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Review article

Scurvy: Past, present and future

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ABSTRACT

This study outlines the major landmarks in the research on scurvy and its relationship to vitamin C. A thorough search including original manuscripts, books and contemporary reviews published in PubMed was conducted using as keywords “scurvy”, “vitamin C”, and “history of medicine”. Observations on scurvy first appear in Egyptian medical scrolls 3500 years ago, and continue through to the discovery of vitamin C and the modern research on the physiological role of ascorbic acid. The observations of great navigators during the 15th and 16th centuries, when scurvy plagued ships' crews, played an important role in clarifying scurvy's etiology. Among the personalities in the history of the disease, James Lind and Albert Szent-Györgyi are most noteworthy, the first for conducting the first clinical trial on the treatment of scurvy with lemon and orange juices, and the second for discovering and identifying vitamin C.

1. First descriptions on scurvy

Scurvy, one of the oldest diseases in human history, is perhaps also one of the few dietary diseases that have excessively tormented human kind. However, it is predominantly connected in history with the voyages of the navigators and explorers of the 15th and 16th centuries.

The first reports of the disease are found in Papyrus of Ebers (1550 BC), where, in addition to diagnosis, treatment is also recommended by eating onions and vegetables, all nowadays known to be rich in vitamin C [1]. The disease is referred to by the general term *lienes magni*, as mentioned by Hippocrates (460 BC–370 BC), Aulus Cornelius Celsus (25 BC–50 AD) [2], Aretaeus of Cappadocia (2nd century AD) [3] in Caelius Aurelianus (5th century AD) [4], Paul of Aegina (625–690 AD) [5] and Avicenna (980–1037 AD) [6]. The first formal description of scurvy, however, is attributed to Hippocrates (Fig. 1); under the term “ileos ematitis” (“ειλεός αιματίτης”): “The symptoms of this disease are the following: the mouth feels bad; the gums are detached from the teeth; blood runs from the nostrils. Sometimes it develops with ulcerations on the legs; some of these heal, others not, and their color is black and the skin is thin” [7].

Other authors of the ancient world employ the use of terms such as “στομακακή” (stomakaki) and “σκελοτυρβή” (skelotirvi) [8], as it is described by Galen (129–199/217 AD) [9]. Pliny the Elder (23–79 AD) using the same terms when describing an illness that struck the Roman soldiers who were based in The Netherlands [10]. Marcellus Empiricus (3rd–4th c. AD), however, referred to scurvy using the term “*oscedo*” and recommended for its treatment the herb *Herba* Britannica [11], while Strabo (63/64 BC–24 AD) described the emergence of an epidemic of scurvy among the Roman troops in Arabia during the reign of Gaius Aelius Gallus [12]. Then until the end of the 14th century, no more reports about scurvy appeared, aside from two reports of an unknown disease like scurvy at the time of the crusades [13,14].

2. The first major exploration and scurvy at sea

Vasco da Gama (1460/69–1524 AD), famous Portuguese navigator, during his circumnavigation of Africa, noticed that many men fell sick showing swelling in the legs, arms and gums, and he also noticed that eating oranges had a beneficial effect [15].

The disease is generally described as “amalati de la boccha” (curse of the mouth), which subsided after the ship replenished fresh foods stocks [14], whereas other reports of scurvy cases come from a traveler Thomas Stevens (1579) [16], the Portuguese navigator Ferdinand Magellan (1480–1521 AD) [17], the English navigator Sir Francis Drake (1540–1596 AD) [18], the French explorers Jacques Cartier (1491–1557 AD) [19] and François Pyrard (1578–1623 AD); Pyrard also reported the results of autopsies in patients who died of scurvy [20]. In 1589, Richard Hakluyt (1552/1553–1616 AD), an English writer, in his work “Principal navigations” uses the word “scurvy” (“*skurvie*”) [21], whereas, in 1586, during the mission of Thomas Candish (1560–1592), similar incidents occurred pointing also the beneficial action of a herb called “*scurvygrass*” (*Cochlearia officinalis or curiosa*) [22].

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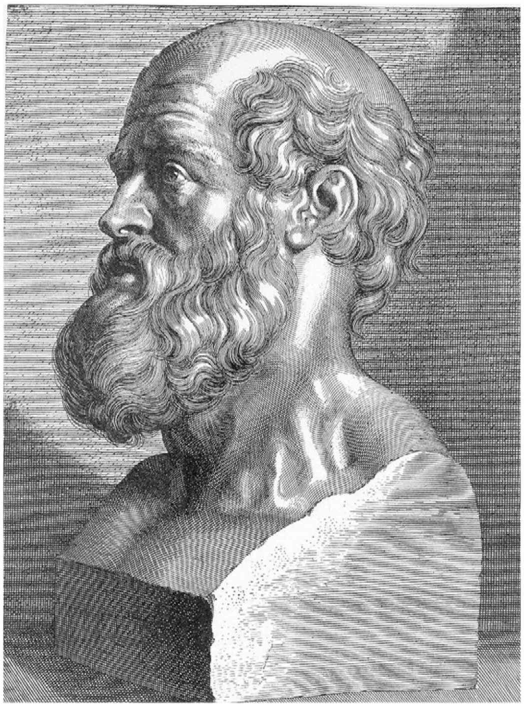

Fig. 1. Hippocrates (460–370 BC) [acquired by public domain at: http://commons.wikimedia.org/wiki/File:Hippocrates_Light.jpg].

Fig. 2. James Lind (1716–1794) [acquired by public domain at: http://oldjll.sustainabilityforhealth.org/trial_records/17th_18th_Century/lind/lind_portrait.html].

3. Scurvy during 16th–18th century — the work of James Lind (1716–1794)

During the time of the large explorations between 16th and 18th centuries, there were numerous reports of the disease in the contemporary medical literature. Among them the most important books are that by the Danish doctor Johannus Echthius, who first uses the word 'scorbutus' in 1556, the manual of Naval Medicine by the English surgeon William Clowes (1540–1604 AD) [23,24], the *Surgeon's mate* by the English military surgeon John Woodall (1570–1643 AD) [25], John Bachstrom's (1688–1742 AD) – a Dutch physician – *Observationes circa scorbutum* [26] and William Cockburn's – a Scottish physician – *Sea Diseases* [27].

The name of James Lind (Fig. 2), an officer of the British Royal Navy during the 18th century, is inextricably linked with the history of research into the disease. To determine which the most effective treatment for scurvy was, he carried out the first clinical trial using control groups of patients; he finally was able to conclude that eating lemons and oranges leads to a spectacular remission of the scurvy disease [28]. In 1753, Lind published his famous treatise on scurvy [29], in which he proposed the manufacturing of a lemon syrup [30]. However, a careful study of the method proposed by James Lind, based on current data, would lead to the manufacture of syrup with little nutritional value, since boiling destroys vitamin C.

4. James Cook (1728–1779) and the theory of "pneumatic chemistry"

The period from 1770 to 1815 is characterized as the period of "pneumatic chemistry," in which began the fundamental discovery that the air is a mixture of gases with different properties. Among those gases, carbon dioxide, under the term *fixed air*, can be dissolved in water and absorbed by chemicals in their solid phase [31].

James Cook, English navigator and explorer, is probably the second Englishman after James Lind whose name was closely connected with the history of scurvy. A careful study of the Cook's strategy reveals that at every opportunity James Cook replenished the food supplies of his ships with green vegetables, sweet potatoes and coconuts [32], a tactic which was confirmed by the accurate observations of James Cook on the diet of crews of different ships [33].

During the same time period, William Cullen (1710–1790 AD), a Scottish physician and chemist, will publish his observations [34] concerning the emission of carbon dioxide by heating limestone and its amount in living tissues [35] that lead to the flourishing of a new field in chemistry, that of *pneumatic chemistry*. A basic principle of this theory is that carbon dioxide is a factor in preventing putrefaction, and, therefore, can be applied in the treatment of scurvy, which is considered to belong to the putrefacting diseases [36].

Soon, however, this theory was proven to be incorrect. In 1786, Thomas Trotter (1760–1832), an English naval physician and author, indicated that the influence of different acids in the course of the disease is due to the ability of different features of various acids to provide the body with oxygen [37], a theory supported also by Thomas Beddoes (1760–1808 AD) [38].

5. The major epidemics of the 19th century: land scurvy and pediatric scurvy

One of the first outbreaks of land scurvy during the 19th century was recorded in the English prisons of Millbank in 1825 (Fig. 3) [39]. In an effort to investigate the causes that led to this outbreak, in 1843, William Bally discovered that those prisoners who developed scurvy were deprived of potatoes and onions in their daily diet [40]. This became more apparent during the potato famine (1845–1888), during which the absence of potatoes from the daily diet of the Irish and British people led to an increase of land scurvy [41].

Around the middle of the 19th century, major outbreaks of scurvy were recorded in California during the gold miner crisis (1848–1850), the Crimean War (1854–1856) and the American Civil War (1861–1865) [42–47]. During the Franco-Prussian War, cases of scurvy were reported during the siege of Paris (1870–1871) [48]. Ernest-Charles Lasègue (1816–1883), a physician at the Salpêtrière, and Alexis-Charles Legroux, a physician to Hotel who studied the occurrence of

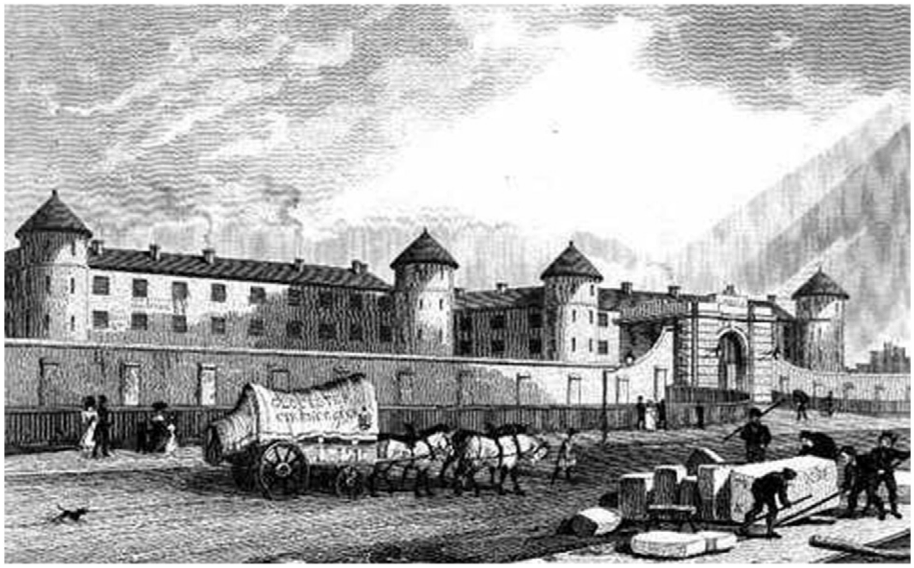

Fig. 3. Millbank prisons (19th century) [acquired by public domain at http://commons.wikimedia.org/wiki/File:Millbank_Thomas_Hosmer_Shepherd_pub_1829.jpg].

scurvy in prisons, established a link between the disease and physical inactivity proportionally to the enclosure time [49].

An alternative theory about the scurvy disease, entitled "Theory of reduced alkalinity" was proposed by a British chemist, Samuel Parkes (1759–1825), who claimed that scurvy results from an imbalance of acid and alkali within the human body [50,51].

Participants in polar exploration also wrote reports containing crucial observations on the disease. Sir William Edward Parry (1790–1855), an English rear-admiral and Arctic explorer, was the first to report cases of scurvy during his missions [52,53]. One of the most famous missions to conquer the South Pole is that of the British Royal Navy under the command of Robert Falcon Scott (1868–1912). Edward Wilson (1872–1912), the mission doctor, reported the first cases of scurvy especially during the first exploration missions [54], which were cured by providing patients with fresh seal meat [55].

The first outbreak of the disease in children was registered in French charities during the period from 1590 to 1640 [56] by William Clowes (1540–1604) [57] and Fabricius Hildanus (1560–1634) [58]. In 1877, the British pediatrician Walter Cheadle (Fig. 4) (1836–1910) diagnosed a case of scurvy in a boy aged 16 months. Cheadle will publish soon two major articles in *Lancet* in 1878 and 1882, emphasizing the absence of milk from the diet, and highlighting the need of fresh milk and mashed potatoes for the speedy recovery of young patients [59,60]. Scurvy in children was thereafter referred to as *Cheadle disease*, or *Barlow disease* in honor of the English physician Sir Thomas Barlow (1845–1945), who, in 1884, published the first comprehensive study on pediatric scurvy [61].

6. Studies of the 20th century, animal experiments and the discovery of vitamin C

The most important studies in the history of scurvy is that of Axel Holst (1860–1931) and Theodor Frolich (1870–1947) in 1907 [62].

In 1912, an English biochemist, Sir Frederick Gowland Hopkins (1861–1947), noticed that rats stopped growing when their diet was based exclusively on crude protein, fat, carbohydrates and salt, while they responded promptly by resuming their growth after receiving fresh cow milk [63]. During the same time, Casimir Funk (1884–1967) attributed scurvy, pellagra, rickets and beriberi to nutritional deficiencies of animal factors, calling them "vitamins" (vital amines) [64].

In 1916, two American biochemists, Elmer McCollum (1879–1967) and Cornelia Kennedy (1881–1969), announced the existence of a fat-soluble factor A and a water-soluble factor B that play an important role in rats' nutrition [65]. A year later, English biologist Hariette Chick (1875–1977), along with Margaret Hume (1887–1968), demonstrated the anti-scorbutic value of milk in guinea pigs that is directly related to its amount [66].

Since 1918, Sir Arthur Harden (1865–1940) and Sylvester Solomon Zilva, biochemists at the Lister Institute, started working systematically on the ascorbic factor of lemon juice [67]. In 1927, Hungarian physiologist, Albert Szent-Györgyi (Fig. 5) (1893–1986) isolated reducing factors from the adrenal glands of guinea pigs, which determined the chemical formula as $C_6H_8O_6$ [68] calling it "hexuronic acid" [69]. From 1928 to 1932, Szent-Györgyi concocted large quantities of hexuronic acid, while an American research team led by a biochemist, Charles Glen King (1886–1988), isolated the ascorbic

Fig. 4. Walter Cheadle (1836–1910) [acquired by public domain at http://hharp.org/library/gosh/gallery/doctors.html].

Fig. 5. Albert Szent-Györgyi (1893–1986) [acquired by public domain at http://profiles.nlm.nih.gov/WG/B/B/F/Y/].

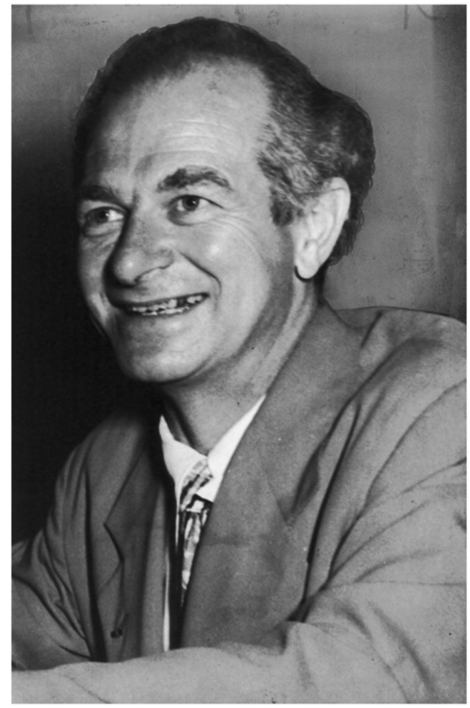

Fig. 6. Linus Pauling (1901–1994) [acquired by public domain at http://commons.wikimedia.org/wiki/File:Pauling.jpg].

factor from lemon juice, identifying it with hexuronic acid [70]. The final structure of vitamin C was published in 1933 by a research team in Birmingham, led by Reginald Herbert [71]. At the same time, the combined works of the British chemists Sir Walter Norman Haworth (1883–1950) and Hirst and of a Swiss research team under the guidance of Tadeusz Reichstein (1897–1996), led to the successful synthesis of ascorbic acid, today known as vitamin C [72–74].

The association between scurvy and ascorbic acid was established in individual studies [75,76], as well as other large multicenter studies in Great Britain [77] and in the United States [78], which also calculated the daily dietary needs for adults as a minimum of 45 mg of vitamin C. The discovery of ascorbic acid's antioxidant properties and its lack of toxicity revolutionized the food industry [79–82].

In 1968, the famous American chemist Linus Pauling (Fig. 6) (1901–1994), who was honored with two Nobel Prizes, supported the view that people suffering from schizophrenia show higher rates of metabolism of ascorbic acid and that large doses of vitamin C might be useful in the treatment of mental illnesses [83]. In his book *Vitamin C and the common cold* Pauling argues that taking 1 g of vitamin C every day prevents the common cold and that vitamin C protects against cardiovascular disease, stroke, cancer and various infections [84].

7. What we know today about vitamin C

It is now known that vitamin C plays an important role in biochemical reactions involving hydroxylation and especially in the biosynthesis of hormones and neuro-transmitters [85]. Those reactions are catalyzed by enzymes known as dioxygenases which employ bivalent ferrum ions as co-factors. The role of ascorbic acid in the biosynthesis of collagen is fully clarified today [85,86]. At least 27 different types of collagen have been described to date. Their molecules consist of 42 distinct polypeptide chains, and more than 20 different proteins have been described to be structurally homologous to collagen proteins. Vitamin C appears to be utilized in the synthesis of glypicans, especially proteoglycans, which are associated with the cell membrane. The main function of those molecules is to regulate interactions between receptor molecules and ligands; moreover, they may contribute significantly to growth and the organism's development [87]. Ascorbic acid also works with redox reactions within cells, since *in vivo* studies appear to link the increase in concentration of ascorbic acid in mitochondria with an increase in dietary content of vitamin C [88,89]. Vitamin C seems to help the reduction of the reactive oxygen species (*ROS*) through oxidation of dehydroascorbic acid [90]. Thus ascorbic acid has anti-apoptotic activity [91] and the increased concentration of ROS seems to be associated with mitochondrial diseases [92], a situation which can be treated with vitamin C [92,93].

In addition to mitochondria, ascorbic acid appears to be associated with the endoplasmic reticulum (*ER*). The L-glyconolactone oxidase seems to catalyze the aerobic transformation of glyconolacton to ascorbic acid with simultaneous production of hydrogen peroxide [94,95]. The role of ascorbic acid in the ER appears to be related with the absorption of ROS, which, in turn, propagate redox reactions within the ER [96]. Under certain conditions, it appears that ascorbic acid may work as a pro-oxidant, as well [97]. This role seems to be particularly harmful, since it may lead to the formation of ROS [98] and glycosylated proteins [99]. However, the role of ascorbic acid in thiol oxidation in rat mitochondria appears to be beneficial [100–102].

In different studies ascorbic acid is added in treatment protocols in combination with other drugs, dietary antioxidants or antioxidant supplements and, therefore, it is not possible to clearly identify its role. In addition, data obtained and the conclusions of the studies are conflicting. There is also no consensus about the therapeutic effects and dosage of vitamin C, and in many studies, small differences recorded between the group receiving vitamin C in comparison to the control groups are not reliable due to the number of participating patients. There are also significant differences in the route of dispensation of vitamin C (per os or intravenously) [90]. Nowadays, although scurvy tends to become a forgotten disease, rare cases do occur especially in people undergoing extreme diets, neglected elder people or kids with poor diet [103–106]. Although vitamin C is considered to be an essential nutrient, several aspects of its use remain a mystery [107]; several randomized controlled trials have shown no effect of antioxidant supplements on hard endpoints such as morbidity and mortality [108]. Further research will be needed in order to fully elucidate the role of vitamin C and its therapeutic role.

Learning points

- Scurvy is a disease as old as human existence.
- First reports on scurvy can be traced back to ancient Egyptian medical papyri and in the texts of Hippocrates.
- Numerous cases of scurvy and outbreaks were recorded during the naval explorations by Portuguese and English navigators.
- James Lind and James Cook are two of the most important figures in the history of the disease during the 17th and 18th centuries.
- The first cases of land scurvy were recorded during the 19th century in the English prisons of Millbank, during the potato famine in Ireland, the Crimean and American Civil War.
- The pediatric scurvy was described for the first time by the British pediatrician Walter Cheadle during the 19th century.
- In 1927, Hungarian physiologist, Albert Szent-Györgyi isolated the ascorbic factor, vitamin C.
- Nowadays, it is well known that vitamin C plays an important role in biochemical reactions involving hydroxylation and especially in the biosynthesis of hormones and neuro-transmitters.
- Ascorbic acid also works with redox reactions within cells.
- Future research on the vitamin C should focus on *in vitro* activity of various physiological and pathological processes, particularly those associated with mitochondrial diseases and alterations of functions of the endoplasmic reticulum.

Conflict of interest

The authors declare no conflict of interest.

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