Christian Eijkman & the Cause of Beriberi

by Douglas Allchin

Visuals || Notes

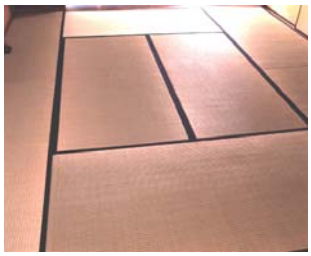
Meet Christian Eijkman, who shared the Nobel Prize in Medicine in 1928. Let's journey with him on the mission of medical research that led to his award.

The year is 1886. It's October. Eijkman embarks with two other doctors from the Netherlands. Their destination is the island of Java, almost halfway around the globe. They pass through the Suez Canal--opened only a few years ago-- and arrive a few weeks later.

Java is part of the Dutch East Indies, one of many important trading colonies around the world. Java and the surrounding islands typically fascinates Europeans:

the exotic forests, with their excpetionally tall trees

There are dense thickets of fibrous rattan vines, harvested by the Javanese and exported to Japan to make tatami mats.



Many crops made the East Indies valuable as a colony to the Netherlands: sugar cane, coffee, cacao and indigo. Many trees have been cleared to grow the crops, imported from other tropical regions.

Life on Java is not the same for the three doctors, even in the Dutch community of Batavia. The tropical heat is everywhere. They also need a taste for rice, a staple in this region of Asia.

Eijkman, age 28, has seen the sights of Java before -- while serving as an officer for the Dutch Army. However, after two years he had contracted malaria and returned to the Netherlands. Malaria is one of many diseases common in the tropics. Cholera, influenza, dysentery and plague are also widespread. So, too, is beriberi.

Beriberi is, in fact, the reason why the medical commission has 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 and muscle weakness.

Patients lose their sense of feeling and control of limbs, often leading to paralysis. 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 have died in various epidemics.

Epidemics of beriberi in Asia have become more frequent. In Japan in 1880-81, one doctor was swamped with so many beriberi patients that the hospital could not accommmodate them all and they overflowed into nearby temples. The Dutch government is now particularly concerned because the local soldiers and even Dutch Navy sailors are suffering -- recently crippling an effort to quell a native uprising in a remote province. They want to find to cure for the disease or--better--prevent it. They have sent the medical commission to find the cause of beriberi. Eijkman will eventually share a Noble Prize for his discoveries on Java.

Disease, Germ Theory and Eijkman

Eijkman and his colleagues are not the first to study the cause of beriberi. Beriberi has been known in southern and eastern Asia for centuries. A Chinese physician described it four thousand years ago. In the East Indies it had been reported as early as the 1630s. 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?*

Dutch medical commission has arrived with new ideas about disease from Europe. Indeed, Eijkman's career nicely reflects 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 by Louis Pasteur and others 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 results from microscopic organisms that infect the body.

In 1880 Koch 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-causinTheg agents. In 1882 and 1883 Koch identified the bacteria that caused tuberculosis, cholera and diptheria.

Outbreaks of beriberi have been common in armies and navies and in prisons, all relatively closed communities. Is the disease therefore infectious, transmitted by some "germ"? That was the hope of the Dutch government, who sent 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. He joined 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 has now brought all these new methods with them. They are thus prepared to find the bacterium that causes beriberi, isolate it and make a vaccine. The scientists are transferring an understanding of germ theory in person from Europe to Java.

Not quite a year later, the group completes its work in Java. They characterize beriberi more precisely in terms of both its clinical symptoms and the nerve degeneration visible microscopically in the tissues. They confirm in their report that a bacterium causes beriberi. But they also discover a new infection pattern. They have not been able to infect one organism directly by injections of blood, unless repeated many times. Whereas most diseases seem to be transmitted through a single exposure to the germ, a person has to reside in an area of beriberi for several weeks to contract the disease. For beriberi, the bacterial agent apparently must be transfered many times. The comission returns home. Eijkman remains, however, to continue the studies and work at the local medical school. He has yet to establish a pure culture of the bacterium and from that, develop a vaccine.

Chicken-feed?

Several years pass as Eijkman continues investigations in his small laboratory. His work has been frustrated because, even using Koch's techniques, he has been unable to isolate the beriberi bacterium in a pure culture. He continues injections of diseased blood, but the results are inconsistent. Are the transfers responsible, or is it just chance? He realizes that he needs many more organisms: some injected, some not. He switches from rabbits to chickens, which are cheaper and easier to raise.

Before long, the chickens exhibit signs of the disease. They walk unsteadily and have difficulty perching. Later they do something chickens rarely do: lay down on their sides! They also have trouble breathing. Yet now the disease occurs among *all* the chickens, even those not injected. Eijkman decides that there must be contagion. He separates the chickens, at first in different cages, and then, when that fails, in different parts of the hospital grounds. No sooner are the chickens isolated than they all recover. Why?

> **THINK [2]**: *Given this unexpected turn of events, what would be an appropriate next step? Where would you look next for clues?*

Eijkman learns quite unexpectedly from his assistant that the chickens have received different food. When the experiments began, the assistant had obtained leftover cooked rice from the military hospital -- a way to save costs. But later a new cook had arrived. He had refused to give "military" rice to "civilian" chickens! The assistant had returned to raw, feed-grade rice.

> **THINK [3]**: *With this information, what would you plan to do next?*

Eijkman must now isolate the difference in the rice. Which factor is responsible? Does the cooked rice spoil overnight? No. Is it the cooking of the rice? No. Is it contaminated water used to cook the rice? Is it the hospital rice itself? There are different varieties of rice. Normally, the local rice, known locally as beras merah, has a reddish cuticle (or pericarp, in botanical terms). You can remove the cuticle, though, by milling or "polishing" the rice. Polished rice has a fancier white appearance and a taste that many people preferred and was used at the hospital. Here, finally, was the relevant difference.

Soon, Eijkman is able to make chickens sick almost at will, simply by controlling their diet. When fed the polished, white rice, healthy chickens soon show symptoms similar to human beriberi. In addition, when fed red rice, they become well again. They recover as well when just the husks or cuticles of the rice--the "rice polishings"--are added to a diet of polished rice. In some cases, the sick chickens regain a normal gait and the ability to fly within a few hours of eating the rice polishings!

Eijkman now has an important clue for finding the bacterium. It must be in the polished rice. This would certainly explain why beriberi was so prevalent in nations where rice was a staple food. Eijkman had clearly not planned to change the chicken's diet, but the chance event revealed valuable information that he and his colleagues had missed during many years of deliberate study.

Yet healthy chickens eating red rice remain healthy, even when living in the presence of other diseased birds. Cross-injections have also been ineffective. Eijkman reasons further that the bacterium must never enter the body. It must create a neurotoxin that is absorbed in the body. The cuticle of the rice must be a neutralizing agent or antidote.

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

> **THINK [4]**: *Imagine that you are among the skeptics of Eijkman's new discovery. How might you interpret these findings in another way? How might Eijkman design a test to respond to your criticism?*

Of Rice and Men

Eijkman continues 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 continues worldwide. Two researchers (one Japanese, one French) independently seem to have isolated the bacterium which caused bubonic plague. In India, over 45,000 people receive a new cholera vaccine. Compared to those not

inoculated, 70 percent fewer die. In 1892, a skeptic of germ theory in Germany swallows a vial of live cholera bacteria to demonstrate his belief that the bacteria does not cause the deadly disease. Indeed, he does not get sick.

Eijkman has still not demonstrated conclusively how polished rice is part of the process in which bacteria cause beriberi in humans. He needs 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?*

Eijkman turns to institutions. There, diets are already determined. The large number of cases will also help ensure that the results are not due to chance or mere coincidence in a small group. He persuades the prison at Tolong, where 5.8% of the population suffers from beriberi, to substitute undermilled, or half-polished, rice for white rice. All cases of beriberi are cured. But as Eijkman notes later, this merely confirms the potential effectiveness of the cure. It does not demonstrate that a bacterium in the polished rice initially causes the disease. This requires comparing individuals who consume the different types of rice.

Eijkman thus enlistes 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 eat either polished rice or half-polished rice, according to local customs. In some cases prisons serve a mixture. Here is a natural experiment, a case where the desired experimental conditions existed on their own. For Eijkman and Vorderman's purpose, the experiment is fortuitously already in progress. Between May and September of 1896, Vorderman leads an exhaustive study of beriberi in one hundred prisons of Java and the small neighboring island of Madura--a survey which embraces nearly two hundred and eighty thousand prisoners. He reports the distribution of beriberi in the 100 prisons and its frequency among prisoners as follows:

[VORDERMANN'S DATA]

	# 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 reported on other 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 is able to show a correlation between diet and beriberi, why are these additional statistics necessary? What purpose does **each** serve?*

Vorderman's data further indicates that beriberi does not correlate with lower altitude (many other diseases were more prevalent among those on lower ground). Nor does the incidence of other diseases match the distribution of beriberi. In four prisons, Vorderman notes further, the number of cases of beriberi has 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?

Eijkman and Vordermann's study is significant in part because of its large scope. But imagine for a moment the native Javanese perspective. Why are so many persons in prison available for scientific study? The Dutch are managing over a quarter million prisoners on one island! Java is one of the most densely populated areas in the world. Still, almost 1 percent of the population is in prison. From the local perspective, the Dutch colonials are invading foreigners. The prisons, all military prisons, reflect how the Dutch deal with Javanese opposition to their occupation -- that is, when thery do not rely on mass executions. Vorderman's survey takes advantage of that exercise of colonial power.

In addition, although more Javanese than Dutch suffer from the disease, the Dutch colonials have more at stake than simply aiding the local population. The disease takes its toll on the local armies and work force. The Dutch thus value a cure primarily for military and economic reasons. Likewise, no one has offered the Javanese the tools or resources to study the disease on their own. Although Eijkman and Vordermann are addressing fundamental biological questions, their research is also motivated by the Dutch economic interests and facilitated by its military presence.

Beriberi after Eijkman

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

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

> **THINK [8]**: *How will Eijkman's and Vorderman's dramatic results become known to others? If you are working elsewhere in Asia, how will you know if someone has been studying beriberi nearby? If you are aware of such work, how do you find out about the results? What about differences in*

language?

Between 1885 and 1906, inspired by Eijkman's conclusions, many researchers search actively for the bacterium or toxin present in rice and try to identify the curative factor in the rice cuticle. Seventeen different researchers claim that they have found the microorganism that causes beriberi. Other researchers, including Koch, search for the infectious agent and fail to find one. They conclude, by contrast, that beriberi is not bacterial at all.

> **THINK [9]**: *From the perspective of someone who thinks that beriberi is infectious, why might Eijkman, Koch and others have failed to isolate the bacterium? Is the 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, now in 1900.*
> *(a) If you are a researcher at this time, with limited time and resources for investigation, will you focus on infection or diet as a cause of beriberi? Why?*
> *(b) If you are a public administrator in Java, with a limited budget, what programs will you support to control the incidence of beriberi? How will you justify to potential critics whether you 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 does scientific uncertainty seem to affect decision-making in different contexts?*

In Java, another Dutch doctor, Gerrit Grijns, succeeds Eijkman at his laboratory. However, after some initial investigations on the curative factor, Grijns finds himself disagreeing with how Eijkman interpreted his own results. For Grijns, it is not the rice that is toxic, nor the polishings that effect a "cure." Rather, something vital seems to be missing from the rice once it is polished. The rice cuticle must contain a critical nutrient. In other words, for Grijns, beriberi is a nutrient deficiency, not the result of some "germ."

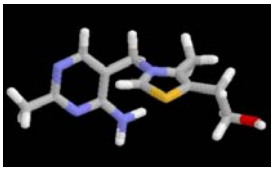
> **THINK [11]**: *How can Grijns explain Eijkman's and Vorderman's data? How would you try to confirm Grijns' theory experimentally?*

Grijns finds that other foods can effectively treat beriberi -- notably *kachang-ijo*, or mung bean. In addition, starchy diets of tapioca root or sago palm can also produce the disease. Rice alone is not responsible. Even a diet without starch -- of overcooked meat -- can cause beriberi. Grijns' results dramatically undermine and reverse many of Eijkman's conclusions. Beriberi patients do not suffer from something in their diet, but from something missing from it. Beriberi is a 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 intersects with independent investigations by biochemists in Europe on nutrition. In England, in 1910-1912, one researcher, Frederick Gowland Hopkins, feeds 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 cease to grow. When given as little as 2 or 3 cubic centimeters of milk per day, they begin to grow again. Such amounts are insignificant in terms of their protein or energy. Hopkins concludes that there are "accessory factors" in the milk that are 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 isolate an anti-beriberi chemical. They recognize more clearly how beriberi and similar diseases are linked to the work on dietary requirements. Scurvy and pellagra, along with beriberi are all deficiency diseases. That is, they result from something essential not present in the diet. Because the vital missing elements seem to include substantial nitrogen, Casimir Funk calls them "vital amines," or vitamines. Later, the specific factors are labeled: vitamin C is associated with scurvy; vitamin B_1, with beriberi; niacin (also in the B complex), with pellagra; and vitamin D, with rickets. Ironically, Eijkman does not accept these conclusions when they are first introduced.

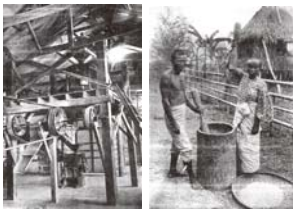


The "beriberi vitamin," named thiamine, is isolated in 1925 by a pair of Dutchmen, Jansen and Donath, again working in Java. From 300 kilograms of rice polishings, they are able to extract a mere 100 milligrams of thiamine. Even in the rice cuticle--which can prevent beriberi--the vitamin is present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

nutrients.

The significance of Eijkman's work in opening the study of vitamins is 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 in Java in the 1880s? Was it a vitamin deficiency? A white-rice diet? Economic conditions that led to poor diet? The introduction of steam mills by the Dutch? Or the whole system of Colonialism that established these conditions? How does each view (biochemical, dietary, social, cultural) imply an alternative way to reduce the frequency of beriberi? What does this tell us about the nature of causation?*

THINK: NOS Reflection Questions

What does the case of Christian Eijkman & the cause of beriberi show about the following aspects of doing biology?

- the role of chance or contingent events (THINK 2)
- theoretical perspectives in interpreting data (THINK 1, 4, 9, 11, 12)
- role and limit of controlled experiments (& distinction between causation and correlation) (THINK 3, 6, 12)
- conceptual change (reinterpretations versus cumulative growth of knowledge) (THINK 11)
- collective nature of discovery (THINK 13) -- Here, students may be invited to list all the individual who contributed something significant to the outcome: the medical commission, Eijkman, his critics,

Vorderman, Grijns, Hopkins, at least.
- scientific communication (THINK 8, & the transfer of Koch's methods by the commission)
- the cultural and economic contexts of science (THINK 5, 10)

Further Reading

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- Vedder, Edward B. 1913. *Beriberi* (New York: W. Wood).
- Williams, Robert. 1961. *Toward the Conquest of Beriberi* (Cambridge, Mass.: Harvard University Press).