 2003, vol 6, pp 1–13

Introduction

Rickets – Past and Present

Ze'ev Hochberg

Pediatric Endocrinology, Meyer Children's Hospital,
Rambam Medical Center, Haifa, Israel

Contents

The name 'rickets' is from the Old English wrickken, to twist. The more technical medical term, rachitis, which comes from Greek, the spine, was suggested by Francis Glisson in 1650, both from similarity of sound and from the part of the body which he thought was one of the first to be affected.

At the turn of the industrial revolution, 'the English disease', resulting from vitamin D deficiency, spread among city-dwelling poor children and became endemic in cities. At the turn of the Internet revolution it appears to be endemic again. The increase in the incidence of vitamin D deficiency is paralleling the primacy of breast-feeding in Western societies as human milk contains only minute amounts of vitamin D. It is more prevalent in black or children of darker complexion and in those who escape well-baby clinics. The three main risk factors are nutritional status [1], breast-feeding and dark skin.

Is Vitamin D a Vitamin or a Hormone?

Vitamin D is not a vitamin in the strict definition because it can be produced by exposure of the skin to sunlight. As such, animals and humans do not have a

dietary requirement for vitamin D when sufficient sunlight is available. However, nutritional vitamin D becomes essential when sunlight is insufficient to meet daily needs. This has become particularly acute as more people reside in urban centers where they are exposed to sub-optimal levels of sunlight. Air pollution, clothes, tall buildings, indoor dwelling, and sunscreens block ultraviolet light from the sun and these factors all reduce the ability of the skin to synthesize vitamin D_3. Moreover, people living far north (or south) of the equator obtain little purposeful ultraviolet radiation during the winter months. The same is true for Middle-Eastern women who remain indoors or cover their entire body from sunlight. Under these conditions vitamin D, and its hormone derivative calcitriol, can be considered a bona fide vitamin in that it must be supplied in the diet [2].

The Unit Definition of Vitamin D

The World Health Organization has defined the 'International Unit' of vitamin D_3 as the activity of 0.025 μg of the international standard preparation of crystalline vitamin D_3. Thus, 1 IU of vitamin D_3 is 0.025 μg, or 65 pmol. The unit definition of the active metabolite calcitriol was set to be equivalent in molar terms to that of the parent vitamin D_3. Thus, 1 unit is 65 pmol of calcitriol; as such the unit of calcitriol is much more active than the unit of vitamin D itself. The vitamin D requirements for children or adults have not been precisely defined. Historically, it was defined on the basis of the vitamin D content in a teaspoon of fish oil, a quantity shown to be sufficient to prevent rickets. A more rigorous scientific definition is unavailable.

Rickets Is a Disease of Growing Children

Osteomalacia, the bone disease in rickets, results from a defect in the mineralization of bone matrix with increased bone mass. It is to be distinguished from osteoporosis where bone mass is decreased, from hypophosphatemic osteopenia of premature infants, and from renal osteodystrophy, which is partly due to calcitriol renal deficiency, but also due to hyperphosphatemic hyperparathyroidism.

When osteomalacia wrecks the growth plate of a growing child, it impairs longitudinal bone growth, producing widening and disorganization of its structure. These result from extensive compensatory proliferation of growth plate cartilage cells, mostly in the periphery of the plate, to give the cup-shaped metaphysis. Whereas cartilage mineralization is excessive, showing as a wide hazy layer on top of the metaphysis, the latter exhibits insufficient mineralization. This type of 'epiphyseal dysplasia' is defined as 'rickets'.

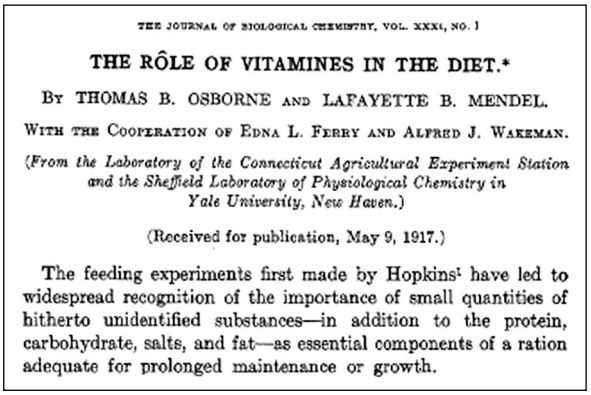
Fig. 1. An elephant mother's milk is the richest of all mammalian milks. Cow's milk is much less nutritious. When captive baby elephants lose their mothers, they are usually fed on powdered cow's milk mixed with rice and bananas. Often, the result is poorly developed bones. This 6-month-old calf has rickets [32].

From the 1911 1st Edition Encyclopedia [3]

'*Rickets*, a constitutional disease of childhood characterized chiefly by a softened condition of the bones and by other evidences of perverted nutrition… The symptoms, which precede the outward manifestation of the disease, are marked disorders of the digestive and alimentary functions. The child's appetite is diminished, and there is frequent vomiting, together with diarrhoea or irregularity of the bowels, the evacuations being clay-coloured and unhealthy. Along with this there is a falling away in flesh. Importance is to be attached to certain other symptoms present in the early stages, namely, profound

Fig. 2. Severe rickets in a child with vitamin D receptor loss-of-function.

sweating of the head and upper parts of the body, particularly during sleep, with at the same time dry heat of the lower parts and a tendency in the child to kick off all coverings and expose the limbs. At the same time there is great tenderness of the bones, as shown by the pain produced on moving or handling the child. Gradually the changes in the shape of the bones become visible, at first chiefly noticed at the ends of the long bones, as in those of the arm, causing enlargements at the wrists, or in the ribs, producing a knobbed appearance at the junction of their ends with the costal cartilages. The bones also from their softened condition tend to become distorted and misshapen, both by the action of the muscles and by the superincumbent weight of the body. Those of the limbs are bent outwards and forwards, and the child becomes “bowlegged” or “in-kneed” often to an extreme degree. The trunk of the body likewise shows various alterations and deformities owing to curvatures of the spine, the flattening of the lateral curves of the ribs, and the projection forwards of the sternum. The cavity of the chest may thus be contracted and the development of the thoracic organs interfered with as well as their functions more or less embarrassed. The pelvis undergoes distortion, which may reduce its capacity to a degree that in the female may afterwards lead to serious difficulties in parturition. The head of the rickety child is large-looking in its upper part, the individual bones of the cranium sometimes remaining long ununited, while the face is small and ill-developed, and the teeth appear late and fall out or decay early. The constitutional conditions of ill health continue, and the nutrition and



THE JOURNAL OF BIOLOGICAL CHEMISTRY, VOL. XXXI, NO. 1

THE RÔLE OF VITAMINES IN THE DIET.*

By THOMAS B. OSBORNE and LAFAYETTE B. MENDEL.

With the Cooperation of Edna L. Ferry and Alfred J. Wakeman.

(*From the Laboratory of the Connecticut Agricultural Experiment Station and the Sheffield Laboratory of Physiological Chemistry in Yale University, New Haven.*)

(Received for publication, May 9, 1917.)

The feeding experiments first made by Hopkins[1] have led to widespread recognition of the importance of small quantities of hitherto unidentified substances—in addition to the protein, carbohydrate, salts, and fat—as essential components of a ration adequate for prolonged maintenance or growth.

Fig. 3. The 1917 report on the role of vitamins in growth.

development of the child are greatly retarded. The disease may terminate in recovery, with more or less of deformity and dwarfing, the bones although altered in shape becoming firmly ossified, and this is the common result in the majority of instances. On the other hand, during the progress of the disease, various intercurrent ailments are apt to arise which may cause death, such as the infectious fevers, bronchitis and other pulmonary affections, chronic hydrocephalus, convulsions, laryngismus, stridulus, etc. An acute form of rickets of rare occurrence (*really a form of scurvy, Z.H.*) has been described by writers on diseases of children, in which all the symptoms are of more rapid development and progress, the result in many instances being fatal. The treatment of rickets is necessarily more hygienic than medicinal, and includes such preventive measures as may be exercised by strict attention to personal health and nutrition on the part of mothers, especially where there appears to be any tendency to a rickety development in any members of the family. Very important also is the avoidance of too prolonged nursing, which by its weakening effects upon the mother's health is calculated to engender the disease in any succeeding children. "At the same time it must be admitted that, when the mother is healthy, her milk abundant, and nursing discontinued before the lapse of the first year, there is no better means of preventing the occurrence of rickets than this method of feeding an infant; the disease, as is well known, being far more frequently met with in children brought up by hand." The management of the child exhibiting any tendency to rickets is of great importance, but can only be alluded to in general terms. The digestive disorders characteristic of the setting in of the disease render necessary the greatest care and watchfulness as to diet. Thus, if the child be not nursed but fed artificially, fresh milk should be almost the only article of diet for at least the first year,

and the chief element for the next. When not digested well, as may at times be shown by its appearance as a curd in the evacuations, it may be diluted with water or limewater, or else discontinued for a short time; carefully-made gruel or barley water being substituted. Many of the so-called "infants' foods" which are now so extensively used appear to be well adapted for their purpose, but when employed too abundantly and to the exclusion of the due amount of milk are often productive of digestive and intestinal disorders, probably from their containing a greater amount of starchy matter than can be utilized. From the end of the first year light animal soups may occasionally be given with advantage. The medicinal remedies most to be relied on are those which improve the digestive functions and minister to nutrition, and include such "agents" as the preparations of iron, quinine, and especially cod-liver oil and phosphorus, and the cautious use of extract of thyroid gland has been advocated by Henoch. Of no less importance, however, are abundance of fresh air, cleanliness, warm clothing, and attention to the general hygiene of the child and to regularity in all its functions. When the disease is showing evidence of advancing, it is desirable to restrain the child from walking, as far as possible. But this precaution may be to some extent rendered unnecessary by the use of splints and other apparatus as supports for the limbs and body, enabling the child to move about without the risk of bending and deformity of the bones which otherwise would probably be the result.'

Historical Background

The origin of vitamin D dates backs 500–750 million years, as it was made by plant plankton. It is transferred along the food chain into animal plankton and into the seafood, where it is stored and concentrated – hence the importance of oil-rich fish and cod liver oil as a source of vitamin D. The physiologic function of vitamin D in these early organisms is unknown. It became important many years later in the evolution of animals with calcified eggs and skeleton.

In terms of human evolution, the original Africoid races required minimal substrate and storage of vitamin D in the tropical environment. Under excessive exposure to sunlight and ultraviolet-B radiation, pre-vitamin D is photoisomerized to biologically inert isomers. In the ice-age environment, white skin was better adapted to vitamin D production. In a frigid northern climate, with many sunless days and shorter hours of daylight, dark or black skin became a liability. Inbreeding within the albinoid group, which continually heightened the albinoid characteristics, made the development of this new human stock possible.

In terms of human history of vitamin D and rickets, the Greek historian, Herodotus (485–426 BC), observed that Persian warriors had much softer skulls than Egyptian warriors and attributed it to the turbans worn by Persians [4] and Hippocrates described a disease resembling rickets in 130 AD. The majority of Roman children in the first century AD seem to have been afflicted with rickets. Soranus of Ephesus (98–138 AD) in 'A Treatise on the Diseases of Women' gave a more complete description [5].

As people began to crowd in narrow streets and sunless, polluted cities, the incidence of rickets increased. Over 90% of children working in mines and many city dwellers were affected with leg bowing. 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, who impressed his co-workers so much that they entrusted him with drafting the whole book, into which their own observations and possibly those of authors like Daniel Whistler were incorporated [6]. 'Tractatus de Rachitide Sive Morbo Puerilii' appeared in 1650 with Glisson as the author [7], Bate and Regemorter as his associates, and with five, additional contributors. As early as 1668, he realized that this was a disease of children [8] with devastating consequences in young women with deformed pelvis, resulting in maternal mortality. It was then known as *the English disease*, *morbus anglicus, morbus anglorum* and *rachitic* [9].

A hundred years later, the French scholar Levacher de la Feutrie (1738–1790) wrote his book on rickets [10]. 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 it's 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 orthopedic devices developed specifically for the treatment of rickets-deformed bones, including leg braces, corsets, and instruments to realign the spine.

In 1822, Sniadecki [11] observed that Warsaw city children had much higher rate of rickets than children from the country and suggested for the first time that this bone disease was caused by lack of sunshine. Two years later, Schutte [12] first reported of the value of cod-liver oil in the treatment of rickets. In the 1890s Palm made recommendations that children sunbath to prevent rickets. He had no idea what healing power was in the rays, but whatever it was, he surmised, these children needed it.

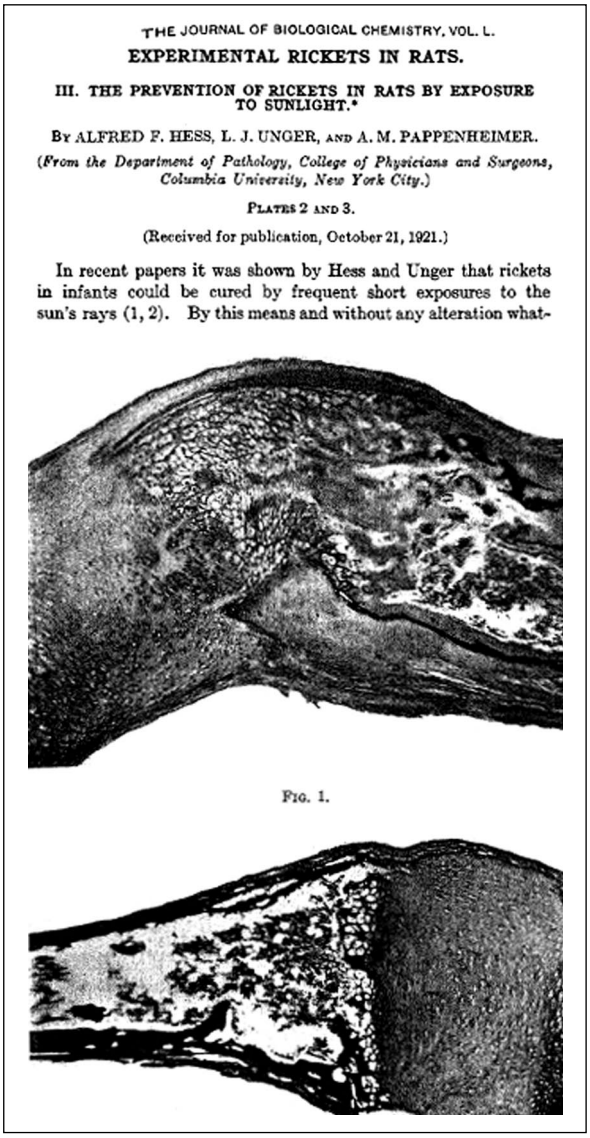
The turn of the 20th century was marked by a debate on small quantities of hitherto unidentified substances that are needed in addition to the protein, carbohydrate, salts and fat for prolonged maintenance of growth [13]. This was difficult to accept at the time and in 1915 the *Journal of Biological Chemistry* published the opinion that 'The assumption that some unknown substances are indispensable for growth is a convenient device for explaining experiments that result in failure – a device that becomes superfluous as soon as the experiment succeeds' [14].

Vitamin D became classified as a vitamin through a historical accident. It was in 1919/20 that Sir Edward Mellanby, working with dogs raised exclusively indoors, devised a diet that allowed him to unequivocally establish that their bone disease, rickets was caused by a deficiency of a trace component present in the diet. In 1921 he wrote, 'The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin' [15]. Shortly thereafter, McCollum [16] observed that by bubbling oxygen through a preparation of the 'fat-soluble vitamin', they were able to distinguish between vitamin A (which was inactivated) and vitamin D (which retained activity) and predicted several years later that the latter was a vitamin which promotes calcium deposition. A year later, this chapter was concluded when Goldblatt and Soames [17] identified that when a precursor of vitamin D in the skin was irradiated with sunlight or ultraviolet light, a substance equivalent to the fat-soluble vitamin was produced and Hess et al. [18] prevented rickets in rats by exposing them to sunlight.

The chemical structure of vitamin D was determined in the 1930s by Windaus et al. [19] in Göttingen, Germany. They discovered that vitamin D_2 is produced by ultraviolet irradiation of ergosterol and vitamin D_3 resulted from the ultraviolet irradiation of 7-dehydrocholesterol. This concept was then utilized by adding vitamin D precursor to milk and other food products, to be irradiated by a mercury arc lamp [20].

As our understanding of mineral and vitamin D metabolism grew, we also learned about possible defects in these events and the advent of molecular biology in this field enhanced our options to diagnose rare forms of rickets. The term 'rickets resistant to vitamin D' was coined in 1937 by Albright et al. [21], as the patients they described presented with changes in mineral metabolism that could only be overcome by very large daily doses of vitamin D.

But how does vitamin D affect calcium deposition to build strong bones? Since the 1950s, scientists had been puzzling over the implications of two findings related to this question [22]. In the early part of that decade, the Swedish researcher Arvid Carlsson (2000 Nobel laureate for his work on signal transduction in the nervous system) made the startling discovery that vitamin D can actually remove calcium from bones when the body needs it. At about the same



THE JOURNAL OF BIOLOGICAL CHEMISTRY, VOL. L.

EXPERIMENTAL RICKETS IN RATS.

III. THE PREVENTION OF RICKETS IN RATS BY EXPOSURE TO SUNLIGHT.*

By ALFRED F. HESS, L. J. UNGER, and A. M. PAPPENHEIMER.

(*From the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York City.*)

Plates 2 and 3.

(Received for publication, October 21, 1921.)

In recent papers it was shown by Hess and Unger that rickets in infants could be cured by frequent short exposures to the sun's rays (1, 2). By this means and without any alteration what-

Fig. 1.

Fig. 4. The 1921 description of the healing effect of sunshine in rickets.

time, the Norwegian biochemist R. Nicolaysen, who had been testing different diets on animals for years, concluded that the uptake of calcium from food is guided by some unknown 'endogenous factor' that alerts the intestines to the body's calcium needs [23].

Table 1. Classification of rickets

	Calcium deficiency	Phosphate deficiency
Nutritional rickets	Calcium deprivation Vitamin D deficiency	Neonatal rickets Antacid misuse Phosphate binders
Absorptive rickets	Malabsorption diseases Bile salts depletion Phenytoin therapy	
Renal rickets	Renal insufficiency Renal tubular acidosis	Fanconi's syndromes (types 1 and 2, secondary) X-linked recessive hypophosphatemic rickets (Dent's disease) Hypercalciuric hypophosphatemic rickets
Metabolic rickets	25OHD-1α-hydroxylase deficiency (vitamin D-dependent rickets) End-organ resistance (hereditary vitamin D-resistant rickets)	X-linked hypophosphatemic rickets Autosomal-dominant hypophosphatemic rickets Tumor-induced osteomalacia

Answers began to emerge with the experiments tracing the activation of Vitamin D. In 1961, Prader et al. [24] reported several examples of a condition for which they coined the term 'hereditary pseudo-deficiency' rickets. Scientists did not have the tools to follow vitamin D metabolism in living subjects until the advent, in the mid-1960s, of new techniques using radioactively labeled substances. Between 1968 and 1971, researchers made great progress in understanding the metabolic processing of vitamin D and its physiological activity. In 1968, a team headed by Hector DeLuca at the University of Wisconsin isolated an active substance identified as 25-hydroxyvitamin D_3, which the team later proved to be produced in the liver [25]. Two years later, Kodicek and David R. Fraser showed that a second active metabolite is produced in the kidney. Finally, in 1971 the chemical structure of this metabolite was identified as 1,25-dihydroxyvitamin D_3 [26], now termed calcitriol. It was now clear that the liver changes vitamin D_3 to 25-hydroxy vitamin D_3, the major circulating form of the vitamin. The kidneys then convert 25-hydroxyvitamin D_3 to 1,25-dihydroxyvitamin D_3, the active form of the vitamin. It turned out that the pseudo-deficiency rickets of Prader et al. [27] was a defect in this last step of renal conversion, and it was termed 'vitamin D-dependent rickets'. The understanding that the kidneys metabolize vitamin D into its active form calcitriol raised the issue whether this was really a vitamin or a hormone. In 1997,

Table 2. Milestones in the history of vitamin D and rickets

750–500 million years ago – vitamin D in plant plankton
300–500 million years ago – calcified skeletons and eggs
2nd century AD – Soranus of Ephesus's describes rickets in Roman children
1645 – Glisson describes the English disease in city children
1822 – Sniadecki identifies the healing power of sunshine
1912 – Hopkins describes the vitamins
1921 – Mellanby describes the fat-soluble vitamin D
1923 – Goldblatt and Soames showed the conversion of a precursor to vitamin D in the skin under the effect of ultraviolet light
1930 – Windaus reports the chemical structure of vitamin D
1937 – Albright describes vitamin D-resistant rickets
1950s – Carlsson and Nicolaysen associate vitamin D with uptake of calcium from food
1968 – DeLuca identifies liver 25-hydroxyvitamin D
1970 – Kodicek and Fraser identify renal calcitriol
1975 – Haussler binds vitamin D to a nuclear receptor
1988 – Baker clones the vitamin D receptor
1997 – Fu et al. clone 25OHD-1α-hydroxylase

Table 3. Antique books on rickets

Whistler D: Morbo puerili Anglorum, quem patrio idiomate indigenae vocant. Lugduni Batavorum, 1645.
Arnold Boate (Bootius, de Boot): Observationes medicae de affectibus omissis. London, Whittaker, 1649.
Glisson F: De Rachitide sive morbo puerili, qui vulgo. The Rickets diciteur. London, 1650.
Glisson F: A Treatise of the Rickets Being a Disease Common to Children. London, 1668.
Levacher de la Feutrie T: Traite du rakitis, ou l'art de redresser les enfants contrefaits. Paris, Lacombe, 1772.
Levacher de la Feutrie T: Du rakitis, ou abrege de son historie: Suivi de propositions aphoristiques sur cette maladie. Paris, Lacombe, 1803.

the group of Walter Miller in UCSF cloned and sequenced the P450c1-alpha cDNA from human keratinocytes [28].

The most recent chapter of vitamin D and rickets started when, in 1975, Mark Haussler at the University of Arizona made the discovery of a protein receptor that binds calcitriol to the nucleus of cells in the intestine [29]. The role of the vitamin D receptor in vitamin D-dependent rickets type-2 was

realized in 1982 [30] and in 1988, the group of Bert O'Malley from California Biotechnology Inc. cloned the vitamin D receptor [31].

References

1 Lulseged S, Fitwi G: Vitamin D deficiency rickets: Socio-demographic and clinical risk factors in children seen at referral hospital in Addis Ababa. East Afr Med J 1999;76:457–461.
2 Utiger RD: The need for more vitamin D. N Engl J Med 1998;228:828–829.
3 http://91.1911encyclopedia.org/R/RI/RICKETS.htm
4 Herodotus, The Histroies, 525 BC.
5 Soranus of Ephesus: Why the Majority of Roman Children Are Distorted; in: Treatise on the Diseases of Women, 98–138 AD.
6 Whistler D: Morbo puerili Anglorum, quem patrio idiomate indigenae vocant The Rickets. Lugduni Batavorum 1645, pp 1–13.
7 Glisson F. De Rachitide sive morbo puerili, qui vulgo The Rickets diciteur. London, 1650, pp 1–416.
8 Glisson F: A Treatise of the Rickets Being a Disease Common to Children. London, 1668, pp 1–373.
9 http://www.whonamedit.com/index.cfm
10 Levacher de la Feutrie T: Traite du rakitis, ou l'art de redresser les enfants contrefaits. Paris, Lacombe, 1772.
11 Mozolowski W. Jedrzej Sniadcki: On the cure of rickets. Nature 1939;143:121.
12 Schutte D: Beobachtungen über den Nutzen des Berger Leberthrans (Oleum jecoris Aselli, von *Gadus asellus* L). Arch Med Erfahr Geb Prakt Med Chir Geburtsh Staatsarzneik 1824;2:79.
13 Hopkins FJ. J Physiol 1912;xliv:425.
14 McCollum EV, Davies M. J Biol Chem 1915;xxiii:181.
15 Mellanby E: An experimental investigation in rickets. Lancet 1919;i:407.
16 McCollum EV, Simmonds N, Becker JE, Shipley PG: Studies on experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biol Chem 1922;53:293.
17 Goldblatt H, Soames KN: A study of rats on a normal diet irradiated daily by the mercury vapor quartz lamp or kept in darkness. Biochem J 1923;17:294.
18 Hess AF, Unger LJ, Pappenheimer AM: Experimental rickets in rats. III. The prevention of rickets in rats by exposure to sunlight. J Biol Chem 1921;L:77.
19 Windaus A, Linsert O, Luttringhaus A, Weidlinch G: Über das krystallistierte Vitamin D_2. Justis Liebigs Ann Chem 1932;492:226.
20 Hess AF, Weinstock M: Antirachitic imparted to inert fluids and green vegetables by ultraviolet irradiation. J Biol Chem 1924;62:301.
21 Albright F, Butler AM, Bloomberg E: Rickets resistant to vitamin D therapy. Am J Dis Child 1937;54:529.
22 http://www.beyonddiscovery.org/content/
23 Nicolaysen R, Eeg-Larsen N. Vitamin Horm 1953;11:29.
24 Prader A, Illig R, Weierli E: Eine besondere Form der primaere Vitamin D resitenden Rachitis mit Hypocalcaemi und autosomal-dominantem Erbgang: Die herediaere pseudo-mangel Rachitis. Helv Paediatr Acta 1961;16:452.
25 Blunt JW, Tanaka Y, DeLuca HF: Biological activity of 25-hydroxycholecalciferol, a metabolite of vitamin D_3. Proc Natl Acad Sci USA 1968;61:1503.
26 Lawson DE, Fraser DR, Kodicek E, et al: Identification of 1,25-dihydroxycholecalciferol, a new kidney hormone controlling calcium metabolism. Nature 1971;230:228.
27 Fraser D, Kooh SW, Kind HP, et al: Pathogenesis of hereditary vitamin-D-dependent rickets: An inborn error of vitamin D metabolism involving defective conversion of 25-hydroxyvitamin D to 1α,25-dihydroxyvitamin D. N Engl J Med 1973;289:817.
28 Fu GK, Lin D, Zhang MYH, et al: Cloning of human 25-hydroxyvitamin D-1-α-hydroxylase and mutations causing vitamin D-dependent rickets type 1. Molec Endocr 1997;11:1961.

29 Brumbaugh PF, Haussler MR: Specific binding of 1α,25-dihydroxycholecalciferol to nuclear components of chick intestine. J Biol Chem 1975;250:1588.
30 Feldman D, Chen T, Cone C, et al: Vitamin D resistant rickets with alopecia: cultured skin fibroblasts exhibit defective cytoplasmic receptors and unresponsiveness to $1,25(OH)_2D_3$. J Clin Endocrinol Metab 1982;55:1020.
31 Baker AR, McDonnell DP, Hughes M, et al: Cloning and expression of full-length cDNA encoding human vitamin D receptor. Proc Natl Acad Sci USA 1988;85:3294.
32 http://www.artbyelephants.com/background.html

Ze'ev Hochberg, MD, DSc
Pediatric Endocrinology
Meyer Children's Hospital, Rambam Medical Center
POB 9602, Haifa 31096 (Israel)
Tel./Fax +972 4 8542157, E-Mail z_hochberg@rambam.health.gov.il