Respiratory Medicine (2006) **100**, 1862–1870

respiratoryMEDICINE

HISTORICAL REVIEW

The history of tuberculosis

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Received 31 July 2006; accepted 9 August 2006

KEYWORDS
Tuberculosis;
Mycobacterium tuberculosis;
History of tuberculosis;
History of medicine

Summary Tuberculosis has claimed its victims throughout much of known human history. It reached epidemic proportions in Europe and North America during the 18th and 19th centuries, earning the sobriquet, ''Captain Among these Men of Death.'' Then it began to decline. Understanding of the pathogenesis of tuberculosis began with the work of Théophile Laennec at the beginning of the 19th century and was further advanced by the demonstration of the transmissibility of *Mycobacterium tuberculosis* infection by Jean-Antoine Villemin in 1865 and the identification of the tubercle bacillus as the etiologic agent by Robert Koch in 1882. Clemens von Pirquet developed the tuberculin skin test in 1907 and 3 years later used it to demonstrate latent tuberculous infection in asymptomatic children. In the late 19th and early 20th centuries sanatoria developed for the treatment of patients with tuberculosis. The rest provided there was supplemented with pulmonary collapse procedures designed to rest infected parts of lungs and to close cavities. Public Health measures to combat the spread of tuberculosis emerged following the discovery of its bacterial cause. BCG vaccination was widely employed following World War I. The modern era of tuberculosis treatment and control was heralded by the discovery of streptomycin in 1944 and isoniazid in 1952.

Tuberculosis is an ancient scourge. It has plagued humankind throughout known history and human prehistory. It has surged in great epidemics and then receded, thus behaving 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.

One can hypothesize that the genus *Mycobacterium* originated more than 150 million years ago.[1] *Mycobacterium ulcerans* has specific habitat requirements and a current geographic distribution that separates its endemic regions widely. Those regions were last in contiguity as part of the Gondwanaland continental land mass during the Jurassic period. Modern techniques of molecular genetics and the sequencing of the genome of several strains of *M. tuberculosis* allow a more rigorous estimation of the time of origin of

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0954-6111/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.rmed.2006.08.006

mycobacteria. This estimation is facilitated by the low mutation rate of *M. tuberculosis*. Gutierrez and her colleagues concluded that an early progenitor of *M. tuberculosis* was present in East Africa as early as 3 million years ago, and they suggest that it may have infected early hominids at that time.[2] It is likely, however, that all modern members of the *M. tuberculosis* complex, including not only *M. tuberculosis* but its African variants *Mycobacterium africanum* and *Mycobacterium canettii* as well as *Mycobacterium bovis*, had a common African ancestor about 35,000–15,000 years ago.[2–4] Modern strains of *M. tuberculosis* appear to have originated from a common ancestor about 20,000–15,000 years ago.[5] Currently circulating strains fall into six major lineages, or clades, all of which are present in East Africa; their global distribution varies, however.[6] Analysis based on the known mutation rate of *M. tuberculosis* indicates that much of the present diversity among these strains originated between 250 and 1000 years ago.[7]

East Africa was, then, the ancestral home of both tubercle bacilli and its human hosts. Archeological evidence for any disease is generally lacking in East Africa. However, tuberculosis in Egypt can be documented more than 5000 years ago. Typical skeletal abnormalities of tuberculosis, including characteristic Pott's deformities, have been found in Egyptian mummies and are clearly depicted in early Egyptian art.[8–11] Among the early descriptions of Egyptian tuberculosis was that of A.J.E. Cave, published in 1939 in the *British Journal of Tuberculosis*.[8] More recently, *M. tuberculosis* DNA has been amplified from tissues of Egyptian mummies leaving no doubt as to the cause of early skeletal disease.[12,13] Written record of Egyptian tuberculosis is limited. No reference to it is present in medical papyri, although the descriptions of diseases in these records is not easily deciphered.[8] Tuberculosis is clearly noted in the Biblical books of Deuteronomy and Leviticus, however, using the ancient Hebrew word *schachepheth*.[14] Tuberculosis was well established in East Africa by the time Europeans reached the area in the 19th century.[15]

Early people began to move out of Africa as early as 1.7 million years ago, but these early migrants were largely replaced by later waves of humans during the past 35,000–89,000 years.[16] One can assume that they took their diseases, including tuberculosis, with them. There are written texts describing tuberculosis in India as early as 3300 years ago and in China 2300 years ago.[10,17] Wandering humans reached Europe and Asia easily, but their move into the Americas was blocked by the Bering Strait. In fact, a land bridge existed connecting Siberia and Alaska until about 10,000 years ago, but this route was largely blocked by glacial ice between about 30,000 and 12,000 years ago. Thus, early venturers into the Western Hemisphere, had limited times in which they could travel by land, but coastal water travel was open to them more generally. Although there remains some disagreement about its precise dating, the Monte Verde site in Chile probably puts human occupation of that South American area as early as 33,000 years ago, with evidence of a tool-making community as early as 12,500 years ago.[18]

Just as in Egypt, archeological evidence of early tuberculosis is found in America.[18–21] Bony tuberculosis, including Pott's disease is well demonstrated in Peruvian mummies. And as in Egypt, *M. tuberculosis* DNA has been recovered from mummified tissues. While the earliest evidence of pre-Columbian tuberculosis in America comes from the Andean Region, there is abundant archeological evidence that the disease occurred throughout the hemisphere prior to the arrival of the first European explorers.[18,22]

Tuberculosis was well known in classical Greece, where it was called phthisis, N24ΦH.[23,24] Hippocrates clearly recognized tuberculosis 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.[25] ''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*.[26] At that time, however, tuberculosis appears not to have been a problem in Alexandria; the African epidemic had waned, at least in Egypt.[24] The Greek physician, Clarissimus Galen, 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.

As Europe entered the middle ages, the written record of tuberculosis becomes sparse. That does not mean that the disease was not present. Indeed, there is archeologic evidence from widespread sites throughout Europe for tuberculosis during the millennium that followed the fall of Rome in the 5th century.[22] St. Francis of Assisi died in 1226 at the age of 44, probably of tuberculosis.[27] A fascinating aspect of tuberculosis during the middle ages is that of scrofula, which European monarchs beginning with Clovis in 496 treated with the ''royal touch.'' Hundreds, and sometimes thousands, of scrofulous individuals were touched by monarchs during the next several hundred years, and a codified ritual for confirming the diagnosis and

bestowing prayers developed in the liturgy of the church.[24] Queen Anne was the last British ruler to touch for scrofula; a young Samuel Johnson was among those upon whom she laid her hands.

As the renaissance swept northward from Italy into Northern Europe, new knowledge emerged, including new knowledge of disease. The great anatomists of Padua were supplanted at the helm of medicine by French giants Jean Nicolas Corvisart, Marie-François-Xavier Bichat, Gaspard Laurent Bayle, and René Théophile Hyacinthe Laennec. It was Laennec, most frequently remembered today for his invention of the stethoscope, who clearly elucidated the pathogenesis of tuberculosis and unified the concept of the disease, whether pulmonary or extrapulmonary.[28–30] His 1819 book, *D'Auscultation Mediate*, was translated into English with considerable editing by John Forbes in 1821.[31] In this work Laennec not only clearly expounded the pathology of tuberculosis but also described most of the physical signs of pulmonary disease and introduced terms to describe those findings that are still in use today. Modern understanding of tuberculosis began with Laennec's treatise.

Laennec's work was possible in large part because of his enormous experience with autopsies of persons dying of tuberculosis at the Hôpital Necker in Paris. By Laennec's era, tuberculosis had surged across Europe in an epidemic tsunami. Death rates in London, Stockholm, and Hamburg approached 800–1000/100,000/year at that time.[32,33] Nor was North America spared. Similar death rates prevailed in American cities of the time.[34]

In the face of such an awesome tuberculosis prevalence, society responded by romanticizing the disease. The wan and pallid facies of the victim of tuberculosis were thought to be attractive. Georges Sand, Frédéric Chopin's lover, called him her "poor melancholy angel." Poet George Lord Byron, who did not himself have tuberculosis, is said to have remarked to a friend, "I should like to die of a consumption." "Why?" countered his friend. "Because the ladies would all say, 'Look at that poor Byron, how interesting he looks in dying!.'"[35] Emily Brontë described the tuberculous heroine in *Wuthering Heights* as "rather thin, but young and fresh complexioned and her eyes sparkled as bright as diamonds."[36] Charles Dickens wrote in describing the death of Smike in *Nicholas Nickleby,* "[As] the mortal part wastes and withers away, so the spirit grows light and sanguine."[37] When commissioned in 1883 to create his famous statue of John Harvard, who gave his name to Harvard University, sculptor Daniel Chester French found there were no existing pictures of Harvard. "But it is recorded," he noted, "that he died at the age of about thirty of consumption…. It is fair to assume that his face would be delicate in modeling and sensitive in expression."[38]

Surrounded by patients with tuberculosis, medical practitioners and scientists struggled to understand its etiology. In Northern Europe tuberculosis was generally considered a heritable disease; in Southern Europe it was felt to be infectious in nature. This dichotomy of views was expressed by Georges Sand in a letter to Francois Rollinat written in 1838 from Mallorca, where she and Chopin had gone hoping the climate would improve Chopin's failing health. They were expelled from Palma by a concerned citizenry, "phthisis being extremely rare in those latitudes and, moreover, considered contagious!."[39] That tuberculosis was, indeed, infectious in nature was probably first suggested in 1790 by Benjamin Marten, who attributed the disease to "some certain species of *animalcula*."[40] French military surgeon Jean-Antoine Villemin convincingly demonstrated the infectious nature of tuberculosis in 1865 when he inoculated a rabbit with "a small amount of purulent liquid from a tuberculous cavity" removed at autopsy from an individual who had died of tuberculosis.[26] Although the animal remained outwardly healthy, it was found to have extensive tuberculosis when sacrificed and autopsied 3 months later. Rabbits, as it happens, are generally resistant to infection with *M. tuberculosis*; Villemin's results might have been even more dramatic had he chosen to inoculate a guinea pig. About the same time, William Budd wrote a letter to Lancet suggesting that tuberculosis "is disseminated through society by specific germs … cast off by persons … suffering from the disease.[41] Evidently unaware of Villemin's work, he based his view on the then known epidemiology of tuberculosis in naive populations.

The history of tuberculosis was changed dramatically on March 24, 1882, when Hermann Heinrich Robert Koch made his justly famous presentation, *Die Aetiologie der Tuberculose*, to the Berlin Physiological Society.[24,42,43] In his presentation, Koch not only presented demonstrations of the tubercle bacillus he had identified but posited his famous postulates, perhaps better called the Koch-Henle postulates, which to this day set the standard for the demonstration of infectious etiology. While a District Health Officer in Wolstein, Koch had previously elucidated the life cycle of anthrax, earning an appointment at the Imperial Health Office in Berlin. Koch's contributions to bacteriology were legion, and he was awarded the Noble Prize in Medicine or Physiology in 1905 for his elucidation of the etiology of tuberculosis.

In 1890, Koch made a presentation to the Tenth International Medical Conference in Berlin in which he said he had isolated a substance from tubercle bacilli that could "render harmless the pathogenic bacteria that are found in a living body and do this without disadvantage to the body."[44] He called this substance tuberculin, and injections of it rapidly came into vogue as a treatment for tuberculosis; they were almost as rapidly discredited as ineffective. Koch injected himself with .25 cm^3 of his concentrated tuberculin and observed that he developed "an unusually violent attack of ague … and rise of body temperature up to 39.6°C."[45] He concluded that his tuberculin might be of use diagnostically, and Danish veterinarians soon were tuberculin-testing cattle.

In 1907, 33-year-old Clemens Freiherr von Pirquet was one of Vienna's leading pediatricians. He had already made the original recognition of serum sickness, and he had coined the terms allergy and allergen. He had first observed and described anamnestic (booster) immune responses. In 1907, after learning of Koch's reaction to his self-injected tuberculin, he used a vaccination lancet to introduce a small amount of diluted tuberculin intracutaneously.[46,47] Two years later he published a more extensive study of tuberculin reactions in which he set forth a cut-point of 5 mm and noted that positive tuberculin reactions reflected latent tuberculosis (a term he introduced) in children who did not manifest tuberculosis.[48] Charles Mantoux introduced the use of a cannulated needle and syringe to inject tuberculin intracutaneously in 1908, and Florence Seibert developed purified protein derivative (PPD) essentially in the form in which it is currently used in a series of investigations at the Phipps Institute of the University of Pennsylvania during the 1930s.

With the availability of well-standardized PPD, careful studies of tuberculin reaction sizes became possible, and such studies led to further knowledge of mycobacterial infections. In 1952 Carroll Palmer and Leroy Bates published a large study of reactions to one test unit of PPD-S (equivalent to 0.4 units of PPD-RT23) in more than 3000 hospitalized tuberculosis patients.[49] Fewer than 1% failed to react. Reactions sizes were normally distributed about a mean and mode of 15 mm; later studies with five units of PPD-S would establish a mean of 17 mm. Three years later, a World Health Organization study group published a report that expanded these skin testing studies to school children in various populations.[50] While the distribution of reaction sizes in tuberculous patients observed by Palmer and Bates was confirmed, this report showed that in high tuberculosis prevalence countries—Ethiopia and the Philippines, for example—a substantial number of healthy school children reacted with reaction sizes similar to those in tuberculous patients. These children had latent tuberculous infections, as first noted by von Pirquet.[48] In some populations, they noted, reaction sizes in these children were skewed towards smaller reactions. That these smaller reactions were due to cross-reacting hypersensitivity to the antigens of environmental mycobacteria was demonstrated experimentally in guinea pigs by Edwards and Palmer.[51] Ultimately Edwards and her colleagues performed tuberculin skin tests of more than 600,000 United States naval recruits.[52] They established conclusively that latent tuberculous infection is common in the United States and preumably in other low tuberculosis prevalence countries, that latent infection could be recognized by tuberculin testing, and that nonspecific tuberculin reactivity was common in certain geographic regions.

While knowledge of tuberculosis advanced with the work of Villemin, Koch, von Pirquet, and others, the tidal wave of disease in Europe and North America ebbed. Mortality rates began to decline in the early and mid-19th century.[33,34,53–55] The explanation for this decline remains elusive. Improved social and living conditions, herd immunity resulting from natural selection of a genetically more resistant population, and improved nutrition have all been offered as hypotheses, but none of these appears adequate to wholly explain the observed decline in tuberculosis rates.[55] Falling case rates were accompanied by an apparent shift of disease occurrence to older individuals. That this shift in age-specific incidence resulted as a legacy of high infection rates in youth of now elderly cohorts was demonstrated first by Anvord and shortly thereafter and independently by Frost.[56,57] The decline has continued to the present time, largely unaffected by the institution of public health programs or effective chemotherapy, and today tuberculosis incidences in Europe and North America are at historic lows. Elsewhere, especially in Subsaharan Africa where it is fueled by AIDS, the tuberculosis epidemic continues unabated.

Regardless of the secular trends that showed a declining tuberculosis problem, ill patients sought comfort and relief. They turned to spas or sanitaria.[24,58] In 1859 Herman Brehmer opened his Heilenstat in the Silesian Mountain village of Gobersdorf where he emphasized a regimen of rest, a rich diet, and carefully supervised exercise. This sanatorium is generally considered the first such facility devoted to the treatment of tuberculosis, although Harriet Ryan Albee had opened the Channing Home in the basement of a Boston church

2 years earlier. Peter Detweiler opened a similar sanatorium in Falkenstein, near Frankfort, Germany, in 1867. The first sanatorium in North America was opened in Asheville, North Carolina, by Joseph Gleitsman. Edward Livingston Trudeau's Adirondack Cottage Sanitarium followed in 1884. These retreats isolated tuberculosis sufferers not only from those whom they might infect but also from matters of the current world, as poignantly portrayed by Thomas Mann in *The Magic Mountain*.[59]

Sanatorium care certainly comforted and brought peace of mind to many sufferers. In 1907 the *British Journal of Tuberculosis*, the antecedent of *Respiratory Medicine*, led off its first issue with an editorial, presumably written by the editor, T.M. Kelynack…

> Fads and fancies have gathered about so called "open-air" treatment, and impossible claims have been made by inexperienced enthusiasts as to the almost miraculous efficacy accruing from sanatorium residence. In spite of all exaggerations and failures, there can be no doubt but that the maintenance of a strictly hygienic course of life offers the best means known to modern medical science for dealing effectually with tuberculosis.[60]

Whether sanatorium care changed the ultimate outcome for diseased persons is not clear. A 5-year follow-up study by G. Lissant Cox of more than 4000 patients in Lancashire County, England published in the *British Journal of Tuberculosis* in 1923 compared patients treated at home with those treated in sanatoria.[61] Among those patients who were sputum-negative at admission, 14% of those treated in sanatoria had died, whereas 38% of those treated at home had succumbed. Among sputum-positive patients, the same death rates were 61% and 81%. The study may have been influenced by selection bias, but its results are dramatic. A careful and statistically sophisticated review of experience at New York State sanatoria similarly found that patients with minimal disease did well; those with far advanced disease did not.[62] Overall the cure rate in New York sanatoria did not differ greatly from the spontaneous cure rates summarized by Grzybowski and Enarson.[63]

If rest was good for the tuberculous body, perhaps rest of diseased lungs would be beneficial. Thus, pulmonary collapse therapy became popular, especially for cavity closure.[24] Sand bags were sometimes used to splint one side of the chest, and Robert Louis Stevenson wrote *A Child's Garden of Verse* with his left hand while his right arm was strapped to his chest in an attempt to control his hemoptysis. In the late 19th and early 20th centuries surgical collapse procedures were widely used in the management of cavitary tuberculosis. Cavity closure, hopefully with sterilization of sputum, was the usual goal of this therapy.

In 1696, Giorgio Baglivi described improvement in a tuberculous patient who incurred a pneumothorax following a sword wound. The first successful therapeutic pneumothorax was induced by F.H. Ramadge in London in 1834; he reported cure of his patient. Carlo Forlanini carefully documented his results with artificial pneumothorax in 1894, and thereafter the procedure became widely used. For lower lobe cavities, pneumoperitoneum was employed. It is probable that pneumothorax was a useful therapy, primarily because it often resulted in cavity closure and sputum conversion to negative. However, there are no controlled studies of its efficacy—it is difficult to know how one would design such trials—and one must rely on reviews of series of treated patients. Writing in the *British Journal of Tuberculosis* in 1939, Oli Hjaltested and Kjeld Törning reported the outcome of 191 patients treated between 1925 and 1931 with pneumothorax at the Öresund Hospital in Copenhagen.[64] All were sputum-positive at the time of initiation of the pneumothorax. At follow-up, 65 had died, 11 were still sputum-positive, eight were still being treated but were otherwise well, and 107 had been discharged from treatment and were well. In 1951, Roger Mitchell published a series of articles reporting the outcome of 557 patients treated at the Trudeau Sanatorium in Saranac Lake, New York with pneumothorax between 1930 and 1939. Of these, 326 were working and well, 60 were chronically ill with tuberculosis or disabled, and 119 were dead of tuberculosis.[65]

Thoracoplasty was first introduced by Swiss surgeon De Cérenville and further popularized by Norwegian physicians Ludloff Brauer and P.L. Friedrich. It gained favor because it could be done without entering the pleural space and incurring the risk of tuberculous empyema. Harvey Beard reviewed the results of 100 patients in an article published in the *British Journal of Tuberculosis and Disease of the Chest* in 1951.[66] Cavity closure and sputum conversion was achieved in 63 of these patients. In 1937, Samuel Freedlander and Sidney Wolpaw reported their results in patients in Cleveland, OH, comparing the outcomes of 85 patients selected for thoracoplasty who accepted the procedure with 58 who refused it.[67] Cavity closure was achieved in 66% of those who underwent thoracoplasty and only 17% of those who refused it.

If tuberculosis was infectious and if sanatorium care could improve the health of its victims and

render them less contagions to the community, then tuberculosis was a matter of public health concern. As a 22-year-old undergraduate college student at Cornell University in Ithaca, New York, in 1881, Herman Biggs was required to write a thesis. He chose to write on public health, an emerging and still rudimentary discipline. After hailing Koch's discovery of the tubercle bacillus as the ''grandest discovery of the age,'' he concluded, ''Then let us join in a cordial hail to the coming centuries, to the time when zymotic diseases have become almost traditional, when life shall be prolonged and the enjoyment of health and immunity from suffering shall be almost universal through the advances in Preventive Medicine and the prevalence and observance of National Sanitary Regulations.''[68] Biggs pursued a career in medicine and public health and became Chief Medical Officer for New York City and later Health Commissioner for the State of New York.[29] In 1889, Biggs was instrumental in convincing the city of New York to require reporting of tuberculosis cases by care providers. Both the public and the medical profession resisted this move, but Koch noted it and congratulated Biggs in a letter in 1906. ''We have much to learn,'' he wrote, ''from what in my opinion appear to be procedures adapted in an extraordinarily practical and adequate manner to the control of tuberculosis as you have carried them out in New York.''[68]

A more direct approach to the public health challenges of tuberculosis was taken by Albert Calmette and his associate Camille Guérin.[69,70] They set out to develop a vaccine against tuberculosis. At the newly established Pasteur Institute of Lille, where Calmette was the founding director, they undertook a herculean effort to attenuate *M. bovis* for use as a vaccine. Surviving the disruptions of World War I, Calmette, now in Paris, was ready to try the vaccine, BCG (Bacille Calmette-Guérin) in 1921. An infant born of a mother dying of pulmonary tuberculosis and placed in the care of a tuberculous grandmother was the first recipient. The child survived and did not develop tuberculosis. Over the next 7 years, more than 100,000 children were immunized, including Calmette's children. The vaccine was readily accepted in much of Europe. It was not widely used in Britain, however, and in 1928 Calmette published a paper in the *British Journal of Tuberculosis* arguing for its use.[71]

As noted previously, tuberculosis incidences were falling rapidly in Europe during the first half of the 20th century, but the ravages of World War I led to a resurgence of the disease. The American Red Cross sponsored an evaluation trip to France by Herman Biggs in 1916–17. ''Tuberculosis offers a problem of stupendous magnitude in France,'' Biggs reported. ''If the war were to end now, there would be between 400,000 and 500,000 cases of tuberculosis to be cared for, and practically no facilities to deal with them.''[68,72] Again, the *British Journal of Tuberculosis* took note of the problem.[72] With support from the Rockefeller Foundation and French voluntary agencies the Comité National de Défense contre la Tuberculose mounted a country-wide public health campaign that brought public health measures to all of France.[73]

During World War I, both the allies and Germans screened their military recruits for tuberculosis using chest radiographs. After the war there followed three decades of mass radiographic screening for tuberculosis detection in civilian populations. In 1945 in the *British Journal of Tuberculosis and Diseases of the Chest*, T.W. and Mostyn Davies described a survey undertaken throughout Wales that reached 21,627 persons.[74] From this large number, 133 cases of tuberculosis were found (0.6%). Small yields of this sort led to the abandonment of mass radiography as less productive than contact investigation.

In 1948, a remarkable campaign to control tuberculosis with sponsorship by UNICEF and the Danish Red Cross was undertaken with Johannes Holm as its director.[75] The effort was based on tuberculin testing followed by BCG vaccination of nonreactors. It began in Poland, but soon spread to other European countries and ultimately to Ecuador. During the next 3 years, nearly 30 million persons were tuberculin tested and nearly 14 million vaccinated with BCG. The program was, in fact, the first disease control program undertaken by an agency of the World Health Organization.

In 1974 the WHO Expert Committee on Tuberculosis issued its Ninth Report, a document that provided policy guidelines for tuberculosis control for the next 2 decades.[76] It discouraged both radiographic screening and tuberculin testing and promoted sputum microscopy of symptomatic individuals and those at risk. It advocated ambulatory therapy and recommended against hospitalization of tuberculosis patients. It strongly encouraged BCG vaccination, setting a target of 70–90% coverage for all persons less than 15–20 years of age. Today, the WHO continues to mount programs for tuberculosis control, but it no longer recommends BCG vaccination except for newborns. In the United States, where BCG has not been widely used, tuberculosis control programs emphasize treatment of latently infected individuals.

Edward Livingston Trudeau, famous for his Adirondack Cottage Sanitarium, was a remarkable man. A victim of tuberculosis himself and the

product of a desultory medical education, he established a research laboratory in conjunction with his Saranac Lake sanatorium and carried out many studies examining the efficacy of his treatment. In a communication to the *British Journal of Tuberculosis* published shortly after his death from tuberculosis, he commented on the prospect of chemotherapy for tuberculosis.[77]

> 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.

Three decades later the outlook for tuberculous patients and the history of tuberculosis changed dramatically with the introduction of the chemotherapy Trudeau foretold. The discovery of para-amino salicylic acid (PAS) by Jorgen Lehmann in 1943 and of thiosemicarbazone by Gerhard Domagk during wartime Germany and culminating in 1945 yielded the first therapeutic agents with efficacy in the treatment of tuberculosis.[78] Both were disappointing only bacteriostatic. In 1944 Albert Schatz, Elizabeth Bugie, and Selman Waksman reported the insolation of streptomycin, the first antibiotic and first bactericidal agent effective against *M. tuberculosis*.[24,78,79] Within a few months it had been used with dramatic results to treat a young woman with tuberculosis.[80] Limited supplies led to limited distribution, and streptomycin was slow to reach Europe. The British Medical Research Council used the first available supplies in 1946 to conduct a pioneering randomized, controlled study of the efficacy of the drug.[81] Fifty-five treated patients were compared with 52 control patients. Improvement was noted in 31 treated and only 16 untreated patients. Deaths occurred in 12 of those treated and 24 of those not given the drug. It was not until 1950, however, that the first report of streptomycin treatment appeared in the *British Journal of Tuberculosis and Diseases of the Chest*.[82]

Isoniazid, the first oral mycobactericidal drug, followed in 1952 and rifamycins in 1957. A new era of tuberculosis treatment had dawned. Sanatoria closed. Truly effective public health measures became possible. Treatment was increasingly expanded to include those with latent tuberculous infections. The history of tuberculosis control entered on a new chapter. Treatment to cure became the goal sought for every afflicted person in the world.

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