

GERHARD HANSEN VS. ALBERT NEISSER: PRIORITY FOR THE INVENTION OF MYCOBACTERIUM LEPRAE AND PROBLEMS OF BIOETHICS

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Introduction. According to the WHO definition, leprosy, also known as Hansen’s disease, is a chronic infectious disease caused by *Mycobacterium leprae*. The disease mainly affects the skin, the peripheral nerves, mucosal surfaces of the upper respiratory tract and the eyes [23]. At the present stage, leprosy belongs to the conditionally eliminated diseases, however, every year there are cases of infection with this disease [20].

A vivid indication that leprosy has been a threat to humans since ancient times is that the biblical texts contain many speculations about this disease, in particular, the thirteenth chapter of Leviticus, which is part of the Pentateuch (Torah), gives a very detailed description of leprosy with an attempt, so to speak, to diagnose differentially. Thus, if a patient has depigmentation of hair and “deep” ulcers, the priest must “diagnose” leprosy and declare the patient unclean [17, 13:3]. In seven days, the priest can distinguish leprosy from herpes or psoriasis [17, 13:6; 17, 13:31]. A rather thorough analysis of skin diseases in sacred texts was made by the Brazilian researchers R. A. M. Frutuoso, G. R. D. Ferreira, S. B. Frutuoso [6], the Russian researchers O. Terletsky and G. Grigoriev [22], as well as the Uzbek scientists I. Karomatov and H. Gulyamov. [14]. However, the interpretation of its etiology and pathogenesis was far from scientific, because it was believed that this disease is a divine punishment for sin and a demonstration of God’s wrath to mortals. A careful reading of this section of the Torah confirms the thesis that the people of the Ancient East often confused leprosy with other skin diseases, there are a large number of synonyms that denote various morphological elements of dermatological manifestations of diseases such as scleroderma, eczema, vitiligo, mycosis, herpes, psoriasis [4].

The disease, whose complications for thousands of years killed tens of thousands of patients who were feared and branded, isolated and expelled from society, remained unexplored until the 1870s and only during the rapid development of microbiology there was a real breakthrough in the diagnosis, treatment and prevention of leprosy. An invaluable contribution to these issues belongs to the Norwegian microbiologist and leprologist, Gerhard Hansen, and the German doctor, microbiologist Albert Neisser, jokingly referred to by his students as the “father of Honococcus”. **The aim of the research** is to study the biographies of Gerhard Hansen and Albert Neisser in the comparative aspect.

Materials and methods. The general scientific methods, including analysis and synthesis, as well as biographical and comparative-biographical methods were used in the study. The research material relied on the biographies of Gerhard Hansen and Albert Neisser.

Results and discussion. Gerhard Henrik Armauer Hansen was the Norwegian bacteriologist who discovered the leprosy agent – *Mycobacterium leprae* (bacillus Hansen) and refuted the theory of heredity of the disease. Gerhard Hansen was born on July 29, 1841 in Bergen in a large family – the boy was the eighth child out of 15 [7]. He studied medicine at the Royal University of Frederick (now Oslo University). He obtained his scientific degree in 1866. For the next two years, G. Hansen worked at the National Hospital of Christiania, as well as in one of fishing communities of the Lofoten Islands. In 1868, G. Hansen returned to his hometown, which at that time was the focus for the Norwegian studies of leprosy, and became an assistant to the famous specialist-leprologist D. Danielssen (Daniel Cornelius Danielssen, 1815-1894) [1], who in 1847 along with dermatologist C. Boeck (Carl Wilhelm Boeck 1808-1875) co-authored a study on leprosy, which played a significant role in the research and treatment of this disease.

Interesting is the fact that D. Danielssen conducted experiments in vivo: he rubbed in his own scratches, or his subordinates, as well as volunteer patients with other diseases, the pus from leprous nodes in patients with leprosy. However, the infection did not occur, although these experiments did not go without a trace for D. Danielssen: he contracted tuberculosis of bones, infected his wife and four children who eventually all died, while D. Danielssen himself lived to almost 80 years of age.

If D. Danielssen mistakenly believed that leprosy was a hereditary disease [1], then G. Hansen, who traveled extensively around Norway and assisted patients, put forward the revolutionary hypothesis at that

time that leprosy was not a hereditary disease but a contagious bacterial disease with a chronic course. Contrary to D. Danielssen's scientific authority, G. Hansen was able to maintain excellent personal relationships with him, and the fact that the organized preventive measures provided a significant reduction in the number of new infections only confirmed his bold assumptions. This was the impetus for G. Hansen to begin his own experimental and epidemiological study. In his first work, dated 1869, G. Hansen used the term “infectious substance” and described leprosy changes. However, poor material equipment did not contribute to the proper formulation of the data obtained experimentally.

In 1870, G. Hansen won a grant and was able to improve his qualification in histopathology in Bonn, where he was supervised by Max Johann Sigismund Schultze, 1825-1974 - a prominent German anatomist, zoologist and histologist. The Franco-Prussian War, which began in the same year, did not contribute to advanced training, so G. Hansen moved to study in Vienna [7; 8, p. 297]. In early 1873, G. Hansen became engaged to the daughter of his mentor D. Danielssen Fanny (Stephanie) (who, like other children of D. Danielssen, would soon die of pulmonary tuberculosis) [1; 7; 12]. At the wedding, the newly wedded couple was presented with a new modern microscope, and G. Hansen zealously began to examine the brown mass characteristic of lepromatous nodes. The result was rapid: on February 28, 1873, he found small sticks that were stacked in equal rows [13]. The scientist presented the results of his research in a work that became epoch-making and a year later was published in the major Norwegian scientific journal, later was translated into English as *Investigations Concerning the Etiology of Leprosy*, and in which he discovered the sticks that were tentatively called “rods” [1].

As R.K. Kannan points out [13], the results of G. Hansen's discovery were ahead of his time: some colleagues were quite skeptical, arguing that he saw the sticks, but whether they cause the disease is unknown, some scholars mocked the scientist, and others opposed him in all possible ways. Despite the fact that G. Hansen did not know how to prove the authenticity of his invention, his experiments aroused considerable interest among many researchers from other countries. For example, it is known that a Swedish veterinarian Edlund tried to appropriate (though unsuccessfully) G. Hansen's invention.

A similar situation occurred with the colleague of the microbiologist-innovator, the future Nobel Prize winner Robert Koch (Robert Koch, 1843-1910) – dermatologist and venereologist A. Neisser (Albert Ludwig Sigismund Neisser, 1855-1916), already famous at that time for discovering the causative agent of gonorrhea, named *Neisseria gonorrhoeae*.

In 1879, A. Neisser came to Norway, and G. Hansen arranged for an honorary guest for a two-month trip around leprosaries, showed him 600 patients and provided a considerable amount of biological preparations. After returning to Breslau, A. Neisser began to stain bacteria previously detected by G. Hansen and hypothesized that these bacteria were infected by agents of leprosy, thereby declaring the priority of opening the leprosy pathogen [15]. Meanwhile, Koch informed G. Hansen of the success of his subordinate and introduced him to a new method by which the sample of infected tissue had to be impregnated with fuchsin for a day, after which the bacilli of the leprosy became bright red and clearly differentiated. It is natural that G. Hansen decided to prove his priority for the discovery, and in 1880 he managed to stain the bacteria of leprosy.

As both G. Hansen himself, and his father-in-law and mentor D. Danielssen were resistant to leprosy, according to E. Koch's suggestion, it was decided to further infect an already sick person in order to obtain biological material to confirm G. Hansen's hypothesis. On November 3, 1879, G. Hansen, as chief leprologist, summoned a 33-year-old leprosy patient Kari Spiessen, who had been ill with leprosy since the age of 16, and, without her voluntary consent, wanted to incise her cornea with an infected scalpel. The patient was initially scared and refused, but Hansen's colleague reassured her and the woman agreed. When this story became widely known in the medical environment, G. Hansen's actions, despite the *pia desideria* of the researcher, were found to be incompatible with the high rank of a doctor, although, on the other hand, the evidence of the scientist's guilt was insufficient to conclude [8; 16]. By the King decree, G. Hansen was deprived of the right to treat patients and was put on trial, although he retained the position of chief leprologist on a social basis until his death [18].

Last but not least, the scandal was triggered by A. Neisser, who published his description of leprosy pathogen and said that although G. Hansen saw the microorganism, he could neither stain it nor prove that it is a bacterium. In addition, A. Neisser referred to D. Danielssen, as if G. Hansen had not shown him his bacillus. These statements were aroused an attack of rage in D. Danielssen, who had collaborated and supported G. Hansen throughout his life [21]. In addition, G. Hansen received unprecedented support from all Norwegian doctors who defended the great Norwegian discovery: the Norwegian medical community,

outraged by these events, insisted that G. Hansen submitted explanatory statements to the European scientific journals in English, German and French. During the trial of G. Hansen, held on May 31, 1880, each of the interrogated medical experts confirmed that G. Hansen acted in the interests of the motherland, medicine and science. Despite the fact that G. Hansen was deprived of the opportunity to treat patients, his authority in the scientific world remained unshakable: G. Hansen held many honorary positions, in particular, since 1874 he occupied the position of director of Bergen Museum of Natural History, was a member of medical unions, and co-founder of the Leprosy profile journal. At Berlin Congress of Leprologists, held in 1897, G. Hansen was recognized as a “famous man” for his brilliant discovery [16, p. 213], referred to by the Norwegians as “unique in Norwegian medicine” [11, p. 424]. G. Hansen died of a heart attack on February 12, 1912. Funeral service of a prominent scientist was held at the museum, which he headed for almost 40 years, and his ashes remain there to this day [10].

Ut supra, another iconic figure in the history of world leprology is Albert Ludwig Sigismund Neisser, the German doctor, microbiologist, who was jokingly referred to by his students as “the father of gonococcus”. A. Neisser was born on January 22, 1855, in the family of Doctor Moritz Neisser (1820-1896) in the small town of Schweidnitz (now the Polish town of Swidnica) near Breslau (modern Polish Wroclaw). The boy's mother died when he was just 1 year old, so he was raised by his stepmother. After graduating from St. Mary Magdalen High School, where his classmate was Paul Ehrlich, the future outstanding immunologist and bacteriologist, Nobel Prize winner in Physiology and Medicine (1854-1915), A. Neisser entered the University of Breslau, which was considered the top German university, and also studied at the University of Erlangen for one semester. In 1877, under the supervision of Michael Biermer (Michael Anton Biermer, 1827-1892), A. Neisser defended his thesis on echinococcosis and received his doctorate degree [19, p. 229].

A. Neisser planned to become a specialist in the field of internal diseases, but due to the fact that his scientific supervisor did not have a vacant position of an assistant, he accidentally got to the dermatological clinic of Heinrich Koebner (1838-1904) and received the position of an assistant of dermatologist Oscar Simon (1845-1892). It was while working at this clinic that 24-year-old A. Neisser discovered the causative agent of gonorrhea in 1879. A. Neisser examined 35 patients: 26 adult patients with typical purulent urethritis, seven clinical cases of neonatal infection, and two with ophthalmic manifestations. Initially, this pathogen was called “micrococcus”, and in 1882 A. Neisser gave it another name – “gonococcus” [2], which was later changed to the modern one – *Neisseria gonorrhoeae*. This discovery was the start of his research career, of which he often jokingly said later: “What would I have been without the gonococcus?” [19, p. 230].

As noted above, in 1879 A. Neisser went to Norway, where the famous leprologist G. Hansen handed him tissue samples of patients with leprosy. After returning to Germany thanks to the latest technology at his disposal, A. Neisser identified the causative agent of this disease [11, p. 230]. However, this invention was accompanied by a high-profile international scandal, as A. Neisser declared his priority of the invention of the leprosy agent, although G. Hansen had done so before. Thanks to R. Koch's intervention, this situation was resolved quite diplomatically. In 1880, A. Neisser received the title of Associate Professor at Leipzig University, and two years later returned to Breslau at the age of 27 to take up the vacant post of his teacher, O. Simon, who died of cancer [19, p. 230].

Over the next three decades, A. Neisser made a brilliant career, not least made possible by the financial support of the all-powerful Prussian education and culture advisor Friedrich Althoff (1839-1908), who sponsored A. Neisser for 27 years. It is because of this support that the dermatological clinic was founded in Breslau in 1892, built by A. Neisser's project – a large, modern 95-seat building with laboratories equipped with state-of-the-art facilities, lecture halls, a zoo, a museum and a library. It is natural that this clinic has become a world-renowned research center.

A. Neisser is known not only as a researcher for gonorrhea, anthrax, actinomycosis, psoriasis, vitiligo, as a scientist who proved the tuberculous origin of lupus, but also, above all, as a scientist who made a significant contribution to the study of syphilis, which was, like leprosy, a huge medico-social problem for centuries.

A series of experimental studies on syphilis via inoculation conducted by A. Neiser led to a high-profile scandal, which, ironically, was similar to the scandal that at one time exploded around the name of another leprosy researcher, G. Hansen. A. Neisser was accused of introducing syphilitic serum without the consent of patients (these were four prostitutes aged from 17 to 20 years) [19, p. 231]. For this experiment, in 1900 A. Neisser was publicly fined 300 marks. However, neither his reputation, nor his medical license,

or his further scientific career suffered a significant impact, as the German medical community supported the scientist [10] (unlike G. Hansen, who was deprived of the right to treat patients by the King's decree and was put to trial). It is worth noting that this scandal undoubtedly had a positive effect, as it was thanks to him that the first government decree was issued, according to which the subjects of experiments had to give informed consent to participate in clinical trials [3].

An important role in further studies of syphilis was played by scientific expeditions of A. Neisser (which he organized at his own expense) to the island of Java and to Botavia (the territory of modern Indonesia), where the Dutch military contingent was temporarily stationed, and many soldiers were ill with syphilis. These expeditions enabled the scientist to experimentally investigate the mechanisms of syphilis transmission, including from a monkey to a human being. A. Neisser has also made it into history as an active fighter for the prevention of sexually transmitted diseases through health education and informing the general public about measures to prevent sexually transmitted diseases and introducing rigid sanitary measures aimed at minimizing the spread of syphilis.

Interestingly, A. Neisser argued for the rigid regulation of prostitution and the strengthening of sanitary measures against the representatives of this profession. In 1899, A. Neisser co-founded the German Dermatological Union, and in 1902, the German Union against Sexually Transmitted Diseases, and he remained its secretary-general until his death. In 1883, A. Neisser married Toni Kauffmann, a descendant of a wealthy Jewish family who became a constant companion in the scientist's life [19, p. 231]. The death of his beloved wife in 1913 had a negative impact on the health of the scientist who had diabetes, nephrolithiasis and cystitis for a long time. In addition, a few years before his death, A. Neisser unsuccessfully fell and broke his hip: he did not fully recover from this injury.

A. Neisser painfully survived the outbreak of World War I and as a patriot of Germany became a signatory to the so-called Manifesto 93 – “Aufruf an die Kulturwelt” (“To the Civilized World”), in which the prominent German figures of science and culture tried to whitewash and justify the war crimes of the Kaiser, committed during the first two months of World War I. In 1916, A. Neisser's health deteriorated sharply after he underwent the bladder removal at Berlin hospital. A. Neisser died of septicemia at the age of 62. He bequeathed his house to the city. In 1920, an art gallery was created in this house. In 1933, the building was seized by the Nazis and housed a hotel that was destroyed during World War II. Fortunately, A. Neisser's works, which were part of the museum funds, were saved by a doctor from Schweinfurt by the name of Brock, and now they are stored in the library of the famous clinic, built by A. Neisser in his time.

Conclusions. Comparative analysis of biographies of the prominent microbiologists G. Hansen and A. Neisser showed that despite the desire to serve science and humanity, adherence to the rules of bioethics, as well as human morality should remain an integral part of the activity of any scientist, a physician in particular. The timely publication of scientific achievements is a significant moment in the event of disputed questions about the priority of a scientific discovery.

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SUMMARY

GERHARD HANSEN VS. ALBERT NEISSER: PRIORITY FOR THE INVENTION OF MYCOBACTERIUM LEPRAE AND PROBLEMS OF BIOETHICS

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The article is interdisciplinary in nature and covers a wide range of issues in the history of medicine, morality and bioethics. Biographies of the Norwegian microbiologist G. Hansen and the German doctor, biologist, syphilologist A. Neisser are presented. The main attention is focused on the scientific achievements of these researchers in terms of infectious diseases and leprosy in particular. The authors focused not only on the significance of scientific discoveries, but also tried to show that any scientist, even an outstanding one, remains a person with his/her unique character, personal life and friendships, authority in the scientific community and mistakes, desire to gain fame and recognition. The main focus is on the scientific achievements of these researchers in the study of infectious diseases and leprosy in particular. The conflict over the priority for discovery of the leprosy pathogen has been highlighted. Attention is given to the conflict regarding the priority in discovery of the causative agent of leprosy. The authors compared the impact of the international scientific scandal on the priority for the discovery of Mycobacterium leprae, which involved virtually the entire scientific community of Europe at the time, on both scientists. It has been shown that most scientists unambiguously sided with G. Hansen, who was not only the author of the revolutionary hypothesis of the contagious and bacterial nature of leprosy at the time, but also the pioneer of the causative agent of this disease, as evidenced by the synonymous name Mycobacterium leprae – bacillus Hansen. Nevertheless, for a prominent scientist, the consequences of an unethical experiment on intentional additional infection of a patient became quite tragic, since he lost his license to practice medicine, and was put to a trial were his actions were found to be incompatible with the high-ranking status of a doctor, even

though he was the unsalaried chief leprologist of Norway until his death. The biography of A. Neisser, who became the culprit of this high-profile scientific scandal, was simultaneously studied. It is shown that a series of A. Neisser's experimental studies on another threatening disease – syphilis, by inoculation also led to a scandal, ironically, similar to that one around the name of Hansen. However, neither his reputation, nor his medical license, or his further scientific career suffered a significant impact, although it has become a precedent for obtaining informed consent from persons taking part in clinical trials. The findings revealed that, despite the desire to serve science and humanity, compliance with the rules of bioethics, as well as human morality, should remain an integral component in the work of any medical scientist.

Key words: leprosy, Gerhard Hansen, Albert Neisser, *Mycobacterium leprae*, problems of bioethics.

РЕЗЮМЕ

ГЕРХАРД ХАНСЕН VS. АЛЬБЕРТ НЕЙССЕР: ПРИОРИТЕТ ИЗОБРЕТЕНИЯ *MYCOBACTERIUM LEPRAE* И ПРОБЛЕМЫ БИОЭТИКИ

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Статья имеет междисциплинарный характер и охватывает широкий круг вопросов истории медицины, морали и биоэтики. Представлены биографии норвежского врача-микробиолога Г. Хансена и немецкого врача, биолога, сифилидолога А. Нейссера. Показано, что любой учёный, даже самый выдающийся, остается человеком с его уникальным характером, личной жизнью и дружескими связями, авторитетом в научном сообществе и фатальными ошибками, желанием достичь славы и признания. Основное внимание акцентировано на научных достижениях этих исследователей инфекционных болезней и лепры в частности. Описан конфликт, связанный с приоритетом открытия возбудителя лепры. Сравнено, какие последствия для Г. Хансена и А. Нейссера имел международный научный скандал относительно приоритета открытия *Mycobacterium leprae*, в который было вовлечено практически всё тогдашнее научное европейское сообщество. Показано, что большинство ученых однозначно встало на сторону Г. Хансена, который был не только автором революционной на то время гипотезы о контагиозно-бактериальной природе лепры, но и первооткрывателем возбудителя этой болезни, о чем свидетельствует синонимичное название *Mycobacterium leprae* – *bacillus Hansen*. Несмотря на это, для выдающегося ученого последствия неэтичного эксперимента с умышленным дополнительным инфицированием пациентки стали довольно трагическими, поскольку он потерял лицензию на медицинскую практику, пережил суд, по решению которого действия Г. Хансена были признаны несовместимыми с высоким званием врача, хотя он до конца жизни занимал должность внештатного главного лепролога Норвегии. Параллельно исследована биография А. Нейссера, который стал виновником этого громкого научного скандала. Показано, что серия экспериментальных исследований другой опасной болезни – сифилиса, – путем инокуляции, проведенных А. Нейссером, также привела к скандалу, который, по иронии судьбы, походил на тот, который в свое время разразился вокруг имени Г. Хансена. Впрочем, ни на репутацию, ни на медицинскую лицензию, ни на дальнейшую научную карьеру А. Нейссера этот досадный случай существенно не повлиял, хотя стал прецедентом для получения информированного согласия лиц, принимающих участие в клинических испытаниях. В выводах отмечается, что, несмотря на желание служить науке и человечеству, соблюдение правил биоэтики, а также человеческой морали должны оставаться неотъемлемой составляющей деятельности любого ученого-медика.

Ключевые слова: лепра, Герхард Хансен, Альберт Нейссер, *Mycobacterium leprae*, проблемы биоэтики.