

## THE HANSEN-NEISSER CONTROVERSY, 1879-1880

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In 1955 Fite and Wade (<sup>2</sup>) published a very interesting paper on the so-called Hansen-Neisser controversy. They gave a clear tribute both to Hansen and Neisser for the discovery and description of *Mycobacterium leprae*. Nevertheless, since most of Hansen's publications were written in Norwegian, I should like to give some supplementary information.

As a young man, aged 27, Hansen began to work in the leprosy hospital in Bergen, Norway. His first scientific paper was a prize essay on the normal and pathologic anatomy of lymph nodes, submitted to the University of Christiania in 1869. For this the university awarded him a gold medal.

It has been said (by Reidar Melsom; see Fite and Wade) that Hansen was awarded the King's Gold Medal in 1869 for a work presented to the university, which was not printed. That is incorrect. It was not the King's Medal, but Professor Skjelderup's Gold Medal that was awarded to him. Michael Skjelderup (1769-1852) was the first professor of medicine at the University of Christiania, and his gold medal is awarded for medical prize essays.<sup>1</sup> The work presented to the university was published, but not until 1871 (<sup>4</sup>). The monetary award which Hansen received in 1871 was not for his study of the lymph nodes; it was a grant given him by the Norwegian Medical Society to study leprosy. That resulted in his 1874 report, describing the discovery of the leprosy bacillus (<sup>5</sup>).

Lymph nodes from leprosy were included in the material of his prize essay. In these nodes, Hansen observed some yellowish granular masses. Following up these observations he found the same yellowish granular masses in nodules from other leprous organs also. These observations were printed as his first publication in 1869 (<sup>3</sup>); this report was mentioned by Fite and Wade, but they regarded it as unimportant compared to the 1874 report. Nevertheless, these observations were the forerunners of the discovery of the leprosy bacillus.

Earlier, Danielssen had described and shown these yellow granular masses in leprous tissue, and he regarded them as characteristic of leprosy. In 1859, when Rudolf Virchow visited Bergen to study leprosy, Danielssen showed him these elements. Virchow, however, interpreted

<sup>1</sup> A Hansen memorial room was inaugurated in the old Bergen leprosy hospital on February 12th, 1962. His medal is kept in this room, to which it was sent as a gift from his daughter-in-law.

them as only fat-degenerated cells, and Danielssen bowed to the authority of Virchow. Hansen, on the other hand, proved that these yellowish granular masses were not degenerated cells, as Virchow had thought, but was of the opinion that they were specific for leprosy. It was in these same yellowish granular masses that he found the rod-shaped structures which led him to his views on the parasitic nature of leprosy.

When Hansen first observed his bacillary forms is uncertain. According to the usual assumption, 1873 was the year in which the observation was made. The first published mention of Hansen's organism which I have found is in a report by H.V. Carter, surgeon-major of the British army in Bombay <sup>(1)</sup>. He visited the Norwegian leprosy asylums in August and September 1873, and in his report he concisely recounts the information which he had obtained there. I quote directly from his report:

At the present day in no other part of the world, so far as I am aware, are there equally complete, well-conducted, and successful leper-asylums as in Norway; and the physicians in charge are often eminent men, versed in modern science and of European repute.

These advantageous conditions form a most striking contrast with what is known of the arrangement and direction of the lazarettos of old. They arise, of course, out of the circumstances of the case; here is a decisive experiment, conducted in the eyes of watchful Europe by a nation which, though small in numbers, has yet acquired a high position in the intellectual ranks of the age.

In conclusion, I have sometimes thought that we should be willing to admit more than one mode of origin of leprosy. It is, however, improbable that so characteristic a disease should be due to several general causes; and the more promising inquiry would be that of its origin from a combination or succession of influences, which separately could not produce the affection.

He continues with the following foot-note:

I take this opportunity of alluding very briefly to the latest investigations with which I have become acquainted, from their great interest and value. Dr. G. A. Hansen of Bergen is engaged in a series of inquiries which cannot but throw much light upon the origin and nature of leprosy. These point to the parasitic origin of the disease; and by Dr. Hansen's kindness I have myself seen the minute organisms (a species of *Bacterium*) which are present in living leprosy matter taken from the interior of a "tubercle." Should these inquiries terminate in demonstration, it would be necessary to reconsider the topics I have just mentioned, for, as Dr. Hansen justly remarks, if leprosy be shown to be a specific disease . . . then its propagation by hereditary transmission must be very limited, because no specific disease presents real hereditary characters. Some might admit that the proofs of heredity in disease are of the hypothetical order; and as regards leprosy it is not, perhaps, impossible to understand most of the signs of supposed heredity on the ground of local infection or personal contagion. I now rejoice to hear that Dr. Hansen's investigations are likely to be soon made public, because of the light they will furnish where illumination is much needed.

After Weigert and Koch had introduced new staining methods, Hansen tried to stain his bacillus employing these methods. While he was carrying out these investigations Albert Neisser, a pupil of Robert Koch, visited Bergen to study leprosy. Hansen demonstrated to him

his rod-shaped bodies and hoped that Neisser could help him with a successful stain, but Neisser also failed. When he left Bergen, he was provided with a large amount of leprosy material, and on returning to Breslau he succeeded in staining the bacilli.

Hansen and Neisser were quite different personalities. Neisser was an enthusiast. Immediately after he, as he says, "to his intense surprise" (7) had found stained bacilli everywhere in the material brought back from Bergen, he described in the same year, 1879, the bacilli he saw as the causative infectious agent of leprosy. But—as mentioned by Fite and Wade—it is his next article, published in 1881 (8), which "must be acknowledged to be an outstanding definitive description of the relation of the bacilli to the lesions and of their etiologic import."

Hansen had a very critical scepticism, and found that it is as well to be on the safe side. His staining methods were very primitive, but the rod-shaped bodies appeared distinctly in nodules treated with osmic acid. As a curiosity it may be mentioned, although actually there is no connection, that osmic acid is the best fixative for electron microscopic study of the leprosy bacillus and other mycobacteria.

In his 1874 report Hansen was very careful in his conclusions. He finished his report with the following thesis:

I have now prepared my topic from all aspects which I at present feel to be involved in it. Everywhere I find conditions which speak in favor of the specificity of leprosy, nothing whatever which distinctly speaks against it, and absolutely nothing which speaks in favor of nonspecificity.

After the appearance of Neisser's first article, Hansen (6) quickly wrote a new report, published in Norwegian, German and English periodicals, partly to maintain his priority in the matter and partly to give additional details. This article ends with an addendum:

Since writing this, I have also succeeded in staining the bacilli nicely in sections from nodules fixed in absolute alcohol, using a more drastic staining method as advised by Dr. Koch. The bacilli are present in all parts of the sections, at times singly, but frequently in groups, corresponding to their position in the cells.

Fite and Wade make the following comment on this article:

If this sounds like a weak article, it is because it is weak. Little new is recorded, and that inadequately. There is no evidence of more than a trivial amount of fresh work. We can but wonder whether between 1874 and 1879, Hansen really appreciated the importance of his observations.

I agree that little new is recorded in the 1880 article, but Hansen himself very well appreciated the importance of his observations. He was convinced that the rod-shaped bodies which he had discovered in 1873 were the causative agent of the disease, but his common and his critical sense told him that this actual fact was still incompletely proved. He knew the postulates which Jacob Henle (1809-1865) had formulated

in 1840 for regarding a microorganism as the causative agent of a disease:<sup>2</sup>

1. The microbe must always be demonstrated in connection with the disease.
2. The microbe must be isolated and studied outside the animal organism.
3. The microbe must cause the same disease which it caused under natural conditions, when it is again injected into an animal organism.

None of these three postulates was fulfilled. Hansen, therefore, in the following years worked steadily with new investigations to prove with certainty that the microorganism discovered really was the causative agent of leprosy. He enlarged his material, and in all the leprosy nodules from the different organs he found the rod-shaped bodies, confirming the first of the three postulates. After Robert Koch in a letter of 1879 had advised him to stain his smears for a longer time, he obtained a staining technique by which it was easier to demonstrate the bacilli. He made numerous vain attempts in the hope of finding a method to cultivate the bacillus on artificial media, and he also tried to transfer the disease to animals and human beings (see below).

As a result of the discovery of the causative agent there had to be a change, not only in the interpretation of the cause of leprosy, but also in the way of combating the disease. In 1875 Hansen was appointed medical officer for leprosy for the whole country. In this position he made proposals for the reform of legislation. In conformity with the investigations he pressed for, all the hygienic precautions against the disease were later fulfilled. The Norwegian leprosy act of 1877 and the amended act of 1885 are the fruits of his indefatigable endeavors.

Having tried several times to transfer leprosy to rabbits without results, Hansen started to inoculate leprosy material in man. In 1879 he inoculated a woman suffering from the anesthetic form of leprosy with material from a leprosy nodule. Nothing happened. However, Hansen had not asked for permission for the experiment, and by sentence of May 31st, 1880, he was deprived of his position as resident physician of the Bergen leprosy hospital. He continued, however, as medical officer for leprosy in Norway until his death in 1912.

In conclusion, I have given this supplementary information to Fite and Wade's publication, mainly in the hope of establishing the fact that Hansen showed no relative inactivity in the study of the bacillus in the years following its discovery in 1873. Hansen was a hard-working man. He was very interested in giving new evidence of the existence of his rod-shaped bodies. He could have written supplementary reports on his negative results, but his critical nature told him to wait in the hope of giving new positive contributions. How many scientists have not tried, without success, both to cultivate and to transfer *M. leprae* to animals and also to man? It has been time wasted, and most of it has never been reported.

<sup>2</sup> Forty years later these requirements became known as Koch's postulates.

Hansen lived at a time when scientists were more widely versed than are the specialists of today. He produced important publications on zoology and marine biology, and wrote several popular scientific essays. In an appendix to this article his publications on leprosy have been collected, with no claim that the list is complete.

## RESUMEN

Para concluir, se ha ofrecido esta información suplementaria de la publicación de Fite y Wade, principalmente con la esperanza de establecer el hecho de que Hansen no desplegó ninguna inactividad relativa en el estudio del bacilo durante los años que siguieron el descubrimiento del mismo en 1873. Hansen era un sujeto que trabajaba con ahinco y se hallaba muy interesado en aportar nuevas pruebas de la existencia de sus cuerpos de forma de bastoncillos. Pudo haber escrito informes suplementarios acerca de sus resultados negativos, pero su naturaleza analítica le indicó que aguardara esperando ofrecer nuevos aportes positivos. ¡Cuántos sabios no han tratado sin éxito tanto de cultivar el *M. leprae* como de traspasarlo a los animales y también al hombre! ¡Ha sido tiempo malgastado, y la mayor parte de la labor no ha sido presentada!

Hansen vivió en una época en que los hombres de ciencia eran más versátiles que los especialistas de hoy día. Produjo él así importantes publicaciones de zoología y biología marina y escribió varios ensayos científicos de índole popular. En un apéndice de este trabajo se han compilado sus publicaciones sobre lepra, sin pretender que la lista sea completa.

## RESUMÉ

En conclusion, j'ai surtout apporté cette information complémentaire à la communication de Fite et Wade, aux fins de démontrer qu'Hansen ne s'est pas détourné de l'étude du bacille dans les années qui ont suivi sa découverte de 1875. Hansen était un grand travailleur. Il était fort intéressé à trouver de nouvelles confirmations de l'existence de ses bâtonnets. Il aurait pu écrire des rapports supplémentaires sur ses résultats négatifs, mais son esprit critique lui conseillait d'attendre dans l'espoir d'apporter de nouvelles contributions positives. Combien de chercheurs n'ont pas essayé, sans succès, et de cultiver *M. leprae*, et de le transmettre à l'animal ainsi qu'à l'homme? Ce fut de temps perdu, et la plupart de ces tentatives n'ont jamais été relatées.

Hansen a vécu en un temps où les chercheurs étaient plus universels que ne le sont les spécialistes d'aujourd'hui. Il a laissé des publications importantes dans le domaine de la zoologie et de la biologie marine, et écrivit plusieurs essais de vulgarisation scientifique. La liste de ses publications sur la lèpre est donnée en appendice à cet article. Cette liste n'a pas la prétention d'être complète.

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3. HANSEN, G. H. A. Foreløbige Bidrag til Spedalskhedens Karakteristik [Preliminary contributions to the characterization of leprosy.] *Nord. Med. Arkiv.* **1** (1869) No. 13, pp. 1-12.
4. HANSEN, G. H. A. Bidrag til Lympheskjertlernes normale og patologiske Anatomi. [Contributions to the normal and pathological anatomy of lymph nodes.] *Christiania, H. L. Jensen, 1871, 47 pp., 5 plates.*

5. HANSEN, G. H. A. Undersøgelser angående Spedalskhedens Årsager [Investigations concerning the etiology of leprosy.] Norsk Mag. F. Laegev. **9** (1874) No. 3.
6. HANSEN, G. H. A. Bacillus leprae. Nord. Med. Arkiv. **12** (1880) No. 3, pp. 1-10.
7. NEISSER, A. Zur Aetiologie der Lepra. Breslauer Ärztl. Zeitschr. **1** (1879) 200-214.
8. NEISSER, A. Weitere Beiträge zur Aetiologie der Lepra. Vorläufige Mittheilung. Virchow's Arch. **84** (1881) 514-542.

## APPENDIX

*Hansen's Publications on Leprosy*

- (1) Foreløbige Bidrag til Spedalskhedens Karakteristik. [Preliminary contributions to the characterization of leprosy.] Nord. Med. Arkiv. **1** (1869) No. 13, pp. 1-12.
- (2) Fortsatte Bidrag til Lepraens (Spedalskhedens) Karakteristik. [Further contributions to the characterization of leprosy.] Nord. Med. Arkiv. **2** (1870) No. 16, pp. 1-32 & No. 21, pp. 1-24.
- (3) Bidrag til Lymphkjerternes normale og patologiske Anatomi. [Contributions to the normal and pathologic anatomy of lymph nodes.] Christiania, H. L. Jensen, 1871; 47 pp., 5 plates.
- (4) Zur Pathologie des Aussatzes. [The pathology of leprosy.] Arch. f. Derm. u. Syph. **3** (1871) 194-211.
- (5) Om vort Kjendskab til Spedalskhedens Aarsager og om vore Forholdsregler mod Sygdommen. [On our knowledge of the etiology of leprosy and our precautions against the disease.] Norsk Mag. f. Laegev. **3** (1872) No. 2, pp. 1-37.
- (6) (with O. B. Bull.) The leprous diseases of the eye. Christiania, Cammermeyer, 1873; 27 pp., 6 plates.
- (7) Undersøgelser angående Spedalskhedens Årsager. [Investigations concerning the etiology of leprosy.] Norsk Mag. f. Laegev. **3** (1874) No. 9, iv.
- (8) On the etiology of leprosy. British and Foreign Med.-Chir. Rev. **55** (1875) 459-489.
- (9) Bacillus leprae. Nord. Med. Arkiv. **12** (1880) No. 3, pp. 1-10.
- (10) Bacillus leprae. Virchow's Archiv. **79** (1880) 32-42.
- (11) The bacillus of leprosy. Quart. J. Microscop. Sci. **20** (1880) 92-102.
- (12) Fortsatte studier over bacillus leprae. [Further studies of bacillus leprae.] Nord. Med. Arkiv. **14** (1882) No. 29, pp. 9-16.
- (13) Studien über Bacillus leprae. [Studies of the leprosy bacillus.] Virchow's Archiv **90** (1882) 542-548.
- (14) Einige Bemerkungen über die Anästhetische Form des Aussatzes. [Some remarks on the anesthetic form of leprosy.] Vierteljahresschr. Derm. p. Syph. **10** (1883) 557-560.
- (15) Om de seneste Undersøgelser af Baciller ved Spedalskhed. [On the latest investigations of bacilli concerning leprosy.] Norsk Mag. f. Laegev. **3** (1883) 256-259.
- (16) Die Aetiologie und Pathologie der Lepra. [The etiology and pathology of leprosy.] Vierteljahresschr. Derm. u. Syph. **11** (1884) 317-336.
- (17) Tvangslov og Stiftelser mod Spedalskhed. [Legislation on and institutions for leprosy.] Med. Revue **2** (1885) 285-290.
- (18) Die Lage der Leprabacillen. [The status of the leprosy bacillus.] Virchow's Archiv **103** (1886) 388-392.
- (19) Die Aetiologie und Pathologie der Lepra. [The etiology and pathology of leprosy.] Congrès périodique international des Sciences Medicales, Copenhague 1886, Vol. III, pp. 27-40.
- (20) Die Erbllichkeit der Lepra. [The heredity of leprosy.] Virchow's Archiv **114** (1880) 560-562.
- (21) Ist die Lepra eine "im Aussterben begriffene" Infectionskrankheit und ist sie erblich? [Is leprosy a dying-out infectious disease, and is it hereditary?] Virchow's Archiv **120** (1890) 476-486.

- (22) Lepröse Testikler. [Leprous testicles.] Festskr. f. D. C. Danielssen. Med. Revue **8** (1891) 21-28.
- (23) Forholdet mellom tuberkulose og lepra. [The relation of tuberculosis to leprosy.] Fohr. Skandinav. Naturforskere 14. Möde, Köbenhavn 1892, pp. 509-515.
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- (25) Leprastudiets fremtidige Stilling i vort Land. [The future position of the study of leprosy in our country.] Med. Revue **12** (1895) 1-5.
- (26) Spedalskheden på Island. [Leprosy on Iceland.] Med. Revue **12** (1895) 5-6.
- (27) (With C. Looft.) Leprosy: In its Clinical and Pathological Aspects. Bristol, Wright, 1895, 145 pp.
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- (32) Nogle Lepraspørgsmaal. [Some leprosy questions.] Med. Revue **14** (1897) 324-325.
- (33) (With C. Looft.) Lepra (Spedalskhed) Klinisk og Pathologisk-Anatomisk Fremstillet. [Leprosy (Spedalskhed) A Clinical and Pathologic-Anatomical Point of View.] Bergen, Grieg, 1897, 92 pp.
- (34) Leprosy in Norway. Internat. Med. Annual, 1897.
- (35) Lidt om Spedalskhed (Lepra). [A few words on leprosy.] Naturen (1897) 324-336.
- (36) Spedalskhedens overførelse. [The transmission of leprosy.] Med. Revue **15** (1898) 297-298.
- (37) Lepraens bekjæmpelse. [The combating of leprosy.] Med. Revue **16** (1899) 106-108.
- (38) A rare case of leprosy. Lepra. Bibliotheca Internationalis **1** (1900) 88-89.
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- (41) Correspondence. Lepra. Bibliotheca Internationalis **3** (1903) 231.
- (42) Lepra. In Kolle-Wassermann: Handbuch der pathogenen Mikroorganismen. Jena, Gustav Fischer, 1903, Vol. II, pp. 178-203.
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- (44) Paraleprose. Deutsche med. Wochenschr. **38** (1904) 1380-1381.
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- (46) Zu Hutchinsons Fisch-Theorie. [On the fish theory of Hutchinson.] Lepra. Bibliotheca Internationalis **7** (1907) 27-28.
- (47) Leprosy in Finmark. Lepra. Bibliotheca Internationalis **7** (1907) 209-210.
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