

Vandenbroucke JP (2003). The contribution of William Fletcher's 1907 report to finding a cause and cure for beriberi.



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William Fletcher's experiment on inmates of a lunatic asylum in Kuala Lumpur, Malaya, lives on in medical memory as the definitive proof that certain types of rice were "either directly or indirectly, a cause of beri-beri" [as the original conclusion in the 1907 report read]. It was a rigorous experiment, mimicking several features of a modern randomized trial.

Also well remembered is the story of Christian Eijkman, who in 1889 proposed the nutritional hypothesis for beriberi, several thousands of miles away from Malaya, in another former colony - the Dutch East Indies. In 1929 Eijkman shared the [Nobel Prize](#) with Sir Frederick Gowland Hopkins, the biochemist in Cambridge, UK. Between Eijkman's original nutritional hypothesis and Fletcher's controlled trial, a number of other observational and intervention studies on humans had been done, several with ingenious attempts to remove bias from the observations.

Eijkman had been sent to the Dutch East Indies in 1886, as part of a commission to study beriberi, and he decided to experiment in chickens. Beriberi was a problem: a progressive neuropathy, leading to gait and sensory disturbances. As in Malaya, it occurred mainly among the inmates of institutions (prisons and asylums), and in the army. The prevailing dogma was that the disease was infectious, so Eijkman had fed chickens with potentially infective material from inmates, to no avail - up to the day in 1889 that the chickens suddenly started to develop a neuropathy that might resemble beriberi, but which disappeared as suddenly as it had come.

When trying to find out what had happened to produce this "epidemic", Eijkman discovered that, for a few weeks, the rice fed to the chickens had been changed by one of his servants from the unpolished to the polished (with husk removed) variety, and then back again. This observation prompted him and his successors in the Dutch East Indies to set in motion new animal experiments, which were later supplemented by observations and interventions in humans. These ultimately led to the idea that rice contained "an anti-beriberi factor". Thanks to the subsequent work of many others in many laboratories over the world, this led to the isolation of one of the vitamins of the B-group, a substance that has to be present in our food to preserve health. If they are deficient in vitamins of the B-group, people develop neuropathies such as beriberi or pellagra.

The story is a more tortuous one than is often thought, however. Eijkman's nutritional hypothesis was controversial, and the debates about the origin of beriberi led to several observational and intervention studies on humans to try to verify whether infection or nutrition was the cause - with rather variable results and interpretations. Many of these studies paid due attention to the potential of [allocation bias](#) and [observation bias](#). One of these stands out: an 1897 observational study on prison inmates done by Adolphe Vorderman, a government physician of the Dutch health inspectorate. He paid scrupulous attention to avoiding bias in his investigations, even the bias of his own memory. [Vorderman's 1897 report](#) is included and commented on separately in the *James Lind Library*.

Knowledge and debates about the origin of beriberi in the Dutch East Indies were adopted in the British Colonies, with much further theorising and numerous studies in inmates and other captive populations (like the army). These ultimately resulted in Fletcher's experiment in which individuals in a lunatic asylum were assigned to one or other of the two different types of rice. It is worth noting that Fletcher's conclusions did not rule out infection, as he gave three possible explanations for the findings: a toxin contained in rice, a deficiency in rice, or the idea that certain rice was not sufficiently nutritious and therefore made people more prone to infection. This led to renewed and more focussed experiments on people as well as on birds, which finally confirmed the early ideas about a nutritional deficiency proposed by Eijkman and further developed by his successor Grijns.

The whole story with its ups and downs and the many "half-way" positions taken by physicians is recounted in the book *BeriBeri, white rice, and vitamin B: a disease, a vitamin and a cure* by Kenneth Carpenter (University of California Press, 2000). The book quotes Eijkman as lamenting "that the workers in the Netherlands Indies had shown

Cite as:

Vandenbroucke JP (2003). The contribution of William Fletcher's 1907 report to finding a cause and cure for beriberi. JLL Bulletin: Commentaries on the history of treatment evaluation (www.jameslindlibrary.org).

how beriberi could be combated, but the disease was still there, while physicians in the British possessions had used that knowledge and applied and extended it" (page 63).

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