

Of Rice and Men

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This case study focuses on Christiaan Eijkman and his search for the cause of beriberi in the Dutch East Indies in 1890s. It highlights chance and error on the path to a Nobel Prize.

In October, 1886, three doctors embarked from the Netherlands on a mission of medical research that would take them almost halfway around the globe. They passed through the Suez Canal--only opened a few years earlier--and arrived a few weeks later in the Dutch East Indies (now Indonesia). On Java and the surrounding islands, they could be fascinated by the exotic wildlife and towering forests, and by dense thickets of fibrous rattan vines, harvested by the Javanese and exported to Japan to make tatami mats. Elsewhere, trees had been cleared to grow crops brought from other tropical regions: sugar cane, coffee, cacao and indigo. These crops made the East Indies valuable as a colony to the Netherlands.

Life on Java would not be the same for the three doctors. Amenities commonplace in Europe were scarce. The tropical heat was everywhere. A typical Dutchman would also have to develop a taste for rice, a staple in this region of Asia.

One of the doctors, Christiaan Eijkman, age 28, had seen the sights of Java before. He had served as an officer for the Dutch Army in Batavia. After two years, he had contracted malaria and returned to the Netherlands. Malaria was one of many diseases common in the tropics. Cholera, influenza, dysentery and plague were also widespread. So, too, was beriberi.

Beriberi was, in fact, the reason why the medical commission had been sent to Java. It is a debilitating disease, indicated by the name itself. In Sinhalese, the word beri means weak, and doubling it intensifies its meaning. Beriberi involves weight loss, muscle weakness, loss of feeling and eventually paralysis in the limbs. Fatigue can give way to confusion, depression and irritability. In some cases fluid collects in the legs, taxing the circulatory system, enlarging the heart and causing heart failure. The disease can be fatal. Anywhere from one to eighty percent of beriberi patients died.

In the late 1800s epidemics of beriberi in Asia became more frequent. In Japan in 1880-81, one doctor was swamped with so many beriberi patients that the hospital could not accommodate them all and they overflowed into nearby temples. The Dutch government was particularly concerned that large numbers of its fleet crews and native workforce were suffering. They wanted to find a cure for the disease or--better--prevent it. They sent the medical commission to find the cause of beriberi. Eijkman would eventually share a Nobel Prize for his discoveries on Java.

Disease, Germ Theory and Eijkman

Eijkman and his colleagues were also not the first to try to identify the cause of beriberi. Beriberi had been known in southern and eastern Asia for centuries. A Chinese physician had described it four thousand years earlier. In the East Indies it had been reported as early as 1642. But no one knew a cure.

THINK [1]: What might have caused the epidemics? What are the possible causes of any disease? How would you confirm one cause versus another?

The Dutch medical commission arrived with new ideas about disease from Europe. Indeed, Eijkman's career nicely reflected the discoveries. When Eijkman first visited the Indies in 1885, he was fulfilling a contract with the military who had helped pay for his medical education. After his return to the Netherlands, however, Eijkman became fascinated by exciting new studies of the role of bacteria in disease. He turned from practicing medicine to pursuing medical research. Eijkman went to Berlin to study with the world leader in the field, Robert Koch. According to Koch's 'germ theory of disease', disease was the result of microscopic organisms that infected the body.

In 1880 Koch had developed an important method for culturing bacteria on a solid medium instead of in a liquid nutrient broth. By spreading out the bacteria on a plate, he could separate the different strains or species of a mixed culture, isolate each one and then breed a pure culture. With this method it became much easier to isolate and identify specific disease-causing agents. In 1882 and 1883 Koch himself identified the bacteria that caused tuberculosis, cholera and diphtheria.

Outbreaks of beriberi were common in armies and navies and in prisons, all relatively closed communities. Was the disease therefore infectious, transmitted by some "germ"? The Dutch government decided in 1886 to send two doctors to Germany to learn the latest techniques directly from Koch and to apply them in the East Indies. Once there, the medical team met Eijkman. Hearing about their mission, he decided to join them. Also in that year, a prominent French researcher, using a method that he had pioneered a few years earlier, created a vaccine for rabies. The Dutch commission took all these new methods with them. They were thus prepared to find the bacterium that caused beriberi, isolate it and make a vaccine. The scientists were themselves vehicles for transferring an understanding of germ theory from Europe to Java.

Just over a year later, the group completed its work in Java. They characterized beriberi more precisely in terms of both its clinical symptoms and the nerve degeneration visible microscopically in the tissues. In their report, they confirmed that a bacterium caused beriberi. But they also discovered a new infection pattern. They had not been able to infect one organism from another. Whereas most diseases were transmitted through a single exposure to the germ, a person had to reside in an area of beriberi for several weeks to contract the disease. For beriberi, the bacterial agent must be transferred many times. The commission returned home, leaving Eijkman on Java to direct the local medical school. He established a small laboratory where he continued the work on beriberi. He had yet to establish a pure culture of the bacterium and from that, develop a vaccine.

Chicken-feed?

Three years passed as Eijkman continued his investigations. Eijkman's work had been frustrated because, even using Koch's techniques, he had been unable to isolate the beriberi bacterium in a pure culture. Then, in 1890, amid his daily activities of directing the medical school, teaching and treating patients, Eijkman made a chance observation. He noticed that chickens in the hospital yard were suffering from conditions similar to his beriberi patients. The chickens walked unsteadily and had difficulty in perching. Later they did some chickens rarely do: laid down on their sides! They also had trouble breathing. He posed the obvious question: could the chickens be infected with the same organisms that caused beriberi?

THINK [2]: What would you plan to do next? How would Eijkman know whether this was the same disease as human beriberi? What, if anything, might Eijkman gain from studying the chickens instead of humans?
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Eijkman did have the chickens promptly moved to another location for further study. When the chickens were moved, though, their health suddenly improved, with no apparent treatment! Why?

THINK [3]: Given this unexpected turn of events, what would be an appropriate next step? Where would you look next for clues?

Eijkman began to search for the factors that might help him to isolate bacterium. He traced one possible difference in the chicken's new home. Previously, the chickens had been served boiled rice leftover from the officers' table in the military hospital. But a new cook had given them a different variety of red rice, known locally as beras merah. Normally, the local rice had a reddish cuticle (or pericarp, in botanical terms). You could remove the cuticle, though, by milling or "polishing" the rice. Polished rice had a fancier white appearance and a taste that many people preferred. The cook had decided, however, that "civilian" chickens did not deserve such special white rice! So he had fed them "half-polished" rice instead.

When Eijkman discovered the change, he had an important clue. The polished rice must be the source of the infection. The white, starchy portion of the rice grain must contain the bacterium for which he had searched for so long. This would certainly explain why beriberi was so prevalent in nations where rice was a staple food. He clearly had not planned to change the chicken's diet, but its effects also did not escape his notice. The chance event revealed valuable information that he and his colleagues had missed during five years of deliberate study.

Soon, Eijkman was able to make chickens sick almost at will, simply by controlling their diet. When fed the polished, white rice, healthy chickens soon showed symptoms similar to human beriberi. In addition, when he fed them red rice, they became well again. They recovered as well when just the husks or cuticles of the rice--the "rice polishings"--were added to a diet of polished rice. In some cases, the sick chickens regained a normal gait and the ability to fly within a few hours of eating the rice polishings! Eijkman reasoned that there must be a neutralizing agent or antidote to the bacterium in the cuticle of the rice. This could explain why healthy chickens eating red rice remained healthy, even when living in the presence of other diseased birds.

Not everyone who heard of Eijkman's conclusions accepted them. Others agreed that the rice Eijkman used was responsible, but perhaps not for the reasons he specified.

THINK [4]: Imagine that you were among the skeptics of Eijkman's new discovery. How might you have interpreted these findings in another way? How might Eijkman have designed a test to respond to your criticism?

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Eijkman continued with his various administrative and teaching duties, while also finding time for his research on beriberi and the toxins it produced. Meanwhile, controversy over the new germ theory of disease continued worldwide. Two researchers (one Japanese, one French) independently seemed to have isolated the bacterium which caused bubonic plague. In India, over 45,000 people had received a new cholera vaccine. Compared to those not inoculated, 70 percent fewer died. In 1892, a skeptic of germ theory in Germany swallowed a vial of live cholera bacteria to demonstrate his belief that the bacteria did not cause the deadly disease. Indeed, he did not get sick.

Eijkman had still not demonstrated conclusively how polished rice was part of the process in which bacteria caused beriberi in humans. He needed a properly controlled experiment.

THINK [5]: How would you construct such an experiment on human diets, while also following basic ethical principles about respect for persons?
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Eijkman turned to institutions. There, diets would already be determined. The large number of cases would also help ensure that the results would not be due to chance or mere coincidence in a small group. He persuaded the prison at Tulong, where 5.8% of the population suffered from beriberi, to substitute undermilled, or half-polished, rice for white rice. All cases of beriberi were cured. But as Eijkman noted later, this merely confirmed the potential effectiveness of the cure. It did not demonstrate that a bacterium in the polished rice had initially caused the disease. This would require comparing individuals who consumed the different types of rice.

Eijkman thus enlisted A. G. Vorderman, supervisor of the Civil Health Department of Java, to help survey the incidence of beriberi on a wide scale. In each prison on Java prisoners ate either polished rice or half-polished rice, according to local customs. In some cases prisons served a mixture. Here was a natural experiment, a case where the desired experimental conditions existed on their own. For Eijkman and Vorderman's purpose, the experiment was fortuitously already in progress. Between May and September of 1896, Vorderman led an exhaustive study of beriberi in one hundred prisons of Java and the small neighboring island of Madura--a survey which embraced nearly two hundred and eighty thousand prisoners. He reported the distribution of beriberi in the 100 prisons and its frequency among prisoners as follows:

	# of prisons	# with beriberi	percentage of prisons w/ beriberi	frequency among prisoners
half-polished rice	35	1	2.7%	1 in 10,000
mixture	13	6	46.1%	1 in 416
polished rice	51	36	70.6%	1 in 39

Vorderman also considered other possible sources of the beriberi bacterium, focusing especially on hygienic factors:

	# of prisons	# of prisons where beriberi found	percentage of prisons w/ beriberi
Age of Buildings	_____		
40-100	26	13	50.0%
21-40	32	11	34.4%
2-10	42	19	45.2%
Floors	_____		
impermeable	58	24	41.4%
partly permeable	13	7	53.9%
permeable	29	12	41.4%%
Ventilation	_____		
good	68	28	41.2%
medium	11	8	72.7%
faulty	21	7	33.3%
Population Density	_____		
sparsely populated	73	32	44.6%
medium	1	1	
overcrowded	26	9	34.6%

THINK [6]: If Vorderman was able to show a correlation between diet and beriberi, why were these additional statistics necessary? What purpose does each serve?

Vorderman's further data indicated that beriberi did not correlate with lower altitude (many other diseases were more prevalent among those on lower ground). Nor did the incidence of other diseases match the distribution of beriberi. In four prisons, Vorderman noted further, the number of cases of beriberi increased with the arrival of a prisoner who already had beriberi.

THINK [7]: What conclusions can be drawn from Vorderman's study beyond what Eijkman could conclude from his study with chickens? (Reconsider especially your earlier assessments.) How do Vorderman's results support Eijkman's and/or other explanations?

Beriberi after Eijkman

Eijkman left Java just as his collaboration with Vorderman was ending--for a second time due to illness. Back in the Netherlands, he continued briefly his studies on beriberi. Unsuccessful in his efforts to isolate the bacterium, he focused on the cure instead. He showed that water and alcohol extracts of the rice cuticle could cure the disease as effectively as the polishes themselves. He confirmed that the curative factor was destroyed when heated over 120 C. It could also pass through a membrane, such as the cell membranes of an intestine. He then turned to other research projects on metabolism, seasons and climate, leaving others to pursue the remaining problems about beriberi.

Beriberi was important enough that research had been occurring in several places besides Java. There were major efforts in Japan, Malaya, and the Philippine Islands. (In Japan's war with Russia in 1904-1905, four thousand soldiers died of beriberi.)

THINK [8]: How would Eijkman's and Vorderman's dramatic results become known to others? In Asia in the 1890s, how would you know if someone else was studying beriberi in a nearby region? If you were aware of such work, how would you find out about the results? What about differences in language?

Between 1885 and 1906, many researchers inspired by Eijkman's conclusions searched actively for the bacterium or toxin present in rice and tried to identify the curative factor in the rice cuticle. Seventeen different researchers claimed to have found the microorganism that caused beriberi. Other researchers, including Koch, had searched for the infectious agent and failed to find one. They concluded, by contrast, that beriberi was not bacterial at all.

THINK [9]: From the perspective of someone who thought that beriberi was infectious, why might Eijkman, Koch and others have failed to isolate the bacterium? Was failure to find a pathogen definitive in this case? Where should the burden of proof lie?

THINK [10]: Consider the conflicting claims about the causes of beriberi around 1900.

(a) If you were a researcher at this time, with limited time and resources for investigation, would you focus on infection or diet as a cause of beriberi? Why?

(b) If you were a public administrator in Java, with a limited budget, what programs would you support to control the incidence of beriberi? How would you justify to potential critics whether you should inform the public about consumption of half-polished rice, improve sanitation of rice storage and transport, wait, or do something else?

Based on your responses, how would you say that scientific uncertainty affects decision-making in different contexts?

In Java, another Dutch doctor, Gerrit Grijns, succeeded Eijkman at his laboratory. Grijns disagreed with how Eijkman had interpreted his results, however. For Grijns, it was not the rice that was toxic, nor the polishings that effected a "cure." Rather, something vital seemed to be missing from the rice once it was polished. The rice cuticle must have contained a critical nutrient. In other words, Grijns saw beriberi as a nutrient deficiency, not as the result of some "germ."

THINK [11]: How would Grijns have explained Eijkman's and Vorderman's data? How would you try to confirm Grijns's theory experimentally?

The results from Grijns's investigations dramatically undermined and reversed many of Eijkman's conclusions. Beriberi patients did not suffer from something in their diet, but from something missing in it. Beriberi was deficiency disease, based on the absence of some essential nutrient present in the rice cuticle.

THINK [12]: How could Vorderman's conclusions have been significant and mistaken at the same time? More generally, what can we conclude about both the value and the limits of a controlled experiment?

The work on beriberi by medical researchers eventually intersected with independent investigations by biochemists in Europe on nutrition. In England, in 1910-1912, one researcher, Frederick Gowland Hopkins, fed young rats highly purified forms of the basic ingredients known to be essential for any diet: proteins, fats, carbohydrates, water and salts. Though apparently fully nourished, the mice ceased to grow. When given as little as 2 or 3 cubic centimeters of milk per day, they began to grow again. Such amounts were insignificant in terms of their protein or energy. The researcher concluded that there were 'accessory factors' in the milk that were necessary, though only in extremely small amounts.

During the same period, several individuals working independently around the globe--Casimir Funk, a Pole working in London, E.S. Edie, also in England, and Umetaro Suzuki in Japan--each isolated an anti-beriberi chemical. They recognized more clearly how beriberi and similar diseases were linked to the work on dietary requirements. Scurvy and pellegra, along with beriberi were all deficiency diseases. That is, they resulted from something essential not present in the diet. Because the vital missing elements included substantial nitrogen, Casimir Funk called them 'vitamines'. Later, the specific factors were labeled as we now know them: vitamin C was associated with scurvy; vitamin B1, with beriberi; niacin (also in the B complex), with pellegra; and vitamin D, with rickets. Ironically, Eijkman did not accept these conclusions when they were first introduced.

The "beriberi vitamin," named thiamine, was isolated in 1925 by a pair of Dutchmen, Jansen and Donath, again working in Java. From 300 kilograms of rice polishings, they were able to extract a mere 100 milligrams of thiamine. Even in the rice cuticle--which could prevent beriberi--the vitamin was present in only a few parts per million. Vitamins, they learned, are not typical nutrients.

The significance of his work in opening the study of vitamins was marked by a Nobel Prize in Medicine in 1929, awarded jointly to Hopkins and Eijkman, then age 81.

THINK [13]: Who discovered vitamins? When? What does it mean to make a discovery in science? As a member of the Nobel Prize Committee, how would you advise giving an award on this occasion?

Why had beriberi suddenly become more prevalent in the early 1870s? During that period, Westerners introduced steam-driven mills to the East. The mills replaced more traditional methods of hand-pounding rice. The highly effective milling process stripped the essential vitamins from the rice with increased efficiency. As steam-milled white rice became more common, so too did the occurrence of beriberi.

THINK [14]: What was the cause of beriberi on a biochemical level? On a dietary level? On a social, cultural or economic level? How does each view imply an alternative way to reduce the frequency of beriberi? How would you answer someone's question, "What caused beriberi?" ?

Further Reading

Carpenter, Kenneth. 2000. Beriberi, White Rice and Vitamin B: A Disease, A Cause and a Cure (Berkeley: Univ. of California Press).

Funk, Casimir. 1912. "The Etiology of the Deficiency Diseases." *Journal of State Medicine* 20:341-368.

Vedder, Edward B. 1913. Beriberi (New York: W. Wood).

Williams, Robert. 1961. *Toward the Conquest of Beriberi* (Cambridge, Mass.: Harvard University Press).

Link to supplement on THINK exercises above:

<http://www1.umn.edu/ships/modules/biol/eijkman2.htm>

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