

History

Tuberculosis (TB) has a long history. It was present before the beginning of recorded history and has influenced the advance of biomedical sciences and healthcare. Its causative agent, *Mycobacterium tuberculosis*, may have killed more persons than any other microbial pathogen.

Primeval tuberculosis

It is presumed that the genus *Mycobacterium* originated more than 150 million years ago. TB was documented in Egypt, India, and China as early as 5,000 years ago. Typical skeletal abnormalities, including Pott's deformities, were found in Egyptian.

Identification of genetic material from *M. tuberculosis* in ancient tissues has provided a powerful tool for the investigation of the incidence and spread of human TB in historic periods. Research on ancient DNA poses extreme technical difficulties because of the minute amounts of DNA remains, their oxidation/hydrolysis, and the extremely high risk of contamination with modern DNA. *Mycobacteria* are assumed to be better preserved than other bacteria due to the resistant lipid-rich cell wall. These bacteria are ideal microorganisms for studying ancient DNA and were the first to be pursued. These investigations have answered important questions. They proved that TB is an ancient disease with a wide geographical distribution. The disease was widespread in Egypt and Rome; it existed in America before Columbus. Another important achievement of the studies on ancient DNA was the confirmation of the TB diagnosis in human remains that showed the typical pathology. *Mycobacterial* DNA was detected in bone lesions in the spine of a male human skeleton from the Iron Age. Molecular methods other than PCR have also been used to demonstrate the presence of the tubercle bacillus in ancient remains, including mycolic acid analysis

Phthisis/consumption

The term phthisis (meaning consumption, to waste away) appeared first in Greek literature. Around 460 BC, Hippocrates identified phthisis as the most widespread disease of the times. It most commonly occurred between 18 and 35 years of age, and was almost always fatal. Although Aristotle (384-322 BC) considered the disease to be contagious, most Greek authors believed it to be hereditary.

The White Plague

The TB epidemic in Europe, later known as the "Great White Plague", probably started at the beginning of the 17th century and continued for the next 200 years. TB was the leading cause of mortality. The high population density and poor sanitary conditions in the enlarging cities of Europe and North America at the time, provided the necessary environment, not met before in world history, for the spread of this

airborne pathogen. The epidemic spread slowly overseas by exploration and colonization. TB existed in America before Columbus' arrival but was rare among the natives. Death rates increased rapidly. TB was also rare among Africans who lived in small villages. After contacts with Europeans, these populations experienced a high mortality rate. There is also evidence of the presence of the disease in pre-historic Asia, but it was only toward the end of the 19th century that peaks in incidence were observed in India and China.

Pathological and anatomical descriptions of the disease began to appear in the 17th century. Franciscus Sylvius was the first to identify the presence of actual tubercles and described specific change in the lungs and other organs of consumptive patients. The name 'tuberculosis' appeared in the medical language at that time. The earliest references to the infectious nature of TB appeared in 17th century.

The discovery of the tubercle bacillus.

In 1865, the French military doctor Jean-Antoine Villemin demonstrated that consumption could be passed from humans to cattle, and from cattle to rabbits. He postulated that a specific microorganism caused the disease. On the evening of March 24, 1882, in Berlin, Robert Koch made his famous presentation. Using solid media made of potato and agar, Koch invented new methods of obtaining pure cultures of bacteria. His colleague Julius Richard Petri developed special flat dishes (Petri dishes), which are still in common use, to keep the cultures.

"Under the microscope the structures of the animal tissues, such as the nucleus and its breakdown products are brown, while the tubercle bacteria are a beautiful blue", he wrote in the paper that followed his dramatic presentation. Showing the presence of the bacillus was not enough. He wanted his audience to note that bacteria were always present in TB infections and could be grown on solid media first appearing to the naked eye in the second week. Then, he showed that, by inoculating guinea pigs with tuberculous material obtained from people and cattle that have died from TB, the disease that developed was the same. Cultures obtained from the experimental animals were identical.

Several years later the partially purified derivative (PPD) of tuberculin was produced which is presently used in the Mantoux test, also known as the Tuberculin Skin Test.

Sanatorium and initial therapies

The introduction of the sanatorium cure provided the first widely practiced approach to anti-tuberculosis treatment in 19 century.

Hermann Brehmer (1826-1889) a Silesian botany student suffering from TB, was instructed by his doctor to seek out a healthier climate. He traveled to the Himalayas where he studied the mountain's flora. He returned home cured and began to study medicine. In 1854, he presented his medical dissertation Tuberculosis is a Curable Disease. Brehmer then opened an in-patient hospital where patients received good nutrition and were continuously exposed to fresh air.

Sanatoria, increasingly found at that time throughout Europe and the US, provided a dual function. Firstly, they protected the general population by isolating the sick persons, who were the source of infection. Secondly, they offered TB patients bedrest, exercise, fresh-air, and good nutrition, all of which assisted the healing process. Many of them improved and returned to "life in the flatland"; many did not.

Probably, it will never be known whether sanatorium treatment was a success or a failure, because no study was undertaken comparing the rates of mortality of sanatorium patients with those of TB patients who were similar in age, sex, and economic position, but who remained untreated or were treated by other methods. During the early '60s, many sanatoria started to close. By the middle of that decade only a few beds remained available for patients suffering from TB. Yet, the real end of the TB sanatorium began even earlier, when the depressing era of helplessness in the face of advanced TB was substituted by active therapy.

In the beginning of 20 century the Italian physician Carlo Forlanini (1847-1918) discovered that the collapse of the affected lung tended to have a favorable impact on the outcome of the disease. He proposed to reduce the lung volume by artificial pneumothorax and surgery, methods that were applied worldwide after 1913.

19th and 20th centuries

A further significant advance came in 1895, when Wilhelm Konrad von Röntgen discovered X-rays. After this, the progress and severity of a patient's disease could be accurately documented and reviewed.

At the beginning of the 20th century, public health authorities realized that TB was preventable and that it was not directly inherited. Several associations were set up to educate the community at large. Books educated people about bad food and bad air. Public health reformers used illustrative posters and stamps as a means of communication, advertisement. This new medium quickly became an effective educational tool in the widespread campaign against TB. Periodic international conferences on TB were held until the outbreak of World War I in 1914. After the war, in 1920, a conference on TB was held in Paris with participation of delegates from 31 countries.

From 1908 until 1919, Albert Calmette and Camille Guérin in France serially passed a pathogenic strain of *M. bovis* 230 times, resulting in an attenuated strain called Bacille Calmette-Guérin or BCG, which was avirulent in animals. BCG was first administered to humans in 1921 and it is still widely applied today.

In 1943, streptomycin, a compound with antibiotic activity, was purified from by Selman Waksman. The drug was active against the tubercle bacillus in vitro and in guinea pigs. It was administered to a human patient at the end of 1944. Two pioneering clinical studies were conducted on the treatment of TB patients with streptomycin, one in Europe and the other in the US. A considerable improvement in the disease was observed in patients on streptomycin therapy, but after the first months, some patients began to deteriorate. These pioneering studies properly interpreted such treatment failure as a consequence of development of resistance to the drug.

Para-aminosalicylic acid (PAS) was produced and first tested as an oral therapy at the end of 1944.

The first patient treated with PAS made a dramatic recovery. The drug proved better than streptomycin, which had nerve toxicity and to which M. tuberculosis could easily develop resistance. In the late '40s, it was demonstrated that combined treatment with streptomycin and PAS was superior to either drug alone. Yet, even with the combination of the two drugs, TB was not defeated. Overall, about 80 % of sufferers from pulmonary TB showed elimination of their germs; but 20 % were not cured, especially those with extensive disease and cavitation.

Two further findings were very important for TB treatment. Between 1944 and 1948, the action of nicotinamide on the TB bacillus was discovered. Isoniazid was soon submitted for clinical testing. It was named a “wonder drug”. Nevertheless, six studies showed that *M. tuberculosis* readily became resistant to isoniazid. The success was achieved by using three drugs together, (streptomycin, PAS, and isoniazid). TB was completely curable.

The general success was based on BCG vaccination, mass radiography screening for early diagnosis of disease, isolation of infectious cases and social measures.

The spirit of optimism was encouraged by the discovery of a series of new anti-tuberculosis drugs: rifamycin, pyrazinamide, ethambutol, cycloserine, and ethionamide. At the end of the '70s, the primary care of TB patients moved from specialized institutions to general hospitals and ambulatory care services.

Earlier studies on TB transmission performed by Wells and Riley. They documented the role of the droplet nuclei in the transmission of TB. They showed that

guiney pigs got infected by inhaling only the air which reached from TB patients. This could be confirmed by comparison of drug susceptibility patterns.

Indeed, the conclusions of those investigations still stand strong. During coughing, sneezing, talking or singing, sputum smear-positive TB patients can eliminate large or small droplets of moisture containing viable bacilli. Large droplets tend to settle quickly onto the floor. Smaller droplets (1-10 μm) remain suspended in the air for prolonged periods of time. It was established that the risk of TB transmission is proportional to the concentration of droplet nuclei in the environment.

Therapy with anti-tuberculosis drugs was identified as the most effective measure for controlling patient's production of infectious particles. Therefore, patients should only require isolation while they were sputum positive and before initiation of specific therapy.

A global health emergency.

Someone in the world is newly infected with TB bacilli every second.

- Overall, one-third of the world's population is currently infected with MBT.
- 5-10 % of people who are infected with TB bacilli (but who are not infected with HIV) become sick or infectious at some time during their life.
- People with HIV and TB infection are much more likely to develop TB.

In Europe and in the US, the general improvement in public health helped to reduce the burden of TB. The disease became greatly controlled but it never quite disappeared. Then, in around 1985, cases of TB began to rise again in industrialized countries. The reasons were

- increase in prison populations
- homelessness
- injection drug use
- crowded housing
- increased immigration from countries where TB continued to be endemic.
- But HIV epidemic was a major factor

Then studies reflected the occurrence of inconsistent or partial treatment, which was going on everywhere. Patients stopped to take all their medicines regularly for the required period for different reasons. Uncompliance frequently results in the emergence of bacteria resistant to drugs.

Multidrugresistant TB, or MDR-TB, refers to M. tuberculosis isolates that are resistant to at least both isoniazid and rifampicin, the two most powerful anti-tuberculosis drugs. MDR-TB takes longer to treat with second-line drugs, which are more expensive and have more side-effects.

HIV-positive patients have the greatest risk. Indeed, the HIV/AIDS epidemic has produced a devastating effect on TB control worldwide. While one out of ten immunocompetent people infected with *M. tuberculosis* will fall sick in their lifetimes, among those with HIV infection, one in ten per year will develop active TB.

In developing countries, the impact of HIV infection on the TB situation, especially is overwhelming. While wealthy industrialized countries with good public health care systems can be expected to keep TB under control, in much of the developing world a catastrophe awaits. The registered number of new cases of TB worldwide correlates with economic conditions: highest incidences are seen in the countries of Africa, Asia, and Latin America.

Supervised treatment, including direct observation of therapy (DOT), was proposed as a means of helping patients to take their drugs regularly and complete treatment, thus achieving cure and preventing the development of drug resistance. The Directly-Observed Treatment, Short-course (DOTS,) strategy was promoted as the official policy of the WHO in 1991. In 2000 the Stop TB Initiative was formed. It announced the following targets:

- By 2005: 70% of people with infectious TB will be diagnosed and 85% of them cured.
- By 2015: the global burden of TB disease (deaths and prevalence) will be reduced by 50% relative to 1990 levels.
- By 2050: The global incidence of TB disease will be less than one per million population (elimination of TB as a global public health problem).

In spite of these global efforts, TB continues to stay a world problem. Extensively drug resistant TB (XDR-TB) was defined as MDR-TB with further resistance to second-line drugs. XDR-TB can develop when these second-line drugs are also mismanaged and, therefore, also become ineffective. A recent survey confirmed XDR-TB to be an actual problem all around the world.

Nowadays, treating TB is effective, even in low income countries, if based on reliable public health practice, including good laboratory infrastructure, appropriate treatment regimens, proper management of drug side-effects and resources to maintain adherence and prevent spread. It is also very important to intensify research efforts devoted to developing effective TB vaccines, as well as shortening the time required to detect drug sensitivity, improving the diagnosis of TB, and creating new, highly effective antituberculosis medications. Without supporting such efforts, we still run the risk of losing the battle against TB.