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Microbiologic Therapy of Tuberculosis: Bacterium termo to Streptomyces griseus

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Abstract

Tuberculosis in the 19th century resulted in 1,000 deaths per 100,000 population per year in European and American cities. There was no effective treatment. In 1885 Professor Arnaldo Cantani of Naples successfully treated a patient with pulmonary tuberculosis using an inhaled spray made from a culture of *Bacterium termo*. Cantani's bacteriotherapy spray was subsequently used by other European physicians with varying success. This mysterious bacterium was later judged to be unclassifiable because the original cultures were probably a mixture of bacteria. In the 20th century two scientists at Rutgers University, Schatz and Waksman, isolated streptomycin from the soil bacterium *Streptomyces griseus*. Streptomycin was shown to be an effective treatment for pulmonary tuberculosis after completion of a controlled trial in England. Microscopic features described for *B. termo* are compatible with *Streptomyces griseus* which may have been an organism present in the *B. termo* mixed culture. The success of the bacteriotherapy spray used by Cantani and others may have been due to the presence of streptomycin elaborated by *S. griseus*.

Keywords: Tuberculosis; Bacteriotherapy; Putrefaction; Soil bacteria; Streptomycin.

Introduction

During the 19th century the disease known as phthisis (from Greek phthiein=to waste away) or consumption became known as the white death or the great white plague (white because of the pallor of those afflicted). The term tuberculosis was used by the German physicians, Johann Lukas Schonlein and Herman Brehmer, to describe the disease with tubercles. The disease ravaged Europe with death rates in the cities of 1,000 per 100,000 inhabitants every year. Cities in the United States suffered similar mortality rates. The disease was poorly understood with some physicians believing it was infectious, while others thought it was hereditary or cancerous [1].

In 1865, a French military surgeon, Jean Antoine Villemin, inoculated a rabbit with purulent liquid from a tuberculous cavity of an autopsied soldier. Three months later he autopsied the healthy appearing rabbit and found extensive tuberculosis [2]. Villemin's experiment demonstrated that tuberculosis was an infectious disease. The infectious nature of tuberculosis was recognized by the English physician, William Budd. In a letter to The Lancet he stated that "tubercle never originates spontaneously, but is perpetuated solely by the law of continuous succession" [3]. However, it was not until March 24, 1882 that Robert Koch announced the discovery of the infectious agent-the tubercle bacillus. Koch was an expert in microscopy and staining techniques and was able to identify the bacilli in tubercles from animals that had died from tuberculosis by adding caustic potash to the methylene blue stain [4].

Bacteriotherapy

While knowledge of the bacterial etiology and transmission of tuberculosis may have slowed the epidemic somewhat, there was still no cure for the infection. In May of 1885, Arnaldo Cantani, Professor of Clinical Medicine at the University of Naples, treated a patient with bacteriotherapy after having found the therapy to be harmless to healthy animals. His patient was a 42-year-old woman with cavitary tuberculosis who was hospitalized with a fever, copious sputum production with tubercle bacilli, and weight loss. "Animals inoculated with the sputum became tuberculous." [5]. On May 4th, Dr. Cantani began daily

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treatment with a spray containing *Bacterium termo* which had been grown in a culture media containing meat broth. With the daily inhalations he observed that the numbers of tubercle bacilli in the expectorated sputum were steadily declining and by June 1st they had disappeared. "Animals inoculated with the sputum no longer became tuberculous" [5]. The patient was improving and gaining weight. He believed that the tubercle bacilli were being replaced by the harmless *B. termo.* The news of his successful treatment of a single patient in Italy quickly spread to England [5] and the United States [6]. In Poland, Dr. Filipovitch treated six patients with advanced pulmonary tuberculosis at the Odessa Town Hospital using the bacteriotherapy as described by Dr. Cantani. He grew a "pure" culture of *B. termo* in meat broth and treated patients twice daily with inhalations. None of the six patients improved and three died. The failure of his bacterial treatment was reported in the British Medical Journal on October 2, 1886 [7]. Having read Dr. Filipovitch's article, A. Primrose Wells, a physician on the Isle of Mann and Licentiate of the Royal College of Surgeons, published his more encouraging experience treating five patients with bacteriotherapy. He prepared his culture of *B. termo* in a meat-infusion broth and administered a fine spray to patients thrice daily. His first patient was a 43-year-old man with advanced cavitary tuberculosis who improved after two weeks and by the end of a month of therapy he was able to return to work. His therapy was continued twice daily for another three weeks. A second patient was a 20-year-old woman with noncavitary tuberculosis who showed considerable improvement after only ten days of therapy. She had travelled some distance to receive her treatment and returned home to care for her sister who had more advanced tuberculosis. Her favorable response convinced her sister to seek the same therapy. Unfortunately, she and two additional patients with advanced tuberculosis did not improve with bacteriotherapy. Two of the patients succumbed to their illness including the sister of the woman successfully treated [8].

Victorian bacteriotherapy

At the time that Professor Arnaldo Cantani and others reported their experiences treating pulmonary tuberculosis with *B. termo* spray, modern microbiology was just beginning. The Victorian cities of the 19th century were overwhelmed with sewage and garbage. Putrefaction was evident in the air, water, and soil. In 1854, John Snow had proven that cholera was spread by sewage contaminated drinking water. The German chemist, Justin von Liebig believed that fermentation, putrefaction, and decomposition resulted from a rearrangement of molecules. So while the decomposition of sewage could become the food of plants it could also lead to zygomatic diseases. Leibig's concept of zygomatic disease was that there were specific modes of putrefaction that were analogous to the specific types of fermentation and these chemical reactions produced disease. Zymes were thought to be chemicals that acted as catalysts for decay. Disease was "a spreading internal rot, that it came from an external rot, and that it could be transferred to others" [9]. It is interesting that Liebig believed that his zygomatic disease could be transferred by purely chemical reactions rather then by microoganisms. John Simon, who served as Britain's senior public health official from 1855 to 1870, was able to unite the new germ theory of Pasteur and Koch with the older chemical theory of Liebig by envisioning both filth and germs as important in causing disease. He thought that filth served as the medium which allowed the disease germs to propagate [9]. Victorian physicians and scientists interested in the study of putrefaction were greatly assisted by the optical magnifications achieved by the compound microscope which unveiled the world of the microbe. Jabez Hogg was an ophthalmologist with great expertise in microscopy and he concluded that bacteria "are the active agents in putrefactive changes" [9].

Ferdinand Julius Cohn (1828-1898) received a doctorate degree in botany from the University of Berlin in 1847. Two years later he returned to his birthplace in Breslau (now Poland) to found the Institute of Plant Physiology and establish a research group at the University of Breslau. During this time the prevailing thought was that all bacteria were derived from one species of plant. About 1875, the practice of culturing bacteria on solid media began to be used by Cohn who then detailed the microscopic features of the cultured bacteria which he used for classification. Cohn was a botanist and thought that bacteria were members of the plant kingdom and were related to algae. He classified bacteria into four groups or tribes based on their microscopic appearance: 1. *Sphaerobacteria* (sphere-shaped), 2. *Microbacteria* (rod-like), 3. *Desmobacteria* (filamentous), and 4. *Spirobacteria* (screw-like). According to Cohn's classification *B. termo* was a member of the *Microbacteria* group. "*B. termo* was specified as the cause of putrefaction" [10]. Cohn believed that, at that time, it was impossible to distinguish "with certainty genera and species among bacteria." However, he was convinced that the bacteria were "divided into species as distinctly as other plants" [11]. The compound microscope and its lenses had greatly improved the ability to observe microorganisms, but even with the oil immersion technique the details of unstained specimens were difficult to discern.

Bacterium termo

Cohn studied *B. termo* which he described as a "schizomycetous organism" that grew in his nutrient solution containing acid potassium and ammonium tartrate. Previous to Cohn's classification of bacteria, the *Schizomycetes* were classified as fission fungi that produced putrefaction and this group included bacteria [11]. The organisms he observed were "short rods (single, in pairs or fours joined end to end) and roundish white Zoogloeae, together with a greenish fluorescence." The name Zoogloea is derived from the Greek word for animal glue and Cohn established the term Zoogloea for "bacteria arranged in gelatinous masses, diffused or more or less crowded together" [11]. Currently the term refers to a specific genus of gram-negative, aerobic, rod-shaped bacteria. He did not observe endospores and thought that the rods were motile and possessing "a single polar flagellum, or in some cases, perhaps, provided with paired or triple flagella" [12]. Erwin Frank Smith cultured *B. termo* adding water and beans to Cohn's nutrient solution. He observed a green fluorescent organism with a polar flagellum [12]. James Cossar Ewart cultivated *B. termo* and observed that "the rods, instead of undergoing fissiparous division, lengthened into filaments, in which in due time spores appeared." He described the spores as "extremely bright almost spherical bodies" which later escaped the filaments and formed zoogloea [13]. William Henry Dallinger observed *B. termo* as having a pair of flagella with one at each end. He experimented with various techniques to achieve success in observing the flagella with his microscope and decided to make measurements of the diameters of the flagella using the width of a line drawn by a finely sharpened pencil as a reference. The average length of *B. termo* was determined by making 100 measurements of 6 different infusions. It was found to be 1/10,000 of an inch (2.54 microns). The width of the body was found to be 1/20,400 of an inch

(1.24 microns). He then observed that it would take 10 flagella to match the width of the rod-shaped organism. A total of 200 measurements with four different microscopic objective lenses of varying magnifications were used to confirm that the mean diameter of a flagellum was 0.00000488526 inches (0.124 microns) [14].

Gustav Hauser was a pathologist at the University of Nuremberg who discovered the bacterial genus *Proteus* in 1885 which he named after the character in Homer's Odyssey. Proteus was able to transform himself into various animals and even water and a tree. The morphologic variability of the bacteria which appeared as bacilli, cocco-bacilli, or filamentous forms inspired Hauser to apply the name *Proteus* for the genus [15]. Hauser "found three different distinct bacilli which he grouped under the common name proteus, which have the putrefying properties ascribed to *Bacillus termo*" [16]. He believed that *B. termo* might also be a member of the *Proteus* genus. The *Proteus* genus includes facultative anaerobic, heterotrophic, proteolytic bacilli that inhabit the gastrointestinal tracts of mammals, reptiles, amphibians, fish, shrimp, and insects. These organisms have been isolated from the soil and from fresh and salt water. The presence of *Proteus* species in water or soil may serve as an indication of fecal pollution. The metabolic actions of these bacteria in the soil may be beneficial to plants by encouraging the growth of rhizobacteria and by neutralizing toxic substances [15].

In 1950 the International Association of Microbiologists met in Rio de Janeiro, Brazil for their Fifth International Congress and established the International Committee on Bacteriological Nomenclature. They considered the possible classification *B. termo* as described by Cohn in 1872. The committee concluded that "the species *B. termo* is not recognized by most bacteriologists at the present time because it probably was not based on a pure culture and is at present unidentifiable" [17].

Discovery of streptomycin

Selman Abraham Waksman was born in Russia and emigrated to the United States in 1910. He entered Rutgers College in 1911 and graduated with a degree in agriculture in 1915 followed by a masters degree in 1916. After receiving a doctorate degree in biochemistry from the University of California, Berkeley in 1918, he then returned to Rutgers as a microbiologist and later became Professor of Microbiology and Head of the Department of Microbiology in 1940 and was elected President of the American Society for Microbiology in 1942. He was particularly interested in soil and marine microbiology which led him to have a particular interest in the *Actinomycetes* and their classification. He noted that they resembled bacteria, but had a "fungus-like form of growth" [18]. In 1943, Waksman recognized the genus *Streptomyces* as a new name for the aerobic, saprophytic *Actinomycetes* which form spores [19]. Waksman received a Nobel Prize in 1952 for his discovery of streptomycin [20].

Albert Israel Schatz graduated from Rutgers University in 1942 with a major in soil science and became a bacteriologist in the U.S. military where he developed an interest in antibiotics. He was discharged from the military the following year with a service-related back injury and returned to Rutgers to seek a doctoral degree working in the laboratory of Selman Waksman. Schatz desired to perform his research project on finding a new antibiotic and took on the task of searching for an antibiotic to treat tuberculosis at the suggestion of two collaborators at the Mayo Clinic, William Hugh Feldman and Horton Corwin Hinshaw. His research resulted in the discovery of a new antibiotic from *Streptomyces griseus* which he named "streptomycin." This research was the subject of his doctoral thesis. Streptomycin exhibited antimicrobial activity against a variety of bacteria including *Mycobacterium tuberculosis* [21,22]. Subsequently, it was found that the addition of meat (beef) extract to the growth media enhanced the production of streptomycin by *S. griseus* allowing for large scale production of the antibiotic [23].

After Feldman and Hinshaw demonstrated that streptomycin inhibited the growth of tubercle bacilli in guinea pigs, treatment of patients with various types of tuberculosis was begun at the Mayo Clinic. A total of 75 patients, including 24 with pulmonary tuberculosis, were studied. While some successes were observed, Dr. Hinshaw believed that additional confirmatory studies would be needed [24]. Shortly thereafter, the Streptomycin in Tuberculosis Trials Committee of the Medical Research Council in England designed a controlled clinical trial of streptomycin for the treatment of pulmonary tuberculosis. Fifty-five patients were treated with intramuscular injections of streptomycin and bedrest and 52 patients were treated with bedrest alone. A majority (51%) of the streptomycin treated patients showed considerable improvement with an additional 18% showing some improvement. Despite the clinical improvement noted in these patients only 15% were bacteriologically negative at six months. Furthermore, strains of tubercle bacilli resistant to streptomycin were isolated from patients by the end of the second month of treatment while their sputum samples remained positive [25].

In an effort to increase the concentration of streptomycin in the lungs, without incurring the adverse effects of higher intramuscular doses, streptomycin was administered by aerosol to twelve children; nine responded favorably [26]. More recently, with the emergence of multiple drug-resistant tuberculosis, inhaled therapy has been further investigated [27].

Battle for life

Louis Pasteur, in a lecture to the French Academy of Sciences in 1877, provided both theoretical and experimental evidence that bacilli caused anthrax [28]. He refuted an earlier study in which blood from a slaughterhouse cow that had died from anthrax was injected into a rabbit. The rabbit died, but no anthrax bacilli were observed at autopsy. Pasteur argued that the organisms involved in the putrefaction process in the cow, which had been dead for over 16 hours, would have displaced the anthrax bacilli. Furthermore, these putrefaction bacteria in the blood of the dead animal could subsequently be pathogenic for a living animal injected with this blood. Pasteur termed this microbial competition "the battle for life" [29]. This concept of bacterial replacement may very well have served as the inspiration for Professor Cantani's experiments with bacteriotherapy.

In the years following Pasteur's lecture, other investigators demonstrated that when anthrax bacilli were added to the soil they were antagonized by other soil microbes. Waksman and Woodruff summarized these studies and added the results of their own work showing that *Actinomyces* isolated from the soil were particularly effective in antagonizing other bacteria. An ether-soluble fraction of a paper filtrate from an *Actinomyces* culture was found to be the substance responsible for inhibiting the growth of multiple test organisms and was then named "actinomycin" [30]. Additional studies resulted in the identification of a new species named *Actinomyces antibioticus* which possessed strong bacteriostatic and bactericidal activity. The active

substance was separated into 2 fractions labelled actinomycin A and actinomycin B [31].

Numerous bacteria, such as *Bacillus subtilis*, *Staphylococcus albus*, *Staphylococcus aureus*, and *Micrococcus tetragenus* have all been shown to inhibit the growth of *M. tuberculosis* when grown simultaneously *in vitro. Micrococcus tetragenus* has also been shown to suppress the growth of *M. tuberculosis in vivo* in animal experiments. Culture filtrates of *Bacillus subtilis* injected into rabbits infected with *M. tuberculosis* prevented disease development without any adverse effects to the rabbits. *B. subtilis* has also been demonstrated to lyse *M. tuberculosis* organisms *in vitro*. A substance called "subtilin," obtained from *B. subtilis,* inhibited the growth of *Mycobacterium tuberculosis* in culture media, and was also effective in treating tuberculosis in guinea pigs. Other bacteria, including *Pseudomonas aeruginosa, Escherichia coli,* and *Micrococcus antibioticus* have been shown to have inhibitory effects on the growth of *M. tuberculosis* [32]. Despite the potential shown by these bacteria and their extracts on *M. tuberculosis in vitro*, and in *in vivo* animal studies, none were further studied for safety and efficacy in treating tuberculosis in humans.

Streptomyces griseus

A. Krainsky first reported *Actinomycetes griseus* which he isolated from Russian soil in 1914, but the outbreak of the First World War prevented access to this culture in the United States. In 1943, Waksman and Henrici introduced the genus *Streptomyces* into the classification of the *Actinomycetes* [19]. Waksman was able to isolate a strain of *S. griseus* from New Jersey soil in 1915 which was similar to the *A.* griseus isolated by Krainsky in Russia the previous year. The mycelium at an early stage of growth had a water-green color with long filaments and little branching. The filaments "fragmented readily into rod-shaped conidia, 1 to 1.5 by 0.8 microns" [33]. Additional strains of *S. griseus* were isolated from soil samples obtained from California, Oregon, and Texas. A variety of strains were tested and only a few were found to produce streptomycin. Furthermore, some of the strains which produced streptomycin "may continuously form inactive substrains" [33,34]. The strain of *S. griseus* which was isolated from New Jersey soil in 1915 was repeatedly subcultured on artificial media was later tested and found not to produce streptomycin. However, since the strain was not tested when it was originally isolated, it is possible that the strain might have mutated from a streptomycin producing strain to a non-producing substrain after repeated culturing. Schatz independently obtained two different strains of *S. griseus* distinct from those previously isolated by Waksman. One strain was isolated from the throat of a sick chicken and given to him by a research student named Doris Jones. A second strain was isolated from a heavily manured soil sample by Schatz a few days after he received the first isolate from Jones. The two strains looked alike, but produced different amounts of streptomycin [35].

Streptomyces species are filamentous, aerobic bacteria that produce spores and inhabit soil, compost, water, and plants. Overall, *Streptomycetes* make up about 40% of soil bacterial species [36]. This species has even been isolated from the soil of the Mount Everest base camp [37]. The structure of *S. griseus* has now been studied using an electron microscope in addition to high magnification with a light microscope [38]. The diameter of the mycelium ranged from 0.3-2 microns with most being from 0.5-1.3 microns. Spores of varying shapes measuring from 0.7-1.9 microns in diameter were observed. Septate hyphae and non-septate filaments were seen. Mature spores often revealed small fragments of transparent film adhering to the outside of the spores. The spores germinate at one or both ends whether in nutrient broth or on solid media.

Figure 1: Arnaldo Cantani (1837-1893) photograph taken before 1890.

Table 1: Tuberculosis and Streptomycin.

Date	Researcher	Discovery or Achievement
1865	Villemin	tuberculosis is infectious
1882	Koch	discovery of tubercle bacillus
1885	Cantani	bacteriotherapy of tuberculosis
1915	Krainsky	discovery of *Actinomycetes griseus*
1944	Schatz	discovery of streptomycin
1948	Marshall	streptomycin treatment of pulmonary tuberculosis
1952	Waksman	Nobel Prize for streptomycin

Conclusion

The studies of Cohn and his contemporaries using basic light microscopy of unstained organisms yielded a variety of descriptions of *B. termo*. Spores were seen by some, but not by others. Flagella were usually seen, but varied in numbers for each bacterium among various observers. The filamentous growth of *S. griseus* might have been mistaken for flagella or the presence of flagellated *Proteus* species might account for the various descriptions of flagella by microscopists of *B. termo*. The bacteria were seen as short rods singly or in short chains and a fluorescent green color was sometimes reported as were zoogloea. The confusing aspects of these reports led microbiologists in 1950 to the conclusion that *B. termo* was likely not a specific organism, but rather a mixture of organisms resulting from cultures that were not pure.

Many years earlier, Gustav Hauser had speculated that *B. termo* might be another species of *Proteus.* He named the genus because of the varied appearance of the bacteria. The most common species, *Proteus vulgaris* and *Proteus mirabilis* both exhibit swarming which could have been what Cohn described as zoogloea. A species of *Proteus* might have been *B. termo* or more likely one of a mixture of organisms responsible for the variety of descriptions of *B. termo made* by different observers.

Actinomycetes puzzled microbiologists for many years because they looked like bacteria, but reproduced like fungi. *S. griseus* has a variety of microscopic appearances. Hyphae become septate and resemble rod-shaped bacteria in chains. Filaments can resemble flagella. Spores with adhering transparent films might resemble Cohn's roundish white zoogloea. The water-green color of *S. griseus* mycelia at an early stage of growth might match the fluorescent green color of *Bacterium termo*. Finally, the sizes of *B. termo* and its flagella are similar to the sizes of *S. griseus* and its filamentous form. It seems possible that the *B. termo* could be the organism later identified as *S. griseus* or more likely another one of the mixture of organisms contaminating the cultures of *B. termo.*

On October 11, 1945 Sir Howard Walter Florey delivered the Lister Memorial Lecture at the Royal College of Surgeons in England. Later that same year Florey, along with Sir Ernst Boris Chain and Sir Alexander Fleming, would share the Nobel Prize for the discovery and development of penicillin. In this memorial lecture, Florey speculated that Lister would have been delighted to know that some of the organisms that he endeavored to eliminate from contaminated wounds with carbolic acid "have been made to yield substances with almost ideal properties for the treatment and prevention of sepsis" [39]. Florey discussed the replacement of the tubercle bacillus with *B. termo* as performed by Cantani in 1885 noting that the *B. termo* "appears to be a mixture of species." Professor Arnaldo Cantani and the other physicians who adopted his bacteriotherapy method all grew the cultures of *B. termo* in broth containing meat. There is no documentation available regarding the original sources of the *B. termo* used by the various physicians to inoculate the meat infusion broth. There is also no cultural or microscopic analysis of the final product used as the bacteriotherapy spray. Furthermore, there is no information on whether the physicians made a single culture of meat infusion broth which was reused multiple times to treat patients with the diluted spray or whether multiple broth cultures were made during the therapy. Many years later, *S. griseus* was found to have optimum production of streptomycin when meat was added to the growth media. Studies have shown that streptomycin has activity against multiple species of bacteria including *M. tuberculosis* and numerous bacilli such as *P. vulgaris* and *E. coli* [21,36]. If the bacteriotherapy spray contained a mixture of organisms, then the streptomycin produced by *S. griseus* could have suppressed the growth of other potential pathogenic organisms. Furthermore, the presumed streptomycin containing spray might have played a role in the improvement of the patients treated by Professor Cantani and Dr. Wells. As noted in the controlled trial of intramuscular streptomycin in England, treatment failures in cases of advanced pulmonary tuberculosis are often experienced; thus the failures of treatment with *B. termo* spray, even if it contained streptomycin elaborated by *S. griseus,* would also be expected in such severe cases. Additionally, studies have shown that strains of *S. griseus* vary in their ability to produce streptomycin with some strains not producing any at all; this could have contributed to the differences in patient clinical outcomes experienced by various physicians.

In the late 1890's, Ernest Duchesne, a 20-year-old French student at the military medical school in Lyon, observed that the Arab stable boys at the army hospital stored their saddles in a dark/damp room to encourage mold to grow on them because it helped heal saddle sores on the horses. He made a solution of the mold and then injected it into guinea pigs. He then injected lethal doses of various bacteria into the guinea pigs and found that the pre-treated animals survived. In 1999, The Lancet published a tribute to Ernest Duchesne and bestowed upon him, and not Alexander Fleming or Selman Waksman, the moniker, "The Father of Antibiotic Therapy" [40]. If *B. termo* was really *S. griseus* or if the "pure" cultures of *B. termo* were contaminated with *S. griseus*, then Arnaldo Cantani may have actually been the first physician to treat an infected patient with an antibiotic. Perhaps the moniker given to Duchesne should be transferred to Cantani?.

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