# The evolution of a neglected disease: tuberculosis discoveries in the centuries

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## Keywords

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## Summary

*Tuberculosis (TB) and humans have coexisted for more than 40,000 years. The word "tuberculosis" derives from "tubercle", the histological lesion which appears in the organs, described by Pott in the late Eighteenth century and found, by molecular biology, in human skeletons dating back to 5000 BC. Early description of TB can be found in the writings of ancient India and China and in the Bible.*

*In ancient Greece tuberculosis was not considered contagious, but Aristotle recognized the contagious nature of the pig's and ox's scrofula. The suspicion that phthisis is a contagious disease and that isolation can reduce the risk of transmission was expressed for the first time by the Arabian Avicenna, in his work "The canon of medicine". In 1699, the Health Council of the Republic of Lucca founded the "sanatorium" concept as place of care and isolation. In 1865 Villemain inoculated tubercular material from a human lymph node into a rabbit, obtaining for the first time the typical tubercular lesions. Some years later, on March 24, 1882, Robert Koch announced to the Berlin Society of Physiology the discovery of Mycobacterium tuberculosis. In the same period Virchow improved awareness of risk factors and correct behaviours among the general population.*

*In 1952 Waksman won the Nobel Prize for the discovery of the first active drug against TB: streptomycin. Nevertheless, drug resistance appeared rapidly some years later and it is still a great challenge in TB fight nowadays.*

Tuberculosis (TB) and humans have coexisted for more than 40,000 years, since *Mycobacterium prototuberculosis*, supposed ancestor of the *Mycobacterium tuberculosis complex* (MTBC), reached the Fertile Crescent. Then, evolving and differentiating into various lineages, it followed the main human migration routes to the present day [1] (Fig. 1).

The word "tuberculosis" derives from "tubercle", the histological lesion which appears in the organs affected by the infection, first described by Sylvius in 1650.

The disease was christened "tuberculosis" by J. Schoenlein in 1839 and later it was observed in the bone by Pott in the late eighteenth century [2]. Tuberculous lesions attributable to Pott's disease were found, by molecular biology, in human skeletons dating back to 5000 BC, as well as in Egyptian mummies of 4000 BC [3].

Oddly enough, despite the high incidence demonstrated by paleo-infectious studies, TB has never been reported in Egyptian papyruses, unlike urinary schistosomiasis and in the same way of smallpox [2, 4]. A description of TB can be found in the writings of ancient India and China, respectively dated around 3300 and 2300 years ago [5, 6].

A clear description of the clinical presentation of TB, "schachepheth" in ancient Hebrew, is found in the books Deuteronomy and Leviticus of the Bible [10]

In ancient Greece, the "phthisis" was a well-known disease described in written testimonies of Herodotus (5th century BC) and in the Hippocratic "Corpus" (III century BC), both characterized by representing with great precision the clinical outset of the disease.

Furthermore, writings were rediscovered that meticulously describe tubercular lesions, the destruction of the lung tissue and the subsequent chronic process accountable for the progressive consumption of patients affected [7].

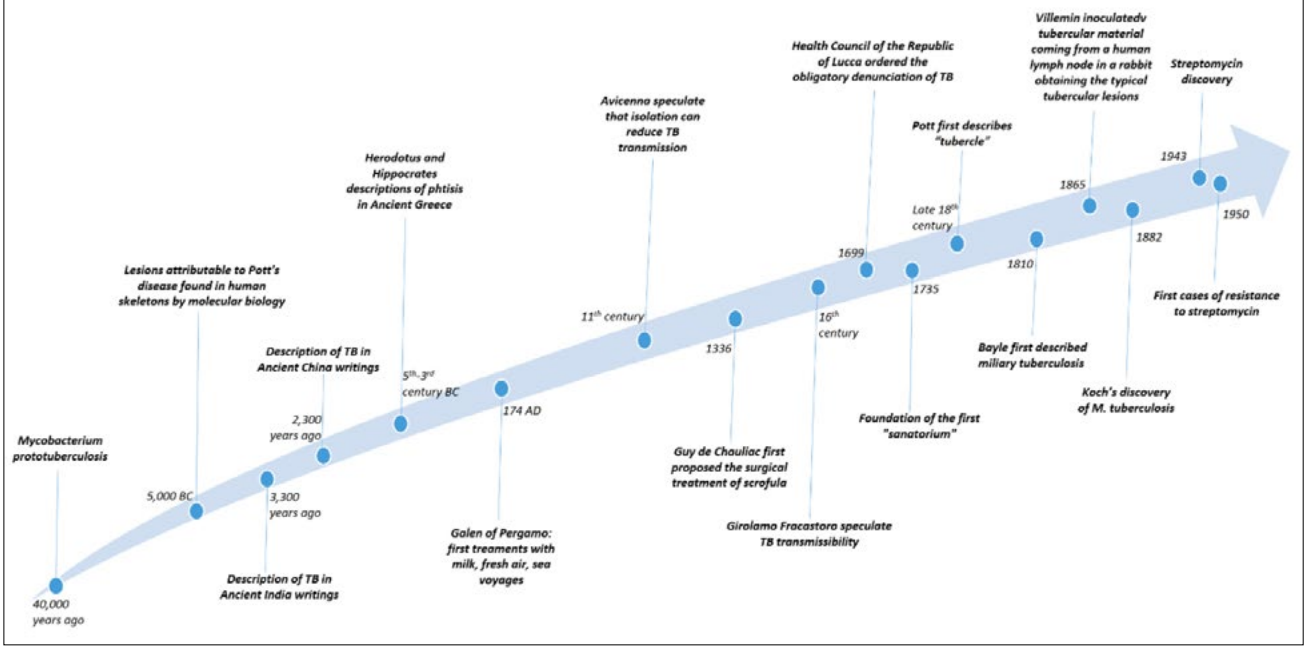
Although at that time the disease was not yet considered contagious, in a passage from his writings Isocrates (4th century BC) wrote about some doubt creeping into the minds of scientists, while Aristotle still recognized only the contagious nature of the pig's and ox's scrofula.

In Roman times, TB is mentioned by Celso, Areteo of Cappadocia and Celio Aureliano. In the complete works of Galen of Pergamum, personal physician of the Roman emperor Marcus Aurelius since 174 AD, a first attempt to treat TB based on milk, fresh air and sea voyages is reported [8].

The Authors of the classical age did not come to understand that even the extrapulmonary manifestations of the disease, such as scrofula, Pott's disease, and tubercular lupus, were to be ascribed to a single etiological agent.

In the following centuries, the Byzantine physicians Alessandro di Tralles, Ezio di Amida and Paolo di Egi-

Fig. 1. Timeline of the main events that characterized tuberculosis' history since its first appearance until the discovery of streptomycin.




na, also described the pulmonary and glandular forms of TB in their treatises. In the Arab world, Avicenna, in his "The canon of medicine", spoke about TB as an "ulcerative, excavating, and summary" disease, and expressed the suspicion that phthisis is a contagious disease. Avicenna was the first to suppose that diabetes was a risk factor for the development of TB and to suggest that the isolation of patients with overt pathology could reduce the risk of transmission [9].

In medieval times, 1336, the French surgeon Guy de Chauliac first proposed the surgical treatment of scrofula by the "myrtle leaf" incision [11].

TB etiology was not known and also therapy was not so clear. In the Middle Ages, it was widely believed that the kings of England and France could cure scrofula simply by touching those affected. To have a clear definition of TB as a contagious disease, we have to wait until the 16th century, when Girolamo Fracastoro, father of the "doctrine of contagion", hypothesized its transmissibility.

The spread of this news created panic among people who began to treat persons with scrofula in the same way as lepers [12]. In 1699, the Health Council of the Republic of Lucca ordered the obligatory denunciation of "persons of any sex and condition affected by etisia" and, in 1735, ordered the isolation and treatment of the consumptives, but forbade their hospitalization in common hospitals, laying the foundation of the "sanatorium" concept as place of care and isolation [13].

In 1671, Franciscus de La Boe recognized the same nature for pulmonary tubercles and scrofula, and he attributed the condition of "tisi" to the suppuration of tubercles in the lung parenchyma, with the formation of caves.

In 1761, Leopold Auenbrugger refined the semiotics of the chest with his treatise on percussion "Inventum novum", facilitating the diagnosis of pulmonary TB [14].

Between the eighteenth and nineteenth centuries in England, due to the increasing incidence of the pathology during the industrial revolution, a great scientific fervour led authors like Willis, Morton, Marten to spread the knowledge of TB [15].

At that time it also became known as the great white plague and the white death, called "white" because of the extreme anaemic pallor of those affected. This term could be also due to its association with youth, innocence and even holiness. Consumptive patients were more frequently affected by TB in case of malnutrition, unsanitary environment and living conditions, that were common risk factors.

In 1810, Bayle was the first to distinguish several anatomopathological entities, describing the presence of tubercles in organs other than the lung and recognizing their possible dissemination to the whole organism, defining it as "miliary tuberculosis".

Louis, supported by 167 autopsies, showed that the tubercles were a specific reaction, where inflammation had only an accessory role [16]. However, Virchow denied the specific nature of the tubercle and, due to his scientific authority and credibility, he delayed the acceptance of a unitary conception of tuberculosis according to what Laennec affirmed.

There was no lack of those who believed in the hereditary character of the disease, such as Linnaeus, who however also argued that pulmonary phthisis was caused "by a real invisible germ of contagion".

A further step forward in thoracic semeiotics was made by Laennec with the invention of auscultation mediated

with the stethoscope, further refining the semiology of the thorax. On December 5, 1865, Villemin informed the French Academy that TB is the effect of a specific causal agent, which he called "virus"; he supported his assertion by the inoculation into a rabbit of tubercular material coming from a human lymph node, obtaining, after some weeks, the typical tubercular lesions in the rabbit [17].

On March 24, 1882, Robert Koch announced to the Berlin Society of Physiology the discovery of *Mycobacterium tuberculosis* and described it with the following words: "Thin, whose length is half-a-quarter of the diameter of a red blood cell, very similar to the lepers' bacillus, but sharper". Once again, Virchow advanced some perplexity on the discovery as the sole explanation for the disease, correctly proposing a larger panel of factors such as poverty, malnourishment, scarce hygiene etc as relevant factors for the development of the disease.

Two German doctors, the bacteriologist Franz Ziehl and the pathologist Friedrich Neelsen first introduced Ziehl-Neelsen stain, demonstrating the typical appearance of acid-fast bacilli.

In the following years, Koch's discovery of the causal agent of TB opened the chance both for the Pasteurian prevention based on the attenuation of the germ and for the search for therapy through the serum of sick people [16], while Virchow's opinions generated also large public health campaigns to improve awareness of risk factors and correct behaviours among the general population.

In 1908, the French scientists Albert Calmette and Camille Guerin grew Koch's bacillus in several mediums to decrease their virulence and increase the capacity to produce immunity.

The BCG vaccine was first used in humans in 1921 when it was given to a child in Paris by Dr Weil-Hale. The baby's mother and grandmother, who had tuberculosis, died just after the baby was born. The baby was given 6 mg. of BCG orally, and he grew in a good health status.

The first active drug against TB to be discovered was streptomycin in 1943, thanks to Waksman who won the Nobel Prize for Physiology and Medicine in 1952 [18]. Unfortunately, since the first streptomycin trial carried out in London in 1950, it became evident that the emergence of drug-resistance appeared rapidly and constituted a contraindication to antibiotic monotherapy [19-21].

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## Conflict of interest statement

The authors declare no conflict of interest.

## Authors' contributions

NR and MM conceived the study, NR, DC, MM, GB drafted the manuscript, NR, DC, ADB revised the manuscript, NR, DC, MM, IB performed a search of the literature, LC, MMD, NR, GB, IB, NLB and ADB revised critically the manuscript. All authors read and approved the last version of the manuscript.

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