Christian Eijkman & the Cause of Beriberi

by Douglas Allchin

Visuals || Illustrated Text

Teaching Notes

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Christian Eijkman shared a Nobel Prize for the discovery of vitamins. His research on beriberi in the Dutch East Indies in 1890s highlighted the role of rice diet, leading to the understanding of specific nutrient deficiencies. Yet originally Eijkman was convinced that beriberi was caused by a microorganism and this assumption guided his work. This case study delves into the fruitfulness of his work, even as his preconceptions guided him into error. The context of Dutch Colonialism also helps frame reflection on funding and ethics in science.

Major NOS features include:

- the role of chance or contingent events
- theoretical perspectives in interpreting data
- role and limit of controlled experiments (& distinction between causation and correlation)
- conceptual change (reinterpretations versus cumulative growth of knowledge)
- collective nature of discovery
- scientific communication
- the cultural and economic contexts of science

THINK Exercises

The primary purpose of these questions is for students to develop scientific thinking skills and to reflect explicitly on the nature of science. The questions are open ended, and the notes here are only guides about the possible diversity of responses. In many cases, the actual history can be a point of comparison (shared *after* the students' own work), but by no means does it indicate an exclusively "correct" answer. Accordingly, the teacher should avoid overt clues or "fishing" for answers, implying that a particular response is expected or considered "more right." The case study should be illustrating the blind, uncertain process of science-in-the-making. To help promote thinking skills, the teacher should encourage (and reward) thoughtful responses, well articulated reasoning, and respectful dialogue among students with different ideas or perspectives. Where the case study here echoes NOS features students have encountered in other case studies, the relationships should be noted and perhaps contribute to deeper discussion. This form of repetition and integration with prior knowledge significantly deepens the NOS lessons.

THINK [1]: What Causes Disease / the Nature of Conceptual Frameworks

There is an epistemic conundrum common in research here: How do you know what to observe or look for if you do not yet know what it is that you are going to find? Certain types of diseases may have diagnostic patterns, but one must be aware of those characters in advance if one is to search for them as "clues." That is, a spectrum of *possible* hypotheses must preceed any target hypothesis about the cause of the disease. This works against finding new disease types, of course.

In the late 1800s various reseachers, 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 whether it was a protozoan, a tiny worm, or a bacterium . Another blamed moldy rice. Yet other researchers implicated diet. But while some concluded that beriberi was due to a deficiency of fats, others thought it was lack of phosphorus or proteins. For one researcher it was insufficient nitrogen, for another an improper balance of nitrogen . How does the scientist determine which of these many reported ideas to trust?

An outbreak of beriberi just a few years earlier (1880-81) in Japan had been well studied by a doctor in the Japanese Navy, Kanehiro Takaki. He collected data about the patients' clothing, living quarters, diet, occupation, economic status, and geographical region, and about seasonal frequency, hoping to find clues. Each, in a sense represented a hypothesis, in the form of a question, about what might have been a causal factor. Indeed, his methods largely reflect epidemiological methods today. Takaki found that:

1. Cases of beriberi were most frequent from the end of spring into summer, but were not isolated to those seasons.
2. The frequency of disease also varied considerably from one ship to another, and from one station to another within a ship.
3. Upper class individuals suffered less than sailors, soldiers, policemen, students and shop boys.
4. The disease was more prevalent in large cities, but even people living in the same area did not suffer equally.

Do these data provide valuable clues? Why?/Why not?

THINK [2]: Unexpected Cures / the Role of Chance

This is an excellent occasion to discuss the role of "chance" in science. Such unplanned events are far more important than the conventional image of "the scientific method" implies. Eijkman could well have decided that chickens were too unpredictable to use. But he saw the potential for tracking an unknown variable. Students may consider what features are necessary to "notice" chance events as significant. Louis Pasteur, for example, is noted for suggesting that "chance favors only the prepared mind." Molecular biologist Max Delbrück coined "the principle of limited sloppiness," suggesting that laboratories should operate with enough informality that careless errors or "chance" events were likely to surface occasionally. This was certainly true of Alexander Fleming's habits--and contributed to his famous findings about penicillin. The series of chance events in Eijkman's case also shows how difficult it can be to proceed without any obvious clues, previous theories, or "working hypothesis" (Chapter *22*).

THINK [3]: Isolating Causes / Controlled Experiments

The key difference is apparently the rice diet. But it is not clear *which* factor in the diet is important. As Eijkman himself considers, it could be the storage of the cooked rice, the cooking (heating), the water used in cooking, the rice type, the absence of a protective covering on the rice grain. Each factor must be "isolated" and tested in turn. The key is to *compare* the presence and absence of a single factor under parallel circumstances: the essence of a controlled experiment.

THINK [4]: Eijkman's Interpretation of Chicken Diet / Model Organisms

Many researchers failed to accept Eijkman's conclusions because they refused to believe that the disease in chickens was the same as the human disease beriberi. This highlights the role of animal models or model organisms in studying human diseases. Chickens are cheaper and can be used in ways that would be morally unacceptable for human subjects. Yet one must ensure that the conclusions can be transfered from one organism to another. Was "chicken polyneuritis" indeed equivalent to human beriberi?

In response to criticism, Eijkman characterized the disease more fully. He examined the chickens' tissues and noted the same degeneration of the nerves that the medical commission had identified in human beriberi. Eijkman also tried to show the connection by transferring the disease from humans to chickens with injections of blood or other body fluids from beriberi patients--but with no luck. This could be explained by the intermediate role of a toxin.

Students have suggested other plausible hypotheses. For example, the milling (polishing) of the rice may have been unhygienic and introduced a "germ" into the starchy white rice, whereas unmilled rice would remain germ-free. That is, there would be no anti-toxin, only a physical protective barrier.

THINK [5]: Human Experiments / Research Ethics

This can be an occasion to underscore the concerns of using human subjects in research -- although the ethical standards in the late 1800s were very different than they are today. An obvious approach to investigate beriberi in humans is to control the diet of two groups of people. Indeed, based on Eijkman's work, in 1906 two researchers (Fraser and Stanton) took a healthy workforce to a previously isolated area of Javanese forest. They fed one half of the workers white rice, the others a more complete diet. They continued until the workers that were fed only rice became ill with beriberi. They then switched diets between the two groups. The first group was cured, while second group became ill. Reversing the diet of the same two groups is an elegant example of the use of control. From today's perspective, there are also obvious ethical problems with Fraser and Stanton's study in deliberately exposing persons to harm (in this case moreover, likely without their consent).

See also comments to follow on the Javanese perspective.

THINK [6]: Vorderman's Statistics / Natural Experiments & Controls

Each part of the supplemental investigation represents a variable that Vorderman wished to rule out as a possible cause. There were other ways a bacterium might spread: water, air, contagion, unhygienic environment. The Eijkman/Vorderman study is classic in exhibiting the idea of a controlled study -- not "controlling" the variables in the lab, but comparing two parallels sets of data that differ by a single variable: what is commonly called a "natural experiment." This is an important illustration of how scientists can sometimes secure the relevant empirical information (limited to one variable) without performing an experiment.

THINK [7]: Vorderman's Results / Sample Size

Vorderman's results addressed many objections about the relevance of chicken polyneuritis to human beriberi (THINK 4). Its large scope -- ample samples of both prisons and prisoners -- helped rule out the role of mere coincidence in the results. Once the results became widely known in the early 1900s, more research began to focus on rice 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.

Nevertheless, as noted in the text, several researchers also continued to search for the bacterium responsible for something in the rice.

THINK [8]: Communicating Eijkman's Findings / Scientific Communication

This case underscores the importance of communication among members of a scientific community. Journals, of course, are the primary channels for formally reporting results. Most journals in the late 1800s were European and even the work of researchers from colonial powers working in Southeast Asia were typically published in these European journals. In addition, Eijkman chose to publish his article in his native Dutch--hardly a language used universally, even at the time.

Students might imagine the various forms by which scientists communicate today (e-mail, telephone, correspondence, local and international conferences) and contrast these with what was available in Eijkman's era. This can highlight further the general cultural and technological contexts of science on a "mundane," but clearly influential level.

THINK [9]: Bacterial Causes / Burden of Proof

As suggested in the question, this case is an excellent occasion to discussion asymmetries in experimental reasoning and the corresponding notion of the "burden of proof." Philosopher Karl Popper is widely known among scientists for his idea of falsification: that we can never logically prove a theory in all cases, but that we can rule it out based on a single counterexample or "falsifying" instance. This may be true logically, but the beriberi case demonstrates the additional experimental dimensions of the problem: how does one know that one has a definitive falsifying instance? If one is searching for an unknown (of unknown properties--and hence, hard to find or identify), for example, how exhaustive must one make the search?

In some cases, by contrast, single specimens or events have been influential scientifically ("golden events" in particle physics; fossils; phylogentically unprecedented animals). In these cases, an individual piece of evidence can demonstrate the plausibility of a previously "improbable" hypothesis or "prove" the existence of an important class of previously unknown phenomena. Both cases--falsification and demonstration--raise the question of expectations, null hypotheses, and burden of proof. This can be especially important in cases of social decision-making under scientific uncertainty.

THINK [10]: Making Decisions about Beriberi in Research & Policy / Uncertainty in Scientific and Social Contexts

The first decision underscores that scientists do not have unlimited resources for pursuing various investigations. Scientists must make choices about which problems to pursue or which hypotheses to test. Further, they must make these choices without the advantage of hindsight--that is, they cannot know which path is the "right" path to pursue in advance. The beriberi case illustrates that a scientific community, through its diversity, might be able to "hedge it bets," by pursuing several different lines of investigation simultaneously. If so, then disagreement in a scientific community may be a productive force, rather than a sign of weakness.

The second decision highlights how public policy must often be decided in contexts of scientific uncertainty. Scientists may have the luxury of withholding judgment; public policy-makers, generally, cannot "wait and see." They have many factors to consider and, therefore, may not always follow the "weight of the scientific evidence." They may need to consider equally avoiding the consequences of possible error. Such cases of uncertainty confront us today. Even professional scientists may disagree over interpretations of the evidence. How do we decide the best policy in the meanwhile? (Chapter *21*).

THINK [11]: Grijns' Interpretation / Alternative Hypotheses & Conceptual Change

Grijns's notion of a deficiency rather than an active cause required a conceptual "gestalt switch"--seeing background as foreground. The disease was caused by the *absence* of an essential nutrient, rather than the *presence* of a disease-causing agent.

For further discussion, consider how Grijns's might have interpreted Takaki's findings, if he had known about them (notes for THINK 1).

THINK [12]: The Significance of Vorderman's Study / Limits of Control

It is hard to find a better example that demonstrates both the power and the limit of scientific investigation. Correlation does not necessarily document causation. The conclusions of a controlled experiment or controlled study are only as good as the controls investigated. Yet this does not invalidate a study in the context where the controls apply. One may contrast the dramatic decrease in beriberi throughout Asia based in changes of diet with the later discovery of thiamine itself.

THINK [13]: Discovery and Nobel Prizes / Scientific Credit

Historian Thomas Kuhn has argued that discovery is a fuzzy concept and that we cannot pinpoint a specific date, time, or place for most discoveries. They are not single events, but complex shifts in conceptual understanding. For example, can Eijkman be credited with discovering vitamins, if he could cure beriberi, but at first rejected the explanation of deficiency diseases? Does Hopkins earn recognition, even though he did not connect specific molecules with specific diseases, as Funk and Suzuki did? Jansen and Donath were the first to actually isolate thiamine, but would they have done so without earlier findings? Nobel Prizes tend to reinforce a common notion that science relies on genius and individuals of exceptional talent. How does the case of beriberi fit with this image of science?

Credit in science is often portrayed as a significant motivating factor, if not for research, then for publicizing findings as soon as they are publically defensible. How does the system of credit motivate scientists? What other motivations might exist? Why do we credit only the first person to publish a discovery? Are there any disdvantages to our system of credit? Should we give prizes or awards in science? --If so, on what basis?

THINK [14]: "The" Cause of Beriberi / Nature of Causality

Here, causes seem to operate on at least four levels simultaneously. This challenges many conventional notions of causality as single, linear and deterministic--proceeding in billiard-ball-like fashion, from one cause to the next.

Reductionistic thinking further leads us to consider the lack of vitamin B_1 as "the" cause of beriberi. Many were able to cure beriberi using Eijkman's (erroneous?) conclusions, long before anyone understood the concept of a vitamin. Why might we tend to privilege one explanation over another?

THINK: NOS Reflection Questions

These reflective quesionts function partly for recall and review but also to help consolidate and thus complete the central NOS lessons of the case study. They are essential to "closing" the lessons and making the NOS thinking explicit and articulate. Relevant earlier discussions are noted.

- 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, 7, 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)