Albert L. Neisser (1855-1916), Microbiologist and Venereologist

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Albert Ludwig Neisser* is remembered mainly as the discoverer of the etiologic agent of gonorrhea and because he is memorialized eponymically with the bacterial genus to which it belongs. The generic name "Neisseria" was already proposed in 1885 by V. Trevisan, an Italian bacteriologist (1), but it was not adopted generally until the 1930s. Thus, for example, *Neisseria meningitides*, first cultured by Anton Weichselbaum (1845-1920, Vienna) in 1887, for long remained *Diplococcus interellularis meningitides*.

Not only are the circumstances of Neisser's professional development of interest, but his scientific career was more complex than a single important discovery. He was born Jan. 22, 1855 in a small Prussian town near the university city of Breslau. His father, Moritz Neisser, was a physician who was widowed during Albert's infancy and he was raised largely by his stepmother. After attending a local elementary school, he attended *Gymnasium* in Breslau. Paul Ehrlich (1854-1915) was a classmate, beginning a life-long relationship. Between 1872 and 1877 he attended the University of Breslau, with some time also at the University of Erlangen (Nurnberg). He obtained his medical degree and license in 1877. Neisser wanted to remain in Breslau and, because the residency that he sought in internal medicine was not available, he accepted a residency in dermatology-venereology. At least the departments of pathology and dermatology lacked the prevailing anti-semitism. The latter department was already highly regarded in 1878, when it was chaired by Oscar Simon (1845-1882). Neisser's interest in the new field of bacteriology probably was stimulated by Ferdinand Cohn (1828-1898), the professor of botany, a pioneer bacteriologist, and the Danish bacteriologist Carl J. Salomonsen (1847-1924), temporarily in Breslau. Neisser knew the pathologists Julius Cohnheim (1839-1884) and Carl Weigert (1845-1904) long enough before they left for the University of Leipzig in 1877 and '78 to learn histologic staining techniques. Upon completion of his training, Neisser in 1880 obtained a junior faculty position at the University of Leipzig. The next two years became the only period during which he was not affiliated with the University of Breslau (2-5).

During his residency the 24 year old Neisser in 1879 made both of his principal discoveries. He demonstrated a morphologically consistent coccus in 26 adults with typical gonorrheal urethritis, seven cases of neonatal infection and two adult cases of ophthalmia. He stained the "micrococci" with methyl violet. Neisser's microscopic finding was soon confirmed, but he was unable to find a reliable culture medium (6). In 1882 Neisser made a more detailed morphologic description and introduced the term "gonococcus (7)." Although gonococci had been demonstrated microscopically in synovial fluid in cases of acute arthritis as early as 1883 (8), Neisser in 1893 became the first to report having grown the gonococcus in culture from synovial fluid (9). The pathologic significance of the gonococcus remained in dispute into the 1890s, mainly because of inability to infect laboratory animals with it.

Simon died unexpectedly in 1882 and, perhaps aided by political influence (5), Neisser at age 27 was recalled from Leipzig to head the dermatology department, a position he retained for the last 34 years of his life. In addition to his clinical and scientific work he became an effective fund-raiser, especially in the Jewish business community. These efforts culminated in 1892 with a new building to accommodate the dermatology-

venereology department (4).

Leprosy

In 1874 G.A. Hansen (1841-1912), a physician at the leprosarium in Bergen, Norway, published his discovery of the possible bacterial cause of leprosy, made the year before (10). An English translation of this Norwegian article was published in 1875 (11). Only two human diseases had at that time been acknowledged to have a bacterial etiology: anthrax in 1850 and relapsing fever in 1868. Thus there was great skepticism about Hansen's allegation, not least by his chief, D.C. Danielssen (1815-1894). Hansen explained in 1880: "Everyone can easily see from the report of my examinations in 1873 that I could assume that bacteria exist in the leprous lesions. But nevertheless, based on these examinations alone, I dared only to express a suspicion that these bacteria are the actual poison that elicits the disease when they enter the body (12)."

How Neisser learned of Hansen's publication is uncertain. However, in July 1879 he traveled to Norway, where leprosy was still endemic and visited three leprosaria. In Bergen he met Hansen with whom he saw many patients and was given cutaneous biopsies and visceral specimens, as well as unstained slide preparations. As soon as Neisser returned to Breslau he prepared slides from this material, stained with fuchsin and with gentian violet, in all of which he could clearly demonstrate the bacilli. In October he presented his findings at a meeting of the Silesian Society for National Culture, which soon thereafter were published in the local Breslau medical journal (13).

A few months later Hansen published an article in German that was intended mainly to defend the priority of his discovery, but acknowledged Neisser's priority in regard to staining of the bacteria. "To explain why these [microscopic] preparations [of biopsies of lepromatous nodules] previously did not succeed I cite a reply from Dr. Koch, whom I had asked for advice: It was either the property of the dyes I had available or the circumstance that I had not dyed energetically enough. This error, as Dr. Koch told me, was also made by Dr. Neisser, so that he only later succeeded in achieving better preparations, which most probably depended on the proven experience of Dr. Koch (12)." In the following year Neisser published a lengthy, illustrated article in the same journal, in which he stated that he had not sought to deny Hansen's priority. However, he had by staining proven the finding about which even Hansen had been uncertain. Neisser considered his clear description of the lepra bacillus to have been a greater scientific contribution than the discovery of the gonococcus (2). He continued research on the bacteriology of leprosy, including unsuccessful attempts at culturing, until 1886 (14, 15).

Clinical dermatology

Between 1883 and 1901 Neisser also published on various problems in clinical dermatology, emphasizing differential diagnosis. The only non-venereal disease after leprosy with which he was concerned for long was lupus vulgaris (cutaneous tuberculosis). His writings on this appeared from 1908 until 1913 and, as with venereal diseases, dealt both with clinical and public health aspects.

Public health and venereal disease control

Throughout his career Neisser was interested not only in the diagnostic and therapeutic aspects of venereal diseases, but also in their public health ramifications. In an 1890 article he revealed his attitude about prostitutes: "Much more is achieved when one recognizes that one is always dealing with sick people, sick not only in the physical, but frequently also in the psychological sense, and very frequently with people who are not automatically detestable, but rather are to be pitied and in need of help." (16) Statistics regarding the admission

to the Breslau City Hospital for gonorrhea were begun in 1886 when the diagnosis accounted for 9.3% of VD admissions. Two years later this diagnosis accounted for 54%, which Neisser attributed to the supplementation of physical examinations with microscopic examination (not cultures) of secretions. This new diagnostic sensitivity created financial problems for the hospital because, on average, admissions for gonorrhea lasted a month (16). Numerous ineffective oral and instilled medications were employed, to which he added Protargol, a silver proteinate for urethral instillation that he had devised (17).

Ten years later he presented various civilian and military statistics regarding the prevalence of gonorrhea and its public health costs. "… [W]ith the enormous distribution of the disease and its severe complications, everyone must feel that it is high time to sound a warning on the matter. Gonorrhea is a social danger for the people and requires the most careful attention from the authorities who are responsible for the public health." (18) In 1899 Neisser became one of the founders of the German Dermatologic Society, and in 1902 he organized the German Society for Combating Venereal Diseases. Most of the publications in his last years pertained to the control of venereal diseases in the civilian and military populations.

Experimentation on transmissibility and immunity of syphilis

In the 1850s experiments had been conducted in which contents of secondary syphilitic lesions were injected into healthy persons to determine whether such lesions are contagious (19) Even then the disastrous results were anticipated by some and caused an ethical scandal, although "syphilization" experiments continued to the end of the century. In 1892 Neisser conducted somewhat similar human experiments on which he reported in 1898 in a review article entitled "What do we know about the serum therapy of syphilis (20)?" Although a microbe was suspected, this investigation preceded the identification of the etiologic agent and development of a serologic diagnostic test. Neisser wanted to test the hypothesis that the disease could be ameliorated or prevented by injections of blood serum from syphilitics from which bacteria had been thoroughly removed. In the less problematic trial, syphilitics in the early stages of the disease were infused intravenously with serum from patients with late syphilis. He concluded that "The result of all of these attempts, 28 in all, should be considered absolutely negative."

While this study was being conducted, three young female in-patients and a 24 year old woman with gonorrhea received a subcutaneous injection of syphilitic serum and developed no signs of syphilis. With this "assurance of safety," four prostitutes ages 17-20, one of whom had gonorrhea, were given an intravenous injection of syphilitic serum. All soon demonstrated signs of secondary syphilis and Neisser concluded that such prophylactic immunization was ineffective.

In March 1900 a disciplinary proceeding against Neisser was held because he had inoculated patients "without having ascertained the consent of these persons or their legal representatives." According to Josef Jadassohn (1863-1936), a former student, Neisser "was so convinced of the correctness of his experiments that he was quite amazed at the attacks he received (21)." He had written in 1898: "The possibility that the intravenous infusions might have been injurious can not be absolutely denied. I of course, am entirely convinced that these prostitutes were infected in another "normal" way (20)." This argument was rejected and Neisser was fined 300 Mark. However, neither his licensure or academic position were affected (22).

Experimental syphilis

Since the 1860s numerous micro-organisms had been claimed to be the pathogen of syphilis (23). In 1904 investigators in Neisser's laboratory showed that the pathogen of syphilis is not a filterable virus (24). In 1903 Elie I. Metchnikoff (1845-1916) and Pierre P. Roux (1853-1933) at the Pasteur Institute succeeded in

infecting chimpanzees with the unknown pathogen of syphilis (25). Neisser soon determined to verify their findings. This work began in September 1903 with chimpanzees from the Breslau zoo, and his first detailed report was published a year later (26). In the absence of a serologic test, before autopsy the question whether an animal had actually been infected depended entirely on the development of symptoms that resembled those of human syphilis. Furthermore, the incubation period was unknown and animals frequently died a few weeks after having had syphilitic human serum or tissue administered, usually of pneumonia.

In 1905 Neisser organized a privately funded expedition to Java (27). This island was chosen because of information that syphilis was more prevalent there than on Borneo or Sumatra. Participants included his wife and at least one of his trainees, Gustav Baermann. This was an enormous undertaking. According to Neisser, at any one time they had 10-20 orangutans, imported from Borneo, 20-30 gibbons and 600-800 monkeys (mainly macaques) in captivity. Many also died, not of pneumonia as in Breslau, but of gastroenteritides. Apes were more easily infected with syphilis than monkeys. The incubation period typically was 3-5 weeks. To test for the dissemination of the pathogen, tissue was taken from various organs of infected animals and inserted into healthy ones. It was found that marrow and, secondly, spleen were the most consistent sites of the pathogen. Blood was never infectious. Although secondary lesions occurred only in apes, it was demonstrated that unresponsiveness did not indicate lack of dissemination in monkeys.

While they were in Java in 1905, Fritz Schaudinnn (1871-1906) and Erich Hoffmann (1868-1959) in Berlin discovered the *Spirochaeta pallida*, the pathogen of syphilis (28). How Neisser learned of this discovery is uncertain, but he at once attempted to verify the finding. This was successful in humans, as well as in a few apes and monkeys. Neisser credited most of this work to Baermann. A government-funded second expedition to Java was made in 1906-07. In this, in addition to continuing the experiments with primates and monkeys, attempts were made to transmit syphilis to other mammals and chickens (29). Success occurred only in guinea pigs, but thereby introduced a more practical animal for syphilis experimentation. This investigation, to which Rudolf Pürckhauer was assigned, continued in Breslau until 1909 (29).

Metchnikoff had concluded from his experiments that the pathogen of syphilis is weakened by passage through several rhesus monkeys. If true, development of an active anti-syphilitic vaccine might become feasible. Beginning during the second Batavia expedition and continuing in Breslau until 1910, Neisser and Bruck experimented with monkeys and guinea pigs to evaluate Metchnikoff's conclusions (30). They disagreed with Metchnikoff and extended the investigation to immunization with killed spirochaetes and serum made from attempts to "immunize" monkeys, horses, cattle and sheep, as well as chickens. They concluded that no immunologic technique provides either preventive or therapeutic benefits.

Serologic testing

In 1903 Jules Bordet (1870-1961) and Octave Gengou (1875-1957) invented the complement fixation test for the identification of cholera vibrios (31). In winter 1905-06 Neisser visited August von Wassermann (1866-1925) at the Robert Koch Institute in Berlin. In the course of their conversation about the complement fixation reaction Neisser suggested that it should be adapted to test for syphilis, since its pathogen was now known (32). As the first source of spirochaetes Neisser provided the liver of a syphilitic fetus and, for testing, sera from syphilitic patients. Wassermann assigned Carl Bruck (1879-1944), then one of his trainees, to develop the test (33). Bruck subsequently joined Neisser's second Java expedition and became a member of his faculty until 1911. A few months after the initial announcement of the test Neisser, Bruck and Schucht reported their preliminary experience. The reaction succeeded in syphilitic apes as well as in patients, although it was positive

in only 70% of symptomatic syphilitics. Some cases became positive on re-testing, but some positive tests when repeated became negative (34). Not surprisingly, the Wassermann test elicited considerable skepticism in the first years of its use (35). Neisser staunchly defended its validity, but did not participate in subsequent research to improve and understand the reaction. In an English language review in 1908 he stated that "Already in hundreds of cases in my own practice the application of [the Wassermann] reaction has given us clear evidence of syphilis…" even in the absence of definite clinical signs (35). Never "in many thousands of examinations" has the reaction occurred in health men.

Treatment of Syphilis

Neisser was satisfied with the efficacy of mercury treatment for syphilis and mainly experimented with its optimal means of administration. He even used the improvement of primary and secondary lesions following an "energetic course of mercury" for the differential diagnosis of syphilis. Nevertheless, he considered mercury to be bacteriostatic, not bactericidal (19). Iodine compounds were also not believed to be spirochaeticidal, but "exert a special curative action on tertiary processes." (34). Nevertheless, with some hesitance, Neisser in 1910 accepted Ehrlich's new arsenical preparation (37). "It is almost funny when some, in their enthusiasm about "606" alone or in combination, take the position that heretofore we have been powerless against syphilis." He considered "606" especially important for cases of intolerance of mercury, cases that appear to have become resistant to mercury, and for various tertiary symptoms. "Arsenobenzol, designated "606," whatever the future may bring to justify the present enthusiasm, is now actually a more or less incredible advance in the treatment of syphilis and in many ways is superior to the old mercury - as valuable as this will continue to be – because of its eminently powerful and eminently rapid spirochaeticidal property." In later publications he became a strong advocate of arsenical therapy.

Final years

Although Neisser became increasingly incapacitated during the last four years of his life, he continued to attend conferences and to publish. In 1912 he suffered an accidental hip fracture from which recovery was slow (38). Next he suffered repeated bouts of renal colic, and diabetes mellitus developed. He finally submitted to surgical nephrolithotomy, but became septic and died on July 30, 1916, 61 years of age.

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• Albert Neisser was not related to Max Neisser (1869-1938), a bacteriologist who also was educated in Breslau, but had his career in Frankfurt am Main.