Overview

The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus

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Keywords

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Summary

Tuberculosis (TB) is a contagious, infectious disease, due to Mycobacterium tuberculosis (MT) that has always been a permanent challenge over the course of human history, because of its severe social implications. It has been hypothesized that the genus Mycobacterium originated more than 150 million years ago. In the Middle Ages, scrofula, a disease affecting cervical lymph nodes, was described as a new clinical form of TB. The illness was known in England and France as "king's evil", and it was widely believed that persons affected could heal after a royal touch. In 1720, for the first time, the infectious origin of TB was conjectured by the English physician Benjamin Marten, while the first successful remedy against TB was the introduction of the sanatorium cure. The famous scientist Robert Koch was able to isolate the tubercle bacillus and presented this extraordinary result to the society of Physiology in Berlin on 24 March 1882. In the decades following this discovery, the Pirquet and Mantoux tuberculin skin tests, Albert Calmette and Camille Guérin BCG vaccine, Selman Waksman streptomycin and other anti-tuberculous drugs were developed.

Introduction

Tuberculosis (TB) is a contagious, infectious disease, due to *Mycobacterium tuberculosis* (MT), which usually lasts throughout the life course and determines the formation of tubercles in different parts of the body [1]. MT has very ancient origins: it has survived over 70,000 years and it currently infects nearly 2 billion people worldwide [2]; with around 10.4 million new cases of TB each year, almost one third of the world's population are carriers of the TB bacillus and are at risk for developing active disease [3].
TB has always been associated with a high mortality rate over the centuries, and also nowadays, it is estimated to be responsible for 1.4 million TB deaths, among infectious diseases after human immunodeficiency virus (HIV) [3].
Due to its infectious nature, complex immunological response, chronic progression and the need for long-term treatment, TB has always been a major health burden; in more recent years, the appearance of multi-drug resistant forms and the current TB-HIV epidemic, associated with its severe social implications, treating and preventing TB have represented a permanent challenge over the course of human history [4, 5].

Ancient times: the first historical records

It has been hypothesized that the genus *Mycobacterium* originated more than 150 million years ago. *Mycobacterium ulcerans,* causing infections since ancient times, requires specific environmental conditions as reflected nowadays in its distribution worldwide [6].
Three million years ago, an early progenitor of MT might have infected early hominids in East Africa [7] and 20.000-15.000 years ago, for the first time, the common ancestor of modern strains of MT might have appeared [8, 9].
Egyptian mummies, dating back to 2400 BC, reveal skeletal deformities typical of tuberculosis; characteristic Pott's lesions are reported and similar abnormalities are clearly illustrated in early Egyptian art [10, 11].
Nevertheless, no evidence about TB lesions is reported in Egyptian papyri. The first written documents describing TB, dating back to 3300 and 2300 years ago, were found in India and in China respectively [12, 13].
Other written documents connected to TB are related to the Hebraism. The ancient Hebrew word *schachepheth* is used in the Biblical books of Deuteronomy and Leviticus in order to describe TB [14]; in the same period, in the Andean region, archeological evidence of early TB, including Pott's deformities, was provided by Peruvian mummies, suggesting that the disease was present even before the colonization of the first European pioneers in South America [15-18].
In the Ancient Greece TB was well known and called Phtisis. Hippocrates described Phtisis as a fatal disease especially for young adults, accurately defining its symptoms and the characteristic tubercular lung lesions.

Excellent discoveries of the early scientists who studied TB were made in the same period: in Greece, Isocrates was the first author supposing that TB was an infectious disease, while Aristotle suggested the contagious nature of "king's evil" in pigs and oxes [19].
In Roman times, TB is mentioned by Celso, Aretaeus of Cappadocia and Caelius Aurelianus, but it is not recognized as sharing the same etiology of extrapulmonary manifestations such as scrofula, Pott's disease and TB lupus.
According to the Greek Clarissimus Galen, who became personal physician of the Roman Emperor Marcus Aurelius in 174 AD, the symptoms of TB include fever, sweating, coughing and blood stained sputum; he recommended fresh air, milk and sea voyages as successful treatments for the disease [20-22].
After the decline of the Roman Empire, TB was widespread in Europe in the VIII and XIX centuries, as witnessed by several archaeological findings [23].
The Byzantine doctors Aetius of Amida, Alexander of Tralles and Paul of Aegina described the pulmonary and glandular forms of TB [24], while in the Arabic Empire, Avicenna supposed the contagious nature of TB.

Middle Ages and Renaissance time: the "king's evil" and the discovery of extra pulmonary TB

In the Middle Ages, scrofula, a disease affecting cervical lymph nodes, was described as a new clinical form of TB. The illness was known in England and France as "king's evil", and it was widely believed that persons affected could heal after a royal touch [25].
In the 12th century, William of Malmesbury reported complementary treatments including visits at royal tombs, the kings' touch or the use of a coin-talisman.
The practice of the king's touch established by English and French kings continued for several years. Queen Anne was the last English monarch to use this practice (1712), George I put an end to it in 1714, while in France it continued up to 1825 [26].
In the Middle Ages, moreover, the French surgeon Guy de Chauliac (1363) for the first time proposed a healing intervention for the cure of the "king's evil" [27].
Guy de Chauliac was also strongly in favour of the removal of scrofulous gland with an engraving, as recommended by Paul of Aegina, who advised the surgical removal of the diseased gland, taking care not to harm vessels or nerves of which the neck region is rich [28].
As far as concerns the contagious nature of TB, a clear definition was first given by Girolamo Fracastoro in the sixteenth century [29].
The exact pathological and anatomical description of the disease was illustrated in 1679 by Francis Sylvius, in his work *Opera Medica*, in which he describes tubercles, their progression to abscesses, cavities and empyema in the lungs and in other sites of consumptive patients [30].
Short afterwards, in Italian health law, in particular in an edict issued by the Republic of Lucca in 1699, there is the first official reference to the infectious nature of the disease [31]. In 1735 the Health Board of the Republic ordered the compulsory notification and isolation of consumptives, forbidding their admission in public hospitals, and establishing specific places for their treatment [29].

XVIII-XIX centuries: the infectious theory and the isolation of the Koch bacillus

In 1720, for the first time, the infectious origin of TB was conjectured by the English physician Benjamin Marten, in his publication "A new theory of Consumption". For the early eighteenth century, Marten's writings display a great degree of epidemiological insight [32].
Both terms consumption and phthisis were used in the 17th and 18th centuries, until in the mid-19th century Johann Lukas Schönlein coined the term "tuberculosis" [33].
In the 18th century in Western Europe, TB had become epidemic with a mortality rate as high as 900 deaths per 100,000 inhabitants per year, more elevated among young people. For this reason, TB was also called "the robber of youth".
During the industrial revolution, the diffusion of particularly problematic social conditions, such as extremely deprived work settings, poorly ventilated and overcrowded housing, primitive sanitation, malnutrition and other risk factors, were intimately associated with the disease [26].
In 1838-39, up to a third of English tradesmen and employees died of TB, whereas the same proportion decreased to a sixth in the upper class [34].
The extreme anemic pallor of people affected by TB was at the origin of the new term "white plague", coined during the 18th century [20, 35].
One hundred years later, TB was defined as "Captain of All These Men of Death" because of its epidemic proportions in Europe and North America, determining one in four deaths.
At the beginning of the 19th century, there was a large scientific debate about different theories concerning the etiopathological origin of phthisis, arguing whether it might be considered: an infectious disease – as generally considered in Southern Europe – an hereditary one – as stated in Northern Europe – or a form of cancer. On the other hand, the discussion was about scrofula, tubercles, and phthisis as separate disease entities or manifestations of the same illness [26].
In 1793, the caseous necrosis, "cheese-like", phthisic abscesses were named "tubercles" by the Scottish pathologist Matthew Baille [36].
In 1810, the French physician Gaspard-Laurent Bayle of Vernet described the disseminated "miliary" TB in his work *Recerches sur la phthisie pulmonaire*, recognizing TB not only as a disease affecting the lung, but a generalized one, clinically defined by coughing, difficulty in breathing, fever and purulent expectoration [37, 38].
In 1819, the French Theophile Laennac identified the presence of consolidation, pleurisy and pulmonary cavitation as pathognomonic signs of pulmonary or extrapulmonary TB [33]. *Mycobacterium tuberculosis* most commonly affects the respiratory tract, but it could also

infect gastrointestinal, bones, joints, nervous systems, lymph nodes, genitourinary tract and skin with inflammatory infiltration, caseation, necrosis, abscesses, fibrosis, formation of tubercles and calcification [39, 40].
He recognized tubercles as the characteristic signs of the first phase of phthisis. He described their first appearance in the lungs, in their "miliary" ("millet seed-like") form, their progressing to larger tubercles containing "cheese-like" ("caseous") material, their breakdown into pus, and eventually forming cavities and empyema.
Extra-pulmonary phthisic tubercles were recognized in the intestines, liver, meninges and other organs, as also described by Sir Percivall Pott, a British surgeon that in 1779 defined as "Pott's disease" the vertebral collapse and spinal cord paralysis caused by TB infection [33, 36, 37, 41, 42].
In 1843, the German physician Philipp Friedrich Hermann Klencke succeeded in the experimental reproduction of human and bovine forms of TB, causing generalized TB in rabbits, through a successful inoculation of material from a miliary tubercle into their liver and lungs [27].
In 1849 Lebert, publishing his work *Traite Pratique des Maladies Scrofuleuses et Tuberculeuses*, suggested that the "King's evil" was a childhood disease that might cause suppuration and ulceration of different body's sites such as skin, ears, eyes, joints, bones, with a different pathogenesis from TB [43].
The first successful remedy against TB was the introduction of the sanatorium cure, described for the first time in 1854 in the doctoral dissertation "Tuberculosis is a curable disease" by Hermann Brehmer, a botany student suffering himself from TB, who reported his healing after a travel to the Himalayan Mountains [44].
Afterwards Brehmer founded an institution in Gorbersdorf, a mountain town situated in a fir forest, in order to cure patients with continuous fresh air and good nutrition. The subsequent sanatoria were built with the same setup and permitted to cure a lot of TB patients in the next decades [45].
The infectious nature of TB was demonstrated in 1865 by Jean-Antoine Villemin, a French military surgeon at the Army Medical School.
He formulated his hypothesis observing that TB was more frequent among soldiers who stationed for long times in barracks than among those in the field.
He also highlighted how healthy army recruits coming from the countryside often became consumptive some months after the beginning of their service.
Villemin's experiments consisted in inoculating a rabbit with "a small amount of purulent liquid from a tuberculous cavity" removed at autopsy from an individual died of TB [20].
As described in Villemin's work *Cause et nature de la tuberculose: son inoculation de l'homme au lapin,* the inoculated animal remained alive and no disease signs were discovered, but at autopsy, three months later, extensive TB was evident [46].
Villemin suggested that phthisis could be similar to glanders, an infectious disease in horses [20, 34, 36, 37, 47].
The infectious theory was well documented in Villemin's work *Études sur la tuberculose. Preuves rationelles et expérimentales de sa spécificité et de son inoculabilité*, dated 1868 [48], in which he stated the presence of TB-like illnesses in different animals [49].
The author also noticed that more crowded urban areas had a higher prevalence of TB and that some parts of the world, like New Zealand and Australia, seemed to have not known TB until the arrival of pioneers.
Some years later, in 1867, Theodor Albrecht Edwin Klebs was one of the early scientists to try to isolate the TB bacillus, sowing tuberculous material on egg white, stored in sterile flasks.
In his experiments, the culture was quickly muddy and it was possible to recognize mobile bacilli, which, after inoculation into the peritoneal cavity, caused the disease in Guinea pigs [50].
The famous scientist Robert Koch was able to isolate the tubercle bacillus. Using the methylene blue staining recommended by Paul Ehrlich, he identified, isolated and cultivated the bacillus in animal serum. Finally he reproduced the disease by inoculating the bacillus into laboratory animals [51].
Robert Koch presented this extraordinary result to the Society of Physiology in Berlin on 24 March 1882, determining a milestone in the fight against TB [52].
In the decades following this discovery, the Pirquet and Mantoux tuberculin skin tests, Albert Calmette and Camille Guérin (BCG) vaccine, Selman Waksman streptomycin and other anti-tuberculous drugs were developed. Koch contributed also to the elucidation of the infectious etiology of TB and for his scientific results, he was awarded the Nobel prize in Medicine in 1905 [33, 51].
Nowadays TB is still a major public health problem, for this reason a combined strategy, based on improving drug treatment, diagnostic instruments, and prevention strategy, is necessary, in order to eradicate *M. Tuberculosis* by the year 2050, as committed by the World Health Organization (WHO) [53].

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Authors' contribution

MM conceived and designed the overview. IB and LG performed a search of the literature and contributed to the draft of the article. NLB revised critically the manuscript. MM supervised the manuscript. All authors read and approved the final version of the manuscript.

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