CHAPTER 11

Christiaan Eijkman & the Cause of Beriberi

DOUGLAS ALLCHIN

☐ INTRODUCTION

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—opened only a few years earlier—and arrived a few weeks later in the Dutch East Indies (now Indonesia). Java and the surrounding islands would have fascinated them with the exotic wildlife, towering forests, and 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 meant that the Netherlands valued the East Indies as a colony.

Life for the three doctors on Java would be very different than in Europe. Western amenities 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 (pronounced "Ike-mahn," Figure 11.1), 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 had 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.

In fact, beriberi was the reason why the medical commission had come to Java. It is a debilitating disease, as indicated by the name itself. For the Javanese, the word *beri* means "weak," and doubling a word intensifies its meaning. Symptoms of beriberi include muscle weakness, weight loss, 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 (see Figure 11.2). The disease can be fatal. At the time, as many as 80 percent of beriberi patients died.

In the late 1800s, epidemics of beriberi in Asia had become more frequent. Members of the Dutch government noted, in particular, that large numbers of their fleet crews and native work force were suffering. They wanted to know how to cure the dis-

FIGURE 11.1 Christiaan Eijkman. c. 1890. *Source:* Koninklijk Instituut voor de Tropen (Royal Tropical Institute) Amsterdam.

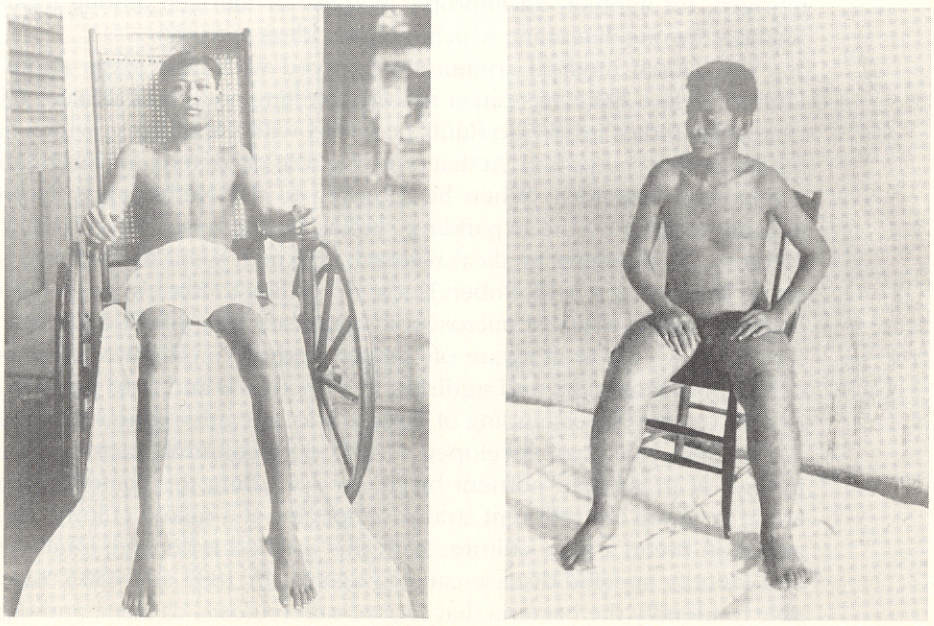

FIGURE 11.2 Beriberi patients. *Source:* (left) Edward B. Vedder, A. M., M.D., *Beriberi*, New York: William Wood, 1913. (right) Herzog, *Phillipine Journal of Science*, 1906.

ease 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

Beriberi was not a new disease in southern and eastern Asia. A Chinese physician had described it over 4,000 years earlier. In the East Indies, it had been reported as early as 1642. But no one knew of a cure.

Eijkman and his colleagues were not alone in trying to identify the cause of beriberi. In Japan in 1880–1881, one doctor was so swamped with beriberi patients that the hospital could not accommodate them all and they overflowed into nearby temples. What had caused the epidemic? The doctor collected data about clothing, living quarters, diet, occupation, economic status, geographical region, and seasonal frequency of the disease, hoping to find clues. How would someone go about identifying the unknown cause? More generally, what can possibly cause disease?

Various researchers, both Asians and Europeans, working in Asia explained the cause of beriberi differently. Some insisted that beriberi was not a specific disease at all, but a combination of other known diseases. Others claimed it was a form of poisoning. They disagreed about which toxin was responsible, however. Was it arsenic, oxalate, carbon dioxide, or some compound produced by a microorganism? Later, some viewed beriberi as an infection, but they disagreed as to whether a protozoan, a tiny worm, or a bacterium was responsible. Another blamed moldy rice. Yet other researchers thought it was diet. But while some concluded that beriberi was due to a deficiency of fats, others implicated lack of phosphorus or proteins. For one researcher, it was insufficient nitrogen; for another, an improper *balance* of nitrogen among foods eaten. (How would someone determine which reported ideas to trust?)

The Dutch medical commission arrived with new ideas about disease from Europe. In fact, Eijkman's career reflected shifting notions of disease. Eijkman had first visited the Indies in 1885 to fulfill a contract with the military, which had helped pay for his medical education. At that time, the role of bacteria in causing disease was still a relatively new idea. When he returned to the Netherlands, however, Eijkman became excited by the expanding studies on the topic. 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. Over a century later, we are well aware of "germs" and the importance of personal hygiene, community sanitation, and sterilization in medicine and food preparation. But in the late 1800s, this understanding of disease was still guiding new discoveries.

In 1880, Koch had developed a method for culturing bacteria on a solid medium instead of in a liquid nutrient broth. By spreading the bacteria across 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 was able to identify the bacteria that caused tuberculosis, cholera, and diphtheria.

Outbreaks of beriberi were common in armies, navies, and prisons, all relatively closed communities. This was typical of infectious diseases transmitted by some

"germ." Thus, when the Dutch government decided to organize a group to go to the East Indies in 1886, it sent two doctors to Germany to learn the latest techniques firsthand from Koch. Once there, they met Eijkman. Hearing about their mission, he decided to join them. In that same year, a prominent French researcher, using a method he had pioneered a few years earlier, created a vaccine for rabies. The Dutch commission took all these new methods with them to search for the bacterium that caused beriberi, isolate it, and make a vaccine. The scientists were themselves vehicles for transferring germ theory from Europe to Java.

Just over a year later, the doctors completed their work on Java. They characterized the clinical symptoms of beriberi more precisely, and reported microscopic observations of nerve degeneration in the tissues. They confirmed that a bacterium caused beriberi. But they also discovered a new infection pattern. They had not been able to infect one organism directly using another. Whereas most diseases were transmitted through a single exposure to the germ, a person had to reside in an area of beriberi infection for several weeks to contract the disease. In the case of beriberi, they reasoned, the bacterial agent had to 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. Even using Koch's techniques, however, he was 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 like those of his beriberi patients. The chickens walked unsteadily and had difficulty perching. Later they lay down on their sides—not a typical posture for chickens! (see Figure 11.3). They also had trouble breathing. He posed the obvious question: Could the chickens be infected with the same organisms that caused beriberi? Eijkman recognized the great potential for

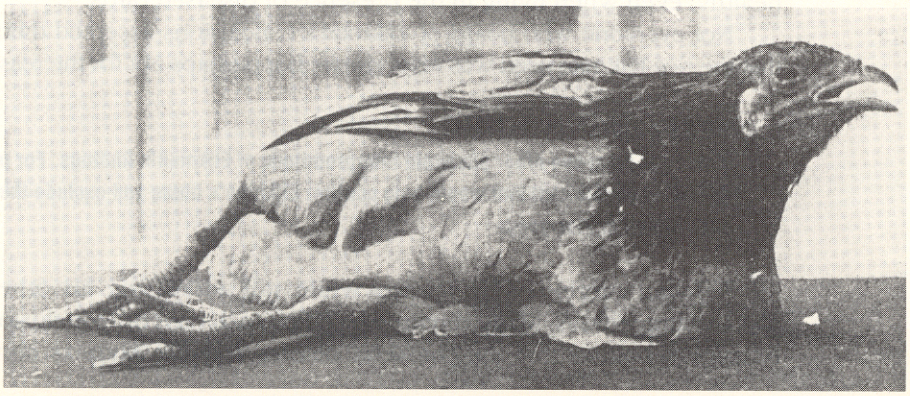

FIGURE 11.3 Chicken with "beriberi." *Source:* from Casimir Funk, *The Vitamines,* Baltimore: Williams and Wilkins Company, 1922.

studying the disease in a population of laboratory animals where he could monitor variables more closely (Chapters 5, 10, and 14 also discuss the use of animal models). He could also change conditions experimentally. Eijkman promptly had the chickens moved to another location for further study.

When the chickens were moved, though, their health suddenly improved, with no apparent treatment! Why? Given this unexpected turn of events, what would be Eijkman's next step? Where would he look for clues?

Eijkman began to search for the factors that might help him to isolate the bacterium. He traced at least one possible difference to the chickens' new home. Previously, the chickens had been served boiled rice left over 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 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. Eijkman had not planned to change the chickens' diet, but neither did its effects 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 those of 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. Eijkman must surely have been impressed that, in some cases, the sick chickens regained a normal gait and the ability to fly within a few hours of eating the rice polishings. He 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 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.

PROBLEM

Identify at least two other plausible interpretations of Eijkman's findings. For one of these, design an experiment that would help confirm Eijkman's ideas and exclude the alternative explanation or vice versa.

Eijkman continued his studies while still addressing his other administrative and teaching duties. Many researchers failed to accept his conclusions because they refused to believe that the chickens' disease was the same as human beriberi. So

Eijkman characterized the disease more fully. He examined the chickens' tissues and noted the same degeneration of the nerves that the commission had identified in human beriberi. Eijkman also wanted to show the connection by transferring the disease from humans to chickens via injections of blood or other body fluids from beriberi patients—but luck failed him. Nor was he able to transfer the disease directly from one chicken to another. He speculated that the microorganism did not enter the blood itself. Instead, it might remain in the intestine, where it could produce a toxin from the starch or something else in the rice grain. The toxin, rather than the microorganism, might then enter the body and poison the nerve cells. Eijkman would have to modify his investigations.

OF RICE AND MEN

Five more years passed as Eijkman continued to search for the beriberi bacterium and the toxins it produced. Meanwhile, two researchers (one Japanese, one French) independently isolated the bacterium that caused bubonic plague. And in India, over 45,000 people received a new cholera vaccine. Compared to those not inoculated, 70 percent fewer died. Germ theory was still controversial, however. In 1892, a skeptic 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 by which bacteria caused beriberi in humans. He needed a properly controlled experiment. Of course, he might well have decided to feed several individuals nothing but polished rice, as he had done with chickens. (Would this have been ethical?) Eijkman turned instead 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 Tolong, where 5.8 percent 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 controls existed without manipulation by the investigators. Fortuitously for Eijkman and Vorderman, the experiment was already in progress. Between May and September of 1896, Vorderman led an exhaustive study of beriberi in 100 prisons on Java and a small neighboring island—a survey that embraced nearly 280,000 prisoners. He reported the distribution of beriberi in the 100 prisons and its frequency among prisoners as follows:

	Number of Prisons	Number with Beriberi	Percentage of Prisons with 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 (why was this comparison important?):

	Number of Prisons	Prisons where Beriberi Found	Percentage of Prisons with Beriberi
Age of buildings			
40–100 years	26	13	50.0%
21–40 years	32	11	34.4%
2–20 years	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 population	1	1	
Overcrowded	26	9	34.6%

Many diseases were more prevalent among those on lower ground. Vorderman also collected data indicating that beriberi did not correlate with lower altitude. Nor did the incidence of other diseases match that 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.

PROBLEM

What conclusions can be drawn from Vorderman's study beyond what Eijkman could conclude from his study with chickens? Reconsider your earlier assessments. How do Vorderman's results support Eijkman's explanation and/or other alternatives?

As a brief aside, consider these studies and the Dutch effort to cure beriberi from a Javanese perspective. First, why were so many prisons available for scientific study? The Dutch were managing over a quarter of a million prisoners on one

island! In the late 1800s, Java was one of the most densely populated areas in the world, with between 30 and 35 million inhabitants. Still, almost 1 percent of the population was in prison. From the local perspective, the Dutch colonials were invading foreigners. The prisons, all military prisons, reflected how the Dutch dealt with the Javanese opposition to their occupation. Vorderman's survey took advantage of that exercise of colonial power.

Second, though more Javanese than Dutch suffered from the disease, the Dutch colonials had more at stake than simply aiding the indigenous population. The disease took its toll on the local work force. Beriberi interfered with the Dutch "trade" in the region. The Dutch thus valued a cure for economic reasons. Likewise, no one had offered the Javanese the tools or resources to study the disease on their own. Though Eijkman and Vorderman addressed fundamental biological questions, their research on this occasion was also motivated by the Dutch economic interests and facilitated by its military presence. Social factors mixed with "pure" science.

BERIBERI AFTER EIJKMAN

Eijkman left Java just as his collaboration with Vorderman was ending—again due to illness. Back in the Netherlands, he briefly continued 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 polishings 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. Eijkman published his results and then turned to other research inspired by his visits to the tropics, leaving others to pursue the remaining mysteries of 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, 4,000 soldiers died of beriberi.) Eijkman's and Vorderman's results were dramatic. But consider how others would have heard about them. If you were studying beriberi in southeast Asia in the 1890s, how would you know that someone else was also studying the same disease in a nearby region? If you were aware of such work, how would you find out about the results? What about differences in language? With no formal network or institution for communicating findings, it is difficult to share ideas, build on the work of others, or benefit from criticism. In this case, there was no scientific community. Research was fragmented, and research news traveled slowly. In fact, most scientific studies sponsored by colonial powers during this period were published in Europe. Eijkman and Vorderman followed this pattern—writing in Dutch, no less.

Nevertheless, in the early 1900s research began to focus more on rice in the diet. Large-scale studies like Vorderman's continued through 1912, in each case confirming the findings on rice. Between 1905 and 1910, major institutions—armies, navies, prisons, insane asylums, and leper colonies—finally began to change their primarily white-rice diets. Many researchers also continued to search for the bacterium or toxin in the rice and the identity of the curative factor in the rice cuticle.

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 essential seemed to be missing from the rice once it was polished. The rice cuticle must have contained some critical nutrient. In other words, Grijns saw beriberi as a nutrient deficiency, not the result of some "germ."

PROBLEM

How would Grijns have explained Eijkman's and Vorderman's data?

Pursuing his alternative hypothesis, Grijns examined the ability of other starchy foods to produce "beriberi" in chickens. Diets of either tapioca root or sago (the starchy pith of a palm) could also produce the disease. If there was a microorganism or toxin, it was certainly not unique to rice. Grijns also looked for other sources of the curative or missing factor. He tested each one by adding it to a chicken's diet of polished white rice. He found that several beans, notably the mongo bean, known locally as *kachang-ijo*, could "cure" or prevent beriberi. Grijns's results dramatically undermined and virtually reversed Eijkman's conclusions. Beriberi patients did not suffer from some disease-causing agent in their diet. Rather, they suffered from some health-related element missing from it.

The work on beriberi by medical researchers eventually intersected with independent investigations on nutrition by biochemists in Europe. 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 "accessory factors" in the milk were necessary, though only in extremely small amounts.

During the same period, several individuals working independently—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 dietary requirements. Scurvy and pellagra, along with beriberi, were all deficiency diseases. That is, they resulted from something essential missing from the diet. Because the vital 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 B_1, with beriberi; niacin (also in the B complex), with pellagra; and vitamin D, with rickets. Ironically, Eijkman did not accept these conclusions when they were first introduced. The significance of his work in furthering the study of vitamins was acknowledged, nevertheless, by a Nobel Prize in 1929, awarded jointly to one of the biochemists (Hopkins) and to Eijkman, then age 81.

☐ *EPILOGUE*

The potentially fatal effects of deficiency diseases demonstrate vividly that vitamins are important in our diet. This may not seem obvious given the small amounts that we need. Just how small these amounts were became clear when the "beriberi vita-

min," thiamine, was isolated in 1925. From 300 kilograms of rice polishings, a pair of Dutchmen (again working in Java) extracted only 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 are not ordinary nutrients.

Biochemically, vitamin B_1 serves as a coenzyme, meaning that it participates in an enzymatic reaction but does not itself catalyze the reaction. Only small amounts are needed because each molecule is used many times. One specific role for thiamine is in the energy pathway between glycolysis and the Krebs cycle (Chapter 7). When the 3-carbon product of glycolysis is split, it releases energy and yields a 2-carbon fragment. This fragment is temporarily attached to a modified thiamine, which (as a coenzyme) transfers it to the first enzyme in the Krebs cycle (see the missing stage in Figure 7.3(B)). Thiamine is therefore critical to virtually every cell in the body. Nerve cells, which use much energy, are strongly affected by its absence, accounting for the clinical symptoms of the disease.

Abundant thiamine is found in the cuticle and bran husk of cereals. Thus today's whole-grain breakfast cereals and breads tout their image as so-called "health foods" in part because they contain the essential B_1 vitamin. Thiamine is present as well in yeast, legumes, and green leafy vegetables. (The thiamine in meats is lost when they are cooked.) Many foods, such as enriched white flour, are supplemented with thiamine. Otherwise, it might be missing from the highly processed diets of many people in industrialized countries.

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 (Figure 11.4). The highly effective

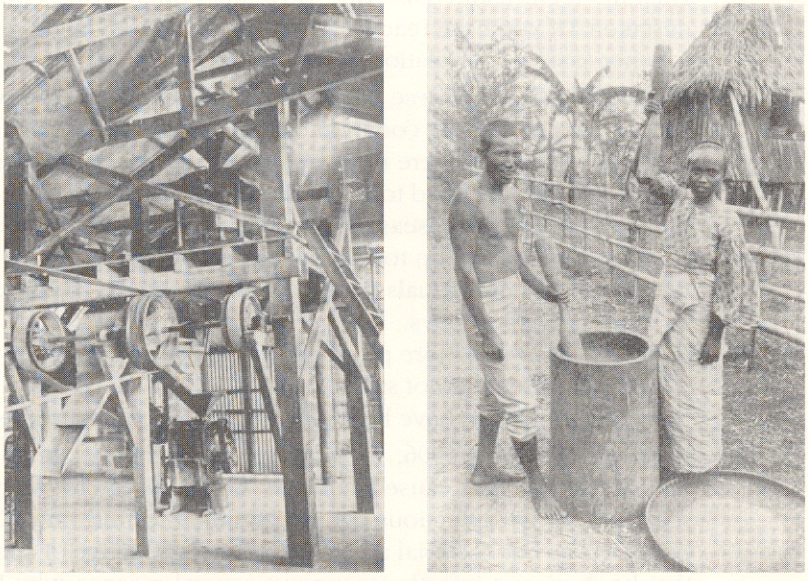

FIGURE 11.4 (A) Steam-powered mill for removing bran and cuticle from rice. (B) Traditional method for hand-pounding rice. The frequency of beriberi increased with the introduction of steam mills. *Source:* Edward B. Vedder, A.M., M.D., *Beriberi*, New York: William Wood, 1913.

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. From different perspectives—biochemical, dietary, and social—what had been the cause, or causes, of beriberi?

QUESTIONS AND ACTIVITIES

1. What does this case show about the following aspects of doing biology?
   — chance or accident
   — theoretical perspectives in interpreting data
   — the distinction between causation and correlation
   — growth of knowledge through small cumulative additions versus through major conceptual reinterpretations
   — the role of individuals versus groups in making a discovery
   — scientific communication and communities of researchers
   — the cultural and economic contexts of science
2. Who discovered vitamins? When? Consider both the contributions and the historical perspectives of Eijkman, Vorderman, Grijns, and others (including Hopkins, Funk, Edie, and Suzuki). Discuss what it means to make a discovery in science. How would you have advised the Nobel Prize committee giving the award on this occasion?
3. Discuss how Grijns's interpretation of Vorderman's data reflects both the importance and the limits of a controlled experiment. How were Vorderman's conclusions significant? Describe how his conclusions could also have been mistaken. (If you have read Chapter 1, 4, or 10, you might relate your comments to other cases of correlation and causation.)
4. A doctor in the Japanese Navy made a number of observations in the early 1880s trying to identify common factors among disease victims. He found that:
   a. Cases of beriberi were most frequent from the end of spring into summer but were not isolated to those seasons.
   b. The frequency of disease also varied considerably from one ship to another and from one station to another within a ship.
   c. Upper-class individuals suffered less than sailors, soldiers, policemen, students, and shop boys.
   d. The disease was more prevalent in large cities, but even people living in the same area did not suffer equally.

   How might Eijkman have later explained these observations?
5. Between 1885 and 1906, 17 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 that beriberi was not bacterial at all. From the perspective of someone who thought that beriberi was infectious, suggest several reasons why Eijkman, Koch, and others might have failed. Was failure to find a pathogen definitive in this case? Where should the burden of proof lie here?

6. Consider the various claims about beriberi, microorganisms, and diet in 1900.
   a. If you were a researcher at this time, what reasons would you have to investigate infection versus diet as a cause of beriberi?
   b. If you were a public administrator in Java in 1900 with a limited budget, what programs would you support to control the incidence of beriberi? Should you inform the public about consumption of half-polished rice, improve sanitation of rice storage and transport, wait, or do something else? How would you respond to potential critics?

   Based on your responses, consider how scientific uncertainty affects different types of decision making.
7. Based on Eijkman's work, two researchers took a healthy work force to a previously isolated area of Javanese forest in 1906. They fed one-half of the workers white rice and the others, a more complete diet. They continued until the workers who were fed only rice became ill with beriberi. They then switched diets between the two groups. The first group was cured, while the second group became ill. Comment on the design of this experiment, both in terms of experimental controls and ethics.
8. Consider the causes of beriberi on different levels. What was the cause of beriberi on a biochemical level? On a dietary level? On a social, cultural, or economic level? How is each perspective associated with an alternative solution for reducing the frequency of beriberi?

SUGGESTED READING

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