



REVIEW

Tuberculosis: a timeless challenge for medicine

E. ARMOCIDA¹, M. MARTINI^{2,3}¹ Department of Medicine and Surgery, University of Parma, Italy; ² Department of Health Sciences, University of Genoa, Italy;³ Unesco Chair “Anthropology of Health - Biosphere and Healing System” University of Genoa, Italy

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Summary

This overview shows how tuberculosis has represented and still represents a continuous challenge for Medicine. Starting from the dawn of medicine, when tuberculosis was called “phthisis” by Hippocrates, passing through the discovery of the tubercles and the creation of the word “tuberculosis”, following the application of the anatomo-clinical method, until the discovery of a microscopic enemy: Mycobacterium tuberculosis. The progressive discovery of the pathological basis of tuberculosis has allowed to devise important therapeutic strategies

in Pre-Antibiotic and Post-Antibiotic Era. In particular, “antibiotic therapy” had to be the end of the challenge between man and tuberculosis. However it was only an illusion. Despite progress in care and prevention, tuberculosis remains one of the world’s leading causes of ill-health and the first cause of death from infectious disease. Nowadays, the drug resistance, individuals with immune deficiencies, the ageing and globalization are just some of the causes responsible for the increasing of the challenge between man and tuberculosis.

Tuberculosis in the history of infectious diseases

History of Medicine is not a discipline destined to culturally enrich only those who work in the health sector. All historians know very well how some medical events have influenced the course of history. In particular, infectious diseases, being interconnected with geo-political, social, economic and war-related issues, have an important historical significance [1]. Some of the classic examples are the plague epidemics that occurred in the 6th, 14th and 17th centuries [2], syphilis considered as the disease imported from the new world [3], the pandemic Spanish influence of 1918 [4] and now the pandemic SARS-CoV-2 (COVID-19).

The diseases listed above have dramatically marked the history of humanity, with events that can be clearly defined with a start date and an end date, except for the COVID-19 which is still ongoing now. Other pathologies, such as malaria [5, 6] and schistosomiasis [7], have taken root as endemic diseases and they have been timeless enemies for some peoples.

Tuberculosis (TB) is an ancient scourge. It has plagued humankind throughout known history and human prehistory. It has surged in great epidemics and then regressed, thus acting like other infectious diseases, but with a time scale that challenges accepted explanations for epidemic cycles. *Mycobacterium tuberculosis* may have killed more persons than any other microbial pathogen [8].

The coexistence of man and tuberculosis: historical and social aspects

Modern strains of *Mycobacterium tuberculosis* appear to have originated from a common ancestor about 15,000-20,000 years ago [9, 10].

The first tuberculosis infections are demonstrated in the most ancient civilizations. Tuberculosis in Egypt has been documented more than 5,000 years ago.

Skeletal abnormalities associated with tuberculosis, including characteristic Pott’s deformities, have been found in Egyptian mummies (confirmed by DNA analysis in mummified tissues) and are clearly depicted in early Egyptian art.

Tuberculosis is clearly noted in the Biblical books of Deuteronomy and Leviticus, however, using the ancient Hebrew word “schachepheth” [8].

In the collective imagination, people living in a condition of socio-economic decay become ill with tuberculosis; this association could have been decisive to create the “Pulcinella” character, a stereotype of the poor peasant.

“Pulcinella”, mainly known in the English-speaking world as “Mr Punch”, is a character from the Italian *Commedia dell’Arte*, whose origins can be traced back to protagonists of Roman Atellan comedy (e.g. Maccus or Bucco), whose grotesque appearances closely resemble the 16th century Neapolitan mask.

This character, as we know him today, originated in Naples (city sadly known for tuberculosis epidemics), most likely representing a poor and hungry, ready to steal food even at the cost of cheating and lying [11, 12].

This character may well be analyzed in an ethnological and anthropological fashion, with his distinctive physical appearance being exaggeratedly hook-nosed, back-humped, and with a paunch/ lumbar lordosis. A similar spinal deformation may be caused by tuberculosis in its form known as Pott’s disease, the most widespread tubercular osteo-articular presentation, capable of affecting every segment of the rachis, albeit more commonly the lowermost section of the thoracic column and the lumbar tract [12].

Traditional puppets with social and somatic characteristics similar to those of “Pulcinella”, a poor peasant with a hump, are present in the folklore of different European states.

Ancient Medicine: when tuberculosis was called phthisis

In the history of medicine, tuberculosis is well suited to study the epistemological path of medical thought, from its origins to the present day.

Tuberculosis was well known by Hippocrates, who is universally recognized as the father of medicine. He clearly recognized tuberculosis, where it was called phthisis, and understood its clinical presentation. “Phthisis makes its attacks chiefly between the age of eighteen and thirty-five,” he wrote in his aphorisms, clearly recognizing the predilection of young adults for active tuberculosis [13]. “Consumption was the most considerable of the diseases which then prevailed, and the only one which proved fatal to many persons,” he wrote in Book I, *Of the Epidemics* [14]. Another Greek physician who has a pivotal role in the history of medicine is Clarissimus Galen. He became physician to Roman Emperor Marcus Aurelius in 174. He wrote of tuberculosis and recommended fresh air, milk, and sea voyages for its treatment, but the disease does not have prominence in his medical texts [8].

The anatomical revolution in the history of tuberculosis

With the beginning of the Middle Ages, scientific progress stopped, even in the medical field. Hippocratic and Galenic knowledge was studied and applied to clinic in a dogmatic manner, being considered absolute truths.

Although starting from the 14th century, Mondino de Liuzzi (1275-1326) began to verify on cadavers the notions handed down by the fathers of medicine, thus starting the experimental sciences.

It has been necessary to wait centuries before the scientific approach had a confirmation in clinical practice and thus physicians abandoned humoral theories. In the study of tuberculosis the transition from the dogmatic to the experimental approach has been particularly slow.

In the 17th century Marcello Malpighi (1628-1694) introduced the use of the microscope in anatomy.

Thanks to this instrument he was able to describe the anatomical structure of the lung [15].

In 1689 the English physician Richard Morton (1637-1698), contemporary of Malpighi, was the first to state that tubercles were always present in the lungs suffering from phthisis [16].

As the result of 900 post-mortem investigations, in 1810 Gaspar Laurent Bayle (1774-1816) described that tubercles could also be detected in organs other than the lung [17, 18]. Thanks to the incessant study of corpse René Théophile Hyacinthe Laennec (1781-1826), who was a colleague to Bayle, laid the foundation for a modern clinic understanding of tuberculosis [8, 19].

In 1819 he published a treatise that not only clearly expounded the pathology of tuberculosis unifying the concept of the disease, whether pulmonary or extrapulmonary, but also described most of the physical signs of pulmonary disease, introducing terms to describe those findings that are still in use today [20].

In 1839 Johann Lukas Schönlein (1793-1864) coined the term “tuberculosis” replacing the terms consumption and phthisis that were used in the 17th and 18th centuries [21].

The discovery of a microscopic enemy: *Mycobacterium tuberculosis*

Although many important anatomopathological and clinical aspects of the tuberculosis were clarified, its etiopathogenesis remained unknown.

In Northern Europe tuberculosis was generally considered a heritable disease; in Southern Europe it was felt to be infectious in nature.

That tuberculosis was, indeed, infectious in nature was probably first suggested in 1720 by Benjamin Marten (c. 1690-1752), who attributed the disease to “some certain species of animalcula” [22]. The infectious nature of phthisis was demonstrated in 1865 by Jean-Antoine Villemin (1827-1892), a French military surgeon at the Army Medical School.

He formulated his hypothesis observing that tuberculosis 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. He infected a rabbit with “a small amount of purulent liquid from a tuberculous cavity” removed at autopsy from an individual who had died of tuberculosis [21].

On the evening of March 24, 1882, Robert Koch (1843-1910) presented the discovery of the infectious cause of tuberculosis at the Berlin Physiological Society.

Koch summarized the importance of his findings, for which he received the 1905 Nobel Prize, in a manuscript published in the *Berliner Klinische Wochenschrift* shortly after his announcement: “In the future the fight against this terrible plague of mankind will deal no longer with an undetermined something, but with a tangible parasite, whose living conditions are for the most part known and can be investigated further” [23, 24].

Koch’s studies on tuberculosis are a milestone in the history of medicine: they inaugurated the beginning of the reign of bacteriology in hygiene.

The social history of medicine has placed Koch’s early work on tuberculosis at the outset of the bacteriological era in hygiene and public health that led to the “medicalization” of entire societies in the late 19th century.

The new bacteriologists’ conception of the pathogens stripped epidemics of any political meaning, turned them into exclusive objects of scientific investigation, lending legitimacy to extended positivism based on medical expertise [25].

Tuberculosis therapy in the Pre-Antibiotic Era

Despite the fundamental diagnostic advances that occurred in the nineteenth century, therapeutic solutions for tuberculosis were still immature.

In the second half of the 19th century, it was a common conviction that specific climatic environments could contribute to cure tuberculosis. Subsequently, the most frequently prescribed remedy for pulmonary forms was a stay in a temperate climate.

In Europe, the first sanatorium was founded in 1854 by Hermann Brehmer in Germany, in Goebersdorf in Slesia, a village on the border between Poland and the Czech Republic. Brehmer stressed the therapeutic effect of the climate in the treatment of phthisis.

The sanatorium regimen planned to cure tuberculosis with Galenic principles of hygiene: isolation, fresh air, exercise and good nutrition.

Eminent physicians supported these remedy for the treatment of the most serious forms of the disease for a few decades [26].

People suffering from tuberculosis became often ill also because of their socio-economic conditions. The correct lifestyle offered in sanatoriums could help patients to rehabilitate themselves and find the strength necessary to defeat the disease. Furthermore, the isolation of tuberculosis carriers protected the population from infection.

These two functions were the only medical goals that could be hoped for from a sanatorium. The seriously ill were unlikely to benefit from staying in the sanatorium [8, 27].

For this reason, in the first half of the 20th century, numerous preventoria were opened.

They had a preventive function: they housed healthy children potentially at risk of infection. In these facilities the guests had the opportunity to respect the main hygienic rules and to feed themselves correctly, as in the sanatorium, keeping themselves healthy [28, 29].

The second therapeutic strategy for the treatment of tuberculosis was the therapeutic pneumothorax. The first successful therapeutic pneumothorax was induced by F.H. Ramadge in London in 1834; he reported complete healing of his patient. Carlo Forlanini (1847-1918) is remembered as the inventor of artificial pneumothorax for treatment of pulmonary tuberculosis. He carefully documented his results with artificial pneumothorax in 1894, and thereafter the procedure became widely used [30]. It is probable that pneumothorax was a useful therapy, primarily because it often resulted in cavity closure and sputum conversion to negative. In 1913 and 1914, Forlanini, thanks to his discovery, was on the shortlist of the Nobel Committee and thus one of the prime candidates for the prestigious prize [31].

However, there are no controlled studies of its efficacy – it is difficult to know how one could design such trials – and one must rely on reviews of series of treated patients [8].

In 1890 Robert Koch developed tuberculin, a glycerine extract of the tubercle bacilli, as a remedy for tuberculosis, but reductions in deaths did not meet those expected of the treatment [25]. However, thanks to the studies of Koch, the

tuberculin skin test has been developed and are still used in the diagnosis of tuberculosis.

In 1900 Albert Calmette and Camille Guérin began their research for an antituberculosis vaccine at the Pasteur Institute in Lille and, in 1921, the time was ripe for a trial of the vaccine, called Bacille Calmette-Guérin (BCG), in man.

Vaccines have changed the history of many infectious diseases, the most illuminating example is the eradication of smallpox. BCG has not had the same luck.

Although the efficacy of the BCG vaccine continues to be controversial, live attenuated BCG is still the only vaccine in use for the prevention of tuberculosis in humans [32].

Antibiotics: turning point in the fight against tuberculosis

The optimism brought by Koch's discovery had no significant consequences in medical practice for over 60 years.

The first truly effective anti-tuberculosis drug arrived in 1943: streptomycin, isolated in the laboratory of Selman Waksman at Rutgers University. In November 1944, a patient with tuberculosis received streptomycin and was declared healed from the disease.

Other cases of successful treatment soon followed [33, 34]. Streptomycin was among the first antibiotic molecules on the market. Again, we find that tuberculosis has been involved in an epochal shift in the history of medicine: the advent of the antibiotic era.

The British Medical Research Council conducted the first large-scale clinical trial of streptomycin in 1948 [35].

This study, said to be the world's first published drug trial that involved the randomization of participants, set the methodologic standard for modern randomized controlled trials. In 1951, isonicotinic acid hydrazide (isoniazid) was tested, followed by the development of pyrazinamide (1952), cycloserine (1952), ethionamide (1956), rifampin (1957), and ethambutol (1962) [34].

The introduction of antibiotics in a short time has radically changed medical practice.

This change can be documented in the medical literature intended for the general practitioner. For example, in Italy the Anton Spartaco Roversi's Manual of Medicine was a consultation pocket book that tried to give an comprehensive overview about medical practice in order to provide a useful bed-side tool for generations of Italian physicians.

In its first editions (1940 and 1944) tuberculosis was finely explained in a systematic manner in every possible manifestation within the chapters divided by organ "With the arrival of effective antibiotic therapies, in the subsequent editions of the book (1954 and 1967) there has been a drastic drop in the number of pages devoted to tuberculosis and its manifestations, indicating a decreased finding of extrapulmonary complications of the disease, and therefore a decreased interest for the general practitioner" [36].

Optimism that tuberculosis would soon be eliminated was not restricted to wealthy countries. At the 1978 International Conference on Primary Health Care in Alma-Ata (now

called Almaty), Kazakhstan, delegates from around the world endorsed the goal of “health for all by the year 2000.” The eradication of smallpox had been announced the previous year, and the future of international public health looked promising to many who were gathered there. But it was not to be.

Tuberculosis therapy in the Post-Antibiotic Era

The enthusiasm for the success of anti-tuberculosis drug therapy stifled the alarm bells that did start to ring around the limits of antibiotic therapy.

Studies on tuberculosis in the 1950s anticipated a problem of great relevance today, anti-antibiotic resistance. Once again, tuberculosis is the protagonist in an epochal change in medicine: the post-antibiotic era. The first national drug-resistance survey in the world, which involved 974 clinical isolates cultured from newly diagnosed cases of tuberculosis in Britain (1955-1956), showed strains that were resistant to streptomycin (2.5%), para-aminosalicylic acid (2.6%), and isoniazid (1.3%) [34]. Tuberculosis, whether caused by drug-susceptible or drug-resistant strains, rarely made even medical headlines, in part because its importance as a cause of death continued to decline in areas in which headlines are written. In such settings, where many of the social determinants of tuberculosis - extreme poverty, severe malnutrition, and overcrowded living conditions - became the exception rather than the norm, some public health experts declared that “virtual elimination of the disease as a public health problem” was in sight [37].

Currently, what are the challenges that tuberculosis offers to us?

Despite progress in care and prevention, tuberculosis remains one of the world’s leading causes of ill-health and death and the top cause of death from an infectious disease globally [38]. The fight against drug resistance is only a tile of an always changing mosaic that needs constant attention and innovation in therapeutic strategies [39, 40].

Globalization is improving circulation of people, goods, but also of microbial agents which may find favorable habitats. Individuals with immune deficiencies represent an ever-increasing population at higher risk of contracting tuberculosis. Co-infection with HIV is also a new scenario where doctors have to fight tuberculosis [41].

At last, we must remember that ageing makes people particularly fragile versus tuberculosis, since it decreases the efficiency of the immune system and increases difficulty in tolerating side effects of anti-tuberculosis drugs, sometimes lethal [42, 43].

As often happens in the management of infectious diseases, only comprehensive approaches that aim to tackle down social determinants of tuberculosis, coupled with scientific progress in diagnostic and therapeutic management of patients with tuberculosis, may allow to eradicate this disease in heavily affected countries [44].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

EA designed the study. EA and MM conceived the study; EA and MM drafted the manuscript, revised the manuscript and performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Emanuele Armocida, Department of Medicine and Surgery, University of Parma, Italy - E-mail: emanuele.armocida@studio.unibo.it

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