The Etiology of Tuberculosis: A Tribute to Robert Koch on the Occasion of the Centenary of His Discovery of the Tubercle Bacillus*

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Announcement of the Discovery

On 24 March 1882 a young Regierungsrat ("government councilor" - a civil service rank) of the Imperial Health Office, Robert Koch, presented a paper on the etiology of tuberculosis to the Physiological Society of Berlin in the library of the university's physiology institute. Basing his studies on investigations by Villemin, Cohnheim, and others who had shown the transmissibility of tuberculosis, Koch had started laboratory experiments with tuberculosis in the summer of 1881 and inoculated the first guinea pigs on 18 August 1881 (10). Within about 8 months he was able to prove the infectious nature of the tubercle bacillus by studying the histology of human and animal tuberculosis. He infected guinea pigs and other animals, developed a method to stain the bacilli in histological specimens and heat-fixed smears of biopsy materials and sputum, grew the bacillus on solid media, and described the airborne transmission. Thus, he fulfilled the postulates of his Gottingen teacher, Jakob Henle, who had stated in 1840 that in order to prove the infectious nature of a disease, a germ must be identified in the affected organism, the germ must be isolated and grown in pure culture, and the disease must be reproduced in experimental animals by these pure cultures with subsequent recovery of the same germ. These postulates are known today as Koch's postulates.

Paul Ehrlich, a young medical assistant in 1882, described this memorable event: "Koch had discovered the tubercle bacillus. It was in a small room of the Physiological Institute where Koch, using simple and clear words and offering numerous preparations and exhibits, demonstrated the etiology of tuberculosis with convincing vigor. Everyone who had attended the lecture was deeply stirred, and I must say that this evening has always been kept in my memory as my greatest scientific experience" (10).

Why was this event so important that 100 years later we still remember it? Tuberculosis was a widespread disease in Europe, and in 1882 tuberculosis mortality amounted to more than 300 cases per 100,000 inhabitants in Prussia and other countries as well. More than one-third of infant deaths and one-half of deaths between 15 and 45 years of age were caused by this disease (11). Its nature was not clear; it was considered to be not infectious, but rather hereditary or neoplastic. The work by Villemin and others on the infectious nature of tuberculosis did not succeed in defeating the earlier theories. Only Koch's convincing experiments and observations "brought the full evidence for the parasitic nature of a human infectious disease, and for the most important one of all." They even convinced Virchow, who earlier had expressed contempt for the "juvenile work" of the "youngsters" at the Imperial Health Office (7). Koch himself stated, "My investigations were performed in the interest of health care to which, as I hope, its greatest benefit will accrue." In addition to describing human tuberculosis, he declared pearl disease of cattle to be bovine tuberculosis.

Effects of the Announcement

Koch's presentation had one interesting immediate reaction. Paul Ehrlich (mentioned above) was so impressed by Koch's demonstration that he

Robert Koch in 1883 (photo courtesy of W. Brehmer, Robert-Koch-Institut des Bundesgesundheitsamtes Berlin)

* Presented at the 21st Annual Swineford Conference at the University of Virginia School of Medicine, Charlottesville, on 16 April 1982.
that he returned to the laboratory right after the lecture and experimented with another staining method (10). Whereas Koch had used an alkaline methylene blue solution which required 20 to 24 h at room temperature and veratrin as a counterstain, Ehrlich used fuchsir or methyl violet in aniline oil (aminobenzene)-saturated water for 15 to 30 min, decolorization with dilute nitric acid, and counterstaining with a blue or yellow dye and obtained better microscopic preparations than Koch did. He reported on his improved stain and the acid-fastness of tubercle bacilli to a meeting of the Society for Internal Medicine in Berlin on 1 May 1882 (9). About 3 months later, Franz Ziehl of the Medical Clinic of Heidelberg University described another staining method for tubercle bacilli; he used methyl violet in carbolic acid (oxygenbenzene or phenol)-water without a counterstain (10). The pathologist Friedrich Carl Neelsen developed the method still used today, but published it only in 1892 in a monograph on pathological and anatomical techniques (Neelsen's staining technique was first mentioned in an article [J. A. Johne, Fortsch. Med. 3:198–202,1885] on a case of congenital tuberculosis [1]). Yet nobody gives credit to Ehrlich today, and we speak about the Ziehl-Neelsen stain!

Koch's paper for the Physiological Society of Berlin was printed a little over 2 weeks later in the Berliner Klinische Wochenschrift of 10 April (4), and the respected Deutsche Medicinische Wochenschrift published an editorial praising Koch (2) and a report by A. Fraenkel on the presentation (3) on 8 April 1882 and another editorial on 15 April 1882 (1). On 20 April Koch demonstrated his microscopic slides and anatomical preparations to the First Medical Congress in Wiesbaden and repeated his paper (8). His findings were discussed by many well-known participants, among them Klebs. During the following year Koch was attacked by many scientists at home and abroad, but nobody could dispute him (5). In 1884 he published an expanded report on his research in Mittheilungen aus dem Kaiserlichen Gesundheitsamt ("Communications from the Imperial Health Office"? (6).

**Koch's Background**

Koch had already gained some fame as a bacteriologist by the time he started his work on tuberculosis, and he was to become the father of modern clinical bacteriology. Therefore, on this occasion to honor his great achievement of discovering the cause of tuberculosis, we should also look at his other accomplishments (7, 12).

Koch was born in 1843 in Clausthal, a mining town in the Harz Mountains, and he studied medicine at Göttingen University from 1862 to 1866. The chemist Wöhler and the anatomist Henle were two of his prominent teachers. After graduation he went to Berlin, but was disappointed that he could not find a position with Virchow and felt that the city was too big and the hospitals too impersonal. He found a temporary assistantship at the general hospital in Hamburg (where he saw the choleravibrio for the first time through a microscope). For a while he held a house physician's position at a psychiatric hospital for children. After his marriage to Emmy Fraatz, in 1867, the position was abolished, and the young couple moved to a small town near Potsdam and then (1869) to Rakwitz, near Posen. He volunteered as a medical officer of the Prussian army in the France-Prussian War in 1870, but was discharged early because the people of Rakwitz needed their physician back. After having passed the competitive examinations for public health physicians, in 1872 he was assigned to Wollstein, near Posen, where he served as a public health officer and general practitioner. In a small laboratory he worked on anthrax, an important public health problem. He developed a method for staining bacteria and studied photomicrography.

In 1878 he published a paper on his studies of the role of microorganisms in wound infections. His work was recognized by his superiors and his friends at the University of Breslau, and in 1880 he was appointed first a visiting physician and then a full member of the Imperial Health Office. He wrote a basic book on bacteriological techniques, studied disinfection, and began work on tuberculosis.

**Further Studies by Koch**

In 1883 he served on the cholera commission in Egypt and India and published his discovery of the cholera bacillus in 1884. In 1885 Koch was appointed director of the new Institute of Hygiene and chairman of the university's Department of Hygiene. He continued to study cholera and tuberculosis, conducted training courses in the new bacteriological techniques, and was involved in many public health problems of the day, such as drinking water supply, sewage disposal, and air quality.

In 1890 he announced to the 10th International Congress of Medicine in Berlin—somewhat prematurely, but giving in to considerable pressure by the German government—that he had found a remedy for tuberculosis with which "the process of disease could be completely stopped without detrimental influence to the body in any other way" (12). He was celebrated (e.g., by being appointed an honorary citizen of Berlin), and great expectations were raised in medical circles and in the public as well. Even Pasteur, with whom he had a rather reserved relationship, congratulated him. Koch was wrong! Tuberculin was not a remedy, but it became an important tool in the diagnosis of tuberculosis. Also, Koch's studies of the reactions of infected animals and humans to challenge with tuberculin or to reinfection ("Koch'scher Grundversuch") became the basis for Pirquet's theory of allergy and eventually for Calmette and Guérin's work on antituberculous vaccination.

To allow Koch to pursue his research without interference by teaching and service obligations, the government built for him the Institute for Infectious Diseases in Berlin, today the Robert Koch Institute. There he worked from 1891 to 1904, continuing his tuberculin studies on...
animals and on patients from the attached infectious disease research ward, first at the Moabit Hospital and later at the Charité. Despite many disappointing results, he pursued the tuberculin "cure" with obsession. He injected himself and his associates, among them Kitaasato and Wassermann. Even his future (second) wife, a 20-year-old model and actress, Hedwig Freiberg, was "challenged...to make sacrifices." He informed her that she "possibly could become rather sick but it probably might not become too bad. In all probability, [she] would not die."

The tuberculin injections left Hedwig Koch with scars for the rest of her life (11). In 1897 Koch reported on a new tuberculin. Of interest to us in his report is the diagnostic use of tuberculin in 1,000 cases and also in cattle. In 1892 he studied cholera in Germany and assisted the government in developing control measures. In 1896 he went to South Africa to study rinderpest (cattle plague) and developed a vaccine. He also investigated malaria, Texas fever, and tsetse disease. In 1897 he went to India to study plague, and at home he investigated leprosy in Mamel, on the Baltic Sea. In 1898 and 1899 he went on malaria expeditions to Italy, Indonesia, and New Guinea, but two other scientists—the Scottish military physician, Ronald Ross, in India and Battista Grassi in Rome—found the Anophelines to be the vector of plasmodia. He was involved in the control of typhoid fever outbreaks in Germany in 1901. From 1903 to 1905 Koch was in Africa to investigate coast fever and horse disease, and he discovered the etiology of African recurrent fever. In 1906-07, when he was 63 years old, he went on a sleeping sickness expedition to East Africa, and in 1908-09 he traveled to the United States and Japan. In 1910 he had several heart attacks, and he died on 27 May 1910 in Baden-Baden. His ashes were buried in a mausoleum in the Robert Koch Institute in Berlin.

Honoring Robert Koch

Koch received many honors. For 30 years (1880 to 1910) he was the chief advisor on the control of epidemic diseases to the imperial government and to Prussia. In 1902 he was inducted in the French Academy of Sciences, replacing Virchow, and in 1905 he received the Nobel Prize. His trip to the United States and Japan in 1908-09 became a triumphal journey. But the major honor extended to Robert Koch is the fact that microbiologists all over the world are still using the basic laboratory techniques developed by him and his associates to diagnose infectious diseases. In this year of the centenary of the discovery of the tubercule bacillus, we shall join our colleagues of the International Union Against Tuberculosis and the World Health Organization in a new start by supporting their challenge to the world: defeat tuberculosis—now and forever. We owe it to Robert Koch and the sick people he worked to cure!

Literature Cited