

History of Tuberculosis. Part 2 - the Sanatoria and the Discoveries of the Tubercle Bacillus

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“If the importance of a disease for mankind is measured by the number of fatalities it causes, then tuberculosis must be considered much more important than those most feared infectious diseases, plague, cholera and the like. One in seven of all human beings dies from tuberculosis.” (Robert Koch, in his address to the Berlin Physiological Society, 24th March 1882)¹

Introduction

Tuberculosis was epidemic in Europe and America in the 18th and 19th centuries, and by the mid 18th century in London and Hamburg, the mortality rates were as high as 1000 per 100,000 per year.² The disease had a predilection for young people and was called the *robber of youth*³, and also for the poorer classes, who were disadvantaged by malnutrition, overcrowding and poor living and working conditions and who died by the millions over those two centuries.^{4, 5}

The ravages of the disease spurred many scientists to find the cause and the cure. Sanatoria were developed in the mid 19th century where patients lived in open alpine or seaside air with good and ample food, but they were not effective at curing the disease and most still died from it.^{2, 6} Scientists and physicians also argued whether phthisis, scrofula and tubercular disease were separate entities or the one disease, and whether they were hereditary, cancer or infectious diseases. In 1865 Jean Antoine Villemin, a French military surgeon, showed by experiments in animals that phthisis was infectious. [2, 5, 6]. The second major breakthrough was the discovery in 1882 by Hermann Heinrich Robert Koch of the cause of tuberculosis – a bacillus he called Tubercle bacillus and which was later renamed *Mycobacterium tuberculosis*.^{2, 6, 7}

Robert Koch's discovery of the tubercle bacillus in 1882

In 1882 Robert Koch, a German physician and one of the founders of bacteriology, discovered the bacillus

that caused tuberculosis. Koch used material from cases of pulmonary, extra-pulmonary and meningeal tubercular disease as well as cases of scrofula. For staining Koch used methylene-blue in a solution of caustic potash. Culture of the bacteria was difficult, he eventually used a medium of coagulated bovine serum developed by John Tyndall, a British microbiologist. Koch then successfully inoculated bacteria from the culture to infect laboratory animals, thus fulfilling the postulates of infectious disease developed by his mentor from Göttingen, Friedrich Gustav Jakob Henle, and which he and Henle later modified to become the Henle-Koch postulates. Koch used his technique to demonstrate the presence of the bacillus in all forms of human and animal tuberculosis proving unequivocally not only that the bacillus was the cause, but the many different forms of tuberculosis were manifestations of the one disease entity.^{2, 6, 7, 8, 9, 10}

Koch delivered his findings in a lecture to the Berlin Physiological Society at the Charité Hospital in Berlin on 24th March 1882 under the title *Die Ätiologie der Tuberkulose*, “The Aetiology of Tuberculosis”.^{1, 6} The audience of Koch's lecture listened in silence and awe and admiration to what must have been an extraordinarily enlightening presentation, afterwards the audience rose to look at Koch's cultures and microscope slides of the bacillus. Paul Ehrlich, then assistant bacteriologist to Professor Friedrich von Frerichs at the Charité Hospital, Berlin, and who later discovered Salvarsan and became the founder of immunology and chemotherapeutics, was present at the lecture and remarked, “I hold that evening to be the most important experience of my scientific life.”¹¹

On 10 April 1882 Koch published his lecture in the *Berliner Medicinische Wochenschrift*, and sent a copy to John Tyndall who in turn published Koch's essential findings in a letter to *The Times* on 22 April 1882. The letter was subsequently reprinted in the *New York Times*, the *New York Tribune* and other newspapers around the world, and within a short time Koch had gained fame in discovering the cause of a scourge that had affected humankind since recorded history.⁷

In 1890 he obtained a concentrated filtrate of liquid cultures of tubercle bacilli which he called *tuberculin* and which he believed was to be an effective vaccine for tuberculosis, however after some years of trying, Koch found this not to be so. In 1907 a Viennese paediatrician, Clemens Freiherr von Pirquet, used cutaneous scratch tests of tuberculin, the Pirquet test, to diagnose children with 'latent tuberculosis', a term which he introduced. Charles Mantoux, a French physician, in 1908 used tuberculin intradermally, the Mantoux test, which replaced Pirquet's test. In the 1930's Florence B. Seibert and Esmond R. Long, two American biochemists, developed a tuberculin purified protein derivative, PPD, which did not produce as many false negative results as 'Koch's substance'. Koch was awarded the Nobel Prize in 1905 for his work on tuberculosis. He died in 1910 in Baden-Baden from heart disease.^{2,6,7}

Koch initially called his bacillus *Tubercle bacillus* and after the publication of his 1882 lecture, it became popularly known as *Koch's bacillus* and tuberculosis became known as *Koch's disease*.⁷ The bacillus was officially renamed *Bacterium tuberculosis* by Friedrich Wilhelm Zopf in 1883, changed to *Bacillus tuberculosis* by Edward Emmanuel Klein in 1884, and to *Mycobacterium tuberculosis* by K.B. Lehman and R. Neumann in 1896 after considering it to belong to a new genus, *Mycobacterium*.¹²

Staining of the bacillus and acid- alcohol fast bacilli

Mycobacterium tuberculosis, as with other Mycobacteria, has a cell wall consisting of glycolipids and lipids which makes the bacteria resistant to chemicals and enzymes, a property which made staining of the bacterium difficult. Koch initially used methylene-blue in an alkaline solution and Bismark brown as a counterstain. In a paper following his address to the Berlin Physiological Society in 1882 Koch remarked :

"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."¹³

Inspired by Koch's lecture, Paul Ehrlich began working on a better method of staining. He used aniline water, fuschin and gentian-violet, applied nitric acid and alcohol to decolourise the background tissue, and heated the slide. He then applied a blue background counterstain which showed up the bacilli which were stained red.^{7, 10}

Later in 1882 Franz Ziehl introduced carbol fuschin instead of aniline and Friedrich Neelson substituted sulphuric acid for nitric acid which stained the

bacillus a brighter red. This was known as the Ziehl-Neelson (ZN) stain. The lipid bacterium cell wall of the bacillus has the property of resisting decolourisation by acid and alcohol and so was known as the acid-alcohol-fast bacillus, AAFB, or acid-fast bacillus, AFB.^{7, 10}

The tuberculosis sanatorium

Fresh air, nutritious food and exercise had been proscribed for phthisis throughout history including by Hippocrates and Aretaeus of Cappadocia. Around the middle of the 19th century, Hermann Brehmer, a German physician, proposed sanatorium treatment (called 'phthisiotherapy'), an 'immune' place where a person could be cured with the aid of fresh rarefied alpine air, plentiful nutritious food, mountain walks, and mountain water douches. Brehmer found such a place in 1857 in a valley in the Sudeten Mountains in Silesia and founded his sanatorium, *Heilanstalt* ("healing place"), in the village of Göbersdorf. Brehmer's treatment included walks on mountain trails to a waterfall where the patient stood underneath a cold mountain stream, the 'forest douche' or *Walddusche*, which he supervised personally to counter any objections to the icy water that his patients might give. In the sanatorium his patients were given nutritious food and milk, Hungarian wine with dinner, and French cognac at bedtime. Brehmer published his treatment in 1857 in his work *Die Chronische Lungenschwindsucht und Tuberkulose der Lunge: Ihre Ursache und ihr Heilung, "The Laws and Healing of Chronic Tuberculosis of the Lung"*.^{2, 6, 14, 15}

Towards the end of the 19th century sanatoria were also built for the poorer classes. They were much less salubrious with plainer food, and the patients had to work and do their own housekeeping. For those who still could not afford a sanatorium, improvisations were made in their home with the patient sleeping outside or in a small outdoor bungalow rugged up against the weather. Rooms in sanatoria were sometimes ventilated with stringent airs – creosote, turpentine and eucalyptus.⁴ Tuberculosis sanatoria became an important treatment in many countries well into the 20th century and many urban hospitals had open air wards as sanatoria. Sanatoria treatment was often beneficial for patients with minimal disease, but many with severe infection still died.^{2, 6}

Other treatments were still being sought, and Paul Ehrlich's discovery in 1909 that syphilis could be cured with an arsphenamine spurred others on to find a chemotherapeutic agent for tuberculosis. Edward Trudeau, medical superintendent of a sanatorium at Adirondack Cottage on Saranac Lake, New York, and who died of tuberculosis in 1916,

stated in a letter posthumously published in the *British Journal of Tuberculosis*:

“My faith in the possibilities of chemotherapy for tuberculosis is based simply on what Ehrlich has demonstrated as possible in syphilis – namely, that a chemical compound could be discovered which killed the germ without injuring the cell ... I see no reason why what has been accomplished in the treatment of syphilis should not be attained in tuberculosis.”¹⁶

Pneumothorax and other surgical treatments

From the late 1880's, sanatoria treatment was supplemented by surgical treatment and collapse therapy, or pneumothorax therapy. The benefit of lung collapse was first suggested in 1771 by Edmond Claude Bourru, librarian, Faculté de Médecine in Paris. In 1885 Edouard Bernard de Cérenville, a Swiss surgeon, and in 1890 Max Schede, a German surgeon, performed thoracoplasty, unilateral partial rib resection to reduce thoracic cavity volume and collapse tuberculous cavities, the principle being to allow them to heal and prevent spread of infection. In 1888 Carlo Forlanini, an Italian physician of Pavia, Lombardy, created the first artificial pneumothorax by collapsing the lung and filling the pleural cavity with nitrogen. Other forms of surgical treatment were used such as lobectomy and segmentectomy, but were commonly complicated by the spread of the infection, fistulas and empyema. In the 1940's the space created by surgical pneumothorax was filled with oil ('oleothorax'). After the introduction of streptomycin in 1945 and other anti-tuberculous drugs, all forms of surgical treatment were abandoned in favour of drug treatment.^{2,6}

The development of the X-ray (the Röntgenogram)

An important contribution to the diagnosis and control of tuberculosis was the discovery in 1895 of X-rays by Wilhelm Konrad von Röntgen. While experimenting with a Crooke's cathode ray tube Röntgen produced a radiation that could produce shadows of metal objects on a photographic plate. Röntgen's technique of utilising these rays to show the body's skeleton with images he called Röntgenograms (he initially called them X-rays but was convinced by his colleagues to change the name) was able to be applied to looking in more detail at internal organs and was very effective at showing tuberculosis in the lung in its various stages, especially the Ghon focus and the apical cavitation and calcification. X-ray screening was introduced for military recruits during

World War I and then for the general population through to World War II where it was again used to screen military recruits. Its efficacy in population screening was found to be very low and was ceased in the 1950's, however it still remained a cheap means of individual diagnostic screening and together with the tuberculin skin sensitivity test played a very significant role in controlling the disease. Röntgen was awarded the Nobel Prize in 1901 for his work.^{2,6,9}

The Bacille Calmette-Guérin (BCG) vaccine

In 1900 two French bacteriologists and *Pastoriens*, Albert Calmette and Camille Guérin, began their research for an antituberculosis vaccine at the Pasteur Institute in Lille. By 1908, by successive sub-culturing a virulent strain of *Mycobacterium bovis* (previously supplied to them by Edmond Nocard, a French veterinarian and microbiologist) on a medium containing ox bile, they were able to produce a non-virulent strain which they formulated into a live attenuated vaccine. By 1919 Calmette and Guérin showed the effectiveness of their vaccine in animals and called their vaccine Bacille Bilie Calmette-Guérin, later abbreviated to Bacille Calmette-Guérin or BCG. In 1921 the first human administration of BCG was performed by two French physicians, Benjamin Weille-Hallé and Raymond Turpin, at the Charité Hospital, Paris, using an oral vaccine. The vaccine was given to an infant born of a mother who died from tuberculosis shortly after giving birth, the child survived and did not contract the disease. The vaccine soon became popular throughout Europe and over the next seven years over one hundred thousand children were immunised.^{2,4,6,17}

In 1930 popular confidence in the vaccine was greatly affected when in Lübeck in Germany 250 children were given a BCG vaccine that had been accidentally contaminated by virulent tubercle bacilli, 73 of the children died in the first year from tuberculosis infection and a further 135 were infected but recovered.^{6,17} World War II was followed by a resurgence of tuberculosis throughout Europe and Asia and in 1948 UNICEF undertook a tuberculosis control program of tuberculin testing and BCG vaccination in children and many countries followed suit.² Routine vaccination was discontinued in the 1970's but is still used in many countries with a high prevalence of tuberculosis to prevent childhood tuberculous meningitis and military disease, and for health care and military personnel and other people at high risk of exposure to tuberculosis.¹⁸

The development of streptomycin and other anti-tuberculous drugs

Tuberculosis was resistant to the sulphonamides of the 1930's and to penicillin of the 1940's. In 1940 Selman Waksman, a Ukrainian born American microbiologist working at Rutgers University with funding from chemical company Merck & Co., isolated actinomycin from *actinomycetes* fungi and in 1942 streptothricin, but these were too toxic to use. In 1943 Waksman and his colleagues Albert Schatz and Elizabeth Bugie obtained streptomycin from *Streptomyces griseus* which was found to be very effective against tuberculosis and much less toxic, and became a standard treatment by 1945. Waksman was awarded the Nobel Prize in 1952 for the discovery. Waksman also coined the term "antibiotic" in 1941 after his discovery of actinomycin.^{2,4,6,8,10}

In 1943 Jorgen Lehmann, a Swedish physician, developed para-aminosalicylic acid (PAS) and in 1945 Gerhard Domagk, a German bacteriologist, developed thiosemicarbazone, both also very effective. Since then other anti-tuberculosis antibiotics have been developed such as isoniazid, rifampicin, ethambutol, and pyrazinamide, and more recently, viomycin and ciprofloxacin which are used in drug resistant infections.^{2,6}

Tuberculosis and AIDS

In the 1980's and 1990's the incidence of tuberculosis surged as a major opportunistic infection in people with HIV infection and AIDS related to their immune system impairment. WHO estimates that in 2012 there were 8.6 million new cases of tuberculosis, of which 1.1 million had HIV co-infection, and 1.3 million died from tuberculosis. The largest number of new cases of tuberculosis occurred in Asia, accounting for 60% of new cases. Sub-Saharan Africa had the highest rate per population with over 260 new cases per 100,000.^{19, 20, 21}

The risk of developing tuberculosis is estimated to be between 12-20 times greater in people living with HIV than those without HIV infection. Worldwide 15% of patients with tuberculosis have HIV co-infection, and up to 50-80% have HIV co-infection in parts of sub-Saharan Africa. Tuberculosis is the leading cause of death in people with HIV infection and AIDS, 1 in 3 people with AIDS die from tuberculosis.^{21, 22} The incidence of HIV-related tuberculosis has declined in developed countries due to effective anti-TB and anti-HIV treatment, but remains a significant health problem in many developing countries.

Drug resistant tuberculosis

In recent decades multidrug resistant tuberculosis (MDR-TB), tuberculosis which does not respond to at least isoniazid and rifampicin, has emerged and is present in most countries. In 2012 WHO estimated there to be 450,000 cases worldwide, most of which were in India, China and the Russian Federation, and 10% had extensively drug resistant tuberculosis (XDR-TB). MDR-TB is on the rise in many countries, but an international initiative financed by UNITAID is currently making progress in improving access in participating countries to diagnostic services for tuberculosis and HIV, and especially to diagnosis of MDR-TB.^{19, 20, 23, 24}

Tuberculosis and the military

Tuberculosis was a major problem in soldiers of the Crimean War of 1853-1856. Florence Nightingale in her paper *On Army Sanitary Reform under the Late Lord Herbert* read at the *Congrès International de Bienfaisance* on 13 June 1862 remarked :

"After the Crimean War, it was found that the death rate among soldiers from consumption alone and its cognate diseases (the monstrous product of breathing foul air) exceeded the death rate from all causes among the civil population."²⁵

Tuberculosis as a medicomilitary problem became more apparent during World War I. Both the Allies and the Germans screened their military recruits for tuberculosis using chest radiographs, however many were still enlisted with latent or active tuberculosis. Before the war ended, 2,000 soldiers had died of tuberculosis in the US Army and was the leading cause of discharge.^{2,25} After World War I the US Army established the Fitzsimons Army Hospital in Denver, Colorado, to cope with the large number of returning Army and Navy veterans with tuberculosis.

Tuberculosis declined in incidence between the two world wars due to better case finding, early diagnosis, and better conditions of living, although X-ray screening was used again during World War II. During the years 1942 to 1945 there were 3,099 soldiers discharged from the US Army for tuberculosis, just over half of all discharges. In one half of those discharges the disease had already been present on enlistment. [26] In 1943 the Valley Forge Hospital was established in Phoenixville, Pennsylvania, to treat returning US military personnel including those with tuberculosis. Following the introduction of streptomycin and other anti-tuberculous drugs, the worldwide prevalence of tuberculosis declined and remained low until its resurgence with HIV in the 1980's.

In the last several decades microepidemics have occurred in small close knit units on US and British Naval ships and land based units deployed overseas. In 1998 an outbreak of 21 cases of active tuberculosis occurred among the ship's sailors and the marine expeditionary unit on a US amphibious ship.²⁷ In 2006 a small outbreak occurred on HMS Ocean, several naval personnel had active tuberculosis and 80 cases of latent infection were identified.²⁸ In 2006 a sailor on USS Ronald Reagan was diagnosed with active pulmonary tuberculosis and 139 sailors and 1 civilian were identified with new latent tuberculosis.²⁹

Overall incidence of tuberculosis in Western militaries is currently low but is higher in militaries of other countries such as South Korea and the Russian Federation. Mancuso & Aaron²⁸ in an analysis of US active military personnel from 1998 to 2012 found that the average annual incidence rate of pulmonary tuberculosis was only 0.6 per 100,000, which was one fifth of the incidence in the US general population. The rate declined from 1.5 per 100,000 in 1998 to 0.35 per 100,000 in 2012. In health care personnel in 2012 the rate was 0.46 per 100,000, an increased risk of 28%, however this was not statistically significant. Interestingly, and reminiscent of the early 20th century experiences, the most common factor associated with diagnosis

during military service was latent infection at the time of enlistment. Military personnel are still at significant risk of acquiring tuberculosis infection because of living and working in close quarters and deployment in regions with a high prevalence of tuberculosis such as Afghanistan, Iraq and South-East Asia, and are particularly at risk of exposure to multidrug resistant tuberculosis (MDR-TB).^{27, 30, 31}

Tuberculosis has been a severe health problem throughout recorded human history, and probably for many thousands of years before that. It has been known by many names including phthisis, consumption, the "white plague" and "the robber of youth". The disease had been romanticised in the 19th century by people such as John Keats, Edgar Allen Poe and Emily Brontë. The nature, cause and cure of the disease had eluded the scientific and medical community until the discoveries by eminent scientists such as René Laennec, Jean Antoine Villemin, Robert Koch and Selman Waksman. Tuberculosis never-the-less remains a significant public health problem worldwide, especially with the emergence of multidrug resistant tuberculosis, and also remains an important medicomilitary issue.

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