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Prevention and treatment of tuberculosis before two great discoveries of the 20th century: the Bacillus Calmette-Guérin vaccine and streptomycin

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ABSTRACT

Introduction and Purpose. Fundamental milestone in fight against tuberculosis is the invention of the effective vaccine, but before Anthony van Leeuwenhoek was the first to observe the bacteria, which opened the door to the first vaccinations in the 19th century. Medicine had battled against infectious diseases in different ways. Some methods can be perceived as a kind of primitive vaccines, which couldn't, however, considerably affect a decrease in the epidemic range, due to their uncommon use and limited effectiveness. The aim of this paper is to analyze the history of tuberculosis and the role of Poland in the fight against it.

Materials and methods. PubMed database was used for review of the literature. The following phrases were searched in English: "tuberculosis", "vaccination", "BCG vaccine", "sanatorium".

Description of the state of knowledge. Poland played an important role in the fight against tuberculosis. It was in the laboratory of Polish pharmacist, where Koch discovered its etiological factor. In the territory of Poland there are prototypes of modern sanatoria for tuberculosis patients. Article also presents old and modern methods of tuberculosis treatment, as the use of specific climatic conditions, which resulted in developing health-resort treatment. A breakthrough in the methods used was the discovery of streptomycin in the middle of the 20th century, which led to the development of pharmacological treatment, nowadays involving the administration of proper combinations of drugs.

Summary. The increasingly strong anti-vaccine movement is slowly destroying what people have been fighting for the centuries. It is worth recalling how we reached milestones in this fight and why immunization is so important for all societies.

Key words

tuberculosis, vaccination, sanatorium, mycoplasma

INTRODUCTION

Mankind has been battling against infectious diseases since its inception. One such disease is tuberculosis caused by Mycobacterium tuberculosis. The first mention of this disease comes from ancient Egypt. The disease is grave, and if left untreated it could lead to extreme emaciation and even death. It is commonly associated with its pulmonary form, but it can also affect other parts of body, such as bones or skin. Poland also played its role in the fight against this disease because it was in the laboratory of a polish pharmacist in Wolsztyn that Robert Koch discovered its etiological factor, later called Koch's bacillus. Currently, scientists face the difficult task of producing new, more effective drugs and improved vaccine to try to eradicate the disease.

BEFORE DISCOVERY OF TUBERCULOSIS BACILLI

Mycobacteriaceae as a family, that appeared nearly 150 million years ago, but the tuberculosis species itself is relatively young and developed 150,000 years ago. The disease itself has been known for millennia [1]. Traces of tuberculosis can be seen on predynastic Egyptian mummies or pre-Columbian Peruvian mummies [2]. On these mummies vertebral damage and spinal deformities typical of tuberculosis can be found [3,4]. The first, weak, evidence of tuberculosis in humans is bone tuberculosis. Changes were found in a skull from Turkey 500,00 years ago. The first undisputed evidence of M. tuberculosis was obtained by PCR sequencing and lipid detection of these bacilli in bone lesions of a 17,000-years-old bison found in Wyoming [5]. The oldest evidence of tuberculosis in humans' dates to the Neolithic. The research was carried out on bones found near the Atlit peninsula in Turkey [5]. The age of the bones is dated to 9250-8160 years ago. For molecular analysis, samples were taken from the remains of a woman buried with an infant. The skeletons, which were in the dark clay, were carefully excavated and cleaned. They showed signs of tuberculosis of bones. DNA fragments were prepared and sequenced by PCR polymerase chain reaction to confirm their identity. Mycobacterium tuberculosis was detected by PCR screening. In addition, both infant and female samples were analyzed by high performance liquid chromatography (HPLC) for the presence of mycolic acids from the mycobacterial cell wall. The anaerobic conditions favored the preservation of the bacterial DNA. The specific genetic complex of M. tuberculosis has been detected at five different loci, including TbD1 with a deletion that is specific to the modern lineage of the bacterium [6,7]. The most of M. tuberculosis detection

tests use bone as the material for diagnosis. Only few percent are based on examination of lung tissue or other soft tissues. This is due to their reduced resistance to time.

Literature from the beginning of writing is full of descriptions of tuberculosis. It is mentioned in Leviticus and Deuteronomy. In the Old Testament this disease was called *consuptio*, which can be interpreted as an exhaustion as a result of illness. *Schachepheth,* an ancient Hebrew term found in these fragments, reffered to a debilitating disease. This word, now known as *schachefet* in modern Hebrew, continues to denote tuberculosis [8, 9].

However, the theory of tuberculosis as a separate lung disease did not emerge until the 18th century, and earlier authors did not distinguish it from other debilitating diseases. The name 'tuberculosis' was suggested by Johann Lukas Schönlein in 1834, when he observed the disease's nodules [3]. There have been different views on tuberculosis over the centuries. Hippocrates thought it was a hereditary disease. Galen was the first to suspect that it could be transmitted from person to person. During the transition from 15th to the 16th centuries, Girolamo Francastoro established, using syphilis as an illustration, that certain diseases can be transmitted through "particles" via direct or indirect contact among individuals. The transmission of *consumption* from a coughing person to a healthy person was almost unbelievable for people living before the 19th century. Tuberculosis was considered a hereditary disease or at most a spontaneous one. It took many years to confirm how tuberculosis was transmitted. This was proved in 1865 by the doctor of the French army, Jean Antoine Villemin. He carried out an experiment on the transmission of tuberculosis from man to rabbit, from cow to rabbit and from rabbit to rabbit. This experience was confirmed by John Sanderson and John Simon, appointed by the distrustful British government [1].

DISCOVERY OF BACILLI

Robert Koch was the discoverer of tuberculosis. He was born in 1843 in Clausthal, a village in the Harz Mountains, as the son of a mining engineer. In 1862 he began to study medicine at the University of Göttingen. In 1872 he settled in Wollheim (now Wolsztyn) [10]. He used the only laboratory available in the city, owned by Józef Jakub Knechtel. A Polish pharmacist provided Koch with expensive and necessary equipment for research, on which both made observations. The laboratory equipment included a Jena microscope, a camera for microphotography and a large collection of tissue samples. In 1876, he outlined the life cycle of anthrax and demonstrated for the first time a link between a specific microorganism and a specific disease [10]. After the researcher's death, Wolsztyn City Council decided to

commemorate his stay in the city with a memory board on the front wall of the building where he lived. In 1877 he was invited to Wroclaw to continue his research on bacteria. His work was extremely productive. At that time, he laid the foundations for modern bacteriological technology, including introduction of glass slides, methods of fixing and staining bacteria and disinfection with hot steam.

He discovered tuberculosis in 1882. He used material taken from freshly growing nodules on the lungs of animals that died three to four weeks after being infected. Such tissues were examined in a standard way. He also crushed the gray nodules, spread them on a glass slide, dried them and examined them for the presence of other microorganisms, which he did not find there. From previous observations, he knew that appropriate dyes, acting on the principle of reaction in an alkaline medium, had to be used in order to separate the bacteria from the surrounding tissues. He used methyl blue for dyeing and added potassium hydroxide to the aqueous solution. After 24 hours of exposure to the colored liquid, delicate mycobacteria appeared. The cultivation of tuberculosis bacilli proved to be very difficult. Finally, he used a bovine serum solid medium developed by Professor John Tyndall. After ten to fifteen days of cultivation, small colonies could be seen through a magnifying lens. He also noted that a similar staining technique was effective for identifying M. leprae, a leprosy bacterium discovered in 1873 by the Norwegian scientist Armauer Hansen. The news of Koch's discovery quickly spread around the world. Overnight, the bacterium and the disease were named after him – Koch's bacillus. This term has permanently entered the medical jargon. From 1885 he was elected professor of Bacteriology in Berlin and the 'Koch Institute' was built for him in 1891. There, Koch's fame attracted many talented scientists, including Wilhelm Löffler, Felix Ehrlich and Karl Joseph Eberth [10].

TUBERCULOSIS RISK FACTORS OVER THE CENTURIES

Tuberculosis as a typical infectious disease has many factors that increase the risk of infection. The most important in the world is HIV (human immunodeficiency virus). Co-infection with HIV and tuberculosis is a major problem, especially in the southern regions of Africa, where the highest percentage of HIV carriers live. Estimate of as many as 700,000 HIV-positive tuberculosis patients. This accounts for 13% of all patients and shows how important the virus of immunodeficiency is as a risk factor [11]. The World Health Organization has determined the level of increased risk of tuberculosis in carriers of the virus to be 15 to 20 times higher than in healthy people [11].

An equally important factor as HIV in terms of increasing the risk of infections is silicosis. It is caused by human inhalation of crystalline silica dust. It has existed since antiquity, but during industrial revolution it became a significant social problem. Before Koch's discovery of tuberculosis, these diseases were often confused. Silicosis occurs primarily in developing countries, where there are no established standards for the maximum allowable concentrations of silica dust. The risk group includes miners, metalworkers, glassworkers, quarries, and ceramic workers. Silicosis usually occurs after about 20 years of exposure, however, with higher concentrations of silica, it can occur even after 5 years [13]. Coniosis occurs as a result of chronic alveolitis. The inflammatory reaction is initiated by alveolar macrophages, which, under the influence of silica dust, activate caspase I, which is dependent on the pro-inflammatory factor Nalp3 [14]. Macrophages lacking this factor are unable to produce pro-inflammatory cytokines or interleukins IL-1ß and IL-18 in response to silica. Silicosis increases the risk of tuberculosis up to 3 times [15, 16].

One of the non-communicable diseases that increase the risk of tuberculosis is diabetes. Physicians noticed this correlation long before tuberculosis was recognized as a separate disease entity. One of the first to notice that diabetes increases the chance of developing *phthisis,* as tuberculosis was then called, was Avicenna [17]. Many studies have been conducted to assess the increased risk of tuberculosis in diabetic patients [18]. In South Korea, a comprehensive study conducted over three years revealed that diabetic patients faced a 3,47 times greater risk of tuberculosis compared to non-diabetic individuals [19]. Similarly, a case-control study carried out using the UK's General Practice Research Database, focusing on tuberculosis cases diagnosed from 1990 to 2001, demonstrated that individuals with diabetes were 4,9 times more prone to developing tuberculosis [20]. In different regions of the world, this correlation affects with different strength. The greatest risk concerns residents of Central America – 6,0, Europe 4,4 and Asia 3,11. The lowest risk is in North America, only 1,46 and in the Caucasian population 1,23 [21, 22, 23]. The mechanism of correlation between diabetes and tuberculosis is not fully known. However, it is assumed to be related to disorders of the immune system in diabetics. Hyperglycemia is associated with reduced production of interferon IFN-y and interleukin-12. IFN-y level is negatively correlated with HbA1c glycated hemoglobin levels. Poorly treated diabetes also increases the severity of tuberculosis [24, 25].

A factor that also increases the risk of tuberculosis is a transplantation. Treatment of tuberculosis in patients after transplantation is extremely difficult because there are many interactions with immunosuppressive drugs, there are no clear

guidelines and there is a high risk of toxicity, especially in liver recipients. Most cases of tuberculosis in recipients are caused by the reactivation of a latent infection under the influence of immunosuppressive drugs necessary after the procedure. There are significant differences between the risk of tuberculosis and the type of organ transplanted. After a kidney transplantation, the risk increases 37 times, and after a heart transplantation, it increases from 20 to 74 times [26 - 30].

Cancer also affects the risk of tuberculosis. The first to describe this relation was Gaspard-Laurent Bayle in 1810 in his work "*Recherches sur la phtisie pulmonaire*". Tuberculosis and cancer are linked to most organs and types of cancer. However, certain disease entities have an increased correlation. The highest correlation applies to Hodgkin's disease (96/10,000 cases), lung cancer (92/10,000) and lymphomas (88/10,000). More cases of tuberculosis occur in patients with blood cancers than solid organ cancers. This is due the fact that patients with blood cancers have reduced immunity not only as a result of radiotherapy or chemotherapy, but also a result of the disease process itself, including, among other, insufficient number of leukocytes [17].

Risk factors are not always related to other diseases or procedures. They often concern socio-economic conditions. In underdeveloped regions of the world, in addition to tuberculosis and HIV, malnutrition is also a serious problem. These issues are closely related. These issues are closely related. Tuberculosis morbidity and mortality are higher in people with low social status. Malnutrition can cause a decrease in immunity, which increases susceptibility to infection. This is due to the reduced amount of macro- and microelements, what affect the immune system. Deficiencies of protein, vitamins A, D, C and E as well as selenium and zinc have a great impact on the onset and course of tuberculosis. The basic indicator of nutrition used in the study was the body mass index (BMI). The conducted research showed an inversely proportional relation between BMI and the incidence of tuberculosis [31].

The last risk factor to be mentioned is smoking. It is generally known that smoking has a negative effect on the lungs and airways, but does it also the risk of tuberculosis? Based on the results of research, it can be said that regular smoking increases the risk of getting the disease by about two times. Smoking also increases the risk of disease recurrence in cured patients. The risk factor is not only the smoking itself, but also the inhalation of tobacco smoke by passive smokers [32].

BACILLUS CALMETE – GUERIN VACCINE

A vaccine is a product of biological origin containing substances capable of inducing immunological processes that determine the creation of permanent and specific immunity without causing toxic effects. The first effective tuberculosis vaccine was developed by Albert Calmette and Camille Guérin. It was named from the first letters of their surnames BCG, or Bacillus Calmette - Guérin. At the beginning of the 20th century, they began research on the Mycobacterium tuberculosis at the Pasteur Institute in Lille. They cultured mycobacteria on a glycerin-potato medium. On such a medium, however, the bacteria tended to stick together, so the scientists decided to add bovine bile to the medium. To their surprise, bacteria grown on such a medium showed less virulence than other subcultures. This accidental observation prompted them to undertake research into a tuberculosis vaccine. In 1913, they planned to start long-term vaccination of cattle, but this plan was put on hold due to the outbreak of World War I. However, the researchers did not stop their work completely. They continued to grow mycobacteria, despite difficulties in accessing the necessary materials. During the German occupation of Lille, the price of potatoes needed to prepare the medium increased dramatically and access to beef bile was difficult. They received the necessary materials thanks to the help of veterinarians working for the German occupier [33].

In 1919, after 11 years of research, they obtained a strain that, when injected into experimental animals, did not induce tuberculosis in them, but did induce immunity. The vaccine was initially called Bacillus Billie Camille-Guérin, but later they decided to drop the word Billie, and this is how the name Bacillus Camille-Guérin, which is still used today, was created. In 1921, after moving to Paris, Calmette decided to test his vaccine on a human. The first administration of the vaccine was performed by Benjamin Weill-Halle and Raymond Turpin at the Charité Hospital in Paris. On July 18, 1921, they administered the BCG vaccine orally to a newborn whose mother died of tuberculosis within hours of giving birth. No side effects associated with the administration of the vaccine have been observed. Bouquet and Negre emulsions were used for vaccination. In 1924-28, 114,000 children in France were vaccinated, most of whom were vaccinated without complications. The method of vaccination turned out to be safe and effective, as evidenced by the statistics. They showed a decrease in tuberculosis mortality in vaccinated children. Vaccination against tuberculosis has also started outside France, e.g., in Spain and Scandinavian countries. [33, 34].

Mentioning the Scandinavian countries, one cannot omit the research conducted by Heimbeck and Scheel. In 1927, Heimbeck gave a speech in which he challenged the notion that most tuberculosis infections occurred in childhood, and that all illnesses later in life were the result of this early infection. He was not groundless, as he presented scientific evidence supporting this theory. From 1924, all nursing students underwent a tuberculin test. More than half (52%) showed no reaction. More importantly, the vast majority developed a tuberculin reaction during their studies, and 40 of them contracted tuberculosis, compared with only three who previously reacted positively. After learning about Calmette and Guérin's work on the BCG vaccine, he decided to use it in tuberculin-negative adults to protect nurses. Also in 1924, Scheel presented the results of an investigation which concluded that the prevalence of tuberculosis among nurses was higher than that of the general population [35].

Calmette used oral administration for vaccination. He claimed that this route of administration was effective only in newborn babies. Heimbeck decided to vaccinate adults by injection. Together with the Swedish pediatrician Arvid Wallgren, they pioneered this method. Heimbeck used subcutaneous administration and claimed that it offered the best opportunities for antibody production. Wallgren used intradermal administration, which was later preferred. In 1930, a conference of the Internationa Union Against Tuberculosis was held in Oslo. During it, Scheel proposed a vaccination plan for students and people aged 15-25 [35]. This conference coincided with a tragic event in Lübeck. It was an event that put the BCG vaccine in a negative light. This year, 251 children were vaccinated there in the first 10 days of life. Almost all of them developed tuberculosis and 72 children died. It turned out that the vaccine was contaminated with a wild, virulent strain of Mycobacterium bovis [33]. The BCG vaccine was approved by the League of Nations Health Committee as the only effective way to prevent tuberculosis [36]. However, the events in Lübeck caused widespread opposition. In consequence, no country has decided to vaccinate its citizens. It was not until the destruction and famine after World War II, which favored tuberculosis epidemics, that the BCG vaccine was used on a large scale in the countries of Europe and Asia [37, 38]. As a result of the international campaign, 30 million vaccines were administered in Europe and as many as 43 million in Japan. Some countries remained skeptical, e.g., the United States, despite positive results from studies conducted on North American Indians. The United Kingdom was also hesitant to use the BCG vaccine and in 1950 vaccinated a large control group – 50,000 teenagers and young adults. Reports have shown vaccine effectiveness in tuberculin-negative individuals at 83% at the start of the vaccination process. This percentage fell over time to 77% [39].

Currently, the number of children vaccinated varies significantly from country to country. This is due to both economic conditions and the country's health policy. Not all countries where the goal is to vaccine all children achieve high rates. They range from 37% in Somalia to 99% in China. In some countries where there is a low risk of tuberculosis, vaccination is not provided at all. The United Kingdom abandoned vaccination in 2005, and the USA has never conducted large-scale tuberculosis vaccination [40]. Some countries, especially republics of the former Soviet Union, use multiple injections of the vaccine during human growth. The first vaccination with the BCG vaccine in Poland took place in 1926. However, it was introduced as compulsory in 1955 [36].

The original vaccine made by Calmette and Guérin was in liquid form. However, this character had many flaws. It did not ensure the full dose for the newborn and was thermolabile, which was a problem in tropical countries. In addition, it had a short lifetime of 2 to 4 weeks. In the 1950s, the lyophilization process began to be used to produce the BCG vaccine. It involves the initial freezing and then vacuum drying of a suspension of cultured live Mycobacterium tuberculosis bacilli. It has many advantages over the primary vaccine. It is thermostable, the storage life is up to 2 years, and administration by injection guarantees control over the precision of dosing. The vaccine should be protected from sunlight as it has a tuberculocidal effect. WHO recommends intradermal administration and this is how the vaccine is administered globally [36].

TREATMENT OF TUBERCULOSIS IN THE PAST

Tuberculosis has accompanied humanity since the dawn of time. Therefore, traces of the fight against this disease can be found in ancient works. Diseases were considered punishment or retribution from the gods for sins and living contrary to tradition. It was also believed that celestial bodies, their arrangement, and phases had an influence on diseases. Tuberculosis epidemics were rare in ancient Egypt, but remains of spinal tuberculosis have been found in many mummies. There are ground to believe that the Deir el-Bahari temple in Luxor served as a tuberculosis sanatorium. This is evidenced by the hieroglyphs carved on the walls describing the treatment of the sick with a rich diet and inhalation of healing balsamic oils. Moreover, in the opening lines of the "*Iliad*" by Homer, the writer mentions how Zeus, the highest of the Greek gods, sends a plague to the soldiers of King Agamemnon.

In ancient Greece, medicine, treatment, and diseases themselves were subject to the process of sacralization. The god who directly looked after medicine was Apollo. The

ancients derived his name from the word '*apollymi*', which means "I destroy, I kill". They saw in him the personification of violent death. The mythical god of the art of medicine itself was Asclepius, the son of Apollo and the nymph Koronis. He studied the art of medicine under the guidance of the centaur Chiron. The symbol of Asclepius is a staff entwined by a serpent, which signifies the rebirth of forces. The cult of Asclepius was widespread throughout the territory of Hellas. Numerous temples and sanctuaries were built for him. Initially small, located near springs or groves, over the years they grew into large centers of not only cult but also healing character. These were places we would now consider spas or hospitals. The most famous of these centers was Epidaurus on the Peloponnese Peninsula. In 1988, the ruins of the sanctuary of Epidaurus were inscribed on the UNESCO World Heritage List. There was also a theater in this center because care was taken not only for physical health, but also for spiritual balance [41]. A few centuries later, the father of medicine – Hippocrates of Kos in his work "*Corpus Hippocraticum*" described several infectious diseases, e.g., mumps, smallpox, malaria, diphtheria, and tuberculosis. Of course, he did not know the etiology of these diseases. He associated them with imbalances between the four basic fluids of the body. He included blood, bile, mucus, and black bile. Hippocrates claimed that the surrounding environment has a measurable impact on human health. He did not recommend rapid climate change to the sick. The exceptions were patients with tuberculosis and other respiratory diseases. He highly recommended baths, air-climate treatments and walks to them. In addition to sea bathing, sunbathing was also popular to strengthen muscles and bones.

Roman doctors saw the advantages of the Alpine climate and the mountains of Lebanon in lung diseases. This theory was also supported by Claudius Galen, who recommended that tuberculosis patients should stay in the mountains. He sent less sick people to Stabia near Vesuvius. The city had an arid climate conducive to the treatment of tuberculosis. For those for whom staying in Stabia did not bring relief, a sea voyage to the extremely dry and warm mountain regions of Egypt and Libya was necessary [42].

Unfortunately, in the darkness of medieval Europe, ancient healing methods were partly forgotten. Arab and Jewish medicine developed rapidly. During this period, lived Avicenna, an outstanding physician who contributed enormous scientific achievements to medicine. Medicine in medieval Europe was initially dealt with by monks. Libraries in monasteries were rich of collections of ancient medical books. The monks were busy copying these books and decorating them, it was an extremely time-consuming job. At the academy in Salerno, Italy, the ancient idea of treating respiratory diseases survived. The period of the so-

called monastic medicine ended in 1095, when at the Synod of Clermont, the right to treatment was taken away from the clergy and transferred to secular hands [41].

After the Middle Ages, there was a period of Renaissance, a time of flourishing science and a return to ancient values. Slowly, the infallibility of ancient physicians began to be undermined. Andreas Vesalius introduced autopsy as a research method. He proved that the anatomy which Galen was describing was that of animals, not humans. He included his observations in *De humani corporis fabrica libri septem*, the first such extensive, illustrated anatomy textbook. Paracelsus was a supporter of the healing power of nature. He believed in "vis medicatrix naturae" which are body's natural defenses. Only when nature alone was not enough did he resort to medicine. In the Renaissance, tuberculosis patients who could not afford to travel for therapeutic purposes tried to create an appropriate atmosphere in their own homes. The floor was covered with a layer of sand, on which freshly cut spruce twigs were placed [42].

Richard Russell was the first to observe the positive effects of treating tuberculosis of the lymph nodes in children during their stay at the seaside. He did this in the 18th century, but his observations were not confirmed according to the scientific standards of the time. Therefore, the German physician Carl Haeberlin is considered to be the founder of modern thalassotherapy. He conducted his research in Wyk auf Föhr – a spa town on the North Sea. The French philosopher Jean J. Rousseau also advocated a return to nature. He regarded the expanding cities as the "abyss of the human race" in which human nature is wasted and forgotten [43].

CLIMATE AID IN THE TREATMENT OF TUBERCULOSIS

Since prehistorical times, people have been travelling for treatment to places with special climatic qualities for treatment. Man used the instinct of animals, which indicated areas of high healing value of nature. Healing centers were established in the vicinity of mineral water springs, on the coast or in the mountains. Numerous sanatoria were established around the world, where chronically ill people, mainly with tuberculosis, were treated. Before the era of antibiotics, the greatest chance of curing tuberculosis was the rest in the right climate and having a proper nutrition. The world's first sanatorium for tuberculosis was founded in 1854 by *Brehmersche Heilanstalt für Lungenkranke* in Sokołowsko, and more precisely in Görbersdorf, because that was the name of this town in Lower Silesia at that time. Initially, a group of several houses grew over time to 300 beds. The patients stayed at a

relatively high altitude of 518 meters above sea level, spent a lot of time outdoor and had a special diet. The method developed by Vincenz Priessnitz was used in the sanatorium. It was all kind of hydrotherapy, e.g. saunas, hot baths or showers [44]. Görbersdorf has been called "Silesian Davos", but this is an incorrect term, because the sanatorium in Davos was founded on the model of Sokołowsko, and not vice versa. After World War II, a health resort with an anti-tuberculosis profile remained, but with the passage of time fewer and fewer patients came there. Currently, the historic hospital building in Sokołowsko is being renovated. The village wants to regain the health resort status it lost years ago. It is worth trying because the Polish Academy of Sciences has confirmed the healing properties of the local climate. The Kuranstalt Spengler-Holsboer sanatorium in Davos, known throughout Europe, was founded by Aleksander Sprengler and Willer Holsboer in 1868. At an altitude of 1,600 meters, the air is extremely clean and dry. It seems to be an ideal place for the treatment of tuberculosis and lung diseases. An interesting image of both the sanatorium and Davos itself can be found in Thomas Mann's novel "The Magic Mountain". The author describes the local air as very fresh, devoid of aroma or moisture. Patients spent long hours lying in the fresh air. When it was winter, they covered themselves with camel skins for warmth. Sanatoriums for tuberculosis were also established on other side of the Atlantic. The first was Adirondack Cottage Sanatorium, founded in 1884. It was founded by Edward Trudeau, who himself fought tuberculosis in his youth, changing the climate to a mountain one. Influenced by the success of the Prussian doctor Brehmer, he decided to open a tuberculosis treatment center, where the therapy consisted of long rest and inhalation of mild, clean mountain air. The sanatorium was paid, but poorer patients could count on big discounts. The success of the resort was not only due to appropriate climate, but also the relatively short distance from large urban centers such as New York, Boston, and Philadelphia. The sanatorium was closed in 1954 after antibiotic therapy was discovered to treat tuberculosis [45].

Doctor Robert George Ferguson was an important figure in the development of sanatorium therapy, as well as the entire anti-tuberculosis treatment. He noted that the only chance to stop the rapid increase in tuberculosis cases among the local community of Saskatchewan province in Canada is to introduce diagnostics, treatment, and hospitalization without the patient's participation in the costs. It was an extremely difficult undertaking for economic reasons. The doctor had to convince both the medical community and, more importantly, politicians to his idea. As one of the members of the commission appointed to investigate the health situation in the province of Saskatchewan, he created a report in 1921 containing guidelines for further treatment of tuberculosis. Among other things, he pointed

out that tuberculosis patients should not be treated in general hospitals, because this does not guarantee the inhibition of the spread of mycobacteria. He argued that the patient as a threat to the health of the public should be treated at the expense of the state, whose duty is to protect its citizens. He even suggested introducing a special tax for this purpose. Most of his postulates were accepted and introduced into Canadian legislation [46]. Ferguson, unlike most American and Canadian doctors, was a supporter of the BCG vaccine, he was the first to vaccinate his own children with it. It was not until 1932 that he was allowed to vaccinate other newborns. Ferguson made a huge contribution to the fight against tuberculosis in North America. In 1936, the infant mortality rate in the first year of life in Saskatchewan was 1,603 per 100,000 births, a large percentage of which was due to tuberculosis, where in 1948, the death rate fell to only 17 per 100,000 births [47].

Tuberculosis therapy centers were established not only in the mountains. In the early 1930s, the magnificent Paimio Sanatorium was built in the forests of Finland. It had a large number of sunny balconies and a roof terrace where patients could lie in the warm. However, they did not lie on ordinary beds or couches, but on specially designed chairs, called Paimio chairs. It is worth paying attention not only to the presence of the sanatorium in the middle of the forest, in the lowlands, but also to interesting architecture of the buildings. It was designed by the famous Finnish architect Alvar Aalto. The building was built in modern style and has many references to the work of Le Corbusier. Aalto decided that the building itself would positively influence the healing process. One of the ideas was to paint the ceiling dark green and remove the light from the lamps from the patients' close field of vision. Patients who spent a lot of time lying down were able to relax more easily. Each of the rooms also had a balcony, located in such a way as to ensure the longest possible access to sunlight. The architect also designed special paths in the forest surrounding the center, where patients were supposed to walk. For Aalto, calmness was the basis needed during therapy. For this reason, all rooms were only double rooms, and their design ensured maximum comfort and silence. Attention was even paid to the shape of the fittings to give the smallest possible splash of water, and thus silence and to the shape of the handles, which were ideally suited to the hand. Aalto also designed furniture for the sanatorium. The most famous is the Paimio chair, which has been continuously produced since 1931. It has a backrest angle that facilitates proper breathing, and it is made of easy-to-clean material, birch plywood. The architect believed that the positive atmosphere inside the sanatorium would facilitate the recovery of the sick. He tried to avoid bright colors and used soft pastel shades. Until 1971, the sanatorium treated only tuberculosis patients, but the appearance of antibiotics drastically reduced the number of

patients. It was therefore decided to rename the sanatorium into a general hospital. In 2005, the building was submitted for inclusion in the UNESCO World Heritage List for its pioneering functionalism [48].

In 1995, another tuberculosis sanatorium built in a. modernist style was added to the UNESCO World. Heritage List. The building in Zonnestraal, built in 1931, was mostly made of transparent materials to let as much sunlight as possible into the patients' rooms. In order to protect against possible overheating of the building, a cooling system was used, which was not a typical solution in those years. This building was the prototype for the style called *heliotherapeutic architecture*. This style did not enjoy long success, as antibiotics were quickly discovered to combat Mycobacterium tuberculosis [49].

In recent decades, due to the possibility of pharmacological treatment of tuberculosis, most tuberculosis sanatoriums have either been closed or converted into general hospitals. One of the last, until its closure in 2012, centers specializing only in the sanatorium treatment of tuberculosis was the A. G. Holley Hospital in Florida. There are still anti-tuberculosis sanatoria in Poland. One of the older ones, operating continuously since 1900, is the "Wysoka Łąka" sanatorium in Kowary in Lower Silesia. The building of the sanatorium has been signed into the register of monuments. It is a beautiful example of eclecticism in architecture [50].

SUMMARY

The work concludes the history of the fight against one of the widespread diseases in the world, which humanity has been struggling with for millennia. Extremely important dates connected with the fight against tuberculosis took place at the turn of the 19th and 20th centuries. The discovery of the etiological agent – Mycobacterium tuberculosis – and the creation of the BCG vaccine turned out to be groundbreaking. Thanks to the cooperation of Albert Calmette and Camille Guerin, a stage began in which humanity began to slowly control the infection and this bacterium. For years, the World Health Organization has been trying to lead to at least a partial eradication of tuberculosis. However, it is not as simple as in the case of, for example, smallpox due to the rapidly developing resistance of microorganisms to chemotherapeutic agents, the decreasing effectiveness of current vaccines and economic difficulties. This review presents how the prevention, and, above all, the treatment of tuberculosis has changed over the years, from ancient patterns of natural medicine to modern

polydrug therapy. If the attempts to create a more effective tuberculosis vaccine succeed, it is possible that one day we will see a world free of this disease.

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