Beriberi, White Rice and Vitamin B

A Disease, a Cause, a Cure

Kenneth J. Carpenter

University of California Press

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Preface

This is a medical detective story: beginning with the investigation of a disease that has killed or crippled at least a million people, and then following up clues that ranged much wider. One outcome was the production of a synthetic chemical that we now, nearly all of us, consume in small quantities each day in our food. The detectives had a variety of professions and spoke different languages. Their work ranged from studying the health of laborers in a primitive jungle to the painstaking dissection of individual grains of rice under a microscope. The integrated story of their struggles and successes, culled from old volumes in scattered libraries, forms the subject of this book.

The disease under investigation was not a fever, but began with a weakness and loss of feeling in the legs, commonly proceeded to a swelling (or dropsy) of the lower half of the body, and could end in heart failure and death. This sequence was first encountered by Western doctors in Indonesia, where the natives called it *beriberi.* It then became clear that the same condition was known in Japan as *kakké,* in Brazil as *perneiras* (disease of the feet), in Louisiana as *maladie des jambes* (disease of the legs) and was occurring among fishermen off the coast of Labrador, and described by physicians as *polyneuritis.*

For the administrators of the European colonies in Southeast Asia toward the end of the nineteenth century, one of the worrying things was that the disease was a particularly serious and increasing problem among the men in their employ, whether as soldiers or civilians. Why should these men be more at risk in hygienically designed barracks than in their own villages, where modern ideas of hygiene were disregarded? The Japanese army, too, in Japan's short war with Russia, had to ship home from Manchuria over ninety thousand men who were suffering from the disease.

In the 1880s and 1890s, germ theory was providing the explanation, and also treatment with vaccines, for a considerable number of

diseases. Naturally, there also began a sustained hunt for the organism causing beriberi, with the eclipse of a few earlier ideas that the disease was caused by an inadequacy of the sufferers' diet and was somewhat analogous to scurvy.

As with other diseases, there have been simplified, semimythical accounts of one "scientist-hero," in this case Christiaan Eijkman, who discovered the cause in a flash of inspiration followed by a single critical trial. It is true that Eijkman, who was attempting in Java to infect chickens with blood from beriberi patients, saw some uninjected chicks developing leg weakness, and that he traced this to their having been fed on cooked white rice. It is less well known that, after failing to reproduce the condition in chickens on his return to Holland, he reverted to believing that the disease was after all an infection, but that individuals' power of resistance to it was influenced by their diet. In fact, the proof that the disease could be explained by a deficiency of thiamin, a vitamin required at a level of no more than about one part in a million parts of diet, was to take more than another forty years.

The isolation of the vitamin was even more difficult than the proverbial task of finding a needle in a haystack. It was more like isolating not one intact needle but the myriad pieces of a needle ground into a powder, and so unstable that it could be destroyed by the manipulations used to separate it. Then there was the further problem of finding out the constitution of the isolated crystals and reconstructing them synthetically. And only when a chemical method of analysis for thiamin had been worked out was it possible to check whether the results fit the hypothesis that diets of low thiamin content were associated with the disease—not only in Asia but wherever else it had occurred.

Finally came the important finding of a biochemical function for thiamin—in the working of an enzyme system for capturing the energy released from the oxidation of sugars. This provided the new concept of a "biochemical lesion" taking place in a vitamin deficiency, and provided the first evidence of a new kind of linkage between clinical disease and biochemical function.

This book provides an example of a long path of scientific research that can be followed by readers without any specialized scientific knowledge. It is also a scholarly account in the sense that references

are given throughout to the original sources of information, so that anyone can follow up specific points of detail. Although the book does include chemical formulae, they are not essential to an understanding of the main story. They are included for the interest of those readers who want to know a little more of how the identification and then the synthesis of the vitamin was achieved.

The early chapters are written from the perspective of investigators at the time, without the use of hindsight. Only in this way can one appreciate the difficulties faced by each successive generation. Moreover, I have concentrated on the actions of the workers in the field and laboratory rather than on underlying social and cultural influences at work in Southeast Asia during a period of colonization, which have been the object of other studies in recent years.

The subject is not entirely a matter of history. It is now realized that the mental degeneration of chronic alcoholics is commonly due to thiamin deficiency, which in turn results from their limited diets and diminished absorption of nutrients. Should thiamin be added to beer and wine, as well as to bread, which would be very inexpensive compared with the cost of keeping the victims in mental hospitals for the remainder of their lives? This is still an unresolved question in the field of public health.

As in any reconstruction of past events, we are indebted to our forebears who have purchased and preserved the publications of previous generations so that they are still available. I have received much help in locating obscure materials from the knowledgeable reference librarians in the Bio-Sciences Library at Berkeley, and also from the staff at the Wellcome Library in London and the Vanderbilt Medical School Special Collections. I have also made use of the impressive work of earlier reviewers of the subject: Le Roy de Méricourt (1868), August Hirsch (1885), Leonard Braddon (1907), Edward Vedder (1913), and Robert R. Williams (1961). The earlier writers were French, German, and British, respectively, and the last two were American. Norio Shimazono and Eisuke Katsura (1965) have also edited valuable reviews of the Japanese literature.

I am indebted to my colleagues Annet Teunis and George Wolf for long sessions of translation from Dutch and German, respectively, and to Patricia Swan, David Fraser, and Barbara Mehne for reading and commenting on draft chapters. Others who helped with individual

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CHAPTER 1

The National Disease of Japan

1875–1885

By 1850 Japan had, by the will of its rulers, been cut off from virtually all contact with the Western world for 250 years. The one exception had been limited trade contact with a small Dutch community that was restricted to a tiny offshore island. Japanese were forbidden to leave the country, and they thought that to have "foreign barbarians" stepping on what they called their "celestial" soil would contaminate it.[1]

By that time several European countries had established profitable trading relations with China, and the United States was anxious to be the first to do the same with Japan. In July 1853, Commodore Matthew Perry, with a fleet of four ships anchored off the Japanese city of Uraga, landed with a show of force and left a statement that he would return early the next year to negotiate a trading treaty. The Japanese authorities, impressed by the fleet's guns, decided that they had better come to terms; when Perry returned, they gave him permission to establish a small American trading enclave at Yokohama, then only a fishing village.[2]

In 1858 the British negotiated a similar treaty, and after that so did other nations. Each small foreign community as it was established usually included a physician who was anxious to learn more about this exotic country. In 1867, with the succession of Emperor Mutsuhito, there began a period of deliberate Westernization.[3] Western books were translated into Japanese, people were sent to Europe to learn new skills, and by 1875 twenty-five Western surgeons and physicians were employed by the Japanese government.[4] In view of the prestige of German medical science in that period, doctors were recruited from the University of Berlin to reorganize the Tokyo Medical School.[5]

A MYSTERIOUS DISEASE CALLED *KAKKÉ*

One of these early Western doctors commented: "One was not long in the country before encountering a formidable and mysterious disease known as *kakké*."[6] Others went so far as to call the illness "the national disease of Japan."[7] In a general review of the diseases encountered in the country, a French doctor wrote: "After smallpox, the *kakké* is certainly the disease that causes the greatest ravages here." He also described its typical progression—the subjects, previously in good health, feel a progressive loss of strength, fall into an apathetic state, and lose their appetite; soon afterward their face becomes puffy, and their ankles swell and become rigid and painful. The edema spreads to the legs and thighs, then to the abdomen. Finally, the subjects lose their voice and die in asphyxial convulsions.[8] Others referred to the earliest sign being a loss of sensation in the foot and calf, such that a patient may not be aware that his sandal has slipped off and he is walking barefoot.[9]

The Japanese doctors, whom the Westerners consulted, said that the best description of the disease as it occurred in Japan was that published in 1804 by Tachibana Nan-kei in his "Notes on Several Diseases." He summarized the seven characteristic signs of the disease as follows:

i. *Kakké* begins to be a problem in April or May, is worst in the rainy, summer period, declines in the fall, and is hardly seen in the winter.
ii. It appears frequently in the Kyoto and Tokyo districts but is rare in other provinces.
iii. It begins with slight swelling and paralysis of the legs, without disturbance of the arms, face, and trunk.
iv. The appetite is not disturbed.
v. There is no fever.
vi. Typically, it is rare among both the nobility and the lower laboring classes such as porters, but it is frequent among the samurai (warrior class) who come to Tokyo from other provinces, and among merchants' servants and artisan handworkers who work the whole day sitting down. Finally, it is common among students who come from elsewhere to attend school.
vii. The *kakké* patient seems almost like a healthy person, but when suddenly *Shiyo-shiu* (pounding of the heart) begins, the case always ends fatally.[10]

Fig. 1.1. A case of "dry beriberi" in a Japanese soldier, showing emaciation of the leg muscles and the characteristic ankle drop (Herzog, 1906a).

These symptoms agreed so closely with those seen by the newly arrived Westerners that they had no doubt that the disease had been present in Japan for a long period (Fig. 1.1).[11] There are also much earlier descriptions of the disease in Chinese medical writings. The Japanese doctors knew of these accounts because Japanese medical science, like much of Japan's culture, derived from early Chinese culture, and the medical texts in Japan were based on traditional Chinese treatises. The word *kakké* is itself derived from two Chinese characters, pronounced *chiao* and *ch'i,* meaning "leg disease."[12] Two texts written soon after A.D. 600 contain descriptions quite similar to the one just set out. In addition, they point out that edema occurs in some cases but not others; they refer to the blunting of sensitivity of the skin on the calves and indicate that severe vomiting may be a precursor of death.[13]

Returning to Japan, a pair of independent doctors wrote, in about 1750, that the serious form of *kakké* described in earlier Chinese texts seemed only to have appeared in Japan in the last twenty years. Previously there had been patients with pain in their legs, but they had all recovered. Now physicians were seeing, in addition, severe edema, heart palpitations, loss of sensation, and a significant number of deaths. These cases were occurring mostly in young men.[14]

Professor Botho Scheube, the first Western scholar to study this material, suggested that the idea that *kakké* had not been a major problem in Japan before 1750 was supported by the fact that a Dutch physician, Dr. Kämpfer, who had special permission to travel in Japan in 1690, made no mention of it in his writing.[15] It certainly seemed that the disease could "come and go" because it had virtually disappeared from China by the time that Western doctors were stationed there after 1850.[16] Yet it was again the subject of investigation in large Chinese cities in the 1930s, as will be described in chapter 8.

TRADITIONAL JAPANESE TREATMENTS

In the feudal structure of traditional Japan, doctors belonged to a special caste, largely hereditary, at the lowest rank of nobility. They had the right to wear a sword in their belt, and a silk jacket embroidered with their family crest, to grow a full beard, and to be judged only by their peers.[17] These doctors were well respected. We have a description of one walking to a house call, with a grave demeanor and wearing a huge pair of spectacles, followed by his servant, wreathed in black silk and carrying a box of medicines. On arrival at the house he is first entertained, like any other guest, with a variety of tidbits and cups of tea. Only when these polite overtures are finally completed will he be permitted to examine his patient.[18]

Squatting on his knees, with the patient lying at floor level, the doctor feels the warmth and dryness of the skin, the pulse at many points on the patient's body, and then, most important, studies the appearance of the face. Routinely, by his gestures he will portray at first rapt attention, then after fifteen minutes or so "uncertainty," then "satisfaction," and finally "delight at having overcome all the difficulties."

When the diagnosis was *kakké,* which was thought to result from edema of the spinal cord, the doctor would treat it with acupuncture, applying needles in the calf, and with moxas applied to the back along

Fig. 1.2. Print of a nineteenth-century Japanese physician in traditional dress (Editions Dacosta, Paris).

the line of the spine.[19] A moxa is a cylinder made of dried parts of a plant (commonly *Artemisia japonica*), held together with glue. It is stuck to a chosen part of the body and then lit to set it smoldering, under the belief that it will draw out toxic gases from the body. People will use moxas for themselves without consulting a doctor, and as a preventive as well as a cure.[20] The pain from the scorching of the skin is also regarded as a counterirritant that stimulates the autonomic nervous system.[21] As the moxa burns down, it raises a blister, which may become infected, thus making the remedy worse than the disease.[22] (This treatment is really no more surprising than the practice of some Western physicians in the same period of bleeding anemic patients to stimulate their bone marrow. Also, "blistering along the back" had

been included in the practice of some Western doctors when treating beriberi in colonial territories.)[23]

THE OPINIONS OF WESTERN DOCTORS

Despite the respect for traditional medicine in Japan, the newly established Western doctors were also much in demand. Most, but not all, of them regarded *kakké* as being at the least strikingly similar to the disease of beriberi that was endemic in many parts of the more tropical Southeast Asia. This was of no particular help, however, since there was no accepted theory regarding either the cause or the treatment of beriberi. Physicians therefore had to make their own decisions about the disease they faced in Japan.

No one suggested that the condition was directly infectious or contagious. Presumably this possibility was ruled out because patients moving into a healthy area did not convey the disease to the people already living there. This was in stark contrast to the experience of cholera, which had spread rapidly through Japan in 1877–79, after its entry from China through two seaports.[24]

However, the most common direct cause of the disease was thought to be a poisonous "miasma" (or "miasm") arising from wet soil.[25] This was the period just before the general acceptance of there being different specific bacteria or other living microorganisms that caused specific diseases. But there was this earlier concept of miasmas, or gaseous poisons, coming from particular areas of soil, usually hot and humid, that reproduced themselves by some kind of catalysis.[26] The concept was used to explain diseases that occurred in certain places, and not in others, and where it was thought dangerous to go out in the night air.[27]

Data collected in Kyoto and Tokyo hospitals certainly confirmed that the disease appeared primarily in the hot, wet summer months of July to September (Fig. 1.3). Most of those arguing for the miasma theory also pointed out that *kakké* occurred only in certain parts of Japan, typically the wetter, coastal areas, and that moving away from those areas was considered a sure way of recovering from the disease.[28] Stuart Eldridge, an American surgeon, believed in the miasma theory but added that the danger "must be capable of being transported, in some manner unknown, to other regions," since the dis-

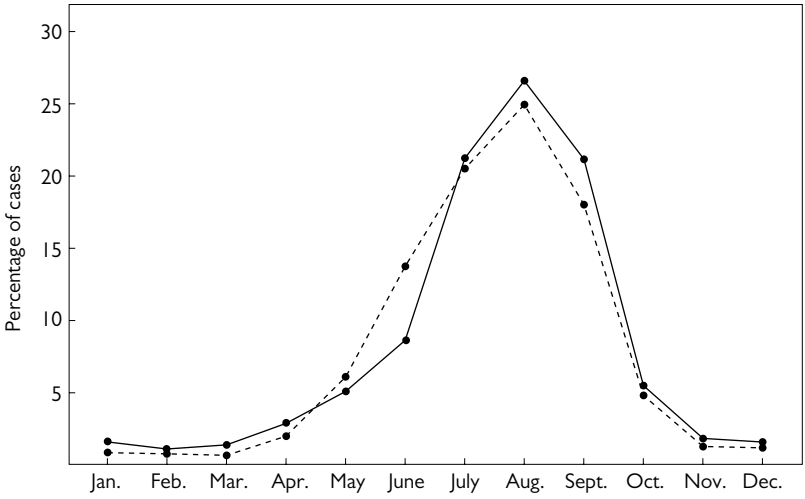


Fig. 1.3. The distribution throughout the months of the year indicating when patients were first diagnosed as suffering from *kakké* (beriberi): *dashed line,* 1,292 outpatients at Kyoto Government Hospital in 1878; *solid line,* 2,996 soldiers in the Tokyo district, 1879 (Scheube 1882–83, pp. 153–54).

ease had recently become common in parts of Japan where it had previously been unknown.[29]

The Western doctors were, perhaps without knowing it, following what had been written over twelve hundred years earlier by the Chinese physician Sun-szu-mo in his book *The Thousand Golden Remedies:*

> *Kakké* is always generated through a poisonous gas formed in the earth, from which heat, air, and moisture arise. The foot always touches the earth, so that the poison enters the foot first and then rises to the leg, arm, abdomen, back, neck and head. . . . Should the poison enter the abdomen, which may or may not swell up, there is a severe shortness of breath, and the patient will die in a few days.[30]

DIET AS A FACTOR

The one physician who argued that miasmas were not responsible for the disease was Albrecht Wernich, who wrote:

> It is a chronic, constitutional disease of blood formation and the vascular system, occurring in people who lack sufficient protein and fat in their diet. In the moist and oppressive summer months they reduce

> their diet so that it consists almost entirely of vegetable foods. People of Japanese descent have a disposition for *kakké.* Most cases are of individuals in their developmental period, which makes great demands on the organism, and in fresh cases one always finds some special stress such as night work, travel, or some other minor disease.[31]

In a further publication Wernich wrote:

> Rice is quite specially responsible for the generation of this disease—not, as had been suggested, because it is eaten in a spoiled state (like ergotism from eating infected rye), but its massive intake inhibits the utilization of other foods. Yet, despite its quantity, it does not provide the nutrients needed for blood formation. Unlike the Chinese who in the north eat fat pork and in the south use coconut oil, the Japanese diet is almost totally lacking in fat. Even though protein-rich items, like fish and bean cheese (tofu), are used in the Japanese diet, they are always taken only in small quantities, and omitted altogether in the oppressive summer months.[32]

In the prevailing "humoral theory," foods were considered "hot," "cold," or "neutral" regardless of the temperature at which they were served; rice and tea were among the few considered to be "cooling." The last three months of pregnancy were also considered a time for eating only "cooling" foods.[33] As one physician put it: "We Japanese lose our appetite in the hot season . . . and prefer a plain diet to meat and other fatty things. . . . fish are subject to putrefaction. We often satisfy ourselves with 'chazuke-meshi' (plain boiled rice mixed with tea)."[34]

Later investigators did not confirm the idea that blood formation was diminished in *kakké*.[35] There were also a number of counterarguments to the idea that the disease was a consequence of a poor diet. The first held that strong, well-nourished people were most at risk, while the poorest-fed, the laboring coolies, seemed to be exempt. In addition, the diet was similar throughout Japan, but the disease occurred only in limited areas.[36]

Duane Simmons, an American physician who had been in Japan since 1860, did not think that an inadequate diet could be the actual cause of *kakké* "because the best fed and the best cared for are its most frequent subjects," but he added:

> I must admit, however, that rice of the better quality is badly borne by those suffering from this disease, while at the same time it is the chief food of those most liable to it. A change, too, from this to a

> coarser food, such as barley and beans, is a measure of great importance in the treatment of the disease. In what the difference consists, unless the latter articles are more laxative than rice, or contain more potash (rice being poor in this respect), I am unable to state.

Later in the same article, he mentioned that the deleterious effect of rice might depend on "the manner in which it is prepared—by entirely depriving it of its outer skin or hull—the universal custom in this country," adding that "the people themselves often use the small red adzuke bean (*Phaseolus radiatus*) as their sole food, with quite satisfactory results in many cases, and I recommend it to my patients."[37] That this was a common practice was confirmed in a later historical review.[38] The head of one department of the Tokyo *kakké* hospital at this time was also using this treatment for early cases and claiming success.[39]

An early Chinese writer, Han Yu (A.D. 768–824), had commented that, while the wheat-eating people in northern China were free of the disease, those living near rivers in the south and eating rice were subject to it.[40] Although the Western writers leave an impression that rice was the universal staple in Japan, statistics for the period indicate that rice made up only about one-half of the national grain consumption, with wheat, barley, and other grains making up the difference. Apparently, farmers would sell the more highly prized rice to urban consumers and themselves eat mostly the other grains.[41] And it was in the cities that the writers were working, and seeing the problem.

Another contributory factor that some Western doctors thought important was the Japanese habit of squatting on the floor rather than sitting on chairs: "They sit with their legs bent under them with the foot extended and turned inward, so that the whole weight of the body compresses the leg on the floor . . . a probable cause of defective innervation of the legs. . . . To sit in any other position is impolite . . . and they would endure considerable discomfort rather than violate propriety."[42] Other possible predisposing causes mentioned by several writers were overcrowding, poor ventilation, lack of exercise, and sexual excess.[43]

BERIBERI IN THE NAVY

A few years after Perry's ultimatum in 1853, a British fleet bombarded a Japanese coastal town in revenge for the murder of an Englishman

visiting the country. The Japanese government then realized that if the country was to retain its independence it needed a modern navy equal to that of any Western power trading in the Pacific. Because the British navy was considered the best developed at that time, shipyards in Britain were given orders to build naval vessels for the Japanese, and British naval officers were invited to become instructors in their new naval cadet school.[44] A British surgeon, William Anderson, was also appointed as professor of medical science in the Naval College, and many Japanese naval surgeons were trained at a private medical school in the south of the country with instructors from Britain.[45]

In contrast, it was the Germans, after their success in the Franco-Prussian War, who were invited to superintend the training and equipment of the Japanese army, and, as mentioned earlier, German scholars had been recruited to lead the official Tokyo Medical School.[46] Thus, in addition to the ordinary rivalry to be expected between the professionals of the two armed services, there was the additional factor of their training being in different languages, and their instructors having come from different medical traditions. This may explain the otherwise bizarre dichotomy in the treatment of their "national disease" in the following twenty-five years.

Kanehiro Takaki was one of the young surgeons recruited into the new Japanese navy in 1870. He wrote in later life that some 75 percent of the patients in the Tokyo naval hospital at that time were suffering from *kakké.* The treatments given ranged from purgatives, digitalis, strychnine, and iron to bloodletting.[47] In 1875 Takaki was selected to receive five further years of postdoctoral training at Saint Thomas's Hospital in London. After his appointment to the naval staff in 1882, he concentrated his attention on the continuing problem of the very high incidence of *kakké* in the navy: from 1878 to 1882, an average of one-third of all the enlisted men had reported sick from it each year.[48] He regarded the Japanese disease as being "beriberi," the name he used for it in his English-language articles.

TAKAKI'S APPROACH

The common idea that the disease was the result of a miasma coming from infected soil must have seemed irrelevant to Takaki when faced with its appearance in one naval ship after another. He examined the

statistics in great detail but could find no correlation between the incidence of the disease and the degree of crowding on the different ships, nor with the kind of weather experienced. The ships were all relatively new and were constructed to the standards of European navies, where *kakké* (or beriberi) was unknown. The patterns of living and working on board were also still in the British tradition. The one possible shortcoming that Takaki saw was that the Japanese sailors' diets did not reach the British and German standards for their nitrogen content.[49]

This requires a little explanation. Humans' functioning tissues are made up largely of protein (plus water); protein contains about 16 percent nitrogen, while carbohydrates and fat contain none. It is much easier to analyze foods for nitrogen than for actual protein, and since the great majority of the nitrogen in foods is present in the form of protein, food chemists commonly multiply the nitrogen content of a food by 6.25 and call that value its "crude protein" content. Nowadays we usually refer to dietary standards for the consumption of protein, and relate these to the crude protein content of the foods eaten, but Takaki was really more correct when he wrote in terms of nitrogen—the quantity actually being measured. We can, of course, convert his values to those more familiar to us. Thus his standard of 345 grains of nitrogen for an adult man doing very heavy work, after conversion from grains to grams and multiplying by 6.25, gives us 140 g as the equivalent amount of dietary protein. This was the standard originally proposed by the German physiologist Carl Voit, based on what reasonably well paid German laborers chose to eat. Voit's standard was generally accepted at the time, although a few years later it was to be challenged and drastically reduced.[50]

Takaki also compared not just the quantity of nitrogen eaten but also the ratio of nitrogen (N) to carbon (C) in the diets of Japanese and European sailors. This was another useful measure because individuals eat different quantities of food, and it was assumed that the bigger man would eat more and also have a proportionally higher need for protein. The Voit standard for an adult doing hard work was for the nitrogen content of the food mix to be at least one-fifteenth that of the carbon content. We can estimate the calorie value of these diets as being approximately 10 kcal/g of total carbon. Protein, when metabolized, has a caloric value of 25 kcal/g of nitrogen. Then the Voit standard is equivalent to a diet in which 16.7 percent of the energy

comes from protein.[51] Takaki estimated that the actual food being eaten by the ordinary sailors in 1883 had only 1 g N per 28 g C, equivalent to protein providing 8.9 percent of the energy. The officers consumed more protein (equivalent to a 12.5 percent value), and they also had much less beriberi.

In 1883 there was a particularly high incidence of the disease on a long training cruise for cadets from Japan to New Zealand, and back via Honolulu. Of the 278 men aboard, 161 developed the disease and 25 died. Takaki pressed the authorities to allow a trial of a modified diet. He finally succeeded in having the next annual training voyage repeated exactly, at the same season in the following year, but with the diet modified to include more meat, condensed milk, bread, and vegetables at the expense of rice, so as to increase its nitrogen content. The Treasury gave a special grant to cover the extra cost of these rations. On this voyage there were no deaths, and only fourteen cases of the disease, all among men who had been unwilling to eat the full rations of meat and milk.[52]

Takaki naturally regarded this outcome as a vindication of his theory that beriberi resulted from a protein-deficient diet, and all the naval ships and depots had their diets changed in a similar way. By 1887 he was able to report that in the previous year there had been no deaths and only three cases of beriberi in the whole navy, compared with over one thousand cases in each year before the changes were begun.[53] For this achievement he received the honor of a personal interview with the mikado (the Japanese emperor) and was later raised to the rank of a baron.

Takaki was not actually the first to have set out to remove the beriberi problem from a group of Asian sailors by changing their diet to a more European pattern. There had been a series of publications that he may (or may not) have read, by Van Leent, a Dutch naval surgeon who had served in a long campaign in the East Indies to subdue a militant group in Atjeh (at the northwestern end of the island of Sumatra). The incidence of beriberi among Javanese serving in the fleet there in 1873 rose to an alarming 60 percent, while for the Europeans it was under 1 percent. Van Leent had observed that when the ships were moored at their base (Palembang), the health of the natives improved almost magically. He attributed this to their being able to supplement their basic rations with fresh eggs, coconut oil, and other food items

that they liked, which had not been possible when they were stationed off Atjeh. He therefore arranged for them to be issued with the diet received by the Dutch sailors, which was richer in both protein and fat. Insisting that this change resulted in a very large drop in the incidence of beriberi, he concluded that the disease was purely a nutritional one, although his data were later disputed.[54] I will return to this in a later chapter.

THE VIRTUES OF BARLEY

Japanese naval prisoners were a special case. Their incidence of beriberi had been the highest of any group under the naval administration, with nearly seventy cases per one hundred men in 1883. During 1884 their ration was changed by having more than half of the rice replaced by barley, and also by small increases in the allowances of meat, fish, and vegetables, and in 1885 there were no further cases. The idea of replacing rice partly with barley had begun in civilian prisons as early as 1875 purely on grounds of economy. However, the civil authorities were surprised to find that wherever the change was introduced the incidence of beriberi had fallen sharply. Takaki again attributed the response to barley to the improvement in overall N:C ratio of the diets from 1:32 to 1:20.[55] He assumed that barley had an N:C ratio of 1:20, as compared with a ratio of 1:50 for rice.[56]

In 1885 the army authorities began to make a similar partial replacement of rice by barley in soldiers' diets, and the incidence of beriberi again fell dramatically.[57] Despite this change, the army's medical men still viewed it not as primarily a nutritional disorder but as an infection that would naturally have periods of epidemic and then of regression. They brushed aside the navy's success by assuming that it had, at the same time as changing diets, made some improvement in hygienic practice whose importance had not been recognized. And, clearly, while it was feasible to disinfect the interior of a ship, the same could not be done for the whole area of soil on which an army camped and marched. The professors in Tokyo University also maintained that the disease either was some kind of infection or was caused by a poison in some dietary constituent, particularly mackerel.[58]

As I describe in chapter 6, beriberi was to reappear in the army as

a serious problem twenty years later during the Russo-Japanese War in Manchuria, where barley was not so easily obtainable. In chapter 8 I will consider how far the early observations in Japan can be explained by modern knowledge. However, some important work was just beginning in 1886 in a Dutch colony, and I will return to that after a description of the production and properties of rice that will continue to play an important part in this history.

CHAPTER 2

Rice as a Staple Food

Rice has been the staple food of hundreds of millions of Asians for millennia and is reverenced for its value. In Malaysia, for example, the word *nasi* is used for food in general and for cooked rice in particular.[1] In Thailand, the general term meaning "to eat" translated literally means "to eat rice."[2] An early European observer in Java wrote of the people: "Their frames are robust and they often labour severely; but under all circumstances, a pound and a quarter of rice, a few spices and a meagre portion of animal food, most frequently fish, is an ample daily allowance for an adult."[3] For nearly two thousand years, "rice has been the heart of Japanese civilization."[4] Nevertheless, its use had been thought of, in the period covered in chapter 1, as being associated in Japan with the deadly disease of beriberi. It was also a common disease in some other parts of Asia where rice was the staple.

Soon controversies were to develop over whether only certain types of rice were associated with the disease, or only rice prepared for consumption in particular ways. It seems useful therefore to insert here a general overview on the subject of rice, the ways in which it is grown and processed, and what was known by 1900 about its chemical composition.

The name "rice" is applied to a wide range of semiaquatic annual grass plants. But, in practice, those cultivated on a large scale all belong to one species, with the formal name *Oryza sativa L.* Within this species are two main types, *japonica* (also known as *sinica*) and *indica,* which are suited to different climatic conditions. The *indica* varieties grow well in more tropical climates, and the thin, elongated grains are typically dry and firm when cooked. The *japonica* types do better in cooler areas, and their shorter grains are stickier and more "mushy" when cooked: desirable characteristics in Korea and Japan.[5] There are also hybrids between the two main varieties. The plant commonly called "wild rice" (*Zizania aquatica*) is another grass but not actually a member of the rice family, even though the grains do resemble rice.

Fig. 2.1. Transplanting young rice plants, growing in water (Labberton, 1910).

Fig. 2.2. A view of flooded rice terraces in the Philippines, showing the great height to which the walls were built to secure a level plot of land. Note the relative size of the workers just visible as specks to the right of the picture (Crow, 1914).

GROWING CONDITIONS

One way in which rice is different from the world's other major grain crops (wheat, corn [maize], barley, etc.) is that the rice plant will grow well in shallow water or even, for some varieties, floating in deep water (Fig. 2.1). This avoids competition from weeds that cannot tol-

erate such conditions. The elaborate terraced fields and irrigation systems constructed over long periods in Asia are designed so that rice plants will be in standing water for at least part of their growing period (Fig. 2.2).[6] Other varieties can be grown economically on dry land provided it contains sufficient moisture. Soil type is less important. In China, for many centuries rice has been the main staple crop in the wetter southern part of the country, whereas wheat and millet have been dominant in the drier northern regions.[7]

Under favorable conditions, the average yield of rice grain per acre is at least equal to that of wheat and corn, and two crops per year were being obtained in some areas as early as A.D. 900.[8] By 1989 the total world production of each of these three crops was on the order of 500 million metric tons per year.[9] Ninety percent of the rice crop was produced in Asia, with South America contributing nearly another 4 percent, and Africa about 2 percent.

PROCESSING OF THE GRAIN

The mature rice seed is harvested, as with other grains, by cutting the stalks, and commonly laying them out to dry completely before threshing. Figure 2.3 shows a panicle (or cluster) of rice with the grains still on it. Threshing separates the grain from the stalk and requires banging or shaking to detach the grain. Traditionally it has been done by either people or cattle trampling on piles, or by knocking sheaves on the edge of a container, with the detached grains falling inside. The grains can then be separated by winnowing—that is, letting the grains and chaff fall through either a natural wind or a forced draft so that the lighter chaff is blown, while the heavier grains fall into a separated heap.

At this stage the grain is called "paddy" (or "rough rice"). The edible part of the grain is still enclosed in a husk (or hull) that is completely indigestible. The traditional way of removing the husk has been by pounding. A portion of paddy is placed in a mortar, that is, a bowl of some kind—perhaps a hollowed-out length of tree trunk. This is then pounded repeatedly with a pestle, usually a heavy pole, to split and separate the husks from the kernel of the grain.[10] The pestle may be brought up and down directly, by hand, or by having it attached to a pivoted beam so that it falls by its own weight and is then lifted again by someone pressing down at the other end of the beam (Fig 2.4).

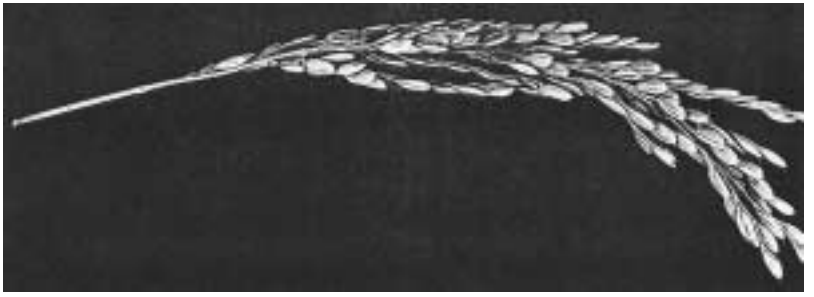


Fig. 2.3. A panicle (or cluster) of a rice plant ready for harvest (U.S. Department of Agriculture).

The pounded grains then have to be winnowed again to allow the broken husks to be blown away from the grains. The husks make up some 20 percent of the weight of the paddy. The grains are now described as "brown rice" and need not be processed any further before being cooked.

In some parts of India (particularly Bengal) it has been traditional first to carry out what is called "parboiling" (or "curing") of the paddy, which results in the husks being separable with less effort. There are different ways of doing this, but typically the paddy is soaked in water for twelve to forty-eight hours, then strained and heated (commonly with steam) until the husks split. It is then dried in the sun, and the husks can be separated from the seed by light rubbing.[11]

The two obvious advantages of parboiling are that it makes it easier to remove the husk, and that the grains are less liable to break up on any subsequent milling because the partly cooked starch has become more gummy. The disadvantage is that the grain is left with a distinctive moldy odor, and often with a discoloration, which people not raised on it from childhood find distasteful.[12]

In broad terms the dehusked rice grain is similar in structure to a dehusked wheat or barley grain, but whereas the latter usually are milled to a flour before being used as a food, rice is almost universally eaten as intact cooked grains. The wheat grain can be ground as it is to produce whole wheat flour and then used for brown bread, or else the outer branny skin of the grain can be separated by roller-milling and then sieving, to yield white flour.

The situation with rice is similar except that if it is desired to remove the brown skin (or pericarp) of the grain it has to be accom-

Fig. 2.4. Village method of pounding rice paddy to remove the hulls (or husks). A tray, used for winnowing the hulls, is in the foreground (Vedder, 1913a).

plished without breaking up the main part of the grain (the endosperm), so as to leave intact white rice (Fig. 2.5). In practice, nearly everyone who eats rice as their staple food, that is, the centerpiece for each of their daily meals, prefers white rice if it is available, and eating it can be a status symbol. White rice also has a longer shelf life than brown rice, which is more liable to be infested with insects and to become rancid.[13] But this is of no importance to villagers who can pound their own fresh paddy for each day's requirement.

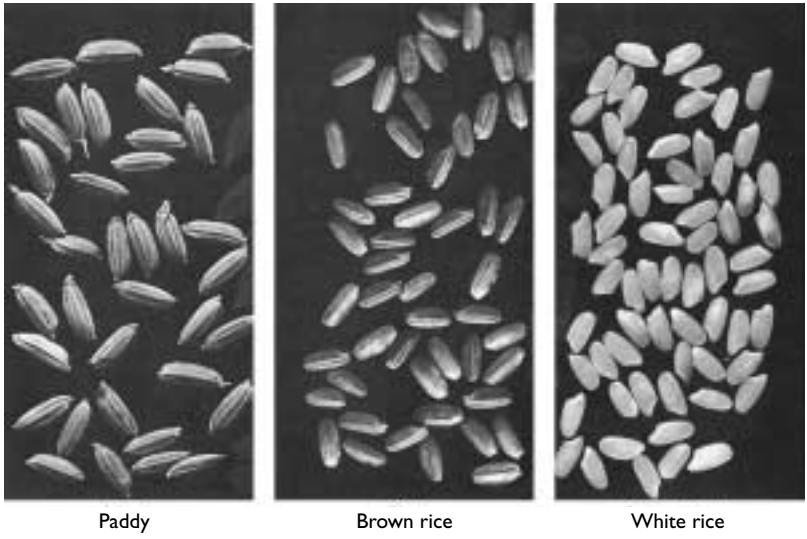


Fig. 2.5. Rice grains at three stages of processing: paddy (with husk or "hull" still attached), brown or "cargo" rice (husk removed, but with skin, "silverskin," or bran surrounding the kernel), and white, peeled, or polished rice (both husk and skin removed) (U.S. Department of Agriculture).

White rice was originally produced, at a high labor cost, in small, hand-driven milling machines. This is thought to have begun in around 1700 in Japan.[14] In Thailand also during the slave-owning period (pre-1905), this labor-intensive process was used by some wealthy families. We also have a later account of a Thai police sergeant who ate only highly polished rice prepared on a hand mill—worked presumably by prisoners or underlings.[15] In practice, since 1870 the production of white rice has been carried out almost entirely in power-driven mills.

When the milling equipment was developed in the second half of the nineteenth century, steam engines provided the power, so that the process was commonly referred to as "steam milling." Of course, the rice itself had no contact with steam during the process. The processing in a steam mill typically begins with paddy, which, after being sieved to remove any rubbish present, is passed into a sheller. Here it is fed into the space between two roughened iron disks, one of which is revolving. They are close enough together so that the husks are cracked and split. The particles of husk are then separated from the brown rice in a forced-draft winnowing machine. The husk particles

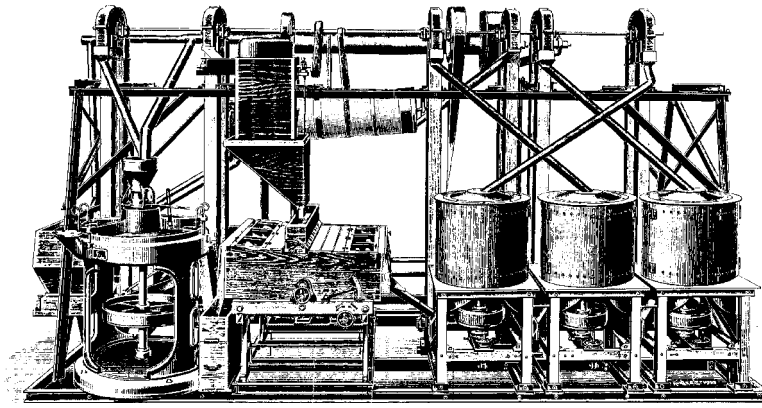


Fig. 2.6. Print of a steam-driven rice mill from a manufacturer's catalogue, ca. 1900. The rice moves from left to right through a dehuller, a fanning machine to winnow away the hulls, and then through three cone mills to remove the bran and yield white rice (Eisenwerk A.G., Hamburg).

can be used immediately as fuel to raise steam for the engine driving the mill. The grain is then passed through a series of two or even three cone mills (Fig. 2.6).Each consists of a vertical cone coated on the outside with emery, a form of corundum (granular aluminum oxide), which revolves in a casing of stout wire cloth. Grains fed from above into the narrow space between the cone and the casing are scoured as they pass down. The particles rubbed off pass through the wires and form the rice bran, which is sold as feed for pigs or other animals. The final cone mill is fitted with a smooth leather or wool lining, so that the grains are "polished" rather than scoured. The polishings removed at this stage may be sold separately from the bran. A further refinement for some markets is to increase the polished appearance by glazing and whitening it with talc, glucose, chalk, or other substances.[16]

Even this description is a simplification because of the need to separate broken and unshelled grains at different stages. The broken grain can be used in making fermented beverages, but it commands a lower price.

Rice deteriorates more quickly in storage if its moisture content is high, that is, over 15 percent. This results from fermentation and fungi and also, if it is stored as brown rice, from weevils and other insects as well as from the more oily bran going rancid. Sun drying is the tra-

ditional process, but in areas where a crop has to be harvested in wet weather, mechanical dryers are now being used.[17]

THE COOKING OF RICE

Wherever rice is the staple food, it is cooked by boiling in water. But nearly always it is first washed (or rinsed) to remove dust and dirt that rises to the surface and can then be poured off. The fastidious cook may give the rice three washings, rubbing the grain at intervals to help remove adhering particles, including any polishing powder that has been added by the millers.[18]

The grains may then be boiled in a large volume of water for twenty minutes or so until they are soft, and the excess water is then poured off.[19] Alternatively, the rice may be cooked in just enough water for it all to be absorbed by the grains. The last few minutes of cooking may then be carried out in a steamer to reduce the risk of the lump burning at the edges.[20]

Because fuel is a big expense for poor Asian families, rice may be cooked only once a day, with breakfast being based on leftover cold rice from the previous day. In a play preserved from the Ming period (A.D. 1388–1644), a Chinese housewife is given the line: "From the moment I get up I am busy about seven things—fuel, rice, oil, salt, soy sauce, vinegar and tea."[21]

THE COMPOSITION OF DIFFERENT GRAINS

At the time of Van Leent and Takaki's writing in the 1880s, it was believed that human nutritional requirements could be summarized as protein, energy (from carbohydrate and fats), and minerals, although it was not considered likely that minerals would ever be limiting in practice. It was also considered debatable as to whether fat, as such, was required in the diet, since it was known that an excess of carbohydrate in the diet was converted into body fat.

Table 2.1 summarizes the representative analyses used by F. W. Pavy in his *Treatise on Food and Dietetics,* first published in England in 1874 and widely quoted for the next twenty-five years.[22] Van Leent was justified in pointing to the low fat content of rice as compared with other grains. Other calculations, not shown here, confirm that the total Asian diets to which he was referring were also considerably

Table 2.1 Early analyses of cereal grains

	Nitrogenous matter	*Fatty matter*	*Starch and sugars*	*Mineral matter*
Rice	7.5	0.8	89.6	0.9
Barley	13.0	2.8	76.4	3.1
Oats	14.4	5.5	69.8	3.3
Maize (corn)	12.5	8.8	72.0	1.3
Wheat (soft)	12.6	1.9	82.6	2.1

SOURCE: Data from Pavy (1881), p. 145. The author points out that cereal grains commonly contain 11 to 18 percent water. The analyses have been recalculated as "percent of total dry matter."

lower in fat than were European diets. Takaki was equally correct in pointing to the low nitrogen content of rice as compared with other cereals, including barley.

It is notable that the analytical tables from this period do not state what degree of processing the samples had received before being analyzed. Nor did either Takaki or Van Leent refer to this aspect. But the following chapter will describe how it was to become of major importance in the next period of research. Later, in chapter 8, I will consider the different portions of a rice grain in more detail.

CHAPTER 3

Studies in the Colonies: A Dutchman's Chickens

1803–1896

Although, as described in chapter 1, the Western maritime nations were slow in making their way into China and Japan, they had much earlier colonized and occupied most of Southeast Asia and its surrounding islands (Fig. 3.1). It was in one of these colonies that the next advance in the understanding of beriberi was to take place.

The Portuguese were the first Europeans to establish bases in the East Indies in the sixteenth century. In a number of letters in this period, missionary priests referred to a local disease called *bere bere,* which they themselves sometimes contracted. In a letter written in 1580 from the Molucca (or Spice) islands we read:

> Father Rodriguez is suffering from an illness called *bere bere.* It begins in the feet and takes away the power of walking; the same happens to the hands, and then goes further to where the heart is affected, when death follows. In the beginning the illness is curable, but once the majority of the body has been affected this is impossible. Because of receiving rapid attention, the Father was cured so that, for the moment, he is healthy again, but he is no longer capable of traveling about the mountainous island of Amboina.[1]

The Dutch replaced the Portuguese in Java and Sumatra at the beginning of the seventeenth century and remained there as the colonial power, except for a short interval during the Napoleonic Wars, until World War II. Now, of course, these islands form the bulk of an independent Indonesia. It is from there that we have the first published reference to beriberi by a Westerner, Jacob de Bont, a physician who went to Java in 1637 and died there only four years later at the age of thirty-nine. He had already written at length on the natural history and diseases of the country, and his writings were published later under his latinized name, Jacobus Bontius.[2] He described sufferers

Fig. 3.1. Schematic map of Southeast Asia and surrounding regions with nineteenth-century place-names.

from beriberi as having lost sensation in their feet and hands. In addition: "Among the chief symptoms of this disease is a lassitude of the whole body . . . languid and depraved. . . . The speech is sometimes so much obstructed that the patient can scarcely pronounce a syllable articulately. . . . Any violent exercise incurs the danger of death. . . . It is especially the product of a rainy season."[3]

He added that he had been told that the name *beriberi* came from a local word meaning *sheep* because the sufferers had a tottering, sheep-like gait. Since then there have been several alternative suggestions regarding its origin: the Singhalese word *bhayree* (meaning weakness): the Hindi word *bharbari* (swelling); or the combination of the Arabic words *buhr* (shortness of breath) and *bahri* (marine).[4] As an early reviewer wrote: "The discordance of views among scholars with a spe-

cial knowledge of dialects makes it unlikely that the question will ever be resolved."[5]

BERIBERI IN SRI LANKA

For the next two hundred years there were scattered reports of the disease occurring both on land in European possessions in Asia and also among native crew members in the navies of the colonial powers. One early report was prepared in 1803 by Dr. Thomas Christie, who was inspector general of hospitals in the British colony of Ceylon (now the Republic of Sri Lanka). The British at this time had control of the island's coasts but were still at war with the inland kingdom of Kandy. Christie wrote that beriberi had resulted in many deaths among both European and native troops engaged in this fighting. Among the Europeans, the disease had broken out inland, where the soldiers' diet had included little other than rice, with a minimum of indifferent beef and no fresh vegetables. The sepoys (native troops) stationed on the coast also suffered. Although they had a bigger selection of foods to choose from, they also lived almost entirely on rice. They were given "ration money" so that they could make their own choice of supplementary foods but preferred to send most of it home to their families.[6]

In both groups the disease was characterized by numbness and frequent paralysis of the legs, often accompanied by edema. As the disease progressed, one saw vomiting, irregularity of the heart, and, in particular, great difficulty in breathing, as a prelude to sudden death. Christie added that some doctors had considered the disease to be only a modification of scurvy. In his opinion this was not the case. "The chief cause of beriberi is certainly a want of stimulating and nourishing diet. . . . However, giving 'acid fruits,' which I find of great value in cases of scurvy, has no effect in beriberi. . . . I can suppose the difference to depend on some nice chemical combination. The deficiency of stimulating animal food seems more often to favor the production of the latter."[7]

Another army surgeon, J. Ridley, painted a dramatic picture of his own experience with the disease in Ceylon some ten years later. He had traveled to a small inland garrison, where a fort was being constructed by four hundred native troops under a European comman-

der, in order to attend to a serious outbreak of beriberi. He found the commander dying of "jungle fever" and five to eight of the men dying each day of beriberi. The descriptions matched those from other outbreaks, but these cases appeared to have progressed unusually quickly: It occurred more than once that some of those who attended the funerals of their comrades one evening were themselves followed to the grave the next."[8]

Ridley ordered the wards for the sick cleaned and fumigated, dosed the patients with calomel (mercurous chloride, used as a purgative) and diuretics (drugs used to stimulate urine production), and had their legs and feet bathed and rubbed. In some serious cases blisters were applied to the back (as in the Japanese practice referred to in chapter 1).[9] The men themselves attributed their misfortunes to their god's displeasure; they had been using some of the timber, supplied for the fort, to build an adjacent temple for their deity, but the commander had put a stop to it.

Ridley, after thirteen days of around-the-clock work, believed that his own tiredness and a feeling of heaviness in his legs were the result of ordinary fatigue. But then he woke "with a sensation of tightness, as if a bar were placed across my breast. . . . I found my legs and feet perfectly numbed and swollen, and the space around my mouth, reaching nearly to my eyes, felt numb. I immediately took a large dose of laudanum [opium tincture] and brandy and subsequently a purgative." Finding the symptoms growing worse, he had his servants carry him on a litter back to his base nearly one hundred miles away. During the journey they would take him from the litter to sit up whenever he had a paroxysm of breathlessness. Later he had fits of vomiting, suppression of urine, and "great anxiety." He also referred to episodes of an "extreme fluttering of the heart" that might occur even when he was reading: "I had the sensation that my heart was suspended by a single thread. . . . My lips were observed to become pale. . . . A violent palpitation succeeded." Finally: "My constitution so much impaired by the disease, and by previous attacks of hepatitis, it was judged necessary to order me to England."[10]

I have reproduced this account at some length because, prior to the experience of World War II prison camps, it seems to have been the only personal description of the disease by a medical man. Ridley gives no suggestion regarding the cause of the problem, although he

does mention that the danger appeared to be greater in some parts of Ceylon than in others. In his report, published five years after the events, he does refer to an earlier writer and adds that "bad water, bad diet and damp have been, I believe, considered as favorable to the production of beri-beri at Trincomale and Palitoopané [two cities in Ceylon]." But he does not comment on whether these factors might have been responsible for the disease in himself or his patients.[11] It appears therefore that Thomas Christie's ideas had not been generally accepted by his medical colleagues.

THE FIRST REVIEWS

One of the first scholarly reviews of beriberi, considering all the available published material, appeared in 1868. The author, Le Roy de Méricourt, was a surgeon in the French navy and had himself been faced with the disease among laborers being shipped on long voyages between colonies in the Orient, Africa, and the West Indies. He reviewed altogether some ninety publications and pointed out that Bontius had made no reference to the appearance of edema in cases of beriberi. Almost all subsequent authors had referred to there being both "dry, paralytic" and "wet, edematous" forms; some had used the term *barbiers* for the dry form, and had diagnosed beriberi only when edema was present.[12] The reviewer commented that there were many reports of cases beginning with paralysis and later developing edema from the legs upward. This led him to consider that there was only one disease, but with varied manifestations. From that time on, the term *barbiers* virtually disappeared from the literature.

De Méricourt also drew attention to reports of the recent appearance of the disease among immigrant workers in Cuban sugar mills and in Brazil.[13] It could, therefore, no longer be considered a purely Asian disease. He also collected all the available statistics from different outbreaks for both incidence and mortality. Under the general heading of "colored races," there were 2,670 cases with 33 percent mortality, but also 215 cases among Europeans with 25 percent mortality. Contrary to the experience in Japan, there was already evidence that Europeans were not always immune to the disease.[14]

On the other hand, in agreement with later experience in Japan, many colonial and naval doctors had expressed their surprise that it was typically the more robust, stout men who succumbed first to the

disease. Also, it had been a consistent finding that children under fifteen were almost exempt, and that women also were generally less susceptible except when they were breast-feeding a baby.[15]

De Méricourt noted that many observers had reported the association of the disease with marshy areas close to the ocean in the Tropics and its greater incidence in rainy seasons, and that they had thought it to be either the result of toxic miasmas rising from the wet soil or a form of rheumatism. However, beriberi had also occurred in some arid areas in India and had broken out at sea when ships were in temperate regions. He concluded that climate could play only a secondary role in weakening people's resistance. It also appeared certain that the disease was not contagious. Nurses and doctors did not develop it from contact with their patients.[16]

He believed that malnutrition was the most important factor. Several physicians had already argued that this caused an alteration in the composition of the blood—so that it was comparable to scurvy in this respect, but obviously it had to be a different change to induce such a different disease. Rice, the staple food of most of the victims, was certainly itself not a fully nutritious food, being deficient in protein, fat, and minerals. The well-being of individuals depended, therefore, on what other foods were eaten to supplement the rice. Those who could afford it and ate fresh fish, meat, and vegetables remained healthy, whereas those who took a minimum of supplements put themselves at risk. This could explain the appearance of the disease after a long period at sea, when fresh foods had been almost exhausted. It also explained the apparent immunity of the senior personnel and cooks, because they had the first pick of whatever supplementary foods were still available. This, rather than true racial differences in susceptibility, explained why Europeans, and also those Indians who were in more privileged positions, had a much lower incidence of beriberi; it also explained the rapid recovery of most sufferers when they reached land, where fresh food was once more available. However, de Méricourt emphasized that it was the quality and not the quantity of the shipboard diets that was inadequate, because the laborers being transported typically gained weight on those long voyages.[17]

Many writers had concluded that there could not be one simple explanation for this puzzling disease, and therefore that it required a combination of stresses to appear. De Méricourt himself thought this

most likely and commented that beriberi occurred most frequently among colored races who, he thought, were ordinarily anemic and predisposed to congestion and edema, and were then subjected both to an inadequate diet and to debilitating climatic stresses. In certain cases the local swellings impinged on the spinal cord, and this produced a progressive paralysis.[18] The important measures for both prevention and cure were the same as those he recommended for scurvy—that the diet be varied and include fresh vegetables and fruits. Those at risk should also be provided with a range of clothing that protected against rapid changes between hot and cold weather.[19]

In the period following the 1869 French review, more material became available, including some of the papers from German physicians working in Japan, which I have already considered in chapter 1. Van Leent, the Dutch naval surgeon, also published data indicating that changing the diet of Javanese sailors to a more European pattern resulted in a significant reduction in the incidence of beriberi from 18 percent to only 3 percent.[20] He agreed with de Méricourt that beriberi was in the same class of diseases as scurvy. But he went on to write (as Christie had done some seventy-five years earlier) that, whereas scurvy was the result of a deficiency of fresh fruit and vegetables, beriberi resulted from a lack of fresh animal material.[21] He argued movingly that it was the duty of doctors to urge that more money be spent for food because it would "lessen the expenditure of men, even though this meant standing up to authorities who were in higher social positions but ignorant of the facts.[22]

In 1883 the German scholar August Hirsch published an impressive review of knowledge about beriberi in the second edition of his classic *Handbook of Historical-Geographical Pathology.* An English translation appeared two years later, and I will use that in citations to this work.[23] Hirsch accepted that diet was an important factor, but for several reasons he did not believe it could be the exclusive cause of beriberi. There were examples of laborers living for long periods on rice and a little dried fish and remaining healthy. Also the disease was limited to certain areas in India, although the diet there was apparently no different from that in other parts of the country. Further, the disease had appeared recently in Brazil without any change in the people's staple food, and the sufferers included people from wealthy, well-fed families.[24]

Hirsch concluded that beriberi was a specific disease "with no clear

analogy to any other disease known to us." It must therefore have "a peculiar and specific cause, . . . not discoverable according to the present state of our knowledge."[25] In his final summing-up he writes: "None of the hypotheses and observations which I have thought it necessary to reproduce . . . have dispelled the obscurity in which the nature of the morbific cause is shrouded. . . . We have not a single fact affording certain proof that the disease is transmissible. . . . I hold it to be still less justifiable . . . to give way precipitately to the modern craze for bacteria in this particular field of enquiry."[26]

THE MICROBIAL THEORY OF DISEASE

In chapter 1 we encountered the concept of diseases being caused by miasmas, poisonous vapors rising from certain damp soils that were able in some way to reproduce themselves by a kind of catalysis or fermentation. In the 1870s evidence began to be accumulated by the French chemist Louis Pasteur and others that diseases could be caused by the spread of living units too small to be seen except with newly improved microscopes. These "microbes," or bacteria, could reproduce within a host and could spread from host to host, either by direct contagion or from ingesting contaminated materials. They could also be killed by strong heat or certain chemical treatments, and scientists no longer believed in their "spontaneous generation."[27]

That was exciting enough because it seemed likely to lead to identification of the sources of epidemics. But it was then also found that, for some diseases, the microbes responsible could be "attenuated" (weakened) by heat or chemical treatment, so that they no longer caused the disease but could still confer resistance to it. It had long been known, of course, that when subjects had once recovered from certain diseases, such as yellow fever or measles, they would not be at risk from another attack even in the midst of a new epidemic. Traditional vaccination against smallpox had also used the phenomenon without its action being understood.[28]

Pasteur's early work on animal disease was with fowl cholera and anthrax in sheep. Robert Koch followed it up in Germany, and then in 1882 isolated the organism responsible for tuberculosis. In 1883 Europe was threatened by another cholera epidemic that had already spread from India to Egypt. The German government set up a Cholera Commission, led by Koch, to go in haste to these countries to find the

organism responsible and its mode of transmission. They did find the organism and reported on their return in 1884 that it was distributed through contaminated drinking water.[29] John Snow had already come to this conclusion thirty years earlier from the epidemiological association of cholera cases in London with the particular water supply that had been used by the victims, but he had not seen an actual causative organism.[30] In any case, Koch became a national hero, and, to quote from another writer, "bacteriology at this period became the center and goal of medical investigations."[31]

THE PEKELHARING COMMISSION

In 1886 the government in Holland received alarming news. A military expedition using a naval flotilla and many native troops had again been sent to Atjeh in northwestern Sumatra to subdue a community that still refused to accept Dutch rule and had been pirating the merchant shipping off its coast. However, offensive operations had been halted because of an alarming increase in cases of beriberi among both soldiers and sailors. The cause of beriberi was, after all, still considered "obscure," and the government must have thought that a commission, similar to Koch's, sent out from Holland with a fresh eye and a knowledge of bacteriology, had at least a chance of finding the answer to this old problem. In other words, the authorities were swept up into what Hirsch had called "the craze for bacteria." Cornelis Pekelharing, professor of pathology at the University of Utrecht, was appointed to lead this commission, with C. Winkler as his assistant.[32]

Pekelharing initially went to Berlin to learn Koch's latest bacteriological techniques at first hand. In Koch's laboratory he met another visiting Dutchman—Christiaan Eijkman, who will be the leading actor in the last portion of this chapter. Eijkman, who was then twenty-eight, had studied medicine at the University of Amsterdam with a military scholarship. He was given an extra year to work in a physiology laboratory, and was then sent out to serve as an army surgeon in the East Indies. After a short period in Java he had become seriously ill with malaria and been given home leave to recover his strength. While on leave he, too, had decided to go to Berlin to improve his knowledge of bacteriology. Pekelharing was so impressed by Eijkman that he arranged to have him assigned to the commission

Fig. 3.2. Contrasting cases of "dry" and "wet" beriberi in the Dutch East Indies (Pekelharing and Winkler, 1888).

to provide additional assistance when the latter returned to the East Indies.

Pekelharing and Winkler spent eight months in the Dutch colony, from November 1886 to August 1887. They began by carrying out careful autopsies and making detailed histological studies of individual tissues from victims of beriberi (Fig. 3.2). There was characteristic degeneration in peripheral nerves, which they considered an explanation of the paralysis and the loss of sensation in the disease.[33] They believed that this degeneration occurred in the early stages, since controlled electric shocks to the legs of patients with only mild symptoms gave smaller muscular responses than when the same shocks were given to healthy subjects.[34]

With regard to the cause of the disease, they wrote: "Beriberi has been attributed to an insufficient nourishment and to misery: but the destruction of the peripheral nervous system on such a large scale is not caused by hunger or grief. The true cause must be something coming from outside, but is it a poison or an infection?"[35] They added that looking for a poison would be difficult, but in looking for a microor-

ganism they did have new techniques that had been successful with other diseases; if they could grow cultures of organisms found in patients, and then reproduce the disease in animals by injecting them with these cultures, this would be clear evidence of the cause. If this approach failed, they would have to return to searching for a poison.[36]

They first studied beriberi patients who had developed the disease in Atjeh and then been brought back to a hospital in Batavia, but in most cases they failed to find bacteria in the patients' blood. When they themselves moved to Atjeh, however, they found bacteria in the patients they studied, but they also found them in healthy subjects chosen as controls, and even in samples of air. It seemed that infection was endemic there, although the characteristics of the bacteria isolated varied considerably. They were also unable to detect bacteria in the degenerated nerve fibers of fatal cases.[37]

The team went on to inject cultures prepared from the blood of beriberi patients into monkeys, rabbits, and dogs. Single injections were found to have no adverse effects. They then gave repeated injections, in some animals as many as twenty times in a six-week period. Six out of seven rabbits treated in this way finally showed some nerve degeneration, as did four out of six dogs. However, some had developed abscesses at the points of injection, and it was possible that these had become independently infected.[38]

Pekelharing concluded that beriberi was an infectious disease of an unusual character because a single exposure to infection was insufficient. However, that seemed to agree with the clinical observation that healthy native soldiers brought to Atjeh rarely became ill with beriberi until they had been there for six weeks, although they must have been exposed to the infections immediately. Repeated reinfection was presumably required for the body's resistance to be overcome. It appeared that the disease was most probably an airborne infection, by an organism that survived only under hot, humid conditions.[39]

To Pekelharing it seemed "scarcely possible to doubt that the micrococcus they had isolated caused beriberi." However, the fact that they, and also other investigators, had found various bacteria in the blood of patients at Atjeh and elsewhere could mean that more than one type was capable of producing "a poison that was indirectly responsible for nerve damage, since no bacteria were detected in the nervous tissue itself."[40]

He believed that, despite the remaining gaps in their work, the way

to deal with the disease was clear. The causative bacteria were in the air of the buildings occupied by the men at risk, and the buildings should therefore be thoroughly disinfected with a solution of mercuric chloride. The reduced incidence of beriberi at Atjeh following the introduction of this procedure further persuaded him of its value.[41] Also, since the bacteria might be active in the surrounding soil, men showing the first sign of beriberi should be moved to an area where the disease did not exist, so that they would not be reinfected. Pekelharing believed that they would not spread the infection because the germs did not multiply in the body and were not excreted—in other words, they had the properties previously attributed to miasmas.

EIJKMAN TAKES OVER

Christiaan Eijkman had been assisting Pekelharing throughout his time in the Indies, and the latter, before leaving, persuaded the authorities to keep Eijkman at work on the beriberi problem, with continued trials of transmitting the disease to animals. As a consequence, he was appointed, at the age of thirty, to be director of a newly established Laboratory for Bacteriology and Pathology (Fig. 3.3). It was to be under the civilian wing of the colonial government, but housed in the two rooms previously used by the commission. These were attached to the military hospital at Weltevreden, a suburb of Batavia (now renamed Djakarta). Eijkman was expected to conduct a range of teaching and other investigations, as well as continuing the study of beriberi. For this work he was given one young assistant, Dr. Johannes van Eecke, who would die seven years later at the age of thirty-five.[42]

In the section of his first annual report for 1888 dealing with beriberi, Eijkman wrote that he had tried to infect a dozen rabbits with cultures of Pekelharing's micrococcus. Each was given twenty successive injections over a month. One died suddenly on the fortieth day without any previous sign of nerve damage. The others showed no notable results. Experiments with a few monkeys were also disappointing. Eijkman concluded that beriberi was a lingering disease, with a considerable time elapsing before its full development. This meant that in infection experiments there was a large chance of other influences interfering. To exclude this source of error, one needed to have many control animals.[43]

Fig. 3.3. Christiaan Eijkman, probably taken at the time of his work on beriberi in Java in the 1880s (courtesy of Chemical Heritage Foundation).

Eijkman's second annual report, for work done in 1889, has recently been republished in English translation together with his two subsequent papers, and I will follow the pagination in this 1990 translation in references to these three papers. Here Eijkman referred only to experiments with chickens. He did not explain the change of species, but it seems likely that he decided to use chickens because they were more economical, to both buy and maintain, in the numbers that he now felt to be necessary. In the second half of the year, after a batch of chickens had been in their facility for twenty to thirty days, they showed a loss of weight and their gait became unsteady, whether or not they had received injections. Although at this stage they still ate eagerly, they had difficulty extending their legs. They then became unable to stand, their breathing slowed, their temperature fell, and death followed (Fig. 3.4). Eijkman added that the disease resembled a condition that had frequently been reported in the East Indies among fowl, pigeons, and ducks.

Autopsies of the chickens showed no gross changes other than ema-

Fig. 3.4. A chicken with polyneuritis (Fraser and Stanton, 1911).

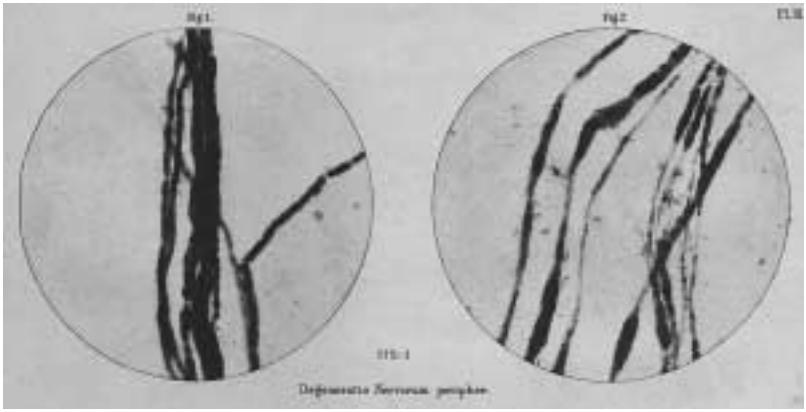


Fig. 3.5. Microphotographs of stained preparations of degenerated nerves from chickens with polyneuritis as a result of eating a polished rice diet. With Marchi's staining procedure, yellowish brown nerve fibers were judged to represent degeneration (Eijkman, 1893c, pl. III).

ciation and fluid around the heart. The brain and spinal cord appeared normal, but microscopic examination of peripheral nerves stained by Marchi's method showed signs of degeneration, most conspicuously in the legs, that resembled the changes seen in the nerves of people who had died of beriberi (Fig. 3.5). Eijkman was not able to culture any consistent type of bacteria from the blood of these chickens.[44]

Because control and injected chickens had been kept together in large cages, Eijkman thought it likely that infection had spread from the injected chickens to the controls. He therefore housed additional

chickens individually in bamboo cages. But these birds, too, began to show the disease regardless of whether they had been injected. It seemed that his entire laboratory premises had become infected. He therefore set up another site, remote from the first, to investigate whether chickens would remain healthy there unless deliberately infected. However, at this time, even the chickens at the original site began to recover and there were no new deaths, "so . . . all material for further experiments fell away."[45]

A DISEASE IN CHICKENS FED HOSPITAL RICE

Surely, at this point most investigators would have given up the use of chickens, whose behavior seemed so uncontrollable, and returned to a mammalian model such as the rabbits used by Pekelharing. But Eijkman felt that the disease in the chickens, which he called "polyneuritis," was sufficiently similar to beriberi to warrant a further effort. He wrote: "Something struck us that had escaped our attention so far." The chickens had been fed a different diet during the five months in which the disease had been developing. In that period (July through November 1889), the man in charge of the chickens had persuaded the cook at the military hospital, without Eijkman being aware of it, to provide him with leftover cooked rice from the previous day, for feeding to the birds. A new cook, who started duty on 21 November, had refused to continue the practice. Thirty years later Eijkman was to say that "he had seen no reason to give military rice to civilian hens."[46] If true, this piece of military rigidity was to have some fortunate consequences. Before and after this period, the birds had been fed on feed-grade uncooked rice, apparently a standard economic practice that the "man in charge" had assumed was satisfactory, and to which Eijkman had paid no attention.

To test whether the change in diet was important, Eijkman transferred a diseased hen from the laboratory to the new site and added it to a cage with two others. Another pair were injected with bacteria cultured earlier from a dead chicken, and a final pair were left as controls. All seven were then fed uncooked feed-grade rice. Four other chickens, which had never been at the laboratory, were fed exclusively "day-after," cooked hospital rice. After five weeks, only the chickens fed the cooked rice were diseased, but all four recovered when returned to the feed-grade rice diet. In a further experiment, chickens

were fed newly cooked hospital rice and again became diseased, but they recovered when transferred to "uncooked hulled rice from our own stock." Eijkman suggested that "cooked rice favored conditions for the development of micro-organisms of a still unknown nature in the intestinal tract, and hence for the formation of a poison causing nerve degeneration." He went on to point out that although there were many points of similarity between the chicken disease, with its peripheral neuritis, and human beriberi, there were also differences—in particular, the overall emaciation and loss of weight of the chickens, which was not seen in beriberi.[47]

For a large portion of 1890 Eijkman was again sick, probably from malaria.[48] In the report for 1891 he wrote that the etiological (i.e., "causation") studies were still in progress, and that he would report only results from his further histological work. He had found some changes in the spinal cord of diseased chickens, but these were "not significant enough to explain the extent and gravity of the disorder." It was the degeneration in the peripheral nerves that appeared most important.[49]

It was only in his 1895 report that Eijkman returned to the etiology of the chicken disease and described the long series of trials that he had conducted over a five-year period. This was important work, for which he received a Nobel Prize in his old age, and it deserves detailed examination. The questions addressed and the answers obtained are summarized in Table 3.1. The first five trials have already been discussed. His first thought at this point was that cooked rice might have deteriorated in some way in the twenty-four hours or so before it was consumed by the birds. However, in trial 6 the disease occurred in the same way in chicks fed freshly cooked hospital rice. Perhaps the cooked rice failed to stimulate the digestive system to absorb the nutrients contained in the rice, and the disease was the result of inanition (semistarvation). Therefore, in trial 7 he underfed chickens on very small amounts of uncooked feed-grade rice. After they had lost a great deal of weight they were killed, but their nerves still showed no degeneration.[50]

Another physician in the East Indies had recently published an argument for "toxic ground water" being the cause of beriberi.[51] Eijkman therefore fed four chickens on hospital rice cooked each day in a porcelain dish with distilled water and gave them water from an artesian well for drinking; but they still developed the usual polyneuritis, and he discarded this possibility.[52]

Table 3.1 The sequence of Eijkman's first experiments

The question asked	*The answer*
1. Was beriberi a transmittable infection?	Chickens injected with bacterial cultures from beriberi patients developed polyneuritis with neural degeneration, but so did the control animals.
2. Were the laboratory premises infected by contact with those injected?	Control chickens, housed separately, still became diseased, so direct contact was unnecessary. The whole premises might be contaminated, although no characteristic bacteria were isolated.
3. Were the laboratory premises infected?	New location selected for additional experiments, but even in the old premises the disease now disappeared.
4. Was it the recent change in the chickens' diet that was important?	Yes, chickens fed leftover cooked hospital rice became diseased, while those fed uncooked feed-grade rice did not.
5. Did the hospital rice contain a preexisting poison?	No, because chickens fed uncooked hospital rice (*for a short time*) remained healthy.
6. Did cooked rice develop a toxin during subsequent storage?	No, even chickens fed freshly cooked hospital rice became ill.
7. Was the disease caused by inanition?	No, starved chickens showed no signs of neural degeneration.
8. Was the cooking water at fault?	No, chickens still became ill when fed hospital rice cooked in distilled water, and drinking artesian water.
9. Could raw hospital rice fed over a longer period cause the disease?	Yes, some chickens developed the disease after extended periods.
10. Was it the variety of rice or the type of processing that was important?	Variety did not matter. The disease occurred only with polished rice.
11. Could raw undermilled rice (with silverskin) cure diseased chickens?	Yes, it did.

Table 3.1 *(continued)*

The question asked	*The answer*
12. Did polished rice acquire a toxin during storage?	No, even freshly polished rice (raw or cooked) caused the disease.
13. Is silverskin still protective when rice is ground and cooked?	Yes.
14. Was stimulation of the intestine by fiber from unpolished rice an important factor?	No, addition of coarse rice husks to cooked polished rice failed to cure diseased chickens.
15. Is it the nutritive salts and/or protein of the silverskin that is important?	No, chickens diseased from being fed tapioca starch responded only for a short period when supplemented with meat that provided as much protein and essential salts as in silverskin.

SOURCE: Modified from Carpenter and Sutherland (1995), p. 159.

In trial 9, Eijkman retested the effect of feeding raw hospital rice to four chickens, which all developed severe signs of polyneuritis. Three died after 25, 30, and 47 days, respectively, and the fourth had to be killed on day 46 when it could no longer stand, even though two chickens showed no serious sign of wasting. In a further repetition, two chickens developed the disease and two others did not. Eijkman contrasted the variable results with uncooked hospital rice with the consistent good results obtained with the raw feed-grain rice, and even the latter's ability to produce cures in affected chickens. It therefore appeared that at least one major factor was the type of rice being fed.

THE SIGNIFICANCE OF SILVERSKIN

This thought led Eijkman to look into the processing used to produce the hospital rice (also called "table rice" or "white rice"). He realized that in addition to the outer husk of the grain being removed, the skin that surrounds the endosperm was also removed in the polishing process. As he writes: "Rice grain enveloped by its silverskin has a less appetizing appearance and feels less smooth to the tongue; therefore the rice is . . . [further treated] to obtain nice-looking, smooth and

white grains."[53] The so-called silverskin gives a grayish or brown color to this type of rice. In contrast, the feed-grade rice that they had used was "red rice," a variety in which the "skin" is red, and which is used mostly for animal feeding so that no trouble is taken to process it further after removing the outer husk.

It therefore seemed likely to Eijkman that the presence of the silverskin was the important difference between the two materials he had been using. This possibility seemed to be confirmed when a chicken that had developed polyneuritis on a diet of cooked table rice recovered after being transferred to the same type of rice that had been only lightly processed so that its silverskin remained.

Eijkman now saw two possibilities: (1) that the skin protected the grain from the intrusion of harmful microorganisms, or (2) that the skin contained "substances indispensable to life and health that are absent or occur in too low concentrations in the nucleus of the rice grain."[54]

One writer had already suggested that beriberi be called "the government disease" and had suggested that natives in their villages remained free from beriberi because they stored their rice crop in the husk, and hand-pounded only enough for their immediate needs, whereas in government establishments milled rice was kept for long periods before use, and once its protective skin had been removed, pathogens had easier access to the starchy endosperm and could multiply there during storage.[55] Eijkman tested this possibility in trial 12 by feeding four chickens on uncooked white rice that had been freshly milled each day, but two of the four birds still developed characteristic signs of the disease. This explanation for the harmful effect of polished rice therefore seemed less likely. Trial 13 used chickens that had become ill as a result of being fed cooked table rice. Some were then fed brown rice (with the silverskin still attached) that had then been milled to a flour, and others were fed cooked red rice. With each treatment the chickens recovered. The virtue of the skin seemed therefore to lie in its chemical composition, rather than its being a physical protector of the inner grain, and the activity apparently survived cooking.

Another possibility considered by Eijkman was that the soft-boiled white rice failed to stimulate the intestinal wall into a proper functioning of the digestive system, which needed some inert material, and that the skin might be providing this. If that were the case, the

outer husk, "consisting primarily of cellulose and silicic acid," should function equally well in this way, but he found in trial 14 that chickens fed cooked table rice were not spared from the disease by the addition of coarse rice husks.

The next possibility was that the skin of the rice was contributing essential protein and/or salts. By coincidence, Eijkman had also been studying the nutritional status and dietary intakes of military units in the East Indies, in relation to the adaptation of Europeans to living in the Tropics.[56] He therefore had the necessary analytic procedures already set up in his laboratory, and a knowledge of the nutritional literature, although at this time he probably did not know of Takaki's work in changing diets in the Japanese navy. (His article had been published in the English-language supplement to a Japanese journal, and had also been the subject of an anonymous editorial article in the *Lancet*, but we know that the medical library in Batavia had only Dutch- and German-language journals.) However, Eijkman also made no reference in his reports at this period to the work of Van Leent, whose papers would have been available and who had repeatedly claimed that beriberi was a purely nutritional disorder arising from the low quantities of protein and fat in the diets issued to Javanese servicemen.[57]

Eijkman found that rice polishings contained 14 percent crude protein, and polished table rice only 7 percent. However, since the weight of the latter was nearly twelve times as great as the polishings from a given quantity of grain, rice with the skin still attached contained no more than 7.6 percent crude protein. Analysis for nutritive minerals, defined as ash that would dissolve in strong acids (so as not to include inert silica), yielded a value of 7.7 percent for the rice polishings and 0.6 and 1.3 percent, respectively, for polished and unpolished rice. Eijkman thought that the higher mineral content of unpolished rice might be important because of published German work in which dogs weakened and became ill when fed a meat powder that had been soaked in hot water so that most of the minerals had been leached out. The author's conclusion had been that "the central nervous system is the first to suffer from the deprivation of mineral constituents."[58]

Eijkman had already, of course, found that semistarvation did not itself lead to the disease, so he now (in trial 15) tried feeding twelve chickens on tapioca starch, which was almost completely lacking in both protein and salts, and again they all developed polyneuritis. This

finding was of interest in itself because it eliminated the idea that the disease was caused by something peculiarly present in rice. Eijkman then went on to use raw meat as a supplementary source of protein and salts. The addition of meat led to an immediate improvement in the condition of sick birds, but this did not persist, and in most cases the disease redeveloped.

Starting again with new birds fed each day on "50 g tapioca starch plus 25 g raw meat," the birds gained weight and grew well but still eventually developed polyneuritis. This also was interesting because it showed that severe weight loss was not an essential characteristic of the chicken disease—a point that had previously worried Eijkman, since it was not characteristic of beriberi. Second, since this diet was richer in both protein and salts than unpolished rice, it seemed clear that the value of the skin could not be explained by its content of either protein or salts. Eijkman was aware of the complexity of different individual minerals in animal tissues, but he seems to have assumed that meat would contribute an ideal mix of the minerals required by animals.[59]

THE TOXIC STARCH HYPOTHESIS

None of the hypotheses considered so far had stood up to the test of experiment. However, one last experience gave Eijkman a further idea—chickens fed on raw meat alone did not develop polyneuritis, although many did eventually die from another condition that he described as a "croupous disorder of the mucous membrane of the nose and eyes." This had plagued many of his previous trials also, and he called it "an intercurrent disease." I will return to this problem in chapter 7.

Eijkman concluded that the common factor in all the treatments that resulted in polyneuritis was starch: tapioca starch alone, starch plus meat, and polished rice (rich in starch). In the absence of starch, either with starvation or giving meat alone, there was no development of polyneuritis. His conclusion, therefore, was that starch had some toxic effect on the chick that needed something present in the rice skin to reverse it.

The weak point in his argument was the result with "meat alone." He mentioned elsewhere in his paper that meat must contain a smaller concentration of the protective factor than was present in the rice skins.

And since the chickens were getting *no* starch when he fed them meat alone, he must have fed more than the 25 g ration of meat that he had given in conjunction with starch—the evidence being that the chickens gained weight. So it was at least possible that the greater quantity of meat did supply the protective factor at the level that chickens needed in the presence of starch. Perhaps the more important factor for Eijkman in framing his hypothesis was the absence of the disease in starved chickens.

He hypothesized that starch was rapidly fermented in the chickens' crop (the storage "bag" in the esophagus that gradually released food into the chickens' true stomach) and that this fermented material then had a toxic effect on the nerves of the chickens. He reported a series of further tests that included feeding monkeys on rice taken from the crops of newly killed chickens, and trying to counteract the protective action of brown rice for chickens by adding lactic acid and ethanol, chosen as fermentation products of starch.[60] The results were disappointing, and I will not describe them in detail. Eijkman had found to his satisfaction that the chicken disease was not caused by a deficiency of either proteins or salts, and the only remaining class of nutritional problem recognized at that time was autointoxication.

There was a general belief at the end of the nineteenth century that diets that were unsuitable in some way could result in gut bacteria producing toxic compounds such as ptomaines.[61] Cases of anemia, for example, were attributed to gut bacteria making iron compounds unavailable.[62] The fact that excessive levels of starch might have another indirect toxic effect as a result of fermentation was in line with the thought of the time. It seems reasonable, therefore, that Eijkman should have attempted to explain his findings in terms of a known (or apparently known) type of effect before going on to any unheard-of type of explanation.

It is remarkable that Eijkman was able to carry out this long series of studies while in chronic ill health from recurring malaria, and with the limited physical facilities that have been described as follows:[63]

> The laboratory in the military hospital where Eijkman worked was small: a main room 5 by 10 m with another small space as an extension and a very small area around it where, under a parapet, there were a darkroom and cages for the chickens. The annex was the workplace of the assistant director Dr. Van Eecke, who dealt mostly with microscopic research. The bigger room held Eijkman's secretary

and the officer of health who was assigned to him from time to time. In the verandah which gave entrance to the lab were the desks and shelves of the administration and the waiting room of the hospital. This contained his ice chest and a sofa, and on the latter Eijkman received his visitors because in the lab there was not enough space to offer someone a chair.

There was no fume hood, but there was another little annex that carried a stone water basin which fed the two water taps in the lab and, by adding a door, it made a closet. This was fitted with a gas pipe which made it possible to heat six to eight Kjeldahl flasks. In case something had to be changed during the digestion process, the experimenter had to take a deep breath, open this primitive fume cupboard, and make the changes as quickly as possible, then close the closet again before taking another breath.[64]

VORDERMAN'S PRISON STUDY

Eijkman still had no direct evidence that his findings with chickens had any relevance to the human disease. However, late in 1895 he had an important conversation with his friend Adolphe Vorderman, another physician in government service in Batavia.[65] He was fourteen years older than Eijkman and had already served in the East Indies for nearly twenty years, first in the navy, and now in the civil government, where he was inspector of prisons for the whole of Java, which is about nine hundred miles long and one hundred miles wide, with roughly the area of Greece. He had already published articles on native food plants in Indonesia and was interested in Eijkman's results with chickens. It occurred to them that there might be an unintended experiment already in progress in the various prisons in Java that were using rice processed in different ways, because it was known that beriberi was a problem in some prisons but not in others (Fig. 3.6). If it were to turn out that the problem occurred where white rice was being used, but not in prisons issuing brown rice, this would provide a confirmation of the value of silverskin, and, of the relevance of the work done with the chicken model.[66]

The standard rations for prisoners everywhere in Java were 750 g rice, one chili pepper, 150 g of a mix of other vegetables, and also either 250 g fresh water buffalo (or ox) meat, 150 g dried meat, or 120 g dried fish on successive days. The type of rice was not specified.[67] Vorderman began by writing a circular letter to each prison governor, ask-

Fig. 3.6. Victims of beriberi (dry form), needing support, in a Javanese prison (Vorderman, 1897).

ing for information on both the incidence of beriberi and the type of rice in use. By March 1896 it seemed clear from the responses that beriberi was almost entirely confined to the prisons where the rations were based on white, decorticated rice. He and Eijkman then persuaded the government to approve a larger study. Eijkman himself was again very sick, probably with malaria, and had to return to Holland, this time for good. But Vorderman set off to spend the next five months visiting all the 101 prisons, taking samples of the rice being used, and recording the apparent healthiness of the accommodation in each.[68]

When the rice samples were examined back in Eijkman's old laboratory in Batavia, it was realized that the deskinning was not "all-or-none."[69] Vorderman therefore defined as "mostly peeled rice" samples in which at least 75 percent of the rice grains had their skins removed, and as "mostly unpeeled" the samples where less than 25 percent of the grains had lost their skins, although for convenience I will still refer to them as "white" and "brown," respectively. Samples with intermediate portions of silverskin were called "mixed rice."

The results of the survey in relation to the records of beriberi for

Table 3.2 Proportion of prisons with beriberi, after their division into different categories

Characteristic	*Considered adverse*		*Considered favorable*	
A. Age of buildings	over 40 years:	13/26 (50%)	under 20 years:	19/42 (45%)
B. Floors	permeable:	12/29 (41%)	impermeable:	24/58 (41%)
C. Ventilation	bad:	7/21 (33%)	good:	28/68 (41%)
D. Population density	high:	9/26 (35%)	low:	32/73 (45%)
E. Geographical position	coastal:	22/33 (67%)	inland:	21/68 (31%)
F. Rice type:	mostly peeled:	36/51 (71%)	mostly unpeeled:	1/37 (3%)
i. Coastal prisons only	mostly peeled:	21/25 (84%)	mostly unpeeled:	1/8 (12%)
ii. Inland prisons only	mostly peeled:	14/26 (54%)	mostly unpeeled:	0/29 (0%)

SOURCE: Vorderman (1897).

NOTE: Altogether 101 prisons were inspected. In each category those considered "intermediate" in character were omitted from this table. Six out of thirteen (i.e., 46 percent) of the prisons receiving intermediate "mixed" rice reported beriberi.

the previous eighteen months are summarized in Table 3.2. There was no indication of an adverse effect from any of the conditions considered unfavorable by people who believed that beriberi was caused by infection and poor hygiene, such as old buildings, permeable flooring, poor ventilation, and overcrowding. On the other hand, there was a dramatic difference when the prisons were classified according to the type of rice that the prisoners received, in favor of those receiving brown rice, as is shown in Figure 3.7.

One complication was that 67 percent of the prisons on the coast had cases of beriberi, but only 31 percent of the inland prisons, so it might be argued that the coastal environment was having an unfavorable effect. However, 22 out of 33 (i.e., 67 percent) of the coastal prisons were using white rice but only 26 out of 55 (i.e., 47 percent) of the inland prisons. In fact, only one coastal prison using brown rice reported any beriberi, and then it was only a single case.

It was difficult to arrive at a fair figure for the proportion of individual prisoners who developed beriberi because many of them had sentences of only a few days, and it was thought that the disease took some four to six months to develop. But taking the crude figures first: out of the more than 96,000 people imprisoned in the institutions using "mostly brown" rice, only 9 (or less than 1 in 10,000) developed beriberi. Of the 150,000 in the "mostly white rice" prisons at some time in the study period, 4,200 (2.8 percent, or 1 in 39) developed beriberi.[70] From the partial data available, it also seems that as many as a quarter of the long-term prisoners developed beriberi in the "white rice" prisons.

Vorderman wondered whether the source of the white rice could be a factor, but the incidence of beriberi was not significantly different in prisons using imported white rice from that in those using locally produced material.[71] Some of the prisons used dried fish imported from Thailand, which in general was inferior in quality and appearance to domestic products, and there had been a suggestion from Japan that eating certain types of fish caused beriberi.[72] However, of the 75 prisons using imported material, 30 (i.e., 40 percent) had beriberi cases, while of the 35 using indigenous material, 11 (i.e., 44 percent) had the disease, so that there was no evidence that the imported material was having any special adverse influence.[73]

Critics, as one might have expected, were to ask why most eaters of white rice did *not* develop the disease. And, with regard to Vor-

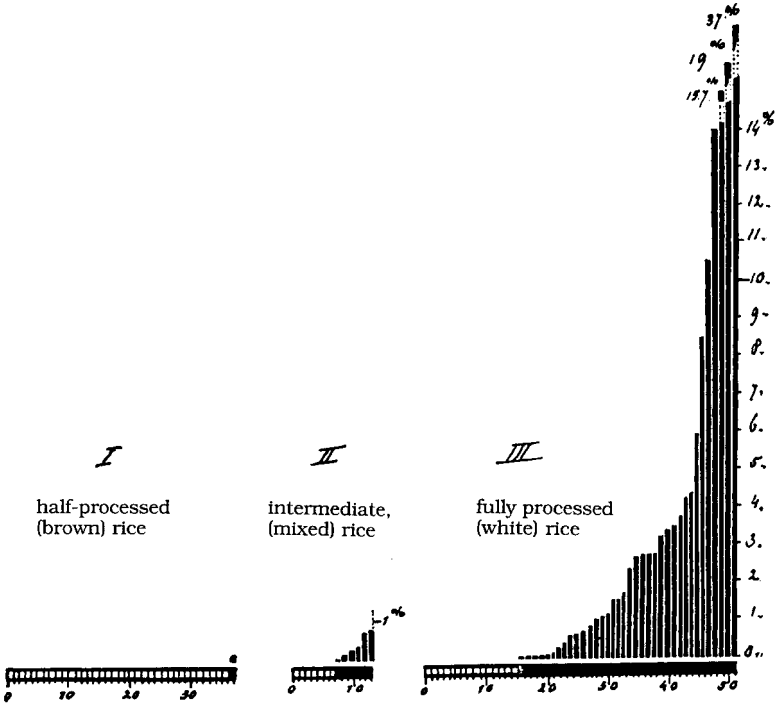


Fig. 3.7. The incidence of beriberi in 101 Javanese prisons according to the type of rice issued to the prisoners (Vorderman, 1897).

derman's actual data: Was it reasonable to assume that the single sample of rice obtained from each prison was truly representative of all the rice that had been issued there for the previous 18 months? Of course, to modern scientists, who are used to working with probabilities to assess the significance of their findings, it would seem obvious that problems such as changes in the character of rice fed would only reduce the clarity of any finding, so that the true relationship between rice quality and beriberi would actually be closer than that measured in the imperfect circumstances of the survey.

There were fifteen prisons where there was no beriberi even though white rice was being used. Vorderman, who believed that the disease was caused by a microorganism, explained this finding as indicating that diet was simply one factor that reduced a subject's resistance to infection from a beriberi organism. In the absence of infection the disease would not develop regardless of diet.[74]

Vorderman himself attempted to strengthen the evidence for the value of rice skin by recording the results in institutions where the rice fed was changed from white to brown. For example, he reported that in one district prison that had been using white rice there had been forty-six cases of beriberi in the previous five months, but there were no more new cases for the following eight months after the use of brown rice was begun. A possible criticism of such findings was that the changes could also be explained on the infection theory by a beriberi epidemic having been in decline in that particular area or institution. It seems that Vorderman did not deliberately change prisoners from brown rice to white rice. This would presumably have been considered unethical and contrary to physicians' duty to do only things that could be expected to improve the health of people under their care. He reported finally that he had been able to persuade the authorities to modify the prison diets so that they included more brown or red rice, and also more beans and other vegetables.[75]

By 1897, therefore, there was evidence that beriberi might not, after all, be a bacterial infection, or at least that subjects were susceptible to the disease only when eating an unbalanced diet—a problem for which a relatively simple solution was available. Eijkman must have felt hopeful, therefore, that after his return to Holland, and when he had demonstrated the production of chicken polyneuritis to his colleagues at Dutch universities, and been able to set out Vorderman's findings, the acceptance of his new ideas about beriberi would follow quite smoothly. But this was not to be, as shall be described in chapter 4.

CHAPTER 4

The Chicken Disease Reinterpreted

1896–1904

Eijkman appears to have recovered his energies in the autumn of 1896, after getting back to Holland. He first published a summary of his work with chickens in a German periodical, which made it available to a wider audience.[1] Then, as soon as he received Vorderman's final report on the results of the prison investigations, he summarized them in articles placed in both a German and a French journal, as well as presenting them to a section of the Royal Scientific Academy in Amsterdam.[2] Naturally, he linked the prison study that showed an association between beriberi and consumption of white rice to the earlier results obtained with chickens regarding the value of the skin that was removed when rice grains were polished.

People with different ideas about the cause of beriberi attacked Eijkman bitterly. In a response, he requoted one such remark: "If one considers that Eijkman apparently needed six years in order to do this work, it must be considered the most inadequate product which can be found in the literature from the Director of a scientific institute."[3] Max Glogner, the original author of this statement, and also a government physician in Java, was no more sparing of Vorderman: "His attempt to secure a place for rice in the etiology of beriberi is to be regarded as totally useless. . . . In the Japanese army the number of illnesses other than beriberi also declined in the period after white rice was reduced in their diets. If Vorderman were to remain logical he would have to conclude that rice was the sole cause of all disease."[4] Glogner himself believed that beriberi was caused by a parasite infection.[5]

When Eijkman criticized Van Dieren's theory that rice contained a nerve poison, he suggested that critics who had never been in the East Indies and studied the disease firsthand should leave the debate to those with such experience. To this Van Dieren replied that the opinions of "colonials" could not be given much weight, since they had

all been eating rice and their brains were therefore damaged.[6] I could quote further personal attacks, but the blow that must have hurt Eijkman most was to come from his own return to experimenting.

DISAPPOINTMENT AT THE ZOO

Eijkman wanted to repeat some of his chicken feeding trials to demonstrate to his colleagues at home both the characteristics of chicken polyneuritis and the preventive value of rice skin. The director of the Amsterdam zoo gave him the facilities he needed, and he began by feeding six chickens on cooked, fully milled white Java rice. Four of them died in the period from two to seven weeks into the experiment. They all lost weight, but none showed the characteristic difficulties in walking that he had seen in Java; nor did histological examination of their nerves show the characteristic degeneration. The two remaining chickens still appeared to be healthy when the experiment was stopped after twenty weeks.[7]

One possible explanation was that the Dutch breed of chicken that Eijkman had used was less susceptible to polyneuritis than Indonesian breeds, and he arranged to have birds shipped over from Java to test this point. But his mind was clearly moving to the alternative explanation that there were "infections" present in Indonesia which were required, in combination with a poor diet, to precipitate both chicken polyneuritis and beriberi. He actually claimed that, in this light, it made the chicken disease more like beriberi rather than less.[8]

However, this new position now put him in opposition to the naval surgeons, both Dutch and Japanese, who had been arguing that the disease had already been proved to be like scurvy, purely the result of an unbalanced diet. He must have realized this, since his next paper featured a withering critique of the work of both Van Leent and Takaki.

Van Leent had written categorically in 1880 that the sole fundamental cause of beriberi was a specific change in the blood, resulting from an equally specific defect in the nutrition of the sufferers.[9] The main evidence that he presented to support this claim came from the naval squadron in which he had been serving. In the years 1870–73 the squadron contained nearly 3,000 European sailors, and in each year their incidence of beriberi was below 1 percent. Among the 750 to 1,000 native crew members the rate was 20 to 26 percent for the first

three years; in 1873, when they were on active service off Atjeh, it rose to 60 percent. The natives, who had previously been issued "Asian rations," were now issued "European rations," and in 1874 their rate of beriberi fell to 7 percent. The main change that this involved was a replacement of one-half of the rice by bread and the addition of more meat (14 oz/day). Van Leent believed that a deficiency of protein and fat in the native ration had caused the disease, and this was corrected by the extra meat.[10]

Eijkman went back to the detailed records available in Amsterdam and argued that they did not in fact provide the clear-cut picture presented by Van Leent. There had been changes in personnel from ship to ship within each year, and the records of illness, particularly among the native crew members, had been incomplete. In addition, he doubted whether the Indonesians actually ate the European rations that had been issued to them. He thought it more likely that they made exchanges with Europeans who also had rice as part of their rations and, in most cases, more than they liked.

Second, Eijkman noted that, although the European sailors always had less beriberi, the incidence tended to fluctuate from year to year in the same directions as it did among the Asians, and he illustrated this with a graph (Fig. 4.1). Since there were no significant changes in the European rations over this period, he regarded the fluctuations as evidence of the importance of some other, nondietary factor.[11]

In regard to the dramatic fall in beriberi in the Japanese navy from 1885 on, Eijkman could only point to the incidence of beriberi among the Japanese sailors having started to fall before their diet had been changed, and that other diseases continued to fall along with beriberi. He concluded, therefore, that there must have been an improvement in general hygiene which could have been at least as important as the change in diet.

He also referred to the decline in beriberi in the Japanese army after 1890, although it had always had a protein intake that met Voit's standards. (Takaki had, of course, attributed beriberi in the navy to insufficient protein.) Therefore, although he did not want to deny the value of improved diet, it could not be considered proven that this was the only factor responsible for the improved health records. In the navy and the army new recruits had proved to be the most susceptible to beriberi, and both services had changed their entry time for new recruits from May to December, so that they no longer had

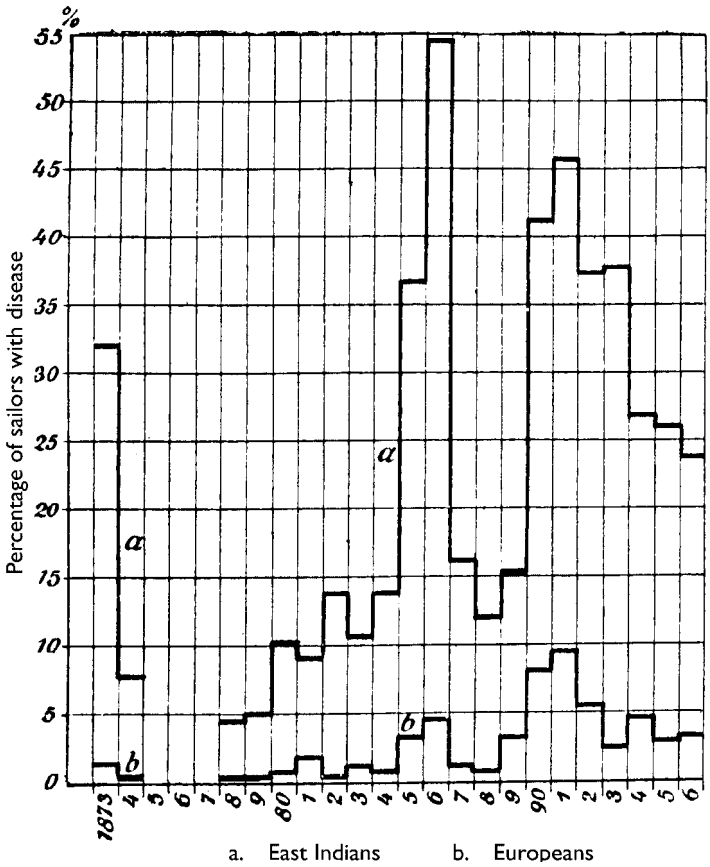


Fig. 4.1. The incidence of beriberi among sailors in the Dutch Indies navy for the years 1873–74 and 1878–98, according to their ethnic group (Eijkman, 1898a).

to face the stress of unaccustomed marches and other exercises during the debilitating heat of summer. He wrote: "It is practically unthinkable that the disappearance of beriberi [in the Japanese navy] was due to the change of diet." Elsewhere in the same study we read: "With so many contradictory findings one cannot conclude anything with certainty." And later: "I see no reason to depart from the standpoint that beriberi is most likely an infection-disease."[12]

This paper, which was printed in three successive issues of the Dutch medical journal, covering sixty-five printed pages, seems uncharacteristic of Eijkman, and the author of his only full-length biog-

raphy ignores it.[13] But an honest work in the history of science must include such convolutions, rather than selecting only those contributions that give it the artificial appearance of a straight line.

Eijkman's studies in the Indies had not been generally appreciated. As a modern Dutch scholar has written: "The criticism of Eijkman's work was typical for the time: often personal accusations were used, sometimes culminating in shouting matches; this was the tropical manner of squabbling."[14] Now that he had apparently changed his ideas so radically, the critics could pounce again: "One month he seeks to persuade us that the disease is a nutritional one, next month that it is an infection. He is his own strongest critic, and his papers cancel each other."[15]

Despite these troubles, in 1898 Eijkman was appointed professor of medicine, medical policy, and judicial medicine at the University of Utrecht.[16] This position has commonly been described as "professor of hygiene." He also received some important advice from his old chief, Cornelis Pekelharing, now his colleague as professor of physiological chemistry and histology at Utrecht. Eijkman was still failing, even with Indonesian birds, to produce polyneuritis, but Pekelharing, after looking at them being offered white rice in the zoo, suggested that they were simply unwilling to eat a normal amount of this food, and that Eijkman should try having them force-fed.

This meant actually pushing food down into their crops, as was commercial practice in the fattening of geese. When this was done, both Dutch and Indonesian birds did develop polyneuritis, and on autopsy their nerves showed the characteristic degeneration.[17] For some reason the birds in Holland preferred to starve rather than to eat white rice. But, with these new results which he had originally hoped for, there was no longer a reason to believe that a local "infection" had played a role in the production of polyneuritis in Indonesia. Ironically, this finding came at a time when he had just published this explanation for the disease *not* appearing in Holland.

Eijkman's main research from this time on was with methods of measuring water purity and hygienic problems in Holland. Although he did carry out some further work on polyneuritis and the properties of the active factor, and he continued to write commentaries from time to time, his pioneering contributions to the understanding of beriberi were at an end.[18] However, the full significance of his experiments was still to be revealed by the work of others.

GERRIT GRIJNS

Back in Batavia, after Eijkman had to return to Holland in early 1896, Gerrit Grijns was appointed to continue the work on chicken polyneuritis. He was seven years younger than Eijkman but had a similar background—medical education at the University of Utrecht, followed by a year in Professor Carl Ludwig's physiology laboratory in Germany (Fig. 4.2). He had originally been appointed in 1893 to assist Eijkman in the latter's physiological studies of the adaptation of Europeans to tropical conditions. But in the following year there was a crisis in the colony. Grijns was recalled to join two military expeditions and only returned to Batavia after the departure of Eijkman, who seems to have taken his notebooks with him in order to write up his more recent work after reaching Holland.[19]

It was perhaps fortunate that Grijns had never worked with Eijkman on the polyneuritis problem, since it meant that he started with no particular preconceptions. The official terms of his commission were to "investigate the . . . properties of the tannin contained in red rice." This did not make much sense to Grijns because it had already been found that the silverskins of non-red varieties of rice were active, and he got permission from his superior to delve more widely into the associations between diet and neuritis. He then began four years of intensive work on the problem. His paper, published in 1901, included descriptions of results with 240 birds, individual by individual.[20] This was republished later in English translation, which I will refer to in citations.[21]

Grijns's first experiment investigated the possibility that chicken polyneuritis was the effect of mineral deficiencies. He made an aqueous extract from the ash obtained by burning fine rice bran, then added it to a diet of boiled white rice on which birds had started to develop polyneuritis. The birds showed no sign of a response, and other birds that had received the diet supplemented with a mixture of salts from the beginning also all developed the disease in less than a month. He concluded that the condition could not be the result of salt-starvation.[22]

He then went on to test whether lack of fat could be the problem, since over 60 percent of the fat in whole rice grains is concentrated in the bran. He supplemented the daily boiled white rice diets of some birds with 0.5 or 1.0 g olive oil, and of others with 0.6 to 1.0 g of ma-

Fig. 4.2. Gerrit Grijns, who took over the beriberi research project in Java in 1896 (courtesy of *Journal of Nutrition*).

terial extracted from fine rice bran with a fat solvent. But these treatments also failed to prevent the birds from developing polyneuritis.[23]

So, if it was not the salts or the fatty material that gave the bran its protective value, and Eijkman's published work had already indicated that it was not the protein, what else could it be? Grijns noted that there was already a suggestion, from the observation that sailors suffering from scurvy were apparently cured by being given *fresh* meat and *fresh* green vegetables, that foods contained, in addition, so far unidentified nutrients. He also referred to the reported difficulties of making a satisfactory substitute for breast milk, even with mixtures having the same analytical values for protein, sugar, fat, and salts.

Grijns next attempted to obtain an active extract from fine rice bran by boiling it in excess water for twenty-four hours and then concentrating the liquor. But the extract showed no activity. He then fed a combination of the extract plus the residue, and it, too, proved inactive. He concluded that the active factor had been destroyed by the method of processing.[24]

Throughout his experiments, Grijns had been plagued (as had Eijkman before him) by a considerable proportion of the birds on test diets developing a fatal condition, which they described as a "croupous inflammation." It occurred regardless of whether the birds were receiving bran, and Grijns regarded it as an endemic infection that they just had to live with.[25] Like Eijkman, he also found that a few birds remained healthy for many months on diets that, for the great majority of birds, led to polyneuritis.

THE VALUE OF BEANS

At this point Grijns decided to investigate whether some other foods might have strong antineuritic activity. He first tested a variety of mung beans (then given the systematic name *Phaseolus radiatus Java* but since renamed *Vigna radiata*), which were known locally as *Katjang idjoe* and were commonly used in Java as a supplementary food for poultry. (We can see from the literature that Vorderman, in his 1893 review of some native food uses, referred to mung beans being used in the treatment of diseases, including beriberi.[26] However, Grijns may not have noticed this.) Six birds were fed boiled white rice, supplemented daily with 10 g of mung beans. Three died with croupous inflammation of the nasopharyngeal cavity and eyes, but the remaining three survived for the full 150-day period of the trial with no sign of neuritis. Two other legumes were also tested in similar trials. Pigeon peas (*Cajanus indicus*), finely ground, proved as effective as the mung beans, but soybeans did not show the same preventive effect. There was no mention of any of the beans being cooked. Since soybeans were richer than either mung beans or pigeon peas in protein and fat as well as minerals, but were less antineuritic, Grijns believed that this confirmed once more that polyneuritis was not caused by any lack of these classes of nutrients.[27]

Grijns then tested whether the mung bean was like the rice grain in having its activity concentrated in the skin. Skins were removed after the beans had been soaked, and the skinned beans were dried again in the sun. Using birds fed on white rice and already suffering from polyneuritis, he found that 10 g of skinned beans per day caused rapid recoveries and, with additional birds, giving 5 g of skins proved equally curative. He concluded that, unlike rice, the activity of the mung beans was *not* concentrated in the skin.[28]

Grijns was also skeptical of Eijkman's idea that the disease was caused by a toxic effect of rice starch. Since the active factor in silverskins had apparently been destroyed by long processing, he tried feeding birds solely on meat that had been autoclaved at 120°C for two hours in order to test whether this would result in polyneuritis in the absence of starch. He used eight fowl for this trial. One died after only nine days without showing the disease, and another survived in apparent health for eleven months, but the remainder developed polyneuritis after two weeks to five months. This was an important result for Grijns: the disease was "wholly independent of the presence of carbohydrate."[29]

If this were the case, however, how could Grijns explain Eijkman's failure to obtain polyneuritis with diets based on potato starch rather than white rice? He thought that it might be caused by the meat that Eijkman had given in combination with the starch, in order to provide adequate protein. Eijkman had not found raw meat to be a rich source of antineuritic activity, but it had shown some. Grijns therefore returned to trials comparing potato flour and white rice, in each case adding autoclaved (i.e., inactivated) mung beans as a protein supplement. Birds developed polyneuritis on each of these treatments at similar time periods. For Grijns this confirmed that there was nothing special about rice starch.[30]

Summing up his conclusions from this period of work (i.e., from 1896 to 1901), Grijns suggested two explanations for the findings of himself and others. The first possibility was that the disease was caused by "a deficiency or partial starvation" and that "for the maintenance of the peripheral nervous system, a certain substance or group of substances is indispensable, which are immaterial for the metabolism of the muscles . . . [so] it may be assumed that very little of them is necessary." The condition was not seen in total starvation, but this could be explained by the bird then, in essence, living on its own tissues (i.e., meat), whose breakdown could release enough of the antineuritic substance(s) to tide it over for a period. Finally, one had to explain why a few birds were able to remain healthy for periods of several months on a diet of white rice. Grijns presumed that white rice still had a significant, although small, antineuritic activity, and that individual birds differed in their requirements, just as humans appeared to differ in how much food they required.

The second possibility was that "there is an agent distributed in nature [most likely a microorganism] which exercises a degenerative influence on the nerves and that it depends on the nature of the foods, whether the peripheral nervous system has enough power of resistance to get the better of this influence." Eijkman's failure to produce polyneuritis in his first trials in the Amsterdam zoo had strengthened the idea that such a microorganism was necessary, but Grijns had now received a further message from Eijkman explaining that with force-feeding he was able to precipitate the disease: so, wrote Grijns, "the possibility of an infection is not excluded, but the principal fact in its favour is removed." In either case, he concluded, "there occur in various natural foods, substances which cannot be absent without serious injury to the peripheral nervous system. . . . These substances are easily disintegrated, which . . . shows that they are very complex substances [and] cannot be replaced by simple chemical compounds."[31]

A CONTROLLED CLINICAL TRIAL

In April 1901, when Grijns's paper had appeared in the local medical journal, a Dr. Roelfsema, the physician responsible for health at the naval harbor at Sabang, was trying to deal with an outbreak of beriberi among the workmen there. He read of Grijns's success in treating hen polyneuritis with mung beans and tried giving them to his patients. He was impressed by their favorable response and in June 1901 sent in a report of his results.[32]

This report was seen in turn by Vorderman, who, in July, was on a visit to the town of Buitenzorg, the site of a mental hospital where beriberi had also been an increasing problem for some months. Hulshoff Pol, the physician in charge, asked Vorderman to inspect the patients there and to assess their diet. He concluded that the patients were well nourished, but recommended that they be given more green vegetables, on the general principle that this was what they had been used to in their own villages. He did not recommend increasing the protein level in other ways, since the native habit was to eat meat only rarely. He also told Pol about the report he had just received from Roelfsema, whose beriberi patients had appeared to respond well to being given mung beans.[33]

Pol decided, in turn, to set up a controlled trial of the value of

Table 4.1 Incidence of beriberi in mental patients receiving different treatments

Pavilions	*Treatment*	*Total present*	*Number*	*Percentage of total*
1, 5, 9	150 g mung beans daily	78	0[a]	0
2, 6, 10	300 g green vegetables daily	86	16	19
3, 7, 11	Regular disinfection	78	33	42
4, 8, 12	No special treatment	58	19	33

SOURCE: Hulshoff Pol (1902), p. 530.
[a]One patient did begin to develop signs of beriberi after the mung bean ration had been reduced to 100 g per day but recovered when it was raised again to 150 g.

both green vegetables and mung beans, and also of the idea, put forward by another physician, that the disease was spread by cockroaches. The hospital's inmates were housed in twelve separate pavilions, arranged in three groups. He therefore allocated one pavilion from each group to each of his four treatments. He used a strong disinfection treatment to eliminate cockroaches from three pavilions. The test was continued for nine months, with the results shown in Table 4.1.

The three groups receiving the beans were clearly protected from the disease, and further tests confirmed that 150 g mung beans daily could be used as a curative treatment as well as for prevention. However, the beans did not have an immunizing effect; within a few weeks of their removal from the diet, the disease could recur. Nor did they restore the activity of severely damaged nerves, but Pol reported that they did reverse the edema and malfunction of the heart.[34]

This must have been very encouraging news for Grijns because it provided strong support for the relevance of his work with chickens, even though Pol himself still regarded the disease as an infection. From 1902 to 1904 Grijns was back in Europe convalescing from a disease he had developed in Batavia, and on his return he was assigned to other work for several more years. Meanwhile, Vorderman had died in 1902 and was replaced by someone uninterested in prisoners' diets so that, for the time being, little more was done about the problem in Java.[35] Nevertheless, to quote from another Dutch writer: "How many kilometers of type have now been dedicated to vitamins and their deficiencies, and how many later researchers owe their fame to their

contributions to a chapter in which the first sentences were written by Eijkman and by Grijns."[36]

Some ten years later, Eijkman lamented that the workers in the Netherlands Indies had shown how beriberi could be combated, but the disease was still there, while physicians in the British possessions had used that knowledge and applied and extended it.[37] And, indeed, I must now turn to the work in progress in Malaysia.

CHAPTER 5

The British Take Their Turn

1902–1909

At the end of the nineteenth century, Britain had a larger empire than any other colonial power. Its territories in tropical latitudes included India and parts of Southeast Asia, Africa, and South America; some early experiences in Sri Lanka have been described in chapter 3. British medical officers therefore had wide experience with tropical diseases, and Britain was the first country to establish schools and training specifically in tropical medicine. The main schools, in London and Liverpool, were directed by Sir Patrick Manson and Sir Ronald Ross, respectively, who had both contributed so importantly to the discovery that malaria was transmitted by the bites of mosquitoes.[1]

Beriberi was the subject of papers in the British literature from many parts of the world. It had been reported to occur, for example, among pearl fisherman off the coast of Australia, policemen in Hong Kong, immigrant laborers in Fiji, prisoners in Singapore, soldiers in Madras, and even (most puzzlingly) in a mental hospital in Ireland. Each writer attempted an explanation of the factor or factors responsible for the outbreak. As one put it: "The literature of beriberi is so great, and at the same time so divergent, and so contradictory are the views and records that have been given, that . . . copious reference to these papers becomes picking and choosing what seems to agree plausibly with the writer's ideas, to the exclusion of other possibly most important material."[2]

There is a comprehensive bibliography of the British papers from this period.[3] The British Medical Association's discussion on beriberi in 1902 will also serve as an introduction to the range of views of beriberi. The opening speaker was Manson himself, who felt it "a somewhat humiliating fact that . . . we are about as ignorant of its true nature . . . as was Bontius over 250 years ago. . . . Recent advances are more in the direction of showing what beriberi is *not* . . . rather than

what it is."[4] However, he then put forward the hypothesis that beriberi would prove to be the effect of a toxin, but one originally produced by a living germ, since the disease could be introduced into a country where it had not previously existed. He did not believe that the patients themselves carried an infection, since blood samples obtained from them by the most careful procedures had proved to be sterile. He believed that Pekelharing and Winkler had been misled, as a result of not having taken adequate precautions against contamination in their blood sampling. Patients received this toxin not from their food or drinking water but either in the air or through their skin, perhaps by way of insects.

The next speaker, from the Indian Medical Service, believed that the disease was an infection that came from consuming moldy rice, either as food or after fermentation into a cheap rice-water liquor, a drink to which many Hindu laborers were addicted. Fowl fed on moldy rice became ill with diarrhea and feather loss, and this speaker said that he could induce the same condition by injecting them with blood from fowl already diseased in this way or from patients with beriberi.[5]

L. W. Sambon, an Italian physician working at the London School of Tropical Medicine, also believed that beriberi was a specific infection but that it existed in the peripheral nerves and was transmitted from person to person by a particular agent. The agent was still unknown, but it might be an insect. Visitors or nurses in hospitals did not become infected.[6]

Ronald Ross reported that arsenic had been found in hair samples from a number of patients with newly acquired beriberi. He accepted that this might be "no more than a curious coincidence"; on the other hand, "it may point to a real connexion . . . [since beriberi] is very like chronic arsenical poisoning."[7] Another speaker argued for it being an infection, and two more that it was related to diet. There was no reference to the work of either Eijkman or Grijns.

RACIAL CONTRASTS IN MALAYSIA

The first major British study of this period also appeared in 1902. The author was Hamilton Wright, who had received his medical training in Canada and was now director of the Institute for Medical Research in the Federated Malay States. (This area is roughly equivalent to the

present-day Malaysia, with the addition of Singapore Island.) Not surprisingly, Wright began by commenting that "there is no disease whose literature leaves one in so great a state of mental confusion." But then he added:

> There is no better field [than the Malay States] in which to investigate this disease: in it are gathered large numbers of several oriental peoples and one can readily compare their habits. . . . It was natural to feel that by a simple process of comparison and exclusion the causative factor of beri-beri may readily be determined. But one is quickly disillusioned. . . . The direct and indirect causes of beri-beri are *not* to be found in the obvious difference in habits or work of the various groups.[8]

Wright's observations can be summarized as follows. The highest incidence of beriberi occurs among the large number of men brought in from China for a fixed period to work in the tin mines. It is true that in some areas tin ore also contains arsenic, but its occurrence bears no relation to the incidence of beriberi, and Chinese men also develop the disease in prison, where there is no contact with arsenic. The laborers typically have a generous diet; imported rice is the staple, together with pork, salted fish, and vegetables grown with human excrement as a fertilizer. None of the mines where the Chinese work seems to have escaped the disease. In one, 800 (out of a workforce of 2,400) died of beriberi in just two years. On the other hand, Chinese who stay on in Malaya as shopkeepers seem to escape the problem.

The Malays rarely develop the disease when living in their own villages. They have cleaner habits and housing than the Chinese laborers, and being Muslims do not eat pork, but they enjoy curries, fish, and fresh fruit. They eat: "rice which differs in no essential point from that eaten by the Chinese who contract beri-beri here, and the Chinese of Rangoon who escape the disease." By contrast, when imprisoned along with Chinese, and living under identical conditions, they prove to be at least as susceptible to beriberi.

Another ethnic group is the Tamils, mostly of low caste, from the Madras area of India, working as contract laborers. They are clean in their habits, bathe daily, and oil their skins twice weekly. They, too, live on rice and curries with meat or fish, and also vegetables so long as they have not been fertilized in the Chinese manner. Their rice also

Table 5.1 Lifestyle differences among three ethnic groups in Malaya

Characteristics	*Chinese*	*Malay*	*Tamil*
Susceptibility to beriberi:			
In ordinary life	+	—[a]	—
In mixed-race prisons	+	+	+
Habits:			
Smoke opium	+	—	—
Drink spirits	—	—	+
Live in crowds	+	—	+
Oil their skin	—	—	+
Eat:			
Mutton, fowl, and fish	+	+	+
Pork	+	—	—
Curry	—	+	+
Vegetables fertilized with human excrement	+	—	—
Type of rice[b]	"Siam"	"Siam"[a]	"Bengal"
Work:			
In tin mines	(mostly)	(seldom)	(seldom)

SOURCE: Modified from Wright (1902), Table 7.
[a]These two classifications were to be disputed by Braddon (1907).
[b]"Siam" rice was ordinary white rice. "Bengal" rice had been parboiled before processing.

differs in having been prepared in the Bengal manner—it was parboiled. They are not afflicted with beriberi. It should be added that the Europeans in Malaya also remain free of the disease.[9]

Table 5.1 is a shortened version of Wright's tabulation of the habits of the three Oriental groups. The only factors that seem to distinguish the group most susceptible to beriberi (i.e., the Chinese) from both of the other groups is that they mostly work in the mines, and that they smoke opium and eat both pork and vegetables fertilized with human excrement, but do not eat curry. He eliminates the mines as a factor because Chinese laborers on estates are also prone to beriberi, as are the Chinese women.

It seemed to Wright that the use of fermented human feces as a fertilizer for vegetables provided a possible route for the spread of a beriberi infection among the Chinese. They cooked their vegetables, af-

ter washing them in water, by heating a large mass of them, with constant turning, and the addition of vegetable oil, in a large pan for half an hour. A specific organism could escape destruction with this procedure. However, in prison kitchens, vegetables were boiled in water for thirty minutes before being served, and Wright confirmed that this treatment left them sterile, so that this would not explain the prevalence of the disease in these institutions.[10] He also noted that "beriberi is almost unknown amongst Chinese market gardeners."[11]

In further tests, Wright collected samples of different types of rice on sale in Malaya and studied the microorganisms that could be cultured from them. He found principally a mold, *Aspergillus niger* and spores of *Bacillus subtilis* on all types of rice, including the pretreated Bengal rice. There was therefore no indication of one kind being worse than another.[12] He also obtained blood samples from forty-eight beriberi patients and from eighteen Chinese free from the disease. Most proved to be sterile, but a few from each group contained bacteria that were "common skin contaminations . . . having no relation to beri-beri."[13]

SEARCH FOR INFECTION IN A PRISON

What Wright considered to be his conclusive investigation was carried out at the two Kuala Lumpur jails. Earlier experiences at these prisons had already been described by the responsible physician. Until January 1895 all the prisoners were held in the original, "old" jail, and there had been no beriberi problem. Then a new jail was opened, and by September the disease had appeared there with thirty-eight cases out of a population of about three hundred while those in the old jail remained free from it. The difference continued and could not be explained by any difference in diet because all the food was now cooked in the kitchen of the new jail, and a portion of it was carried by cart each day to the old jail. The new jail was built on the site of an old Chinese graveyard for laborers who had been working in nearby mines; local opinion held that the disease was coming from the infected ground that had been disturbed.[14]

Wright was given authority in May 1901 to use the new jail for experimental observations, and he arranged for all the prisoners to remain and work entirely within the prison confines. He also eliminated

fish from their diet, since some writers had thought this was a source of the disease. The standard daily diet now included 21 oz of white rice, 7 oz of mixed green vegetables, 2 oz of sprouted beans, and 6 oz of meat together with coconut oil and curry powder. Because of their religious restrictions, the Tamils received mutton, the Malays beef, and the Chinese beef and pork on alternate days. All the foods supplied to the kitchens were regularly inspected. The rice was cultured, and no unusual microorganisms were found, and the rice was never moldy. "Before being delivered to the prisoners for their midday and evening meals, it was steamed for two and a half hours under two atmospheres of pressure, while that for the morning meal was boiled from 8 P.M. to 5 A.M. to form *congee* [porridge], a treatment sufficient to exterminate all known organisms and destroy all known toxins." The N:C ratio in the diet was estimated to be 1:12 and so met Voit's standard for protein.[15]

Wright divided the prisoners into two main parties according to whether they had ever shown signs of beriberi. Those who had (group 1) were housed in one set of buildings, the remainder (group 2) in another. For the next eleven months, new arrivals continued to be divided in the same way. Group 1 contained an average of some 220, but over the eleven months of the study, a total of 1,406 men spent some time in it, so that many clearly were there only for quite short periods. Ninety cases of beriberi arose during their stay, corresponding to 6.4 percent of the total. Seventy-three (81 percent) of these cases developed during the period of the northeast monsoon, from October to February, and most occurred in men rated as being "robust." Their occupations included "butcher, baker, barber and brothel keeper," and they included men of all three main nationalities.

A small third group, made up of a constant batch of thirty-four long-term Chinese prisoners who had never shown signs of beriberi, was housed in the administration block, which had not previously been used for this purpose. They also worked away from the others, cutting grass and carrying water at the wardens' quarters just outside the main prison buildings. Wright believed that it was still impossible for these men to supplement their diet from outside sources. Over the eleven-month period, none developed the disease.[16]

His first conclusion from these results was that the disease was independent of diet, since group 3, which received the same diet as the

others, remained immune. It therefore must have come from an infection latent in the buildings (i.e., those housing groups 1 and 2) that had been used by successive prisoners for some years. Although the men bathed each day after work and before receiving their evening meal, they were then locked in their cells until breakfast the following morning, which was eaten again with their fingers, in their cell, without any opportunity to wash, even if they had had a bowel movement in their cell during the night.

Wright's theory of the disease was as follows:

> Due to a specific organism that remains dormant in certain localities, but having gained entrance to the body by the mouth it multiplies locally (in the stomach or duodenum chiefly), gives rise to a local lesion and produces a toxin that, gaining the general circulation, acts on the peripheral terminations of . . . vital neurones to cause a bilateral symmetrical atrophy, and that finally the organism escapes in the faeces to again lie dormant in places.

He added that the germ, though dormant, survives under favorable conditions (high humidity?) but is immediately destroyed by the action of direct sunlight. In the body it remains active for three to four weeks.[17]

Wright then used monkeys in an attempt to demonstrate the presence of these germs. In each of eight cells in which prisoners had previously developed beriberi, he housed a monkey and had it fed on fruit that had been smeared with dust from the floor. After ten weeks one of these monkeys, after showing increasing weakness, became almost wholly paralyzed. It was then killed and was found to have an infection from an abrasion in the neck, but this did not seem sufficient to explain the degeneration seen in some nerves that Wright considered to be characteristic of beriberi. Four other monkeys developed similar lesions later.[18]

In 1903 Hamilton Wright published a detailed study of the medical history and, in some cases, the autopsy findings of a series of beriberi patients. He drew attention to the disease characteristically beginning with a loss of appetite, followed by a dull pain and vague sensations of gastric irritation. Several days later, signs of nerve and cardiac damage developed. Postmortem findings of congestion and necrosis on the lining of the stomach and duodenum strengthened Wright's belief that this was the site of the primary infection, which,

in turn, was the source of a toxin that damaged the nerves.[19] His theory was, of course, consistent with the blood of patients being sterile. This paper was completed after Wright had left Malaya for a position at Johns Hopkins University.

Herbert Durham, who had come from the London School of Tropical Medicine at this time to study the problem in Malaya, did not believe that Wright's monkeys kept in filthy cells had developed beriberi. In biting terms, more characteristic of that period than our own, he wrote that "the looseness of his report may be sufficient indication of the looseness of the observations on which it was founded." Durham had also tried to infect monkeys with dust from the cells of prisoners who had developed beriberi, but he had failed to produce signs of typical nerve damage.[20]

Wright added a postscript to his work in a further paper summarizing the experience in the Kuala Lumpur jail in the twenty months after he had left Malaysia. In the fall of 1902 there had been nineteen new, acute cases of beriberi per month, but in the following sixteen months the rate had fallen dramatically to only one per month. This change could not be explained by a general decline of the disease in the area, since Wright had also learned that the district hospital in the city had continued to admit some fifty to eighty new cases each month. He regarded the results in the prison as confirmation of the value of the changes in hygienic practices that he had recommended on the basis of beriberi being an infectious disease. And: "Since the prisoners were also on a diet of lower nitrogen content than in the previous year or so . . . this should set at rest the question of diet as a factor in the causation of beri-beri."[21]

G. A. O. Travers, the state surgeon for the area, immediately replied, saying that "it was essential in the interest of medical science, that all statements made in connection with . . . measures to control a disease should be correct in every detail." Wright, before he left, "had made 17 recommendations. Of these only one was actually carried out—the enlargement of the ventilation spaces in the cells, and none of the altered cells was occupied until January 1903, by which time beri-beri had practically disappeared." Wright had claimed that the arrangements for defecation within the cells had been changed from previously unhygienic ones. Travers, who had direct responsibility for prison hygiene, knew that there had been no change from an arrangement that was already satisfactory.[22]

STORED RICE AS A SOURCE OF TOXINS

Leonard Braddon, who had a long experience with beriberi during his service as a government medical officer in Malaya, also believed that Wright had misinterpreted his observations. Braddon first set out his views in reports to the Colonial Office from 1900 to 1904, and then at considerable length in a scholarly book published in 1907.[23] He argued that Wright had been mistaken, as to fact, in three important stages in reaching his conclusion that beriberi was a *place* disease rather than a *diet* disease. First, on going back to the original records of sickness in the new and old jails at Kuala Lumpur, he found that the differences were less clear-cut than Wright had claimed. The old jail had had significant outbreaks of beriberi, and the higher incidence in the new jail could be explained by its greater proportion of long-term prisoners, who were much more prone to the disease than those incarcerated for only a few weeks.[24] Second, the disease, as described by Wright in the monkeys kept in dirty, infected prison cells did not correspond to beriberi but to a different kind of septic neuritis.[25]

Finally, he believed that Wright had erred, in his comparisons of racial lifestyles, in claiming that Malays were less susceptible than Chinese to beriberi even when eating the same type of rice. It was Braddon's experience that Malays living in their traditional *kampangs* (villages or encampments) were exempt, but there they used homegrown rice freshly hand-pounded for each day's consumption. When they were employed in the mines, they ate the same imported, or "Siam," rice as the Chinese laborers and suffered from beriberi in the same proportions as the Chinese did.[26]

With this amendment to the comparative table (Table 5.1), one can see that beriberi was occurring only among those eating imported white (Siam) rice and not among those eating either freshly pounded rice or imported, parboiled (Bengal) rice. The differences between hand-pounded and machine-milled rice have already been discussed in chapter 2, and Braddon quotes from Vorderman's book in this connection.[27]

The so-called Bengal procedure for processing rice had not been encountered by the Dutch workers in Indonesia. However, as described in chapter 2, this involved parboiling. Rice grains still in their husk (i.e., paddy) are soaked in cold water for twelve to seventy-two hours and then are steamed, or boiled with a small quantity of water

for a short period, until the husks burst. The material is then dried, usually by spreading it out in the sun, and finally winnowed to remove the husk. It may then be further milled to remove the skin. But Braddon believed that, as a result of this pretreatment, the inner (aleurone) layer of the skin had adhered tighter to the endosperm, so that it remained even after further milling and contributed both nutritional gluten (protein) and a stronger coating that resisted infection of the endosperm, the inner portion of the grain. The additional milling makes the product more expensive and is not used for the cheaper grades typically eaten by the Tamil laborers.[28] Braddon described such rice as "cured," but it is more usually described as "parboiled." The names "Bengal" or "Indian" rice were in use in Malaya at the time, but they referred to the process rather than the place of origin, since much of it was made by parboiling Malayan rice. Similarly, "Siam" rice was used to refer to any white rice produced without parboiling, whatever its source.

Braddon's theory was that stale, "Siam" rice contained a toxin, produced by a fungus that had established itself on the porous surface of the rice endosperm. This toxin was probably a water-soluble alkaloid, and, when regularly ingested in sufficient quantities over a long period, it produced the toxic effects recognized as beriberi. Freshly prepared rice was nontoxic because the fungi that are naturally present had not had time to produce significant quantities of the toxin. "Bengal" rice was safe because the preliminary boiling had destroyed the toxin-producing fungi.[29]

Braddon also sets out his reasons for rejecting alternative theories. Eijkman's and Grijns's idea that white rice was deficient in some unknown essential factor seemed to be contradicted by his experience that peoples eating fresh rice remained free from beriberi. (Incidentally, this seems to be the first reference by any of the workers in Malaya to the publications of these two Dutch researchers.) Braddon attributes Vorderman's finding that prisons where brown (or red) rice was used were free from the disease to the pericarp coat having provided an obstacle to the fungus establishing itself on the starchy endosperm.[30] As regards outbreaks described as beriberi under conditions where stale rice was *not* the staple food, he believed that in some cases they represented some other form of neuritis, but that under certain conditions other stored grains could become a source of the fungi more commonly found on rice. Most cases of ship beriberi were

"a distinct if closely allied disorder . . . in which dropsy is a common factor."[31]

C. W. Daniels, who had succeeded Hamilton Wright as director of the Institute for Medical Research in Malaya, was not persuaded by Braddon's arguments. In particular, he believed that the parboiling process, which involved passing steam into a closed container holding the wet rice for no more than ten minutes, "fell far short of the treatment required for sterilization" and that "rice prepared in this way yields a larger variety of moulds and bacteria than rice prepared in the local fashion." He still believed that beriberi was an infectious disease.[32]

TWO CONTROLLED TRIALS

In June 1907, when Braddon's book was probably already being printed, another study was published that was of direct relevance to his theory. Two years earlier an epidemic of beriberi had broken out in the Kuala Lumpur insane asylum. Of the 219 inmates in 1905, 94 developed the disease and 27 died from it. The staple of the inmates' diet was Siam-type white rice. William Fletcher, the responsible physician, had not been convinced by Braddon of the superiority of Bengal-type parboiled rice, and he thought there was an opportunity here to submit the idea to a critical test and, as he expected, to put an end to it.[33]

The asylum inmates were housed in two identical buildings on opposite sides of a walled quadrangle. In December of that year, after all the inmates with beriberi had been removed to the district hospital, the remainder were lined up to be numbered. Fletcher then housed the odd-numbered ones in one building, and the even-numbered in the other. As new inmates were admitted, they, too, were assigned alternately to one group or the other until there was a total of 120 in each group. They ate in the same dining hall but at different times. One group continued to receive their old diet, based on "Siam" rice; the other received the same quantity of parboiled rice imported from Bengal. Both the Siam and the Bengal types of rice were of the best quality available, which presumably meant that the Bengal rice had also been fully milled, and each was cooked by the procedure followed by its normal consumers. Thus the Siam rice was cooked in the Chinese procedure with just enough water for it all to be absorbed as the grains

Table 5.2 Health records of mental patients fed different types of rice in Malaya

	White rice ("Siam") group	*Parboiled rice ("Bengal") group*
Cases of beriberi	36[a]	0
Deaths from beriberi	18	0
Deaths from dysentery, etc.	21	27

SOURCE: Fletcher (1907), p. 1778.
NOTE: There were 120 patients in each group.
[a]Ten of these individuals were transferred to the parboiled rice group, and all ten then recovered.

cooked. The Indian rice was cooked by the Tamil procedure with excess water that was then poured off before the rice was served. As Fletcher pointed out, this could be an important difference if the cause of beriberi is a water-soluble poison in the rice that is eaten.[34] This aspect does not seem to have been considered by Braddon.

By June 1906 many cases of beriberi had developed in the Siam rice group, but none in the group receiving parboiled rice. In case this was the result of one building having become infected, the inmates were all switched from one building to the other, but beriberi continued to appear only in the group receiving Siam rice.[35] The results, as of the end of December, are shown in Table 5.2.

In a more detailed report on his experiment, Fletcher wrote that during 1907 the same differences continued, with more sick patients being transferred from Siam rice to parboiled rice, and recovering. He concluded that the transfer of the inmates from one building to the other seemed to show dramatically that the disease could not be attributed to infection of a place, but rather was the result of unsuitable diet. Braddon's belief in the advantage of parboiled rice had been strikingly confirmed. However, he added that Braddon's theory was not necessarily correct: the results could be explained by the ordinary white rice being "deficient in dietetic value."[36]

Henry Fraser, an M.D. of Aberdeen University who had received postdoctoral training in Germany, was sent out in 1906 to succeed Daniels as director of the Institute for Medical Research. In the following year he was given the assistance of a Canadian physician, Thomas Stanton, who had been on Sir Patrick Manson's staff at the London School of Tropical Medicine. They decided to follow up

Fletcher's experiment with a trial using workers engaged in road building in an area remote from any previous outbreaks of beriberi, as well as from settlements where they might be able to supplement their diets. The men were all laborers from Java who had originally been receiving a diet based on "Siam" rice. Then, when some cases of beriberi had developed, this had been changed to parboiled rice. They disliked its musty flavor and repeatedly asked to go back to uncured white rice, even though the possible danger had been pointed out to them.

In view of the uncertainty regarding the nature of beriberi, Fraser and Stanton believed that it would be ethical to give one-half of the men their wish, provided that their subsequent health was closely supervised.[37] In April 1907 the men were examined to confirm that they were healthy and then were divided into two parties, each of approximately 150, and moved farther along the route of the road to two new sets of well-ventilated, well-drained quarters in virgin jungle, some miles apart. The man who was later to be Sir Thomas Stanton, chief medical adviser to the British Colonial Office, now "lived for the best part of a year in a little thatched hut which stood in a clearing in the jungle at the dead end of the new road, many miles from civilization and its comforts: here he kept a lookout for cases of beriberi among the coolies, and dispatched daily specimens of their food sealed up in wooden boxes to Fraser in Kuala Lumpur."[38] After an additional month on parboiled rice, party 1 was changed to ordinary white rice. Their daily rations were typical for such laborers—21.3 oz rice, 4.25 oz dried salt fish, onions, potatoes, coconut oil, coconut, and condiments—and were calculated to contain altogether 91.5 g crude protein for those receiving uncured white rice and 93.5 g for those receiving parboiled rice. These levels compared well with the European standard at that time of 90 g protein for a man weighing about 100 lb.[39]

No case of beriberi developed until the laborers had been eating white rice for nearly three months, but by mid-October, twelve cases had developed in party 1, but none in the other party. Fraser and Stanton then decided to reverse the diets. From then until the following May (1908), no more cases developed in party 1, but party 2, now greatly reduced in number by the completion of contracts, did begin to have cases after four months on white rice. Taking both periods together, 20 people out of 220 had developed beriberi while consuming ordinary white rice, whereas none of 273 had done so while consuming parboiled rice.[40]

This study therefore confirmed Fletcher's findings. In addition, it showed that men could develop beriberi when receiving white rice while also removed from any source of possible infection. This complemented Fletcher's findings that men receiving parboiled rice remained free from beriberi despite living in a building in which there had been a recent outbreak of the disease.

DUTCH IDEAS CONFIRMED

Thus Braddon's idea of the superiority of parboiled rice seemed established, and it was already being used in public institutions in Malaya with good results. But was his explanation, in terms of a toxin, the correct one? Fraser and Stanton were doubtful. From examination of stained histological sections of rice grains cooked in different ways, they concluded that parboiled rice grains, even after milling, still contained a significant proportion of their original pericarp. Using chickens, they therefore set out to test whether the results of their human study could be explained on the basis of Grijns's belief that white rice lacked an essential trace nutrient, which was relatively richly supplied in the pericarp. (The authors are using the botanical term "pericarp" for what Eijkman had called the skin or silverskin of the rice grain, although the term "pericarp" really applies only to the outer layer of the skin, as will be explained in chapter 8, together with a further diagram.)

In summary, Fraser and Stanton reported that the birds did not develop polyneuritis when fed on parboiled rice; but when the same material had been extracted with alcohol, the birds did succumb. With white rice, the birds developed the disease both when the material had been stored and also when a series of freshly prepared batches was used. However, the addition of either rice polishings or alcohol extracts from parboiled rice apparently protected them from the disease.[41] These results were entirely consistent with the early work and conclusions of Grijns and were inconsistent with the toxin theory. Braddon's dismissal of the Dutch worker's ideas came, as mentioned earlier, from his assumption that the only significant difference between the hand-pounded rice (on which Malays remained healthy) and the imported machine-milled rice was that the former was eaten fresh and the latter when it was stale. He had ignored the point emphasized earlier by Eijkman and Vorderman that hand-pounding left a much greater portion of the pericarp (or skin) adhering to the grain.

Braddon was quite angry at the praise given to Fraser and Stanton's work in an editorial in the *Journal of Tropical Medicine and Hygiene.* His reply, published in the journal, said that "the two men had not contributed a single new or independent observation of *any* facts [as to] the origins or spread of beri-beri. . . . They have done some excellent work on the chemical differences between rice which does, and which does not, produce beri-beri. . . . But as regards the practical, the epidemiological aspects of the beri-beri question, they have added nothing new or original to the issue."[42]

One can certainly understand Braddon's point of view. For ten years he had been presenting evidence that beriberi was the result of eating a particular kind of rice. He had made an exhaustive study of the evidence and analyzed it in relation to the many competing theories about the cause of the disease. In all this time the workers at the Institute for Medical Research had written to the effect that Braddon was wrong and that beriberi was an infection, perhaps with a hidden implication that they knew better because they were scientists and he was only a district medical officer. But now that he had been proved right, surely he should receive the kinds of honor and respect that had been accorded to Manson and Ross for their contributions to the control of malaria, whereas it was already beginning to look as though the spotlight would be misdirected to the staff of the institute.[43]

In their first paper, Fraser and Stanton had acknowledged "the important services rendered by Dr. Braddon, in obtaining government approval for the project . . . and placing at our disposal his unrivalled knowledge of . . . the beri-beri problem."[44] Also, as we shall see, their explanation of the clinical findings that resulted from eating white rice did greatly change the actions that could be taken to prevent the disease from occurring. White rice could remain a staple food so long as the remainder of the diet included a rich source of the vital factor(s) that it lacked. The polishings from the rice mills were one source, and the Dutch workers had already shown that beans could serve as another source.[45] The workers in Malaya therefore ended up in agreement with, and reinforcement of, the earlier conclusions of the Dutch workers, although they came to it independently and in a roundabout manner.

Finally, Fraser and Stanton followed up a suggestion by a German worker that the active substance in the supplements to white rice might be an organic compound of phosphorus.[46] They found that, in-

deed, the total phosphorus content of different forms of rice did, at least, serve as an indicator of their protection against fowl polyneuritis. White rice contained approximately 0.12 percent, and parboiled rice 0.20 percent, phosphorus; rice polishings had 1.8 percent. Since it had already been found that about 3.5 g of polishings had to be added to a fowl's daily ration of 60 g white rice to keep it healthy, it was now seen that this also raised the phosphorus content of the mix to that present in the parboiled rice. They therefore recommended that cheap and rapid analyses for phosphorus could be used to evaluate rice from different sources as an indirect indicator of its protective value for humans also.[47]

British workers continued to contribute significantly after 1909, but from then on it was as part of an international effort whose beginning will be described in the following chapter.

CHAPTER 6

The Americans Call a Meeting

1910–1912

The Philippine Islands, to the north of Indonesia, had been a Spanish colony for many years, until the Spanish-American War of 1898. American authorities then took over the territory and suppressed an independence movement, so that it became a colony, in effect if not in title. The U.S. Army of Occupation quickly became acutely aware of the local problems of tropical diseases, and a vigorous effort was begun to study them. The U.S. government was anxious to show that it would not behave like a traditional colonial power. One public health officer assigned to work in the Philippines wrote:

> The health of the people is the vital question of the Islands . . . but it is not alone the problem of the Bureau of Health. Every branch of the government has its part to perform. . . . good roads, agricultural improvements . . . will gradually bring about a better standard of living; education particularly along the lines of hygiene and sanitation . . . all are as important as is the actual holding in check of epidemics and disease. . . . How to do the most and the best with a limited income is still an acute question.[1]

This was a farsighted statement that bears repetition nearly one hundred years later.

With regard to beriberi specifically, the situation had similarities to what has been described earlier for Indonesia and Malaya. Rice was the major staple, and incomes were low. There were also many Chinese living in the Islands, eating rather differently from the Filipinos. Beriberi does not seem to have been a long-standing problem, but there had been a serious outbreak in Manila, the capital, in the winter of 1882–83. It followed an epidemic of cholera, and it was reported that people were then afraid to eat fish because of contamination of the rivers, and also fruit and vegetables because of their laxative effect, so that their diet was reduced to little but rice.[2]

Since 1900 there had been more outbreaks, which seemed to occur only in the areas where imported, polished rice was being used. With a rapidly increasing population, there had been a great increase in rice imports, all of it having been machine-milled and polished in the country of origin, predominantly Vietnam.[3]

There was a big problem with beriberi in the central Philippine prison in 1902, with over five thousand cases and over two hundred deaths. Physicians investigating the problem noticed that "prisoners who worked in the kitchens or the hospital very seldom contracted the disease; . . . they retained more than their share of vegetables, milk etc." New ration scales had been introduced at the end of 1901, with just over 1 lb of rice/head/day, and one-third that amount of bread. In October 1902 the rations were changed again, with the rice reduced by half and the bread and potatoes greatly increased. By the end of the year the epidemic had ended.[4]

The disease had a direct impact on the U.S. Army when it occurred among their native troops—the Philippine Scouts. By 1908, 12 percent of them had been admitted to the hospital with beriberi. In 1910 the Medical Board, on the basis of its reading of both the Dutch and the British work on the disease, reported that it was making a change in the troops' diet, which they expected would overcome the problem.[5] I will return to the outcome of this change later in the chapter.

THE FIRST INTERNATIONAL MEETING

As the newcomers to the special problems of disease in the Tropics, the Americans probably realized most acutely the advantage of an exchange of ideas with others who had had a longer experience of them. At any rate, the first meeting of the newly formed Far Eastern Association of Tropical Medicine was held in Manila in March 1910, so it seems most likely that it was the medical authorities in the Philippines who had taken the initiative as well as issuing the invitations. An invitation also went to Japan, although it is not a tropical country, presumably because it shared some of the medical problems of the Southeast Asian region. Delegates from at least nine countries attended, and beriberi was the first subject to be discussed.

The Dutch East Indies were represented by J. De Haan, now director of the institute at Weltverden where Grijns was also working. He reported that further controlled studies with mung beans had confirmed

their value in both curing and preventing beriberi in institutions.[6] Grijns had also continued attempts to concentrate the active factor in mung beans, but it appeared to be easily destroyed by the extraction procedures used.[7] Regarding the possibility that the human and/or the chicken disease involved an infection, their recent work had given no support to the idea. It had not proved possible to transmit the chicken disease by feeding the flesh of diseased birds to healthy ones, or even by transfusing blood or inserting degenerated nerves into healthy birds.[8] Attempts to find specific antibodies in humans with beriberi and in fowl with polyneuritis had also yielded negative results.[9] The Dutch workers had therefore come to the conclusion that beriberi was a purely nutritional disorder.

Henry Fraser, the delegate from Malaya, was, as expected, in general agreement with De Haan. In their most recent work with fowl, he and Thomas Stanton had found no evidence that storage changed the value of white rice significantly. The virtue of parboiling was not that it kept the grain from deterioration but that, as normally marketed, it retained more of the valuable silverskin. White rice was not "bad," but it required other materials to balance its deficiencies. One good source was rice polishings.[10] (It has been alleged that Fraser and Stanton's belief that the disease was purely a nutritional deficiency had been fortified by their failure, in repeated experiments, to transmit any hypothetical "infection" from beriberi patients to healthy subjects. All mention of such work was supposedly suppressed by the Malayan government, since it could have been considered unethical.[11] I mention the allegation but have seen no evidence to support it.)

Campbell Highet, principal medical officer in Bangkok, was the delegate from Siam (now Thailand). In that country, too, the disease had appeared first in the city jail in 1890 but had then occurred only rarely until 1900. But in the first eight years of the new century, there had been nearly twenty-three thousand cases of beriberi among public servants (army, navy, police, etc.) and over one thousand deaths. Highet agreed that it attacked those who ate white, machine-milled rice. Steam mills had proliferated in Siam since 1890. This was partly because slavery had been abolished in 1905, and it was slaves, typically, who had been used in the past to do the hand milling. Having to pay servants for this labor had now made it cheaper to buy commercial white rice. Highet's last point was a protest against the use of the term "Siam" rice. This was a trade name for rice that had been

processed in a particular way, and the rice might have come from any of a number of countries. Misunderstanding on this point, now that this type of rice was in disfavor, was unfair to Siam as a rice-exporting country.[12]

Dr. Aldo Castellani from Ceylon (now Sri Lanka) admired the experimental work done in Malaysia and the Philippines, but he felt that the rice theory did not explain everything: "In Ceylon there are half a million Indian coolies who eat the same rice as those in India; in fact the greater part is imported from India; still, not a single case has occurred in Ceylon. . . . may it not be that the general debility caused by excessive intake of white rice renders the individual more liable to be infected by the specific parasite causing beriberi?"[13]

Dr. Shibayama, the delegate from Japan, believed that a "one-sided or monotonous diet is only the predisposing cause of beriberi; the true cause must be sought in other directions." He added that it was "not unreasonable to assume that the microorganisms of beriberi are only present in the Orient." It had been Japanese experience that people could still develop beriberi when receiving 5 oz of mung beans daily, or even unpolished rice.[14]

Francis Clark, from Hong Kong, said that, in order to strengthen the hands of medical officers, he wished at the end of the discussion to move a resolution that would yield a practical result.[15] The editor of the proceedings added in a footnote that the following resolution was finally passed: "*Resolved.* That in the opinion of this Association sufficient evidence has now been produced in support of the view that beriberi is associated with the continuous consumption of white (polished) rice as the staple article of diet, and the Association accordingly desires to bring this matter to the notice of the various Governments concerned."

An explanation for the enigmatic phrase "finally passed" was provided, two years later, in a paper by Strong and Crowell: "There was considerable opposition to the passage of this resolution in this form on the ground that it was not sufficiently conservative from a scientific standpoint in relation to our present knowledge. . . . its passage was only secured at a final business meeting after the association had adjourned from Manila to Baguio . . . [with] only a portion of the members present."[16] It seems likely that the Japanese delegation was among those absent.

Another problem for the delegates was, of course, to decide what positive advice to give their governments on their return. Fraser and Stanton had suggested that people could continue to eat white rice but should supplement their diet with rice polishings.[17] Highet believed this to be impractical:

> How can we expect the ordinary native to gauge the proportion of polishings required to make up for the deficiency in the white rice? . . . Further, unless very carefully prepared, rice polishings contain much mineral debris from the grinders, dust, filth, etc. . . . The Siamese in public service declined to eat parboiled rice owing to its stale, musty flavor. A substitute had to be provided in place of white rice, and this was found in the hand-milled grain.[18]

In this context, "hand-milled" presumably meant "hand-pounded."

It was reported that in the Philippines the governor-general had already issued an order by which "the use of polished rice in all public institutions is forbidden."[19] I will return to the effect of this order later in the chapter.

AND WHAT OF THE FRENCH?

The one major colonial power in Southeast Asia that did not send a representative to the meeting in Manila was France. This may have been because the French medical officers had not yet agreed on the statement they would make about the cause of beriberi and how to prevent it, and had referred the matter back to Paris. It was certainly not because their colonies were free of the problem, nor because their medical officers were indifferent to it. The 1910 volume of the French *Bulletin de la Société de Pathologie Exotique* contains no less than nineteen communications on the subject.

Between 1900 and 1909, the predominant belief of French writers was that the disease was an infection. One monograph, published in Paris in 1905, states: "Beriberi is an infectious, contagious and epidemic disease of the Tropics, characterized at times by the presence in the blood of a particular micrococcus," and later that "changing the diet has not given the results one is led to expect by believers in the *nutritional* theory; it only increases the general resistance of the patient, as in other diseases such as malaria."[20] A second monograph, published in the same year, begins its conclusions as follows: "Beri-

beri seems certainly to be a microbial disease and not a nutritional one; it is without doubt an infection and not an intoxication [*empoisonnement*]. . . . Only the theory of infection by a pathogenic microbe appears likely and conforms with the facts." In the text the author explains why: "The immediate cause is a spore-forming bacteria."[21] This belief may reflect the prestige and the influence of Pasteur's work in the previous century.

However, some medical officers in the French colonies had reported the elimination of a beriberi problem purely by dietary means. As early as 1899, Petit, the army surgeon responsible for the health of a thousand Senegalese infantrymen in Madagascar, knew something of Eijkman's work. When 250 of these men were sick with beriberi, he supplemented their white rice with a proportion of rice bran. They protested that they were being given "food meant for mules" but soon saw that they were doing better than men in other units whose diets had not been changed and who were continuing to get sick. Petit concluded that the bran had a neutralizing effect on the poisons present in bad white rice. Other army units had hoped to remove the problem by replacing salt fish in the rations with fresh meat and by adding fat, but these changes had not proved useful.[22]

Another report described the problem that occurred in the small French island of Réunion in the Indian Ocean in 1903–4 among workers on the sugarcane estates. The author wrote that the problem arose after the usual supply of Indian rice had been cut off, and the islanders instead had had to import a much more highly polished type of rice from Cochin-China (Vietnam). When supplies from India were resumed, the epidemic diminished and then disappeared. The author added, in an unexpected comment, that some of the sufferers from the Chinese labor force were "mathematicians and lettered men, delicate and refined, who had been lured to the island where they were put to work cutting sugarcane for ten hours a day in the full sun."[23]

Another physician reported that in the main prison in Saigon, in the period from 1899 to 1903, when the diet was based on machine-milled white rice, on average eighty-two prisoners died each year from a population of under three hundred, mostly from beriberi. As a consequence, the prison governor had begun to release long-term prisoners before the end of their sentence, explaining that "these men had been sentenced to a prison term, not to death." The government

then sent to Java for advice about what could be done.[24] After changing the prison diet to hand-pounded rice, the death rate fell to seven per year, despite an increase in the prison population. Comparable results were then obtained in another prison in the area, where the death rate from beriberi specifically fell from thirty per year to zero after the same change in diet.[25]

At a meeting of the Society for Exotic Pathology in Paris in March 1910, its president set up a seven-member commission to collect information in the countries where beriberi existed and to make a report.[26] This procedure had already been followed for several other tropical diseases, and the French government apparently regarded the society as the appropriate body for such work. The commission presented its report in October 1911; it occupied thirty printed pages and began by reviewing the experience of the disease in the French colonies, of which three examples have just been given, and also of work done in Java, Malaya, and Japan.

The association of the disease with white rice was thought to result from the grain losing its protective coating so that during storage in hot, moist conditions an unknown "pathogenic agent" got into it. Some workers believed that rice bran was effective because it contained "an antidote to beriberi." However, in view of the equal effectiveness of some beans as a preventive, other workers believed that the bran and beans were contributing "special indispensable nutrient materials for the proper functioning of peripheral nerves."[27]

The commission agreed that a *necessary condition* of the disease appearing was the use of white rice as the principal ingredient of the diet. However, it questioned whether this was a *sufficient condition*, or whether some other factor was required to elicit the disease—a factor that could become active under these conditions. The commission believed that the latter was the case, and that overcrowding and defective social conditions were equally essential for beriberi to appear; beriberi was a disease of prisons and asylums, or any grouping of natives housed en masse. They added: "It was a strange anomaly that the traditional scanty and squalid straw huts of the natives were less dangerous: beriberi was a disease of masonry and brick, in which there was high humidity and insufficient light and ventilation. . . . It is extremely interesting that at the time of an epidemic it is enough to disperse the group and let them return to their normal life" (Fig. 6.1).[28]

However, they also said:

Fig. 6.1. "Squalid and scanty straw huts," in which soldiers typically recovered from beriberi (Crow, 1914).

> What is strange in a disease which proceeds by epidemic outbursts and takes hold in particular seats, so that it appears to have an infectious origin, is that the most rigorous disinfection . . . does not suffice, of itself, to extinguish it or retard its extension. . . . The essential, primary cause is still unknown, and despite the hard work of competent scientists there is still uncertainty and a whole field of hypotheses. . . . Epidemics show inexplicable oscillations.[29]

In its conclusions, the commission recommended a variety of procedures to prevent outbreaks: "better hygiene and the provision of warm bedding where it becomes cold at night, more opportunity for physical exercise, but not overworking people beyond their capacity. After an outbreak has occurred in an institution where people are concentrated together they should all, sick and healthy, be dispersed into the open air in straw huts." But then the report concludes (with capitalization as in the original): "The disease can be prevented (and cured) if the ONLY CHANGE is improving the diet either by the addition of fresh provisions and green vegetables or BY THE SIMPLE REPLACEMENT OF WHITE RICE IN THE RATION BY BROWN RICE PREPARED IN THE NATIVE MANNER."[30]

This report may be seen either as a genuine synthesis of different views or as a compromise in which no one lost face. It still allows for

beriberi being an infection but at the same time says that, in practice, all one really needs to do to prevent it is to change the dietary staple from white rice to brown.

THE JAPANESE BERIBERI COMMISSION

The Japanese, too, had a commission in being at the time of the Manila meeting, which reported in 1911. They did not attempt a synthesis, however, but merely reported a continuing diversity of views.

Chapter 1 of this book described the Japanese experience up to the disappearance of beriberi from that nation's navy in 1885 after Takaki's introduction of revised rations of higher protein content. Takaki's critics argued that it was really concurrent improvements in hygiene aboard ship that were responsible for the improvements, and they even hinted that the same improvement occurred in those naval barracks where the diet had remained unchanged. In any case, the navy continued to be essentially free from the disease, even during the 1904–5 period of the Russo-Japanese War.[31]

In stark contrast, beriberi was the major cause of sickness among the Japanese army during the war. Estimates of the number of cases range from ninety thousand to two hundred thousand, and this was thought to have been a factor in the Japanese High Command's being happy to end the fighting in 1905 with limited gains (Fig. 6.2).[32]

The army medical department was in the hands of graduates from the medical school under German influence, which had a firm belief in the infectious nature of beriberi. Maximilian Herzog, an American surgeon stationed in the Philippines, was given permission to observe the work of a military hospital in Japan to which seven hundred beriberi patients had been moved. The surgeon-in-charge, who had previously been professor of infectious diseases in Tokyo, was trying to isolate from the blood of patients a "coccus bacterium," which he believed to be the cause of the disease. It was isolated repeatedly from patients' urine, but not from blood. Herzog also reproduced in his paper three typical case histories at another hospital. The therapies used were "magnesium sulfate and hydrochloric acid" or "infusion of digitalis with potassium acetate." No mention was made of the patients' diet. Professor M. Miura, the government's chief consultant on beriberi, believed that the disease came from an infection conveyed by

Fig. 6.2. Warmly dressed Japanese soldiers in Manchuria during the Russo-Japanese War. Over ninety thousand of the men in this army succumbed to beriberi and were evacuated to hospitals in Japan (Hare, 1905).

food. Herzog himself had been unable to reproduce the disease by injecting the suspect coccus into animals.[33]

Those who considered beriberi to be a nutritional disease saw the army's experience in a different light. As described in chapter 1, it had been found in the 1880s that when barley, which was cheaper than rice, was used to replace part of the rice ration for prisoners, their health records improved, and beriberi in particular almost disappeared. Soldiers' rations were then changed in the same way. Since this effected an economy, the change was noncontroversial. However, when the Japanese army was fighting Russian forces in Manchuria, it was at any rate easier to obtain just white rice for them, and no longer to use barley. This provided a nutritional explanation for the extraordinary epidemic.[34]

Miura accepted that diet had some influence on the soldiers' resistance to beriberi, as it did with other diseases. However, other stresses appeared more important, and during the fighting for Port

Arthur these included diarrhea from bad water, lack of proper housing, sleeping in ditches, and the usual seasonal effects. The navy could maintain more hygienic conditions in its ships, but, even so, its claim of almost complete freedom from beriberi should be "taken with a grain of salt. . . . they prefer to close their eyes to it." He added that there must also be racial differences in susceptibility, since none of the thousands of Russian prisoners of war were found to have the disease.[35]

Later observations of outbreaks in Japan itself continued to be viewed according to the prior beliefs of investigators. Some assumed that the appearance of the disease in inland parts of the country was the consequence of improved transportation, which had encouraged coastal people infected with beriberi to move into these regions.[36] Another writer, who believed that the disease had a nutritional cause, explained the spread as the result of imported white rice being shipped into areas that were previously dependent on local crops.[37]

Although some Japanese workers had been able to reproduce Eijkman's experiments with hens, there was also the criticism that polyneuritis could not be equated with beriberi because the hens showed nervous changes only after becoming emaciated, whereas in humans the disease appeared in those who were well nourished and even plump.[38]

FURTHER PROGRESS IN THE PHILIPPINES

By 1912, the Americans had completed several more studies. The first was with the Philippine Scouts, the military force of five thousand Filipinos under U.S. officers, which had been set up in 1903. As stated earlier, in each of the two years prior to 1910, over 10 percent of the Scouts had been diagnosed as having beriberi. Their standard daily ration issue then included 20 oz of white rice. The Medical Board decided that the ration should be modified first to include less rice and more beans and vegetables and then, in a decision effective from August to November 1910, the imported white rice was replaced by "Filipino no. 2 rice," which was a mixture of red and white rice, milled to remove only a part of the pericarp.

In 1910 as a whole, only 1 percent of the Scouts developed beriberi, nearly all in the first three months of the year, while the incidence of the disease had not fallen in either the Filipino police force,

whose rations were unchanged, or in the general population. The improved health of the Scouts was therefore attributed to the change in their rations.

In November, however, counterorders were received to return to white rice. There had been complaints to Washington from the units because the no. 2 (or second-grade) rice not only was less highly milled but also contained broken grains and dirt, as well as some unhusked kernels. In addition, it did not keep well during the time required to ship it to where the troops were stationed. In light of this experience, the Medical Board worked with millers to have them produce a higher quality undermilled product. Siam was also, at the time the report was written, offering an undermilled rice, of good appearance and guaranteed to contain at least 0.23 percent phosphorus (used as an indicator of its pericarp content).[39]

In 1912 the results were published from a large study in the Manila prison. The subjects were twenty-nine men who were all under sentence of death but had agreed to volunteer. Presumably this earned them a stay in their execution. Another inducement was that they would be allowed unlimited free cigarettes and cigars for the period of the study. However, they were also warned that they might develop beriberi.[40]

Seventeen of the men received the basic diet, containing about 600 g polished white rice per day, together with smaller quantities of bread, bananas, bacon, and onions, varying from day to day. It had been planned for another group to receive cooked white rice to which uncooked rice polishings would be stirred in just before being served. The polishings were obtained from a special mill and were free from the grain weevils common in ordinary commercial samples. Nevertheless, the men said that the mix gave them stomachaches, and they refused to eat it, preferring to go hungry and lose weight. After thirteen days the organizers gave them cooked unpolished (red) rice instead. Another group of six received white rice with the addition of a concentrate, prepared by alcoholic extraction of rice polishings that had been found to cure birds with polyneuritis.[41]

The study was continued for approximately one hundred days. All but one man lost weight, regardless of which treatment they were on, for at least the first five weeks of the trial by an average of about 8 lb. The one man who did not lose weight died on the seventy-seventh day, and autopsy examination confirmed that he had acute beriberi;

Table 6.1 Results of ninety-seven days of feeding three test diets in a Philippine prison

		Number of subjects					
			Beriberi cases			Percent affected	
Group	*Type of rice*	*Total*	*Fatal*	*Definite*	*Slight*	*Seriously*	*To any extent*
A	Polished	17	1	8	2	53	65
B	Unpolished	6	0	0	2	0	33
C	Polished + "extract"	6	0	0	2	0	33

SOURCE: Data from Strong and Crowell (1912).

he was one of the 17 prisoners on the basic diet. Altogether, including the subject who died, 8 of the 17 men receiving the basal diet were diagnosed as definitely having beriberi, and 2 more had shown some slight, preliminary signs. In neither of the other groups was there a definite case of the disease, though in each group 2 of the 6 had shown similar slight preliminary signs.[42] The results are summarized in Table 6.1.

The authors concluded that the alcoholic extract had some protective effect, but since each daily dose corresponded, if recovery of the hypothetical "anti-beriberi" substance was complete, to the amount in over 3 kg of unpolished rice, they believed that much of it had been lost. Similarly, they were disappointed in what appeared to be the only partial protection provided by the unpolished (red) rice, although it contained 0.3 percent phosphorus, which Fraser and Stanton had judged to be an indicator of its being fully protective against beriberi.[43] However, the clear production of the disease in nearly half of those on the basic diet convinced the authors that the disease was not an infection, since the hygienic precautions had been very strict in the special high-security unit of the prison, and the food was all freshly cooked and served immediately.[44]

This human experiment differed from the others described previously in that subjects were deliberately assigned to a treatment expected to produce a disease, *and* they were not changed to a "remedial" treatment on the first appearance of the disease having been produced. Richard Strong, the first author of the study, had also conducted earlier trials at the prison that had been the subject of protest in the United States.[45] His reply to criticism of the present experiment

might be that he had ordered a change in the diet of the man who died, but by then he had lost all appetite. Also, the fact that the men were, in any case, under sentence of death may have made him less solicitous of their lives.

The Japanese worker, J. Tsuzuki, was also preparing alcoholic extracts of rice bran at this time and, after testing them with animals, was giving them with success to beriberi patients.[46]

INFANTILE BERIBERI

Although women in general in Southeast Asia did not seem to develop beriberi to the same extent as men, they were at particular risk in the last trimester of pregnancy and after childbirth. There was also a very high incidence among the breast-fed babies of such women of a disease known in the Philippines as *taon.* Not only was there a very high death rate there among infants—nearly 50 percent in the first year—but, contrary to the general experience elsewhere, the death rate among breast-fed babies was higher than for artificially fed babies. It seemed almost as though their mother's milk had become poisonous.[47] Doctors seeing such infants had been recommending that they be transferred to artificial feeding with canned cow's milk.

A Japanese physician had already published similar findings in 1898, based on experience with over forty cases in infants. The mothers had all had either florid or incipient beriberi, and Hirota found that the sick infants would almost all recover their health within a week if they suckled from a healthy wet nurse or were given cow's milk. He, too, had concluded that their own mothers' milk had become poisonous.[48]

Weston Chamberlain and Edward Vedder, of the U.S. Army Medical Corps, believed that the *taon* babies were themselves suffering from a deficiency of the "anti-beriberi factor." Obviously, with infants under three months of age, there was no question of their being able to ingest rice polishings. There was therefore an immediate need for some kind of concentrate of protective material. They tried an extract of rice polishings, of the same kind as the one that had proved at least partially protective in the prison experiment just described.

Chamberlain and Vedder's published paper reported the results of treating fifteen infants in this way. The sickness had typically begun with vomiting, followed by restlessness, edema of the face and legs,

a stoppage of urine secretion, and difficulty in drawing breath. The treatment was to give the infants twenty drops of "extract" every two hours while they were awake. In every case the response was almost immediate; urine began to flow again, the child fell into a deep sleep, and after a few days the edema had disappeared. The authors wrote that they believed that the rapid responses seen in their work provided "the final link in the chain of evidence" of beriberi being a deficiency condition rather than the result of either infection or toxicity.[49]

In 1913 the government's Bureau of Science began routine preparation of an extract of *tikitiki* (rice polishings) for distribution to doctors treating *taon* babies. It was prepared by mixing good-quality *tikitiki* with 90 percent alcohol for twenty-four hours, then squeezing out the fluid and evaporating it gently to remove the alcohol. The residue was in two layers; the fatty material floating on top was rejected because it had been found to be inactive in chicken assays. About 25 ml of the lower watery layer was obtained per kilogram of *tikitiki.* Adding 60 ml of water gave a further precipitate. This was filtered off, and the liquid was bottled and sterilized at 60°C on three successive days.[50] The process was modified slightly over time, and by 1921 the Bureau of Science was producing ten thousand bottles of extract per year. Even this met only a small portion of the demand, but it was thought to have been a major factor in reducing the death rate from infantile beriberi in Manila from about 10 percent of all births in 1914–16 to about 2 percent in 1927–30.[51]

THE SECOND INTERNATIONAL MEETING

The Far Eastern Association of Tropical Medicine held its second meeting in Hong Kong in January 1912, and again beriberi was the first topic of discussion. There were a number of presentations by speakers who believed that the primary cause of the disease was some kind of infection. Noel Davis, a British medical officer in the Chinese "treaty port" of Shanghai, said that his observations of the disease did not seem explicable in terms of nutritional deficiency. In Shanghai, outbreaks had occurred where men (police recruits, prisoners, tram drivers) slept together in dormitories infected with bedbugs. After vigorous measures had been taken to eliminate the bedbugs, there were no further outbreaks. Three healthy volunteers had also deliberately been exposed to bugs that had previously been feeding on beriberi

victims. One of the volunteers developed beriberi after three weeks, another showed mild symptoms after four weeks, and the third remained healthy. It appeared, therefore, that bugs could carry the infection, and that individuals varied in their resistance.[52]

However, despite the opinions of individual speakers, there was now general agreement from the national delegations, including those from French Indo-China, Japan, and China, that the disease was commonly associated with the consumption of polished (white) rice and that, for whatever reason, addition of rice bran to the diet, or the replacement of white rice by less highly milled material, prevented the appearance of the disease.

Victor Heiser, director of health for the Philippines, said: "The time has come to bring this knowledge to the attention of all Governments concerned. . . . people are dying of beriberi by the thousands and the knowledge by which this can be prevented is at our command."[53] He believed that the association should pass a resolution advising governments to put a tax on white rice sufficient to encourage poor people to change to using brown rice that would now be cheaper. If wealthier people continued to use white rice, that should not create any problem because they also would be consuming a more varied diet that would provide alternative sources of the factor(s) present in the rice silverskin.[54]

Others argued that this approach was impractical because brown rice deteriorated more quickly during transport and storage, and there was no supply of brown rice at the retail level to which consumers could turn.[55] It was agreed that research should be continued in milling procedures that would yield clean grain with enough silverskin retained so that, on analysis, it contained at least 0.175 percent phosphorus (equivalent to 0.4 percent phosphorus pentoxide), the level that Fraser and Stanton had found to be an indirect indicator of nutritional quality as judged by their chicken tests.

Finally, the association agreed on the importance of discovering the chemical nature of the active material in rice bran. That line of work will be the subject of the next chapter.

CHAPTER 7

The Isolation and Construction of a Vitamin

1912–1938

If only the identity of the active factor in the rice polishings could be discovered, other more concentrated sources might be found, or it might even be possible to manufacture it. This could make it much easier to treat cases of infantile beriberi in particular. Eijkman had found that the factor was dialyzable (i.e., that it could pass through fine membranes), which showed that it was not a huge molecule like a protein; this was encouraging, although its being destroyed by heat, especially in alkaline conditions, was obviously going to be a problem in isolating it, as a step to its identification.[1]

EARLY ATTEMPTS AT IDENTIFICATION

One approach was to make educated guesses about what the factor might be, and to try out these possible compounds for their activity in curing birds with polyneuritis. As mentioned earlier, a German scientist, H. Schaumann, had predicted that the activity would turn out to arise from one or more organic phosphorus compounds. His reasons were (1) that nerves are particularly rich in organic phosphorus compounds; (2) that white rice has a low phosphorus content, but rice bran is much richer in it; and (3) the common assumption that the animal kingdom has to obtain every class of organic compound preformed from the vegetable kingdom.[2] Schaumann thought that phosphonucleic acids were the key factors in rice bran. However, these hopes did not bear fruit. None of a range of phosphorus compounds (including phytin, lecithin, and nucleic acids) was found to be active, nor was any of a range of other compounds.[3] Schaumann did, however, show that yeast was another rich source of the factor, and that pigeons could be used as a convenient assay species in place of fowls (Fig. 7.1).[4]

The job that had to be tackled, therefore, was to try to separate the

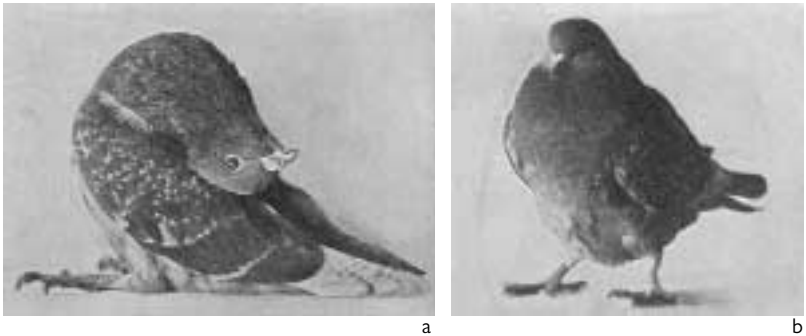


Fig. 7.1. (*a*) A pigeon showing characteristic head retraction after it has been fed on white rice for two to three weeks. (*b*) The same pigeon three hours after receiving a vitamin extract (Funk, 1922).

active factor from the whole range of other compounds present in *tikitiki* extract. This meant treating it in some way, to separate it into two parts, and feeding each part to birds. If only one portion showed activity, that portion had to be fractionated again, until finally pure crystals could be obtained that showed full curative activity. Then would begin the further job of identifying the chemistry of the crystals.

One group pioneering this kind of approach was working at the Agricultural College of the Imperial University, Tokyo. Umetaro Suzuki and his colleagues were able to prepare a fraction, which they named "oryzanin" (*oryzo* being the Latin name for rice), 5 to 10 mg of which given daily to a chicken fed on polished rice would keep it free from polyneuritis.[5] At the time they believed that they had a pure crystalline salt, but later they realized that it was still contaminated with adenine and other impurities.[6] In 1993 Suzuki's memory was honored in Japan by the issue of a postage stamp carrying his portrait (Fig. 7.2).

Another early leader in this kind of work was Edward Vedder in Manila, a physician in the U.S. Army Medical Corps, who had been appointed to the Board of Tropical Diseases.[7] He concentrated his attention on beriberi and was convinced that it represented a nutritional deficiency. As an army officer he had to serve in one post for a three-year tour and then usually move elsewhere. By 1912 he had completed a second tour in Manila. In the following year, spent in the United States, he prepared and published an impressive monograph on the disease.[8] In this publication he reviewed the findings in many coun-

Fig. 7.2. A Japanese postage stamp issued to honor Umetaro Suzuki for his early preparation of a concentrated extract from rice bran for the treatment of beriberi (courtesy of the Ohmer Library of the Chemical Heritage Foundation, Philadelphia).

tries and marshaled the evidence for his belief that dietary deficiency could explain every outbreak of beriberi, despite the contrary beliefs of many observers at the time. We know, from later references, that this book was important in drawing the attention of nutritional workers in the United States to the findings that had been made in this connection in Southeast Asia.[9]

Vedder also left behind someone who would prove to be an important force for the identification of the active factor. In 1909 he had recruited Robert R. Williams to assist him in this work. Williams had grown up in India as the oldest child of Baptist missionaries. After obtaining a chemistry degree in Chicago in 1908, he had come to the Philippines as a schoolteacher but a year later joined the government's Bureau of Science in Manila.[10] He and Vedder confirmed that the active factor was extractable in hot, dilute alcohol and was stable to acid but easily destroyed by alkalis. He also found that it was absorbed, but not destroyed, by animal charcoal, since portions of the charcoal subsequently fed to sick birds resulted in their cure.[11]

CASIMIR FUNK'S "VITAMINE"

Williams then went back to the United States for a period of advanced training in chemistry. On his early return in 1912, he and Vedder had

a shock. Their work had apparently already been completed by somebody else, according to a paper published in England late in 1911, that had now reached the Philippines. A young Pole, working in London, reported that he had isolated the active substance from rice polishings in crystalline form, and that it was an organic base containing 7.7 percent nitrogen, 55.6 percent carbon, and no phosphorus. Only one-twentieth of a gram (or 50 mg) was needed as the daily dose to cure a pigeon—the species chosen for his assays.[12]

The author, Casimir Funk (born in 1884), had grown up in a Poland that was then under a Russian government that was trying to eradicate the Polish language and nationalist feelings. His father, a physician, was able to send Casimir at the age of sixteen to continue his studies in Switzerland, first in Geneva, then moving to Berne to specialize in organic chemistry and obtain a doctoral degree at the early age of twenty! He moved in 1904 to the Pasteur Institute in Paris, one of the few places having a chair of biochemistry; then in 1906 to Berlin to work on amino acids with Emil Abderhalden, and again in 1910 to the Lister Institute in London.[13]

In London Funk had the opportunity to work and publish as a sole author with the proviso that original papers were approved by the institute's director. The grant that he received was to support his work in identifying the anti-beriberi factor in rice polishings, which his chief expected to be an amino acid. He soon realized that it was something else and was required only in very small amounts. In 1912 he received an invitation to prepare a review article for a journal, and this did not require official approval. He therefore took the opportunity to introduce the term VITAMINE for the active (i.e., vital) factor, a term that the director had not approved of his using in his earlier paper. He believed it to be an organic base, and a basic nature in an organic compound had always been found to come from its containing an amine group (i.e., ammonia with one or more hydrogens replaced by carbon bonds). The new name was therefore an abbreviation for a "vital amine."[14]

With a leap of faith, or imagination, Funk then went on to suggest that two other diseases—scurvy and pellagra—were also caused by deficiency of different "vitamines." This paper has since come to be regarded as a classic and has been reprinted in *Milestones in Nutrition.*[15] But, although Funk's term "vitamine" (shortened now to "vitamin") has remained, his original claim to have isolated a vitamin was not confirmed.

In 1913 Funk moved again, to the laboratory of London's Cancer Hospital Research Institute. This institution provided better facilities, but the results he obtained there were rather different. His original crystalline material now appeared to be a mixture, and, although he later separated three separate crystalline materials and reported that two of them appeared to be needed to produce cures, this also could not be confirmed in further work carried out with the assistance of Jack Drummond, a young British scientist who was to be famous in later life.[16]

After the outbreak of World War I in August 1914, Funk felt that foreigners were less welcome in England. He moved once more, this time to the United States, and obtained employment to work on problems of organic chemical production, and then on endocrines as well as vitamins. His life continued to be one of movement from place to place. A biographer has judged that, because of his background, Funk always felt himself a stranger, and that "his imagination was sometimes more that of a poet than of a scientist, and often his ideas were ahead of what was warranted by established scientific work."[17] Nevertheless, his introduction of the term "vitamine" undoubtedly drew attention to this new field of research as something of much broader importance than the prevention of one particular tropical disease.

THE PROBLEM NOT SOLVED

In 1915 Williams published an editorial plea to Funk to provide the details of the revised method for preparing his vitamine that had been promised in an article two years earlier.[18] These details were never to appear, but some of Funk's published separation steps were to prove useful. In particular, the addition of phosphotungstic acid to the initial extract completely precipitated the activity, while leaving most of the extracted material in solution. The precipitate could then be separated, and the "activity" brought back into solution by the action of barium hydroxide, although it was still mixed with other compounds.

By 1916 Williams had made more than forty attempts to obtain pure vitamine from large quantities of rice polishings, but none was successful.[19] Many years later he recalled how discouraging this work had been, but its importance was brought home to him by urgent requests from local doctors to bring them something to save a baby with an

acute case of infantile beriberi. He remembered "a youthful mother whose blue-faced baby was dying in her arms; with a teaspoon I fed it some 2 or 3 ml of the best concentrate I had. . . . soon the breathing became quieter. . . . within 3 hours the infant nuzzled at its mother's breast, nursed hungrily and fell into quiet sleep."[20]

Since one of the materials isolated by Funk had proved to be nicotinic acid, which seemed to have shown some activity in a number of tests, Williams tried out both the compound itself and some of its derivatives. He, too, felt that he obtained some improvement in the condition of his experimental birds with these compounds.[21] But in 1915 the authorities in the Philippines decided to allocate more government positions to Filipinos, and Williams's employment in Manila was terminated. He moved to the U.S. Department of Agriculture's Bureau of Chemistry in Washington, D.C., and for two more years was able to use part of his time for his old interest. He continued to explore the biological activity of pyridine compounds related to nicotinic acid in curative tests with pigeons. He concluded that alpha-hydroxypyridine in 5-mg doses did have some curative effect in a number of tests and suggested that the variability of response could be the result of the molecule being unstable and changing from one form to another.[22]

With the entry of the United States into World War I in 1917, Williams was transferred to war work and could not return to his old interest until the 1920s. By then there had been related scientific developments that now need to be considered.

THE DEFICIENCIES OF PURIFIED RAT DIETS

Prior to 1910, a number of workers in Germany, under the leadership of Professor Gustav von Bunge, had tried to rear young mice and rats on diets made up solely of "purified" ingredients—protein, fat, carbohydrate, and minerals. They repeatedly found that their animals did not grow to maturity.[23] Bunge explained these failures as being caused by the ingredients having been "denatured" during their preparation.[24]

In 1905 Cornelis Pekelharing, whose earlier work on the Dutch Beriberi Commission was discussed in chapter 3, gave a lecture that was published in the main Dutch medical periodical. "Buried there," one might say, on the twelfth page of the article, was the following:

> When mice are fed on casein, egg albumin, rice flour and a complete salt mixture, with water to drink, for the first few days all is well . . . but soon appetite diminishes and in four weeks all are dead. But if given milk to drink, or even the whey from which casein and fat have been eliminated, they keep in good health. There is a still unknown substance in milk. My repeated efforts over the last few years to separate this substance have failed, so I shall say no more about it.[25]

And he never did. This statement, in Dutch of course, remained unknown to English-speaking workers until a fellow Dutchman published a translation twenty-one years later.[26]

By a strange coincidence, Gowland Hopkins of Cambridge University made a somewhat similar statement in the following year—again toward the end of a published lecture, and with no hint in its title: "The Analyst and the Medical Man." After referring to his already published work on tryptophan being an essential nutrient for mice, he went on to say that

> No animal can live upon a mixture of pure protein, fat and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. . . . In diseases such as rickets, and particularly in scurvy, we have had for long years knowledge of a dietetic factor; but though we know how to benefit these conditions empirically, the real errors in the diet are to this day quite obscure. They are, however, certainly of the kind which comprise these minimal qualitative factors that I am considering. . . . later developments of the science of dietetics will deal with factors highly complex and at present unknown.[27]

Hopkins gave no description of any further tests that he had carried out, nor did he say specifically that he had any data of his own in addition to what he had read of the findings of others. However, he does seem to have been the first to suggest a link between the growth failure of young rats or mice and the reason for human diseases such as scurvy and rickets. He did not, at that time, know of the work of Eijkman and Grijns relating to beriberi, and one would hardly need to refer to these remarks made in 1906 if they did not seem to have given him a chronological priority over others when he was selected to receive a Nobel Prize in 1929, together with Eijkman, "for the discovery of vitamins."

In his Nobel acceptance speech he explained that he had worked

with mice in 1906–7. By 1909 he had changed to rats and was attempting to extract and identify the active growth promoter in yeast for his diet based on casein and butterfat. He believed at that time that his findings would not be taken seriously unless he had identified the factor. In 1910 he had a breakdown in health, and on returning to work in 1911, he continued rat growth studies with and without small quantities of milk supplementing a modified basal diet of casein, lard, cane sugar, starch, and salts.[28] The special features of these studies were that:

a. the milk was given separately from the basal diet, so that there could be no question of a monotonous diet having been made more palatable,
b. energy intakes and digestibility were measured,
c. individual rat values were recorded, with statistical analysis of their variability, and
d. "control" animals were used in every trial, and treatments were reversed after unsupplemented animals began to lose weight, showing that these particular animals had the ability to grow, provided that they received small quantities of milk.

The evidence was clear that the growth cessation and decline in weight on the basal diet were not explained by a failure of appetite, or poor digestibility of the food, as had been suggested by skeptical readers of earlier results.[29] The mean growth results were also plotted in simple figures (e.g., Fig. 7.3) that were to be reproduced over and over in textbooks for many years. This may have helped Hopkins to gain the reputation, at least in Europe, of being the spiritual father of vitamin research.[30]

In 1908, Elmer McCollum at the University of Wisconsin began to experiment with feeding purified diets to young rats, his first published results being concerned with the ability of rats to utilize inorganic phosphate for the synthesis of the organic phosphorus compounds in their tissues.[31] In the following year Thomas Osborne and Lafayette Mendel in Connecticut also began to study the ability of young rats to grow when receiving only a single protein source.[32]

Initially there was some confusion and controversy between the two groups, and also with Gowland Hopkins, over whether unknown factors were really essential to sustain growth. However, it was finally realized that the casein and lactose used in many "purified" mixes still contained traces of these unknown milk factors unless they had been

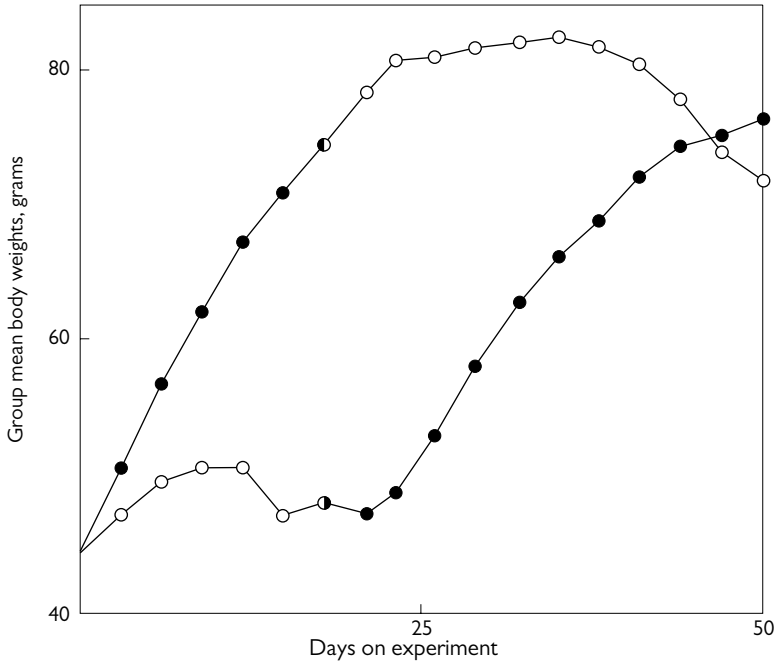


Fig. 7.3. The weights over time of two groups, each of eight young male rats, fed a diet of casein, starch, cane sugar, lard, and salts. *Solid circles,* with 3 ml milk each day; *open circles,* without a supplement. The milk supplement was switched on the eighteenth day (Hopkins, 1912).

exhaustively extracted with alcohol.[33] It was agreed that, for sustained growth, young rats needed to receive both a factor found in cod liver oil and butter, named "fat-soluble A," and another, present in yeast, wheat germ, and nonfat milk powder, named "water-soluble B."[34]

These findings stimulated an extraordinary amount of additional research and also of public interest in Europe and America.[35] "Vitamins" were to be the major topic of nutritional study for the next thirty years, and many books have been written on the subject.[36] Funk was to comment later: "In our opinion the name 'Vitamine,' proposed by us in 1912, contributed in no small measure to the dissemination of these ideas. . . . [It] served as a catchword that meant something even to the uninitiated."[37] Williams, too, was to write that "the much maligned name, vitamin(e), . . . was a stroke of genius. . . . such a captivating word was necessary to focus the attention of the public and, in turn, of science upon the possibilities of the field."[38]

In the present context our interest must focus on just one aspect: the question of whether "factor B" for rats was the same as the "antineuritic factor" required by birds.

IS VITAMIN B THE SAME THING?

McCollum, who originated the term "water-soluble B" as a factor required for the growth of rats, was confident that it was the same factor that others had been studying for its protective power against beriberi and chicken polyneuritis.[39] To doubt it must have seemed an unnecessary complication. His reasons were that the sources of high activity were the same for each, solubility in different solvents seemed to be identical, and the "extracts" active against polyneuritis appeared to support growth in rats also. However, others warned that identity was not strictly proved, and it was prudent to keep an open mind: "An undue simplification based on insufficient evidence would lead to confusion and impede progress."[40]

For another ten years any number of experiments were carried out comparing the activity of different preparations and combinations of preparations for rats and for birds—usually pigeons by now rather than fowl.[41] Finally, by about 1927 it seemed clear that yeast autoclaved enough to destroy its antineuritic activity still improved the growth of rats fed on purified diets, and that growth was again improved by the further addition of extracts from cornmeal, which had high antineuritic activity but were of no value as the sole supplement for rats. It was concluded that "vitamin B" consisted of at least two separate factors.[42]

The factor remaining in autoclaved yeast was now named either vitamin G or vitamin B_2, with the antineuritic factor being coded B_1. There were soon indications that even B_2 was really a mixture of several factors and was renamed the "B_2 complex," but that is a subject beyond our present interest.

IMPROVED ASSAYS

The implications of these new findings for the study of what we can now call vitamin B_1 were considerable. By adding autoclaved yeast (as well as cod liver oil to provide "fat-soluble A") to basal assay diets, assays could be made more specific. Eijkman and Grijns had both

reported that some of their birds, after a long period on rice diets of different kinds, would develop a "croupous inflammation." It is now realized that this is a sign of vitamin A deficiency, which develops only after a bird's preexisting reserve of the vitamin has been depleted.

Birds were, however, still an extremely fortunate choice for their purpose. The original chicken diets of Eijkman and Grijns also included the small amount of B_1 that remained in polished rice, but with this species symptoms of B_1 deficiency appeared before those of deficiencies of the other nutrients which are also present in polished rice only in low concentrations. Species obviously differed greatly in this respect. When Axel Holst tried to use guinea pigs as a model species for studying beriberi, they rapidly developed a condition which he realized was analogous to scurvy.[43] This was an important finding because there had previously been no experimental model for studying this disease.[44] When monkeys were fed on white rice for several months, no signs of a specific deficiency resulted.[45]

It was also coming to be realized that the curative assay with pigeons could give misleading results. As early as 1913, Eijkman had reported obtaining a short-term response from giving a simple solution of potassium and sodium chlorides.[46] Others found that there could also be temporary recoveries after administering glucose, changing the environmental temperature, or giving various stimulants.[47] This problem was thought to explain Williams's reports of variable responses by pigeons to a variety of pyridine compounds, which were retested later under more stringent conditions and found to be inactive.[48] It may also explain Funk's problems in reproducing his early results.

In view of these problems, some workers changed to using rats for B_1 assays and measuring their response in weight gain after they had begun to lose weight and to show signs of paralysis on a purified diet supplemented with cod liver oil and autoclaved yeast.[49] Typical results with one rat are shown in Figure 7.4. Another consistent effect of B_1 deficiency in rats was bradycardia (a reduction in the heart rate), and in one laboratory the period for which a supplement corrected this was found to be a more precise assay response than weight gain.[50]

There was some controversy over whether rats deficient in vitamin B_1 did develop a condition of polyneuritis comparable to that seen in birds. The outcome was that they would do so provided that

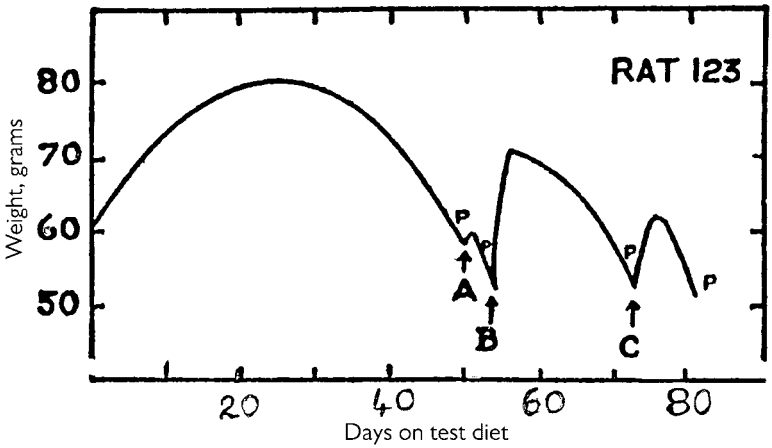


Fig. 7.4. Typical results with one rat using a vitamin B_1 assay procedure with autoclaved yeast in the basal diet (Smith, 1930). Three different preparations were compared at a single dose of 6.5 mg. Preparation A restored weight for two days, B for seventeen days, and C for eight days. When other rats gave similar results it was concluded that Preparation B was the most potent and A the least. The letter "P" indicates the times at which the rat showed signs of paralysis.

they received plenty of B_2 and just a little B_1; but if the diet was completely devoid of B_1, they lost their appetite and died before developing signs of neuritis.[51] Even with pigeons it was found that a condition more like human beriberi, with edema and an enlarged heart as well as leg weakness, could be induced if white rice were supplemented with other grains to increase the vitamin content of the diet slightly.[52]

One disturbing finding with rats was that some could apparently grow and remain healthy without any significant amount of vitamin B_1 in their diets. This phenomenon was called "refection." The carbohydrate source in these rats' diets was raw rice starch or raw potato starch.[53] These forms of starch were known to be difficult to digest, so that a proportion reached the cecum and large intestine, where they could form a source of energy for the bacteria present. It was thought, therefore, that in some rats there were strains of bacteria present which synthesized thiamin, and the vitamin could then be absorbed through the intestinal wall into the bloodstream. It was known that ruminant animals, like cows and sheep, obtained water-soluble vitamins from microbial synthesis in their rumen, and subsequent digestion of the

microbes in the true stomach and small intestine. Much later it was discovered that even rats housed in a cage with a raised wire screen floor were able to grip a fecal pellet as it was being excreted and then ingest it, and that this activity could provide a sufficient source of the vitamin. However, when coprophagy (eating feces) was prevented by taping a cup device to the rat's tail, it still became deficient regardless of what carbohydrate source was included in its diet.[54] Therefore, it now appeared that thiamin was not absorbed directly from the large intestine.[55]

It was generally agreed that "preventive" assays were preferable to "curative" ones. But to use them meant having enough test material to feed one's animals for several weeks rather than for a single curative dose, and also having to wait much longer for an estimate of the test material's potency.

The Dutch scientist B. C. P. Jansen found a way around this problem. He had taken over work on the isolation of the vitamin in Java in the 1920s, using the much-improved laboratories of the new Eijkman Institute, which had replaced the makeshift facilities of the earlier investigators (Fig. 7.5). He developed a preventive assay, using a small ricebird found locally in large numbers. This was the bondol (*Munia maja*), which ate only about 2 g rice per day, compared with 12 g for a pigeon or even more for a fowl. When they were fed on polished rice (which had been washed in running water for two days) together with salts and cod liver oil, these birds almost invariably developed polyneuritis in nine to thirteen days. The preliminary soaking of the rice had been found to speed the depletion period, presumably because the small quantity of residual B_1 had largely diffused out into the water. A daily supplement of 0.1 g rice polishings was found to be enough to keep the birds healthy for fifteen to twenty-three days. Thus an assay using as many as ten birds still required only "10 by 0.1 by 23," approximately 25 g rice polishings, or an amount of a concentrate with the same total potency.[56] This therefore was a preventive assay but one that required only a small quantity of test material.

In 1931 the Health Organization of the League of Nations adopted as an International Standard a large batch of clay that had an extract of rice polishings absorbed onto it. Portions were distributed to various laboratories so that they could compare the potency of different

Fig. 7.5. The Eijkman Institute in Batavia where Jansen and Donath obtained the first vitamin B crystals in 1926. It replaced the primitive facilities Eijkman and Grijns used (courtesy of Research Corporation).

materials with a common standard. One International Unit (IU) of activity was defined as the potency of 10 mg of the standard clay. For the remainder of the decade, authors used these units to describe the potency of the materials that they had either assayed or given to beriberi patients.[57]

CRYSTALS OF "VITAMIN" AT LAST

In the fifteen years since Funk's first claim to have isolated antineuritic crystals, many groups had continued to work on the problem—in Britain, Germany, Holland, Japan, Java, Malaysia, the Philippines, the United States, and perhaps elsewhere, and certainly with more than one group in both Britain and the United States. By 1925 several groups had obtained products that would cure pigeons in doses of between 2 and 6 mg per day, but they still could not claim complete separation from impurities.[58]

Funk, writing a decade after his original claim, now emphasized the difficulty of the work:

> In the starting material the vitamine(s) are associated with large amounts of inactive substances. When we mix a small quantity of a *known* substance with a large quantity of another *known* substance

> we still find it difficult to effect a separation. Here we are dealing with cellular constituents whose chemical nature is still insufficiently known: on concentration of the vitamin there is a corresponding concentration of impurities. . . . Even when we isolate a well defined crystalline substance there is the objection that it may be inactive material that has absorbed a small quantity of vitamine.[59]

We now know that there is only about a teaspoonful of vitamin in a ton of rice bran. However, B. C. P. Jansen and W. F. Donath in Java, after many attempts, reported in 1926 having finally obtained a small quantity of crystals with a potency such that, added to washed rice at a ratio of only one to a million, they maintained ricebirds in good health, and only one-hundredth of a milligram (i.e., 10 micrograms, or mcg) was needed as a curative pigeon dose.[60]

In view of earlier authors' claims having been unverified and treated skeptically, they sent some of their crystals to other laboratories for testing. A vial containing 40 mg went to Eijkman in Holland. If we remember that a level teaspoonful of salt weighs about 5 g (or 5,000 mg), what he received was less than one hundredth of that amount. Nevertheless, it was enough for him to be able to confirm the potency of the material for pigeons, and to report that polyneuritic fowl were cured by the addition of two parts per million of the crystals to their polished rice.[61]

R. R. Williams and colleagues, now working near New York City, also received a small quantity and confirmed its potency, with both their rats and pigeons responding to doses of 40 mcg of material.[62] However, when they followed the isolation procedure described by the Dutch workers, they did not obtain the same yields, nor any actual crystals of active material. Williams commented later: "Our failure to confirm his results fully may have been due to differences in our fuller's earth [clay] or the purity of some of our reagents. . . . So complicated and intricate a process can scarcely be described sufficiently fully."[63]

The procedure was certainly complex, involving sixteen steps. After the initial extraction of 300 kg (or roughly 660 lb) of rice polishings with water, the active factor was first absorbed from the extract onto a special kind of clay, then washed out with barium hydroxide and successively precipitated with silver nitrate, phosphotungstic acid, platinic chloride, acetone, and picrolonic acid. After each precipitation and filtration, the factor had to be redissolved, in most cases

with barium hydroxide. Finally, 100 mg of crystals were obtained with hydrochloric acid. From comparative bioassays of the crystals and starting material, it appeared that over 90 percent of the vitamin originally present had been lost during the process.

Even Jansen and Donath had difficulties in obtaining crystals in subsequent runs. But a small sample of what they had, in the form of a salt with hydrochloric acid, was subjected to a preliminary microanalysis for carbon, hydrogen, and nitrogen. Assuming that the only other element would be oxygen, as was the case for all the organic bases known at that time, the result corresponded reasonably well to an empirical formula of $C_6N_2H_{10}O{\cdot}HCl$.[64]

WHAT WERE THE CRYSTALS?

Jansen attempted to synthesize material that corresponded in composition to his empirical formula, but none was biologically active. And even though his crystals were five hundred times as active as Funk's first material, it was still not clear that it was the ultimate vitamin.

Over the next seven to eight years, other workers, trying different modifications of the Java procedure, gradually developed less laborious separations that also gave bigger yields, but of the same crystals, as judged by their physical properties (Fig. 7.6).[65] By 1931 A. Windaus, a chemist at the University of Göttingen, was collaborating with a group at I. G. Farben Industrie, the large German chemical firm. The group prepared crystals from yeast that proved to be identical with those of Jansen and Donath but found that, in addition to carbon, hydrogen, nitrogen, and oxygen, the molecule contained an atom of sulphur.[66] This put an entirely new complexion on the possible structure of the molecule.

We now have to return to R. R. Williams, who had begun his studies of the vitamin back in 1909 in Manila. In the 1920s he was the chemical director at Bell Telephone Laboratories in New Jersey and was concerned with quite different problems. Nevertheless, he was determined to get back to the characterization of vitamin B_1. He worked first in the evenings and on weekends, in laboratory space in the basement of New York Hospital, taking preparations home for testing on the pigeons he was keeping in his garage. He could then review their overnight responses while drinking his breakfast coffee. A grant from the Fleischman Yeast Company of a few hundred dollars per year

Fig. 7.6. Crystals of thiamin obtained by R. R. Williams in 1933 (Williams, 1956; courtesy of Research Corporation).

helped pay his expenses in the early 1920s. Then, from 1927, he received further support from the Carnegie Institution for supplies and payment to student assistants. His colleague Robert Waterman, from Bell Laboratories, volunteered to work without pay. With the worsening of the Great Depression, they had more free time, because the Bell Company chose to reduce the working week (and pay in proportion) first to four and then to three days, rather than making any staff completely unemployed. They were allocated more space at Teachers College, Columbia University, and then the use of facilities at the university's Chemical Engineering Laboratory.[67]

In 1933 they had obtained sufficient crystalline vitamin to begin to study its chemistry. By then at least three groups in other countries were also studying the same material, so that its identification became something of a race. The groups agreed that the molecule was twice as large as Jansen and Donath had supposed, with the formula for the hydrochloride salt being $C_{12}H_{16}N_4OS{\cdot}2(HCl)$.[68]

SUCCESSFUL SYNTHESIS

Obviously, with a molecule of this size there are almost innumerable ways in which the eighteen multivalent atoms might be joined together. The organic chemist's normal procedure, therefore, is to try first to split it into two smaller fragments that could be more easily identified. At this point Williams had a bit of good luck: he remembered that some twenty years earlier, in order to prevent bacterial growth in an extract, he had added sodium sulfite, and that this had resulted in its complete loss of vitamin activity. He now added sodium sulfite to a solution of the pure vitamin. Again, the activity was lost, and one new material appeared as a precipitate, and another was left in solution.[69]

Many more months of intricate, and at times frustrating, work followed, with Williams obtaining the help of different specialists in the New York area and also the cooperation of Merck and Company, the pharmaceutical manufacturers whose plant and laboratories were only a few miles from Bell Laboratories and could provide him with excellent facilities for both chemical work and animal testing. Joseph Cline, a young organic chemist on the Merck staff, made a particularly important contribution. The value of the cooperation for Merck was that, if commercial synthesis of the vitamin became possible, its chemists would have the know-how to give them a head start.[70] The I. G. Farben company, collaborating with Windaus in Germany, must have had the same idea.

Some of the chemical work involved in identifying the molecule is summarized in Appendix A. There were several slightly different ideas regarding the structure of the vitamin as the work advanced in different laboratories. But it was made much more certain with the successful synthesis by the American group in 1936 of a biologically active compound with identical physical properties to the material isolated from both rice polishings and yeast (Fig. 7.7).[71] It had been "constructed" by condensing together five small molecules in a series of reactions.

The same molecule was synthesized in slightly different ways within a short period in both Germany and Britain.[72] With the isolation of "vitamin B_1," it was first named "aneurin" (for *an*ti-*neur*itic vitam*in*) in Europe, but it was agreed internationally a few years later to call it "thiamine" (or, more recently, "thiamin"). In chemistry *thio*

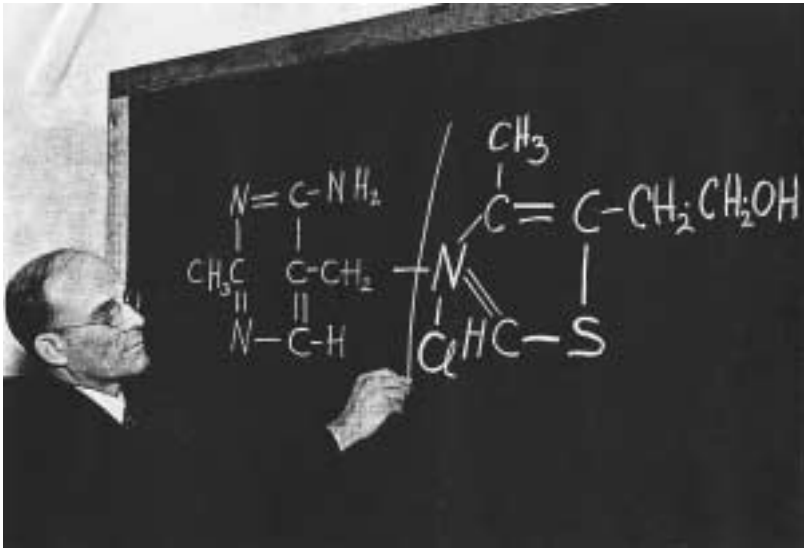


Fig. 7.7. R. R. Williams demonstrating the structure of thiamin and how he used sodium sulfite to split it into two portions that could then be identified (Addinall, 1940; courtesy of Merck & Co.).

stands for sulfur (from the Greek *theion*), and the abbreviated name signifies that this is the "sulfur-containing vitamin(e)." Both synthetic and natural samples of this material had potency for rats such that 3 mg were approximately equivalent to 1,000 IUs of activity.[73]

CLINICAL TESTING

The final test for the synthetic material was, of course, its value in human cases of beriberi. One of the first reports came from Singapore, where a hospital had been receiving a large number of beriberi cases in the acute cardiac stage. (Westernization of Japanese and Chinese terms tends to be inconsistent. Here the stage was called *shoshin*, whereas Scheube, quoted in chapter 1, called it *shiyo-shiu*.) There was agreement that this condition almost always ended fatally. R. B. Hawes and his colleagues wrote in 1937 that their experience in Singapore had been that 80 to 90 percent of their patients died in agony within twelve hours after admission. However, since the crystalline vitamin had become available, only twenty-three of the most recent one hundred patients had died, and none of the last ten patients who

had received higher doses (5–8 mg) of the vitamin by injection. Both the natural and the synthetic preparation had proved effective. The improvement in blood pressure and heart rate occurred within one to two hours of receiving the dose.[74]

At a meeting in England the following year, Hawes said that, with the synthetic material now available at a reduced cost, all the cases could receive large doses. He was amazed, after injecting one apparently dying patient in the morning, to see when he returned in the afternoon that the patient had made his way the length of the ward to get a cup of tea.[75] In the discussion that followed his talk, another physician commented that the effect of the vitamin on pathetic cases of infantile beriberi was also truly magical, and that it was a pity that the chemists who had made these things possible could not see the cures with their own eyes.

Indeed, this was certainly a great achievement, and the outcome of dedicated work by a great many people in different parts of the world over a period of fifty years. I am reminded of remarks made by someone who had contributed to the successful synthesis of vitamin A some ten years later: "After so many years victory has come and the romance of high hopes and bitter disappointment will in a few years simply be recorded in textbooks of organic chemistry in a few terse sentences."[76]

But can a simple shortage of thiamin explain all the past observations of beriberi? That will be the subject of the next chapter.

CHAPTER 8

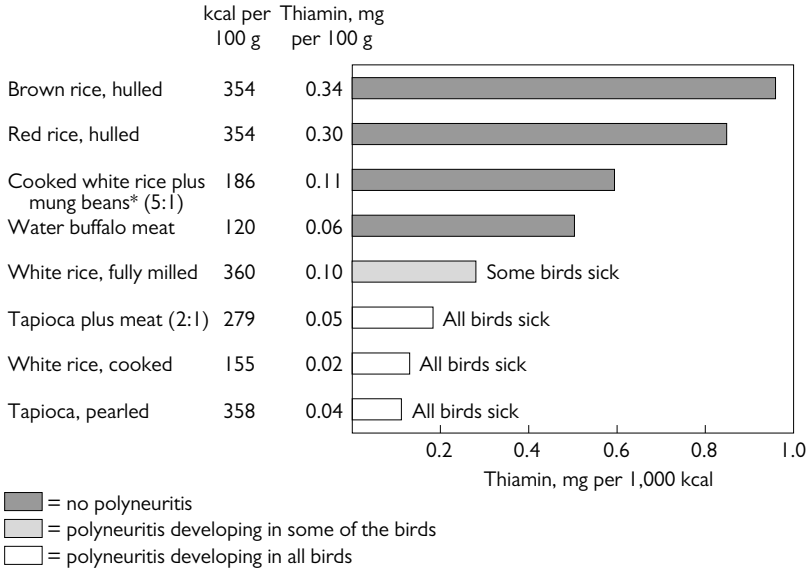
Chemical Analyses of Foods

Explanations and Surprises

The previous chapter ended with the synthesis of a substance having the physical properties of the vitamin isolated from rice polishings, and the same potency in the treatment or prevention of beriberi and also in preventing or curing "vitamin B_1 deficiency" in rats and pigeons. However, there remained a question of whether white rice, or other diets that appeared to provoke beriberi, were simply lacking in thiamin. It was still possible that they contained some "antithiamin" material. Because an ordinary bioassay could not distinguish the two possibilities, some independent technique for measuring the thiamin content of different foods was needed.

CHEMICAL ANALYSES FOR THIAMIN

It is obviously a problem to find a means of measuring the concentration of a particular chemical that may be present as only one part in a million in a complex food. However, it was discovered in 1935 that when thiamin was treated with a mild oxidizing agent it reacted to form a strongly fluorescent compound, which was named "thiochrome."[1] This was then used as the basis for the chemical analysis of foods.[2] Many groups worked to develop a reliable procedure.[3] There were two basic concerns, as with any procedure of this kind—one was to extract into solution all the thiamin present in the test material, and the second was to prevent any other compounds in the test material from contributing fluorescence that would then be wrongly attributed to the vitamin. Some of the methods commonly used to minimize these problems are summarized in Appendix A. However, any value from chemical analysis is only an indirect estimate, and one always has to be aware of some possible problem, particularly with foods not previously studied.



* Mung beans alone have been found to contain 1.69 mg thiamin per 1,000 kcal.

Fig. 8.1. Estimated thiamin concentration of diets used in Eijkman's early chicken trials in relation to their outcome.

Given these cautions, we can review the findings from analysis of the main foods used in different parts of the world.

THE EARLY CHICKEN DIETS

I will begin by comparing the estimated thiamin contents of the various chicken diets used by Eijkman and Grijns in their early experiments. Obviously there are no analyses of the actual batches of materials used by these workers. The best we can do is to take typical (or average) analytical values for the same types of material, compiled from the literature. The values used to create Figure 8.1 were taken from the FAO "Food Composition Tables for Use in East Asia."[4] The values for thiamin in individual foods are given as milligrams (mg) per 100 g. Since the amount of any diet eaten is, at least approximately, the quantity required to meet an animal's (or our own) energy needs, the relative adequacy of different diets in supplying thiamin is better

expressed as milligrams of thiamin per 1,000 kilocalories (kcal). In these units, if rice were to lose none of its thiamin during cooking, the value would remain the same despite its having taken up a large quantity of water.

From Figure 8.1 we see that the three diets estimated to contain less than 0.4 mg thiamin per 1,000 kcal were all associated with the development of polyneuritis. Those estimated to contain higher concentrations of thiamin remained free from polyneuritis, although some did die, after a long period, from a croupous condition that we can now characterize as being caused by vitamin A deficiency.[5] The diets used at that time did not, of course, include any source of vitamin A such as the cod liver oil added to later diets. These analyses appear, therefore, to supply a satisfactory explanation of the results obtained by Eijkman and Grijns, and it appears that the birds used in these trials needed about 0.3 to 0.4 mg thiamin per 1,000 kcal.

Just one result is not explained in terms of thiamin analyses. Grijns obtained disappointing growth with raw soybeans as a supplement to cooked rice. Soy is another fairly rich source of thiamin (0.96 mg/100 g) but these beans in the raw state are also now known to contain potent growth inhibitors for poultry, and this could explain their poor performance in Grijns's trial.[6]

THE FRAGILITY OF THE VITAMIN

As mentioned in chapter 4, Grijns found that both meat and mung beans had lost their antineuritic activity after they were autoclaved for two hours, and that rice bran boiled in water for twenty-four hours was also inactive. He concluded that the active compounds "are easily disintegrated, which shows that they are very complex substances."[7] Then, as described in chapter 7, later workers had used autoclaved yeast in assay diets because it had lost its antineuritic activity but remained a rich source of other growth factors for rats and chickens.

Chemical analyses have been able to confirm that the losses in activity in autoclaved materials are explained by destruction of the vitamin.[8] As expected, the rate of destruction rises with increased temperature, but this is not the only factor. Under acidic conditions losses were reduced, and under alkaline conditions they were greatly increased. Thus, when powdered rice was boiled in an excess of distilled water for twenty-five minutes, 10 percent of its thiamin was destroyed;

the corresponding loss when an alkaline well water was used was 75 percent. This water contained bicarbonates and, as it boiled, carbon dioxide was lost, so that the alkalinity increased.[9] However, the degree of loss also depends to some extent on the actual salts with which the vitamin is in contact. Chapter 7 has referred to the effect of sulfites in rapidly splitting the thiamin molecule, and it appears that the molecule splits at the same point with simple heating.[10] The vitamin also seems to be protected to some extent by the proteins and other compounds to which it may be attached in a natural food. A large number of papers on this topic are referred to and summarized in two comprehensive reviews where thiamin has been characterized as the least stable of all the vitamins.[11]

RICE AND OTHER STAPLES

Returning to rice itself, averages can, of course, include a wide range of individual values. The literature contains suggestions that rice from some regions might be particularly likely to cause beriberi. Unfortunately, there has been no systematic comparison in a single laboratory of samples from many countries, and it can be dangerous to make comparisons between results obtained in different laboratories. For example, in North America twenty laboratories collaborated in analyses of wheat flour for thiamin. The mean average values for the same set of samples ranged from 0.53 to 0.82 mg/100 g in the different laboratories.[12] It seems inevitable, therefore, that some of the variation in published values for rice samples is the result of differences in analytical techniques, or in the care with which they are carried out. Given that qualification, we can say that, combining individual values from fourteen laboratories, the range for brown rice runs from 0.25 to 0.60 mg/100 g, but with the great majority of values being between 0.3 and 0.45. There was no clear evidence for high-yielding varieties being significantly different from others, nor for glutinous rice differing from other varieties.[13]

There are conflicting reports about the loss of thiamin in rice during storage, but reviewers have concluded that nine months of storage of either paddy or brown rice in a hot country can be expected to result in a 10 to 15 percent loss.[14] However, when brown rice is attacked by insects, the loss may be much greater because the insects have eaten the outer layers preferentially.[15] On the other hand, Jansen

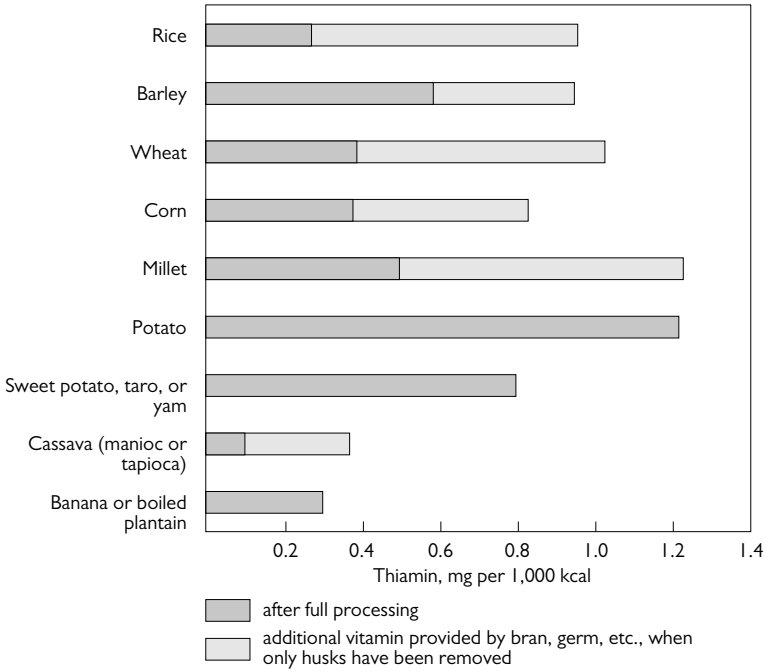


Fig. 8.2. Representative analytical values for the thiamin content of different staple foods after husking only and after full processing, and also for some staple root crops and other foods. Sago meal is not shown because it contains only an insignificant amount of thiamin.

found that rice that had been stored in the husk for one hundred years still kept his birds free from polyneuritis.[16]

If the relatively low analytical value for white rice can explain the incidence of beriberi in rice eaters, does chemical analysis also explain the rarity of the disease in parts of the world where different staples are consumed?

Representative analyses for the other main staple foods (taken from the source used for Fig. 8.1) are set out in Figure 8.2, both as "whole grain" (i.e., merely husked) and when fully milled, as in white wheaten flour, white rice, pearled barley, and degermed corn meal. We see that the thiamin content of all grains has been greatly reduced by milling. White rice is, on average, the lowest, at about 0.27 mg/1,000 kcal, but white wheaten flour and degermed corn also have calculated values less than 0.4 mg/1,000 kcal, and some analyses of white flour have given values as low as 0.24 mg/1,000 kcal.[17] Such low values are

not really unexpected, since early workers had reported that feeding white flour to pigeons could result in their developing polyneuritis.[18] There also have been well-authenticated outbreaks of beriberi in ships and institutions where white wheaten flour was the staple, rather than rice. I will return to this subject in a later section.

The virtual disappearance of beriberi in Japanese prisons and barracks after a portion of the white rice ration was replaced by barley is also explained by barley's higher thiamin content. The values in Figure 8.2 for potatoes are surprisingly high, and sweet potatoes, taros, and yams also appear to be good sources of the vitamin. In contrast is the severe deficiency of sago, and also of cassava flour and plantains, two staples in areas of Brazil where beriberi has been endemic, as will be discussed in the next chapter.

THE EFFECT OF WASHING RICE

The values tabulated for rice are for uncooked material. Eijkman's early results did indicate that birds receiving cooked white rice developed polyneuritis sooner, and more consistently, than those that received the same material uncooked. However, his only reaction seems to have been the conclusion that cooking was not essential for the disease to appear, and from then on he used only uncooked rice in his further studies in Indonesia.

A German worker in the early 1900s looked into this matter again. He found that, when he used white rice that had been merely washed (the normal preliminary before rice is cooked) and then redried, his pigeons died after only twelve days, compared with thirty to forty days with unwashed material.[19] Workers in Japan and India confirmed this result with a number of rice samples,[20] and in Jansen and Donath's description of their early isolation of vitamin crystals they commented that their work in Batavia had been greatly speeded by using washed white rice as the basal diet for their biological assays.[21]

In 1933 Andre Van Veen set out results from his own further bioassays in Batavia, concluding that "a too exclusive attention has been paid to the degree of polishing of rice, and not enough to how it is prepared in the kitchen for consumption." From his studies it appeared that white rice could lose as much as half of its remaining activity through long washing.[22] Yang, working in Shanghai, where beriberi was a problem, reported in 1938 that results with the new

procedure for chemical analysis confirmed that washing rice caused it to lose approximately half of its thiamin.[23]

Benjamin Platt followed up this finding with a clinical trial. In Shanghai at that time there were a number of hostels in which boys from outside of the city lived and ate while they were employed in nearby factories, and beriberi had been a problem in many of these hostels. Platt's trial was organized in a hostel housing seventy-five boys. There was no change in their diet except that the fully milled rice was freshly processed, had no polishing powder added to it, and was cooked in the ordinary way but without the usual preliminary washing step. The study continued for six months, including six weeks of summer weather when the disease was most prevalent. Although signs of beriberi continued to appear in other hostels, the boys in the study remained healthy, and independent observers reported that they had "a spirit of cheerfulness and increased well-being" that was in contrast to the "apathetic and cheerless" appearance of the boys in the other groups, many of whom continued to show edema in their legs.[24] Further work in Shanghai was put to an end by the Sino-Japanese fighting.

On his return to England, Platt summarized his findings in a report to the British government and referred also to an earlier experience that he had heard of: there had been a monastery and a nunnery where the same simple diets were eaten, but only the nuns were troubled with beriberi. The sole difference to which this could be attributed was that the less fastidious monks did not bother to wash their rice before cooking it. He concluded that people could live on white rice and still avoid beriberi even without thiamin supplements provided that they did not wash the rice before cooking, and that they consumed common complementary foods, such as 6 oz of dried beans or 3 oz of peanuts, that would contribute an additional 0.45 mg thiamin to their daily diet.[25]

THE EFFECTS OF COOKING RICE

If merely washing rice grains in cold water causes such a loss of thiamin, one would think that cooking the grains in hot water would cause an even greater loss of this water-soluble vitamin, so that the elimination of washing would be of no importance for the final prod-

uct. As described in chapter 2, however, there are two quite different common procedures for cooking rice. In one, the grains are cooked in a large volume of water, and then the remaining excess is poured off. In the other, just enough water is used so that it is absorbed into the cooked grains and none is discarded.

This is an important difference. American workers found that cooking unwashed white rice in a double boiler by the second procedure caused little or no loss, whereas cooking rice with eight times its own volume of water and then draining led to a 54 percent loss. Repeated washing of a similar uncooked sample gave a 43 percent loss.[26] In another study in India, after white rice had lost 50 to 60 percent of its thiamin from three washings, half of even that remaining was lost by cooking in excess water, so that what was eaten after such procedures would apparently have only 20 to 25 percent of the thiamin present in the rice that had been purchased.[27] Other results confirm the large losses from cooking in excess water.[28] In one study in Thailand, the combined effects of thorough washing followed by cooking in excess water led to an average retention of only 11 percent of the thiamin originally present; the same washing followed by cooking in minimal water gave 46 percent retention. As a consequence, the final concentration of vitamin in the cooked rice was many times as great with the second procedure.[29]

These results certainly confirm Van Veen's comment in 1933 that how rice was processed in the home should receive as much attention as how it had been processed before purchase. In most of the papers cited for losses in cooking white rice, there are analogous results for "brown," or hand-pounded, rice. The percentage losses are generally similar for the two materials. Given that the initial thiamin value for brown rice is some four times higher than for white rice, it follows that the ratios for the cooked materials are similar, so that brown rice retains its advantage at whatever point the comparison is made.

White wheat flour that has been baked into bread (using yeast) has been found to lose only some 20 percent of its original thiamin.[30] Thus, although it was originally similar in vitamin content to white rice, bread as the product finally consumed is considerably richer (per kilocalorie) than the same rice after cooking. However, some other ways of cooking wheat can cause greater losses; these will be discussed in the following chapter.

THE EFFECTS OF PARBOILING RICE

Chapter 5 made reference to the finding that rice that had been parboiled and redried before milling appeared to provide protection from beriberi. This had been the observation in Malaya, as a result of comparing the health of ethnic groups eating rice prepared in different ways, and the difference was confirmed in a well-controlled trial, as discussed already in chapter 5.[31]

Animal assays confirmed that, after subsequent milling to remove the skin, the product still had a vitamin activity in animal assays that was similar to that of brown rice, and much superior to that of ordinary white rice.[32] When chemical analysis became possible, Aykroyd and colleagues milled both ordinary brown rice and parboiled rice in successive stages, and analyzed the milled grains with the results set out in Figure 8.3.[33] We see that without any milling the parboiled sample is slightly inferior, but as milling proceeds, less of the thiamin is lost from the parboiled sample. This indicates that the initial soaking stage in the parboiling procedure had caused most of the thiamin present in the outer portions of the grain to diffuse inward, into the endosperm, so that it was not lost by the mechanical milling.

A serious outbreak of beriberi occurred in the Singapore Criminal Prison in 1918 even though the prisoners were receiving parboiled rice. On further investigation, however, it was found that the rice was being cooked by steam under high pressure and temperature—a condition already known to destroy the anti-beriberi property of a food. When the cooking procedure was changed to ordinary steaming, no further cases appeared.[34]

WHERE IS THIAMIN CONCENTRATED IN THE RICE GRAIN?

This may seem an unnecessary question because it had surely already been settled when Eijkman found that his chickens would develop polyneuritis when fed on white rice, but not on brown rice whose grains still had their coating of silverskin, as he called it. The concentration of the active factors in the skin seemed to be confirmed by the potency of the polishings removed during the final milling to produce white rice.

The first suggestion that the skin might not be the richest part of

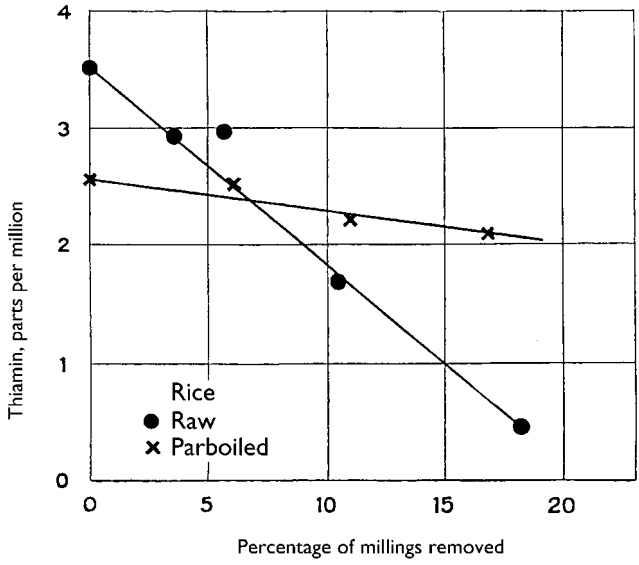


Fig. 8.3. The thiamin contents of raw and parboiled rice after milling to different extents (Aykroyd et al., 1940).

the grain was made in 1915. As described in the previous chapter, McCollum, in Wisconsin, had been the first to demonstrate the need of young rats for a water-soluble factor "B" and was convinced that it was the same substance as that required to prevent polyneuritis in birds. When wheat germ was found to be a particularly rich source of this factor, McCollum suggested that the germ might similarly prove to be the richest portion of the rice grain.[35]

The germ in a grain of rice is very small, making up only some 2 percent of its weight. However, workers in London separated a small amount by hand, one grain at a time, and used it in a curative assay with pigeons. The results indicated that the germ was indeed five to ten times as potent as rice bran, and they concluded that "in both the rice and wheat grain, the antineuritic vitamin is concentrated mainly in the germ."[36] There is a human story concealed here. During World War I, the senior staff of the Lister Institute in London were male physicians who had gone overseas to work in army medical laboratories. Left behind were the relatively junior women on the staff, who now had an opportunity to show what they could do. Their leader was Harriette Chick, a chemist by training.[37] She and Margaret Hume per-

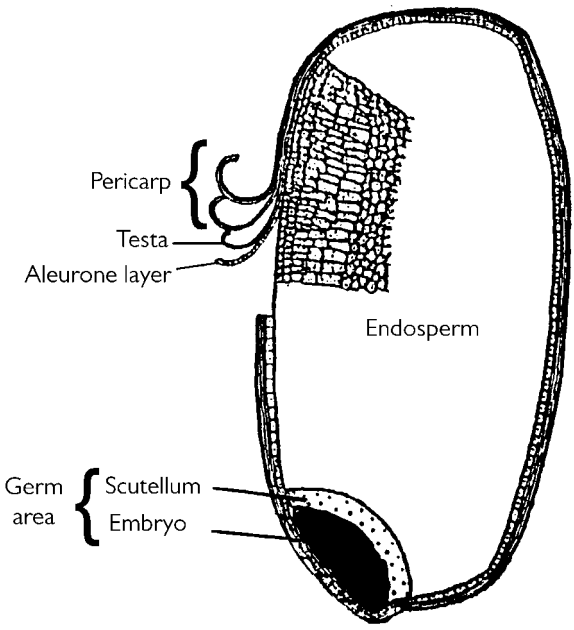


Fig. 8.4. Diagram illustrating Hinton's dissection of the rice grain.

formed the painstaking separation of the rice germ and carried out the assays, thus becoming the earliest independent women investigators to be mentioned in this story. Chick also went on to carry out careful bioassays with guinea pigs and showed that McCollum had been mistaken in his conclusion that guinea pig scurvy was caused by "intestinal intoxication."[38] The achievements of women in many fields in this crisis period in the United Kingdom led to a complete reappraisal of their proper place in a society that previously had not even allowed them to vote.

Chick and Hume's report was quoted in two important reviews.[39] And Japanese workers, as shall be described in chapter 11, followed up their observation, but it appeared to be forgotten by Western scientists. In 1941, British workers in Malaya reported what they considered a finding with "far-reaching implications," that some 50 percent of the thiamin in the rice grain appeared to be concentrated in its tiny germ.[40] Malaya was then invaded by the Japanese, but a cereal scientist working in England carried out more microdissections, dividing the crude "germ" into the actual embryo and the scutellum

Table 8.1 The thiamin contributed by the different parts of a sample of dehusked rice grains

Dissected parts of rice grain		*Proportion by weight (%)*	*Thiamin*		
			Concentration in fraction (mg/100g)	*Contribution to 100 g grain (mg)*	
Pericarp + testa + aleurone layers		6	3.1	0.186	
Germ area	Embryo	1	5.9	0.059	0.248
	Scutellum	1	18.9	0.189	
Endosperm		92	0.05	0.046	
Total		100		0.480	

SOURCE: Modified from Hinton (1948a).

layer immediately between it and the endosperm (Fig. 8.4).[41] Together they provided more than half of the total thiamin in the grain, with by far the greater part coming from the scutellum. The full results are set out in Table 8.1. Harriette Chick's "germ" presumably comprised both fractions.

As Altson and Simpson pointed out, this does mean that workers who were judging the products from different rice milling procedures by the proportion of silverskin remaining could have been misled.[42] There would certainly be an advantage for a milling procedure that could remove the silverskin, so as to provide the favored appearance, without removing the germ (including scutellum) from its groove in the rice grain. An isolated comment in a 1940 paper from India notes that the germ is usually lost during the hand pounding of rice.[43] This statement is surprising in view of the good reputation of such material for keeping people free from beriberi, and I am not aware of any study on the point. It was quickly suggested after publication of the results from Hinton's microdissections that parboiling might result in a more nutritious product because the preliminary steaming of rice grains "glued" the scutellum more firmly to the endosperm so that it would no longer be detached during the subsequent milling.[44] We will postpone a full discussion of the possible significance of this until chapter 11.

Dissection of the rice grain also showed that Eijkman's "silverskin" has several layers (Fig. 8.4). Fraser and Stanton had written as early

as 1913 that the outer layer (or "pericarp") of the skin was of little value, and that "it was the removal of the sub-pericarpal (or 'aleurone') layer which was harmful."[45] They had come to this conclusion from comparing the value for chickens of rice samples milled to varying extents and comparing the results with microscopic examinations of transverse sections of sample grains. They also believed that the virtue of "parboiled rice" was that the aleurone layer had become glued to the endosperm and was not removed in ordinary milling. Hinton was not able to separate the layers completely for individual analysis, but for the wheat grain he did find that the aleurone layer was by far the richest.

Even within the rice endosperm it appears that there is less of the vitamin in its core.[46] When samples of commercial white rice were passed through an experimental mill that abraded further thin layers, it was found, by analysis, that one-half of the thiamin was present in the outer layers comprising only 8 to 9 percent of its weight.[47] This does mean that when samples of white rice are compared, differences in thiamin content may be due to their degree of milling as much as to genetic or cultural differences.

MEAT, BEANS, AND OTHER VEGETABLES

It was estimated, as will be described later, that in the United States in 1940 the average daily intake of meat and fish combined was about 5 oz, or 140 g. Meat from the water buffalo, which Eijkman and Grijns had found was not a rich supplement to rice, contains about 0.06 mg thiamin/100 g, or 0.085 mg in 5 oz. Beef has been found to have about the same concentration, as has meat from sheep, goats, whales, horses, dogs, squirrels, moose, muskrats, opossums, and beavers.[48] Samples of meat from rabbits, deer, and caribou, however, have given values that are three to four times as high, and meat from pigs and raccoons is even higher, at some eight to ten times the value for beef. Organs such as liver and kidney show less species differences and in most cases have been found to contain 0.2 to 0.3 mg/100 g.[49]

Obviously, only the high value for pork is of much practical significance, but it is interesting that the comparative values for different species do not seem to fit any simple classification such as "ruminants" having lower values than "nonruminants," since dogs,

cattle, and horses are all in the same "low" group. The high values obtained with pork cannot be explained by some other factor distorting the chemical analysis; its special value had already been discovered from biological assays, before a method of chemical analysis had been developed.[50]

As one would expect, detailed studies of material from hog carcasses have shown that pure pig fat contains no thiamin. Commercial cuts have given values ranging from 1.0 mg/100 g for the leanest to 0.23 mg/100 g for extremely fat portions. The modern hog farmer attempts to produce lean carcasses, which obtain higher prices; in the past, however, before hydrogenated vegetable shortening was available, the ideal marketable pig was very fat and was valued as a source of lard as well as of meat, so that it would have had less thiamin. Interestingly, the traditional salting and smoking of pig meat to produce bacon and ham seems to cause relatively little loss of the vitamin. Cooking pork causes reductions in analytical values for thiamin—some 20 to 25 percent when thin slices are fried, and some 50 to 60 percent with other cooking methods.[51] However, this may be due in part to thiamin being "bound" and unextractable, although it is still nutritionally available, as judged by rat assays.[52] Pork has long been an important food in China, but it is considered "unclean" and is not eaten by Orthodox Jews or Muslims.

Poultry meat tends to contain a little more thiamin than beef, but not by much. Fish generally have given similar values to beef, with a tendency for the fatty fish (herring, sardine, etc.) to be lower, but salmon and trout (which are from the same family) and also oysters have yielded higher values, between 0.25 and 0.35 mg/100 g. Eggs are a poorer source, with only 0.06 mg/100 g (two large eggs), and this is all in the yolk; this seems surprising, since the egg is the sole food for the rapidly growing chick. Cow's milk, with about 0.04 mg/100 g (or 0.1 mg/cup), is also not a concentrated source of the vitamin, but because of the quantity consumed it can, as we will see, make an appreciable contribution to the total intake of thiamin in human diets.

We have already seen evidence of the high value of grain legumes, and analysis has confirmed this finding for all kinds of dry peas and beans, which have approximately 0.5 mg/100 g (or 1.2 mg/cup). Peanuts are particularly rich, at nearly 1.0 mg/100 g, but most of this

is lost when they are roasted. Other nuts have given values near 0.25 mg/100 g. There do not seem to be any outstandingly rich sources of thiamin among the nonleguminous vegetables and fruit, with values ranging from 0.03 to 0.16 mg/100 g.

The only highly concentrated source of thiamin, apart from the germ fraction of grains, is dried brewer's yeast, with 15 mg/100 g. Large doses of yeast can cause intestinal upsets, but 1 mg of thiamin is supplied by as little as 7 g, or about a tablespoonful. This applies only to killed yeast, since live yeast cells have been found not to release their thiamin in the digestive tract.[53] Marmite, a proprietary yeast extract that is high in salt and is popular in Britain as a savory spread on bread and butter, is also rich in thiamin, with about 3 mg/100 g, but the actual quantity used is again very small.[54]

THE THIAMIN IN MIXED DIETS

R. R. Williams and colleagues made some early estimates of the thiamin in an "average 1940 American diet."[55] Their calculations are simplified and summarized in Table 8.2. It is interesting to see their general conclusion that each of their four main food groups contributed a similar amount to the total. I have added a second set of estimates for the same diet but based on the more recent chemical analyses that have been collated by specialists at the U.S. Department of Agriculture.[56]

Since the 1940 diet is intended to be an average one, we can use a rough average for the different kinds of fish that would have been available at that time; similarly, we can assume that pork is "medium fat." Williams's values for the energy contributed by peas and beans show that they are the "green" (high-moisture) materials, with correspondingly lower values than for dry legumes.

It is interesting, and a little chastening, to see the differences between the two sets of estimates. In particular, I have estimated considerably higher intakes from pork and from potatoes. At the earlier date, fewer analyses had been reported for cooked foods, and the Williams group may have assumed greater losses of the vitamin than have now been found to occur.

It is interesting to see that anyone rejecting pork entirely in favor

Table 8.2 Estimates of thiamin present in a representative daily diet in the United States in 1940

	Weight (g)	*Energy (kcal)*	*Thiamin (mg)*	
			Original estimate	*New estimate*
White bread	260	680	0.122	0.148
Other cereals	36	119	0.053	0.029
Sugar	97	384	—	—
Group total		1,182	0.175	0.177
Pork (including bacon)	46	198	0.159	0.276
Other meats	77	154	0.021	0.062
Fish	20	14	0.010	0.020
Group total		366	0.190	0.358
Milk	365	222	0.124	0.146
Cheese	8	30	0.003	0.003
Eggs	34	48	0.023	0.034
Group total		300	0.150	0.183
Potatoes	138	100	0.057	0.121
Peas, beans	40	44	0.042	0.060
Other vegetables	171	87	0.044	0.103
Fruit	181	96	0.065	0.063
Group total		327	0.208	0.347
Fats and oils	40	319	—	—
Miscellaneous	4	28	0.001	0.001
Grand total		2,522	0.724	1.066

SOURCE: Data from Lane, Johnson, and Williams (1942).

of beef or poultry would apparently have lowered their overall thiamin intake by some 20 percent. On the other hand, if the same diet were eaten now, with white bread in the United States being compulsorily enriched with synthetic thiamin, it would have contained an additional 1.0 mg from this source alone.

Chapter 10 will return to a description of how researchers arrived at estimates of the thiamin requirements for a human population. But

for the moment we can take it that an individual needs about 1 mg per day. Since the original calculation for the 1940 diet gave a lower value, it is understandable that it gave rise to concern that people in the United States might be marginally deficient and "below par," even though they showed no specific symptoms of a vitamin deficiency.

In the next chapter I will consider examples of severe beriberi that have occurred where rice was not the staple, and even in institutions in the "developed world" of northern Europe and the United States.

CHAPTER 9

Beriberi without White Rice

Up to this point, a reader might reasonably conclude that beriberi had been associated only with diets based on white rice. But that would not be correct. The first Westerners who wrote of the disease were probably the Portuguese priests in the Molucca Islands in the sixteenth century, as mentioned at the beginning of chapter 3. And there is no doubt that the local staple food, which they themselves used, was not rice but sago meal. Father Viera wrote to his superior in Rome in 1559 that "the bread which is used here severely disturbs our constitution; it is made from the marrow of the sago palm. . . . frequent diseases among us are caused in great part by the lack of things needed to maintain human life."[1] The meal was prepared from material within the stem of the sago palm by mashing it with water and then sieving it so that the fine starch passed through and could be collected and dried. As mentioned earlier, sago meal contains little or no thiamin (Fig. 8.1), but it remained a staple in that area into the twentieth century.[2] Repeated reports of beriberi among the Moluccans were collected by early investigators.[3]

PROBLEMS OF FISHERMEN AND SAILORS

Labrador is on the northeastern coast of Canada, and, if one considers only inhabited areas, is about as far as one can get from Southeast Asia, the site of the beriberi outbreaks discussed in previous chapters. But it was here in 1904 that Dr. Cluny McPherson, the sole doctor at the Mission Hospital for Deep Sea Fishermen, had four men brought to him from a fishing vessel, in various stages of paralysis of the legs, but with no fever. One seemed critically ill and died of heart failure a few days later. McPherson wrote later: "I studied the cases thoroughly and the only diagnosis I could come up with was beriberi . . . but I felt it could hardly be correct." When his supervisor, Dr. Wilfred Grenfell, visited the hospital, this diagnosis was greeted with hoots

of laughter: "Where do you think you are, Mac, in Japan or Malaya? You should not let isolation distort your perspective."[4] Later, after he had reviewed the evidence, Grenfell apologized.

In fact, we can see from the literature that since 1880 there had been a number of reports of beriberi appearing in vessels engaged in fishing for cod off the Grand Banks in the North Atlantic.[5] One physician thought the most likely cause of the trouble was an infection from handling fish.[6] Another related it to the inadequate diet on some vessels.[7] However, it could have had nothing to do with rice, which was not used on these ships. I will return to the problems in this area later in the chapter.

Even earlier there had been many reports of beriberi occurring at sea, but in nearly all cases the outbreaks had occurred among Asians, who were eating diets already associated with the disease in their own countries.[8] However, this did not apply to the serious problem on Norwegian sailing ships, which seemed to arise only after the Norwegian government had, in 1895, ordered what it considered to be an improvement in the rations provided to the crews. Prior to that time, the men had normally received rye bread biscuits baked with yeast, and for dinner salt meat and peas. Since then they had been given soft bread, prepared on board by baking white flour with baking powder rather than yeast, dried potatoes, and at dinner canned meat or canned fish, with peas provided only once or twice a week. Beriberi had often broken out when men had consumed these rations for long periods, even when they had also been receiving lime juice.[9]

To learn more about the Dutch work in progress at that time, Axel Holst, a professor of hygiene and bacteriology in Norway's Christiana University, visited Grijns's laboratory in Batavia. There he saw the production of polyneuritis in fowls and returned home to continue similar studies in Norway. He tried first to use guinea pigs, reasoning that a mammalian species was closer to humans. With these he realized that the condition he had produced was analogous not to beriberi but to scurvy—an extremely important finding whose significance I have discussed elsewhere.[10] He then turned to using pigeons as the model species for beriberi and found that feeding white bread baked without yeast produced polyneuritis in his birds, whereas with rye bread they remained healthy.[11] This is in agreement with the findings in two other laboratories.[12] Holst, knowing that the Dutch in Indonesia had found other legumes to be effective in preventing both

polyneuritis and beriberi, recommended that the standard sailors' ration should include peas every day.[13] Later analyses were to confirm the high thiamin content of peas, and also that rye bread was a relatively good source of the vitamin.[14]

OUTBREAKS IN BRAZIL

Returning to the Tropics, there had been many reports of beriberi appearing as a new disease in Brazil in the 1880s, particularly in the Bahia area.[15] A professor at the French School of Naval Medicine presented two comprehensive reviews of physicians' reports of outbreaks of the disease there, and of their thoughts regarding its cause.[16] The descriptions of the disease agree closely with those from Japan, although they were too early to have been influenced by papers from that country. The authors were struck, as was the case elsewhere, by robust men seeming to be most at risk, and also people with sedentary work such as clerks and the "lettered classes." No race was exempt, but it seemed that immigrants had to have been in the country for several months before they were in danger of developing the condition. Children under fifteen were almost exempt, as were women except toward the end of pregnancy and when breast-feeding. Finally, several physicians commented on the importance of people with the first sign of the disease moving to a different part of the country or taking a voyage to Europe.[17]

Professor Féris refers to the belief of physicians elsewhere, and even some in Brazil, that the disease is the result of some sort of malnutrition, particularly as a result of the excessive use of rice.[18] He writes that, although beriberi was a problem in areas of Brazil where rice was a staple, it also existed in areas where little or none was eaten, and it had been particularly serious among soldiers who certainly received none in their rations. On the other hand, slaves, who one would expect to be the most poorly fed group, were not particularly prone to it. He concluded that "it is absolutely impossible to incriminate malnutrition when one sees that the wealthy are actually at the greatest risk."[19] He agreed with writers who had concluded that attacks were brought on by abrupt changes of temperature, for example, being chilled when wearing sweaty clothes. As in Japan, abuse of alcohol and sexual excess were also considered contributory causes. One physician attached importance to "the unnatural habit of having sexual

intercourse while standing up," on the basis of one patient having told him that his symptoms always felt worse afterward. Féris agreed about the predisposing influence of alcohol and quoted an old proverb: "Eating, drinking and the pleasures of Venus, all in moderation."[20]

In his enumeration of possible treatments, Féris makes no mention of changes in diet and, apart from changing place, he lists only the use of laxatives and diuretics. He refers to one doctor having used "blistering on parts of the spine, which he found to be helpful." This, of course, is similar to Japanese moxibustion, described in chapter 1, but Féris does not endorse it and warns against the danger of it leading to an infection. However, he does support the use of small doses of both strychnine and arsenic as stimulants.[21]

Féris says very little about the typical dietary pattern of beriberi sufferers. From other sources, however, one learns that the Bahia area, where beriberi was most serious, had most of its usable land turned over to sugar production by 1870 at the cost of mixed farming and cattle production. The typical diet was then characterized by cassava (also known as manioc or tapioca) meal, plantains (starchy bananas), imported salt cod and dried beef, together with molasses.[22] An Englishman working in northern Brazil in the 1800s commented: "Manioc is to Brazil what wheat is to Europeans and North Americans."[23] As indicated in the previous chapter, it is extremely low in thiamin. Raw cod is relatively rich, but only some 25 percent appears to survive the salting and drying. Then, prior to cooking, it has to be soaked for several days, which would leach out still more of the vitamin. All of the characteristic foods are therefore low in thiamin, and the appearance of beriberi is not unexpected. There are also comments that slaves actually had a better-than-average diet because they were allowed to cultivate small plots of their own, and grew a variety of vegetables that they, but not their masters, enjoyed.[24]

PHYSICIANS THEMSELVES AFFLICTED

Thirty years after the appearance of Féris's reviews, an American physician, Carl Lovelace, described his experiences as one of the doctors responsible for the health of the 5,000 men engaged, at any one time, on the five-year project of building a railroad through jungle country in northern Brazil.[25] Malaria and yellow fever were serious problems, but, in addition, nearly 1,000 workers were admitted to the

hospital with the diagnosis of beriberi in all its varieties. Six otherwise healthy American physicians, out of the thirty-six employed over the period, also contracted the disease (a proportion as high as for any other group concerned with the project), and yet they had typically limited their use of rice because of its bad reputation, and "lived on a full, protein-rich diet." The disease also affected a number of officers living "first class" on the company's riverboat. The period from July to December was "the beriberi season," and it seemed clear that some camps had a greater proportion of victims than did others.

In a second paper, Lovelace confirmed that he had read Fraser and Stanton's work and its confirmation in the Philippines, to the effect that replacing white rice with brown rice in the diets of laborers or soldiers in Southeast Asia would prevent outbreaks of the disease. Since the use of white rice could not explain the problem in Brazil, he suggested that a condition of "multiple neuritis" could be induced in a number of ways, and that the term "beriberi" really covered a group of diseases.[26]

Edward Vedder, whose work in the Philippines has already been discussed, quickly responded to this idea.[27] He pointed out that it had not been the conclusion from the Asian experiments that white rice positively induced beriberi: "Any other diet in which a deficiency of the proper vitamines exist will do as well." Further, the rice in this example was replaced with white flour, which had also failed to protect against polyneuritis in animal assays, and the animal protein came from dried or canned meat or fish, which would have lost most of its "vitamine." The only protective element in the diet, therefore, was beans, "and these were probably consumed in insufficient quantity to neutralize the great deficiency in the remainder of the ration."

Lovelace, meanwhile, had been succeeded by another physician who changed the diet of the railway workers by increasing the variety of fresh fruits and legumes, and replacing white rice and cassava flour with Irish and sweet potatoes. It was reported, after two years, that beriberi had virtually disappeared.[28]

OUTBREAKS IN WESTERN INSTITUTIONS

Vedder, in the same period, also criticized writers who had argued that earlier outbreaks of beriberi in prisons or mental hospitals in Europe or the United States could not possibly have been caused by any

problem in the diet.[29] Connolly Norman, for example, listed a number of reported outbreaks in mental hospitals in temperate climates, as a prelude to describing the outbreaks of beriberi from 1894 on, in the asylum in Dublin where he was the medical superintendent.[30] In three epidemic periods, over a five-year span, there were altogether 534 cases with 44 deaths. Very little rice was used in the kitchens, and the only change in the diet pattern before the outbreaks began was the introduction, for Friday dinners, of ling (fish of the cod family)—first the imported dried variety, and then the fresh fish. But this seemed irrelevant, since the epileptics did not receive it, and they had the highest incidence of the disease.[31] In a supplementary note, Norman gave more details about the regular diet, which included 8 oz of meat each day, potatoes for eight months of the year, other fresh vegetables, and a good quantity of bread. In response to criticism that the diet might be deficient in fat, some butter had recently been included, as well as fatter cuts of meat.[32] Norman felt that malnutrition could not be the cause of the problem, and that it was more likely to be related to the overcrowding and poor hygiene in this, as also in the other asylums where the disease had occurred.[33]

Another good description of a similar problem in this period came from the asylum in Tuscaloosa, Alabama, which had seventy-one cases in 1895 and 1896. Again, the highest incidence was among the epileptics (thirty-two out of a population of eighty). No case occurred among the six to seven hundred employed on the institute's farm, out of a total of twelve hundred inmates. Their diet was said to be plentiful, but with no excess of starchy food, and actually to have been improved prior to the first outbreak of the disease.[34]

The first serious outbreak, with twelve cases, occurred in November and December 1895, and the second, with fifty-eight cases, occurred in September and October 1896. Bondurant drew his readers' attention to each of these outbreaks having followed the dry season, when the usual supply of water from a local spring became inadequate. In these times supplementary water was drawn from a local river. In 1894 and 1895 a dam was being built below the point at which water was taken, and after that there had been little current in the river as the level slowly rose; thus the sewage flowing into the river between the drawing point and the dam could have drifted back and contaminated the water brought to the asylum. The relation over time be-

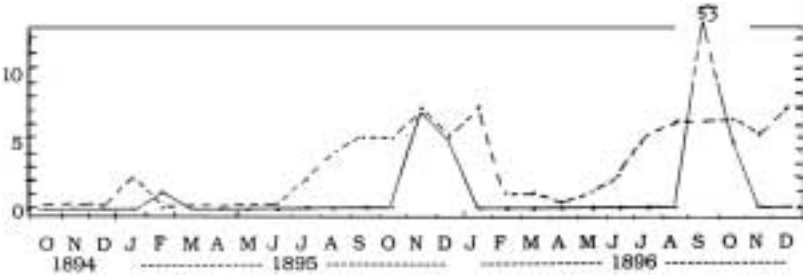


Fig. 9.1. Plot of the number of cases of beriberi appearing in the Tuscaloosa asylum (solid line) and the number of times the hospital tank was filled with river water that may have been contaminated with sewage, month by month (dashed line) (Bondurant, 1897).

tween the use of river water and the incidence of beriberi was plotted by Bondurant (Fig. 9.1). Since there was also an increase in cases of malaria in the asylum after the construction of the dam had begun, he considered it reasonable to conclude that "the exciting cause of the disease developed in the recently dammed up river"; the disease had not developed in the nearby town because "the toxicity of the active factor was only sufficient to cause the disease in those most prone to it—the inactive epileptics and other degenerates who alone supplied the material for the development of the malady."[35] One feels that if Bondurant's ideas had been confirmed by the experience of others, his well-argued paper would have become a classic.

Vedder, commenting in a general way on the reports stating that institutional diets were always satisfactory, wrote that no medical superintendent would ever write that a dietary for which he had some responsibility could be inadequate. Further, although white flour and potatoes were often interchangeable, according to the season, as important sources of energy in the diets, it was only potatoes that were antineuritic.[36] Also, one wonders whether seriously disturbed patients always ate everything in the dietary, or were even offered all the available foods.

THE DISEASE IN THE BRITISH ARMY

The next outbreak of "beriberi without rice" to receive detailed attention occurred among British troops operating in Iraq (then called

Mesopotamia) in 1916–17 during World War I. It was at first thought that the symptoms were the result of an infection because the rations issued were essentially the same as those issued to other army units whose members remained in good health. On more detailed examination, however, it was discovered that the oatmeal issued to the affected units had contained weevils and been discarded. Further, it was reported that the water available for cooking was so "hard" that lentils boiled in it never became soft and were also discarded, and it took five hours of cooking to prepare a stew of meat and potatoes—long enough, it was thought, for destruction of the vitamin originally present. Finally, the bread issue was made from white flour.[37]

After consultation among the army physicians, the troops were supplied with water from a different river and were given an extract of yeast each day; also a proportion of whole wheat flour was used for making their bread. The problem then disappeared. The conclusion therefore was that the primary cause of beriberi was a deficient diet, although a high incidence of both malaria and dysentery among the troops was probably a contributory cause.[38]

INVESTIGATIONS IN NEWFOUNDLAND

In the late 1920s attention returned to Labrador and Newfoundland, where it appeared that there had long been, and still were, serious problems of vitamin deficiencies among the families living on these coasts as well as among those fishing at sea (Fig. 9.2). As early as 1912, a physician who had been working in northern Newfoundland for five years reported that he had found beriberi to be a common problem in springtime among poor people who had been reduced by the end of winter to a diet of "bread and tea." In the previous summer and autumn they had bartered their catches of fish for a six-month supply of food—mostly white flour and molasses. According to the physician,

> The harsh conditions of life make it difficult to grow potatoes or green vegetables, and game is scarce. The problem may begin with tingling in the legs and arms; then, if the subject's diet is not improved, it can advance to paralysis. . . . But the same patient put on a diet of whole wheat flour, beans and peas, will get perfectly well in two months. . . . The "old stagers" of this country, who remember the days when "brown flour" was the diet staple, say this problem was unknown among them.[39]

Fig. 9.2. An isolated "outport" in Newfoundland that is frozen in during the winter months (Williams-Waterman Fund, 1950; courtesy of Research Corporation).

Wallace Aykroyd has already been mentioned in an earlier chapter in connection with his later work on nutritional problems in India, but his earliest contact with deficiency conditions took place in Newfoundland. On his first tour of duty there as a house surgeon, he organized the successful treatment of night blindness with cod liver oil.[40] It seems ironic that vitamin A deficiency could have occurred among fishing folk who could prepare a rich source of this material for themselves from the cod they caught.[41]

After a period of work on B vitamins in London, Aykroyd returned to Newfoundland on a research fellowship that enabled him to concentrate on the beriberi problem.[42] He confirmed the earlier observation that the disease was related to poverty. For example, the records showed that in 1916 and 1917, when there was relative prosperity because the price obtained for fish catches was high, only 1.2 percent of the patient admissions to Saint Anthony's Hospital were for beriberi, whereas the corresponding figure for the previous two years had been 6.2 percent.[43] Three-quarters of the patients had come in April, May, and June.

Aykroyd was able to obtain fairly good data for the winter diets of

Table 9.1 Estimates of the median daily food and thiamin intakes during winter of adults in families in Newfoundland where at least one person developed beriberi

	g	*Kcal*	*Thiamin (mg)*
White flour, biscuit	513	1,872	0.560 (0.280)[a]
Salt beef and pork	72	183	0.225 (0.122)[a]
Salt fish	134	185	—
Fresh game	24	36	0.015
Margarine	22	160	—
Molasses	27	64	0.020
Sugar	5	20	—
Dry beans and peas	26	87	0.115
Cranberries	125	65	0.050
Total		2,628	0.985 (0.602)[a]

SOURCE: The food intake data are taken from Aykroyd (1930). The thiamin intakes have been calculated using current analyses.

[a]Alternative estimates assuming that much of the flour was cooked with baking powder and lost most of its thiamin, and that only one-fourth (instead of one-half) of the meat was pork.

families in which at least one member had developed beriberi. This was possible because, as indicated earlier, each autumn the families living in the "outports" had to calculate how much they needed to buy in bulk before winter set in and the bays froze, so that no further supplies would be available. The supplies still consisted mainly of white flour, salt beef and pork, salt fish, margarine, and molasses, together in some cases with beans and peas. Apparently they did not have yeast for baking. Table 9.1 sets out median values from the data collected by Aykroyd for thirteen such families and converted to "supplies per adult per day," with children from one to nine years old counted as "half an adult." He also had to make estimates of the small amount of game that some of the families had obtained and any consumption of vegetables. However, most of the families in the group had no fresh vegetables, so they do not appear in the table; nor did any of them have milk.

To the original data, I have added literature values for the thiamin content of each type of food, and then estimated an individual's overall daily intake of thiamin from such a diet. The result depends greatly on two estimates. The first is the proportion of what Aykroyd listed as "salt beef and pork" that was actually pork, since this is now

known to be so much richer than beef in thiamin, as discussed in chapter 8. The second is the proportion of the flour cooked with baking soda and/or baking powder rather than with yeast, because the former has been reported to cause destruction of most of the vitamin, particularly when there is no sour milk to add to the mix, which becomes alkaline during the cooking. This was observed first in assays of white bread with pigeons and rats.[44] Then the effect was studied in detail using chemical analyses and a variety of baking conditions: as expected, the destruction was greatest when the product was alkaline at the end of the baking period.[45]

At least some of the families are likely to have had mainly bread with very low thiamin content and to have eaten relatively little pork, so that their intake would have been only one-half of that estimated for the average U.S. diet in 1940, that was considered in the previous chapter.

In resurveys of families in Newfoundland in 1948, there was much less evidence of even mild indications of beriberi. This was attributed to the supply of white flour having been fortified since 1946 with three B vitamins (thiamin, riboflavin, and niacin).[46]

EPIDEMIC DROPSY

This condition was confined to parts of India and to Indians living abroad. It was characterized by edema starting in the legs, together with a skin rash and fever.[47] Since beriberi itself was accepted as taking different forms— "wet" or "dry"—many physicians regarded epidemic dropsy as yet another form of beriberi.[48] This made it more difficult for workers in India to accept the idea that beriberi was always explained by the deficiency of a diet based on polished rice. First, epidemic dropsy occurred among people eating parboiled rice, and, second, there would be a sudden epidemic in an area, after a period of years with no cases, and with no evidence of any change in the local diet prior to the epidemic.

One line of thought sprang from the disease seeming to appear only among Bengalis, because one special characteristic of their traditional diet was that they used mustard oil for cooking, whereas other Indian groups preferred oils such as sesame and coconut. Could it be that some merchants were adulterating mustard oil with a small proportion of a cheaper mineral oil? This led investigators to run chemical

tests on batches of oil in households where the disease had broken out. And in fact, although no mineral oil was found, some color reactions were given by the suspect oils that were not given by pure samples.[49]

The seeds being crushed to produce the oil were then examined, and it was found that among the black mustard seeds were some slightly different ones that were identified as coming from a weed, *Argemone mexicana*, a kind of poppy, that had come originally from the New World and was now proliferating in India. The addition was thought to have been a deliberate adulteration by farmers, since the weed produced seeds at a different time of the year than the mustard plant.[50] At any rate, tests with both animals and human volunteers showed this plant's oil to be highly toxic, producing the characteristics of epidemic dropsy; the active agent was found to be sanguinarine, a known toxic alkaloid.[51]

The successful elucidation of this disease removed one complication for students of beriberi in India. It also confirmed that people who had formed theories explaining beriberi in terms of some kind of "toxin" had a not unreasonable idea, since another similar disease could now be explained on this basis.

ANTIVITAMINS IN FOODS

New problems that lead ultimately to new knowledge can arise in unexpected places. In the spring of 1932, J. R. Chastek had been successfully rearing foxes for their fur at a number of ranches in a rural area some twenty-five miles west of Minneapolis, Minnesota, when a strange disease broke out at the same time at each location. The animals began to lose their appetite, then to move stiffly; finally, they were unable to move at all, except for having convulsions just before they died. Young pups, suckling their mothers, died even more quickly. Autopsies of adult animals showed abnormal hearts and changes in the central nervous system.[52]

The same disease then began to appear, or to be recognized, on other fox farms in the United States and Scandinavia, and was named "Chastek paralysis." The reader will have guessed by now, in view of its inclusion here, that this illness would turn out to be another form of thiamin deficiency.

But why was it occurring? The specialist breeders knew that furs of good quality could be obtained only by using high-quality diets

rich in protein. Chastek, like others, had been using mostly frozen horse meat and a small proportion of frozen fish, together with cereals, carrots, and small amounts of liver and cod liver oil; they were ground in a mill to a homogeneous mix from which the foxes could not pick and choose.

The only change in his mix prior to the outbreak had been an increase in the fish content of the mix from 7 to 20 percent, using whole freshwater carp that had been frozen soon after being caught. When Chastek reverted to his previous mix, the epidemic died down, but when a few new animals were tested with the higher level of fish they, too, developed the disease. The other outbreaks were also associated with diets containing a high level of fish. Second, because of the nervous changes in the animals, some received injections of thiamin and recovered.[53] In 1943 these observations were discussed in the *New England Journal of Medicine,* and it was suggested, in view of so many poor diets in Southeast Asia including fish as well as rice, that the fish might be equally responsible for the endemic beriberi in the area.[54]

With more years of research the source of the problem was narrowed down. A considerable proportion of freshwater fish and a few marine species were found to contain an enzyme, now named "thiaminase," that split (or hydrolyzed) the thiamin molecules into their two ring structures, just as sulphite was known to do. This enzyme was present in the viscera (especially the intestine and spleen) of the fish but not in the muscle (i.e., the fillets). It was inactivated by cooking and also by pepsin (a protein-splitting enzyme) present in both animal and human stomachs.[55] It appeared, therefore, that the thiamin contributed by the other items in the mixed fox diets was being destroyed during the preparation of the wet, homogenized mix and its subsequent shipping to the individual ranches prior to its consumption. This combination of conditions is unlikely to be encountered in human dietaries—we normally do not pregrind fish and store it mixed with other foods; we also usually take only fish muscle, and eat it cooked. In further trials with foxes it was found that if fish was consumed on alternate days with a nonfish mix,[56] the disease did not develop. This was consistent with the "antithiamin" constituent not being absorbed into the tissues.

A similar problem was found to occur in cats that had been fed exclusively on a canned commercial food that was manufactured from a mix of whole raw fish (of different species) ground up with cereals,

and then autoclaved in cans. The thiamin present initially was thought to have been destroyed during the period between the mixing and the canning.[57]

Although the final conclusion had been that fish thiaminase was almost certainly not a practical problem for humans, its discovery triggered a search for possible antithiamin factors in every kind of food. One of the first findings was that the well-known condition of "bracken poisoning" or "staggers" in horses, as a result of eating the green fern *Pteridium aquilium,* was also a condition of thiamin deficiency. As with the raw fish, a thiaminase enzyme was obtained from the fronds. Raw fronds were found to produce thiamin deficiency in rats also, but cooked bracken proved to be harmless.[58]

At the same time Japanese scientists reported the discovery of bacteria in some human feces that had thiaminase activity.[59] There was concern that the presence of such bacteria might be another factor contributing to the occurrence of beriberi in Japan.[60] However, thiamin present in foods consumed in a meal is normally absorbed in the small intestine, and only undigested food residues then move into the large intestine, where gut bacteria reside. Further studies failed to show an increased risk of beriberi in subjects from whom thiaminase bacteria could be cultivated.[61]

HEAT-STABLE ANTITHIAMINS?

Although thiaminases did not seem to be a practical problem for humans since they occurred only in foods that are normally eaten after being cooked, investigators began to look in foods for the possible presence of heat-stable compounds with antithiamin activity. What they found was that adding thiamin to even heated extracts from many plants resulted in much of the thiamin failing to be found on subsequent analysis of the mixtures by the thiochrome method.[62] Such results, even with tea, coffee, and betel nuts, which some Asians were addicted to chewing, led experimenters to hypothesize that these things might precipitate thiamin deficiency even when the diet would otherwise be adequate.[63]

Fractionation of the extracts showed that the chemicals responsible for the effect were usually caffeic acid or other compounds of the same type (polyphenols). However, it was discovered that the main mechanisms were (1) the conversion of thiamin to thiamin disulfide,

that was reconverted when eaten and absorbed, back into thiamin, and (2) the effect of the polyphenols in blocking the oxidation step required in the thiochrome procedure, so that even thiamin still present in the mixture was not being measured. Rat growth assays showed no loss of biological activity of thiamin when it was mixed with these extracts.[64]

The investigations occupied several workers for many years. It seems particularly unfortunate, therefore, that an Indian paper published in 1950 that fully described the problems affecting the thiochrome procedure in the presence of plant extracts seems to have been ignored for ten to fifteen years, while the problem was reinvestigated in laboratories in the Western world.[65]

Comparable studies with heat-stable fractions of meat and fish that had been reported, on the basis of chemical analyses, to block thiamin were also found finally not to result in any significant loss of bioavailable thiamin.[66] It appeared unlikely, therefore, that antivitamins would be a significant factor in producing thiamin deficiency in humans. The preceding conclusion applied only to naturally occurring materials. Chemists have succeeded in synthesizing molecules with slight differences from thiamin that block the action of the vitamin, and rapidly produce a deficiency condition in animals. Two such molecules are described in Appendix B, together with a description of the "allithiamin" molecules that have some advantages over thiamin itself as nutritional supplements.

CHRONIC ALCOHOLISM

A proportion of chronic alcoholics have long been known to develop a neuritis, which remains even when the subject is not actually intoxicated. This condition usually affects the feet and legs first, and the descriptions of it follow almost exactly those of the early signs of beriberi. Indeed, a physician who had returned to a general hospital in England after having spent some time in China expressed the opinion in 1890 that it was impossible to distinguish the two conditions.[67] In 1901, Hamilton Wright wrote from Malaya that "the peripheral neuritis of alcoholism in so many respects resembles beri-beric neuritis."[68] In the following year, Manson, in a lecture review of beriberi (referred to in chapter 4), commented that "clinically, beriberi is a multiple peripheral neuritis . . . but peripheral neuritis is a symptom rather than

a disease. . . . undoubtedly there are cases arising from alcohol . . . and from tin and arsenic as well as from organic poisons."[69]

The first person to suggest that polyneuritis among alcoholics might actually be beriberi was George Shattuck of the Harvard Medical School in 1928.[70] He based his suggestion on the likelihood that alcoholics were "failing to take or to assimilate food containing a sufficient quantity of vitamin B."[71] Four years later a Swiss physician suggested that the disorders seen in alcoholics appeared to be a combination of pellagra and beriberi, and were caused by a deficient intake of vitamin B.[72]

In 1933 another Harvard group reported the results of feeding forty such patients on a diet abundantly rich in vitamins and minerals. They wrote that they had no objective "yardstick" by which to measure results, but it was their "distinct impression that under this regime recovery has been observed more uniformly and with greater rapidity than previously." They concluded, because of the symptoms, that vitamin B_1 was particularly important.[73]

In 1935 another Harvard physician wrote that he had persuaded ten hospitalized patients to eat a diet rich in vitamins by saying that this was the condition for their continuing to receive their usual daily alcohol intake, 1 pint to 1 quart (475–950 ml) of whiskey. After nine weeks all participants were essentially normal, except for the mental state in two subjects that was only "improved." The physician concluded that alcohol could not be directly responsible for the neuritis, which was actually caused by dietary deficiency.[74]

In 1936 a group working in New York reported that they had been able to obtain reasonably good dietary records for forty-two alcohol addicts. They found that every one of the twenty-six with neuritis had apparently had a diet inadequate in vitamin B_1, while the remainder, who were free of neuritis, had all had an adequate intake. This group also concluded that "alcohol has no direct toxic action on the peripheral nerves, and polyneuritis in the alcohol addict is due to vitamin B deficiency."[75] In a further paper the same group reported the results of treating their subjects; one did not respond even to high doses of the vitamin, and it was thought possible that "her pathological changes had advanced so far as to be irreversible," but most showed rapid improvement when given four times the normal requirement of vitamin B_1, while those given only the bare requirement showed little change.[76] To jump ahead for a moment, it was reported

later that alcoholics also showed an impaired ability to absorb thiamin from the small intestine so that, of a 4-mg dose, for example, only 1 mg might be absorbed.[77]

In a longer study in New York, 520 subjects with polyneuritis were treated with 3 to 10 mg thiamin per day. Sixty-one percent of the subjects became symptom-free, 36 percent were partially improved, and 3 percent were unimproved. On average it took three weeks for improvement to be seen. After the thiamin supplements ceased, their beneficial effects continued only for a period. By one year after their stoppage, 50 percent of the patients had lost all or part of their relief, but 90 percent of them responded again to a further treatment with thiamin. The author did not say specifically that the subjects were alcoholics but in his introduction wrote: "In the West, the ever present group of alcoholics afforded ample material for study of the same clinical entity [polyneuritis]."[78]

Another study used the records of Boston City Hospital to compare how long alcoholics with polyneuritis were kept in the hospital in the period 1920–29, when they had received just the ordinary hospital diet, with their stays in the period 1930–38, when they also received vitamin supplements. There was no difference. The author judged that the interns in charge of the wards in each period would have used the same criterion for the patients' release (that they could walk unaided) and concluded, understandably, that vitamin supplements constituted an unnecessary expense.[79] However, the vitamin supplements consisted of fruit juice, eggnog, salads, cod liver oil, and yeast tablets. Only the last item would have been a rich source of thiamin, and even that would have been largely unavailable if the yeast were "live." The results therefore cannot be said to contradict the other reports of benefits from administering high doses of thiamin.

In 1937 a third Harvard group posed a rhetorical question: "If alcoholic polyneuritis . . . is related to a deficiency of vitamin B_1, why is it not associated with . . . cardiovascular dysfunctions such as occur in patients with beriberi in other parts of the world?" The authors' own reply was that they had indeed found such cases—"within a period of two years we have personally studied 35 patients from a total of over 5,000 hospital admissions." The condition of these patients corresponded to the descriptions of cardiac beriberi in the Orient, as did the response to large doses (up to 50 mg) of thiamin.[80] Over the following thirty-five years, a number of papers reported similar cases

among alcoholics in different parts of the United States, Europe, and Australia, all confirming the benefits from large doses of thiamin.[81]

Several authors have emphasized that heart problems in alcoholics can have different characteristics from those seen in the Oriental *shoshin* condition, perhaps as a consequence of direct damage to the heart muscle from alcohol, combined with a thiamin deficiency. They advised that thiamin should be administered as a routine "to any patient in whom heart failure is present without clear evidence of cause."[82]

Another condition seen in a small proportion (around 3 percent) of chronic alcoholics was a brain disorder known as Wernicke's encephalopathy after the first person to have described it in 1881. Among its characteristics were an inability to control movement of the eyeballs (ophthalmoplegia and nystagmus), drowsiness, disorientation, and a staggering walk (ataxia). Many individuals with this condition died, and, on autopsy, characteristic changes were seen in specific portions of the brain.[83] The disorder sometimes leads to memory loss and a psychological state known as Korsakoff's psychosis. Because of this, some writers refer to a combined Wernicke-Korsakoff syndrome.[84]

In 1940 a Harvard neurologist reported that he had found changes in the brains of vitamin B_1-deficient pigeons that corresponded to those found in alcoholics who had died of Wernicke's disease.[85] This observation led naturally to the idea that the disease in humans might also be the consequence of a thiamin deficiency. In the following year a New York group, which had previously worked with neuritic patients, studied twenty-seven cases of Wernicke's disease. They reported that eye movement rapidly returned to normal after thiamin dosage, but it was less certain that there was a response to the mental changes.[86] In further studies of similar patients, thiamin again produced rapid correction of eye problems and the staggering gait in most subjects. The patients who did not respond well seemed to have complications caused by liver disease.[87]

Wernicke's disease does not seem to have been seen in cases of beriberi associated with polished rice consumption in Asia. It could therefore seem to occur in humans only as the result of a combination of alcohol poisoning and thiamin deficiency, but it has now been found to occur in other situations also.

INTRAVENOUS FEEDING AND SEMISTARVATION

"Total parenteral nutrition" (TPN) is the term used for supplying all of an individual's nutritional requirements by intravenous infusion when he or she is not able to take in, or digest, food by mouth. Obviously, for maintenance over a long period, this means supplying the full range of vitamins and minerals, as well as protein, essential fatty acids, and energy. However, when someone needs nourishment for only a few days—as after gastrointestinal surgery—it has been customary for the infusion to be limited to glucose, amino acids, and major minerals.

Sometimes this kind of nutritional infusion has continued for longer than originally expected, and the need for trace nutrient supplements has been overlooked. In 1975 a fourteen-year-old boy who had been nourished in this way for four weeks became somnolent and showed changes in eye movement characteristic of Wernicke's disease. Treatment with 20 mg thiamin per day was then started. Within two days eye mobility and consciousness improved, and after a week the boy's staggering gait was improving and his eyes and speech were normal.[88] Similar experiences have been reported from Germany, Australia, and various parts of the United States. It is also clear now that some patients died before their thiamin deficiency was recognized.[89]

The TPN conditions described here involved, in almost every case, absolutely no thiamin intake, in contrast to the merely low intake on diets containing mostly polished rice. Another condition of zero intake was the use of starvation for the correction of extreme obesity. In 1965 a thirty-five-year-old man weighing 335 pounds, but with no medical abnormalities other than shortness of breath, had apparently been consuming some 6,000 kcal per day. He volunteered to take part in a study in a metabolic ward and for four weeks received a 500-kcal diet (without vitamin supplements) and for the next four weeks received only water, plus a potassium supplement. Then, because he was feeling nauseated, he was given 90 g glucose per day for a week. He developed double vision and then became lethargic, confused, and irritable. But two hours after receiving a first injection of 400 mg thiamin, he was sitting up and enjoying a meal, and the next day he was

completely alert and oriented. In four more obese patients starved for one or more months, no such evidence of a thiamin deficiency was observed. However, the authors concluded that one could not rely on the "wasting" of tissues always releasing enough thiamin during starvation, and that in the future ample vitamin supplementation should be provided during starvation.[90]

The usual signs of Wernicke's disease have also appeared in nonobese patients who fasted voluntarily for long periods. One was a baptist pastor in Singapore who fasted for six weeks for spiritual reasons. During the final week his speech was no longer rational, and he was then admitted to hospital only partly conscious. Within a day of being injected with thiamin, he regained consciousness and could answer questions.[91] In Denmark a prisoner went on hunger strike for seven weeks, except for occasional cups of tea with sugar. At the end of this time he was fed by stomach tube, but he vomited and was disoriented, with limited eye movement, and he was unable to walk. After receiving vitamin therapy, he was able and willing to eat, and his eye movements became normal.[92]

Unintended virtual starvation can also occur when people suffer for a long period from repeated vomiting, sometimes described as "being unable to keep food down," often as a side effect of pregnancy. In 1933 I. S. Wechsler, working in New York, suggested that the polyneuritis often found in such people could be the consequence of a lack of vitamins, rather than of an infection, although at that time he could not point to lack of any particular vitamin.[93]

In 1939 two physicians at the Mayo Clinic pointed out that cases of Wernicke's disease were seen in people who had suffered from repeated vomiting, referring both to the earlier literature and to their own experience. They added, without giving details, that "large doses of vitamins B and C have effected a cure of this condition in some of our cases."[94]

In the same year a paper from Scotland also drew attention to Wernicke's disease, accompanied by polyneuritis, not being found only in alcoholics; it suggested that the nonalcoholic patients all had some kind of gastric disease or "pregnancy vomiting." The authors suggested that the patients were primarily deficient in thiamin, and in their next paper they described the successful treatment of the condition with the vitamin.[95] On the other hand, it was reported from Germany that ten patients with Wernicke's encephalopathy showed no

improvement when treated with high doses of thiamin, nor did chemical tests before treatment started indicate that the patients were deficient in this vitamin. The authors concluded that the disorder was not always to be explained as a deficiency of thiamin.[96]

THE FUNCTIONS OF THIAMIN RECONSIDERED

The findings in thiamin deficiency just reviewed are in contrast to the early reports of avian polyneuritis, where Eijkman had concluded that the disorder was explained by degeneration of peripheral nerves, apparently without any significant damage to the central nervous system. Nevertheless, in later work, neurologists reported finding abnormalities in the brains of thiamin-deficient cats, foxes, monkeys, and pigeons that corresponded to those seen in Wernicke's disease.[97]

In the 1930s the effect in rats of a diet specifically deficient in thiamin was described as follows: "about the 28th to 40th day . . . incoordination in the movements of the hind legs, . . . palsied shaking or bobbing of the head, . . . apparent blindness, . . . finally intermittent convulsive seizures" and then death. On autopsy, hemorrhages and generalized congestion were observed in the brain. Some blackened material was seen in the nerves of deficient rats (stained by the method used by Eijkman as seen in Fig. 3.2) but no more than in control groups. The experimenters wrote that "in sharp contrast with the negative findings in the peripheral nerves are the definite changes found in the central nervous system." A control group given each day the same amount of food as was eaten by the deficient rats lost the same amount of weight but showed none of the nervous signs.[98]

The evidence from animal experiments now all seemed to point to the primary disturbance in severe deficiency being in the central nervous system. It seemed as if it was only in mild deficiency, with enough thiamin available for the central nervous system, that there was a gradual degeneration in peripheral nerves, as seen in Asian cases of beriberi.[99]

The correction of the head retraction in pigeons within an hour or so of their receiving a source of thiamin was much too rapid to be explained by the regeneration of nerves, as was the recovery of eye movement in Wernicke's encephalopathy. Thiamin's role here would seem therefore to relate to function rather than structure.[100] The same would have to be said for the rapid recovery of heart func-

tion in patients at death's door with *shosin* beriberi, when injected with thiamin.[101]

Beginning in the 1920s, biochemical studies began to reveal that at any rate one function of thiamin was to act as an essential part of some enzymes required for the utilization of energy from carbohydrates. This was an important discovery because there had previously been no evidence to explain how vitamins, needed in such microscopic quantities, might actually function in the body. Despite the importance of the work, it is presented in Appendix B rather than here so that readers with no background in biological chemistry will not be put off. Some of the immediate practical uses of this knowledge will be illustrated in the following chapter.

CHAPTER 10

How Much Thiamin Do We Need?

Anyone trying to evaluate a diet for its nutritional adequacy needs to know how much it contains of the individual nutrients and whether these amounts meet the requirement in each case. We do not ordinarily think of this matter in relation to our habitual diets, but it would become obvious if, say, we were to be responsible for devising dehydrated rations for people going on a sledding expedition in Arctic regions. We would clearly need a standard that would be adequate not just for the average person but also for those who had above-average requirements. And how far might needs differ according to race, age, sex, and other factors?

RACIAL DIFFERENCES AMONG HUMANS?

As noted in chapter 1, the first Western physicians studying beriberi in Japan thought that its not being seen among European residents indicated a racial difference in susceptibility, either genetic or because of behavioral differences such as avoiding the Japanese practice of squatting with their weight pressing on their lower legs. This belief was weakened by the increasing evidence of a dietary explanation for the disease, combined with the fact that Europeans living in the East were largely able to afford their own traditional type of diet. In addition, a small number of cases had occurred among European sailors in the Dutch East Indian navy. Also, in Louisiana, a group of farmers of French descent who had adopted intensive rice farming developed beriberi, with the typical signs described in Asia. Apparently, after their harvest had been milled, they took home a portion as white rice and lived on that, fried with bacon fat, as almost their sole food for several months; this was the season when their "disease of the legs" appeared.[1]

The situation of Europeans in Asia was totally changed for those taken as prisoners of war by the Japanese in World War II. They were

now suddenly at the bottom rung of the social ladder and were restricted to a diet of white rice and little else for a long period. Many years earlier, Fraser and Stanton had concluded from their studies with Malaysian laborers that it took some ninety days on a "white rice" diet before beriberi symptoms appeared.[2] Interestingly, it was exactly at this time that the first cases of wet beriberi began to appear in British civilians who had been put into an internment camp in Hong Kong (Fig. 10.1). In the following four months the condition appeared in over two hundred inmates—or about 9 percent of those interned. It seemed certain that the edema was the result of thiamin deficiency in these cases, since administering the small amount of thiamin originally available relieved the condition in those to whom it was given in doses of 3 mg every other day.[3]

In the same camp there were also thirty cases of "dry" or "neuritic" beriberi, with loss of feeling and partial paralysis in the legs. Response to thiamin injections was slow, as had been the general experience with Asian patients. It was also felt that patients responded better to a mixture of B vitamins than to thiamin alone, indicating a multiple vitamin deficiency. And certainly there were direct indications of riboflavin deficiency in many inmates.[4]

Another set of careful records was maintained by the physicians in the Australian army group imprisoned in the Changi camp on Singapore Island. Edema was a common problem, but, because the response to supplements of corned beef (used as a source of extra protein) was much greater than to supplements of rice polishings (used as a source of thiamin), it was concluded that the edema was mainly the result of protein deficiency, combined with an overall caloric deficiency, so that even dietary protein was being used as an additional source of energy.[5]

However, in the same camp, 130 cases were diagnosed, because of the accompanying signs, as being true "wet" beriberi, and a further 135 cases were diagnosed as neuritic beriberi: "presenting the classical picture of a symmetrical neuritis of the lower limbs . . . disorders of sensation were the rule." There were also sudden deaths from cardiac beriberi.[6]

The U.S. soldiers imprisoned in the Philippines also suffered from extremely limited diets, supplying a total of 900 to 2,000 kcal per day and less than 30 g protein in the worst periods. Edema was extremely common but was again diagnosed as being mainly the result of a pro-

Fig. 10.1. Wet beriberi in European civilians interned in Hong Kong during World War II (Smith, 1947; courtesy of Nutrition Society).

tein deficiency.[7] One difference from the Australians' diet was that the rice issued to the U.S. prisoners was only partially milled, so that about half of the silverskin had remained attached to the grains. This was probably a long-term effect of U.S. government projects, begun twenty-five years earlier, to develop such a milling procedure in the Philippines for the standard rice issued to government employees (as

described in chapter 5). At any rate, less than 2 percent of the men in the camps developed neuritic beriberi characterized by motor paralysis of the feet.[8]

In contrast, over 75 percent of the men reported a condition of "painful feet," with extreme tenderness and "burning pain." About one-half of these subjects also had severely diminished vision and an enlarged blind spot. The author of the report quoted here classified these cases as beriberi but acknowledged that "the results of therapeutic tests were inconclusive."[9] One group of ninety-six prisoners with severe "painful feet" syndrome was selected for intensive study by a Japanese doctor and was given different treatments for a three-week period. The twelve men who received daily injections of 20 mg thiamin showed no improvement over the next two months as compared with men receiving only a placebo. Those who received a full range of vitamins and liver extract finally showed a slightly greater improvement. All the prisoners continued to receive their inadequate diet, contributing about 1,600 kcal, during the study.[10]

An apparently identical "painful feet" syndrome was seen in five hundred men of the British military group imprisoned in Singapore; no treatment was universally effective, but injections of nicotinamide, followed by supplements of rice polishings, were the most helpful.[11] The cause of the condition remains a mystery, as does the "burning foot" syndrome that was seen in Spain during the civil war a few years earlier.[12]

VARIATIONS IN DEFICIENCY SYMPTOMS

There are many other reports of disease patterns among prisoners of war at this time. But the selections given here should suffice to demonstrate that, on a white rice diet, beriberi appears as quickly and as seriously in people of European descent as it does in others. On the other hand, it remains difficult to understand the striking individual differences. As physicians who worked in the camps have written: "The uniformity of environment, work, diet and even of type of individual in the camps, emphasized the mystery. . . . why, of a group of apparently similar men, on diets similarly deficient in vitamin B_1, one should get neuritis, another edema, a third should die suddenly of heart failure, and a fourth be apparently well, cannot as yet be explained."[13]

In trials in Java and Malaya with Asian laborers, as described in earlier chapters, there had been similar findings, that is, that only a proportion of the subjects on a white rice diet developed the disease. There was less attention then as to why the remainder remained healthy—perhaps because the trials were of relatively short duration, and the subjects were from varied backgrounds. Sometimes the appearance of beriberi has been related to a previous stress. Thus, in Hong Kong 55 percent of the prisoners with dysentery went on to develop beriberi.[14] On the other hand, it was a common comment in studies reported in chapters 1 and 4 that *robust* men were the most susceptible.

Of the four hundred cases diagnosed as beriberi in the military camp on Singapore Island, fifty-two were confirmed as showing Wernicke's encephalopathy.[15] There was, of course, no alcohol at the camp. Forty-five of the fifty-two cases appeared after protracted attacks of dysentery, with three weeks or more without solid food. Three more men had difficulty in eating rice as the staple food, and the remaining four had had long-standing infections.[16] The physicians at the camp concluded that Wernicke's disease appeared as the result of a sudden, acute depletion of thiamin.[17]

The first symptom in this group was typically loss of appetite, followed by vomiting and then nystagmus (uncontrolled jerky movements of the eyeballs) and double vision. In many cases there was no other sign of beriberi at this time. Of the fifty-two patients studied in detail, twenty-one died, and the remainder recovered after treatment with thiamin in various forms. The term "cerebral beriberi" was coined to describe the condition. A further set of some 130 men were treated with thiamin when they first showed any indication of nystagmus, and they recovered without further investigation.[18]

EXPERIMENTAL THIAMIN DEPLETION

From 1939 on, there were a number of studies in the United States in which volunteers received thiamin-deficient diets. The largest series included twenty women of European descent, together with a larger number of controls. The subjects were not told when their standard diet was, or was not, being supplemented with thiamin.

The Mayo Clinic physicians in charge of this investigation were surprised by the outcome. After only two weeks on diets containing no

more than 0.15 mg thiamin, but designed to contain all the other known nutrients in adequate amounts, four of the women had become apathetic and fatigued and had no appetite. After six weeks they were nauseated and dizzy. After ten weeks they were vomiting and showing a slow heartbeat at rest and sustained blood pyruvic acid levels after exercise. After the participants received thiamin supplements, appetite and other characteristics all returned to normal.[19]

The physicians were surprised because they had not seen any evidence of edema, or of cardiac dilation or neuritic pain, "which is regarded as a conspicuous feature of beriberi."[20] In fact, their observations suggested to them that "the isolated withdrawal of thiamine from the diet does not produce beriberi," that is, the Asian disease whose characteristics had been described so often in the literature. Other studies with both men and women subjects also led to the rapid appearance of mental symptoms.[21]

In a further study, the Mayo Clinic group, after concluding that "neither acute, severe deprivation, nor moderate, prolonged deprivation of thiamine produced the classic syndrome of beriberi," tried the effect of providing a very deficient diet (containing 0.2 mg thiamin) to two women subjects but also giving them an additional boost of 1 mg thiamin every two weeks.[22] As before, nausea and apathy developed after a few weeks, and both subjects showed characteristically raised levels of pyruvic acid in the blood. After ninety days, the subjects found it difficult to rise from the squatting position, and they had pain in their legs, with "objective evidence of dysfunction of nervous pathways. . . . the neuropathy consisted of defects of the sensory nervous pathways, loss of tendon reflexes and paralysis of muscles of the legs. . . . it responded to administration of large doses of thiamin, but only after many weeks."[23] There was no mention of nystagmus or ophthalmoplegia having been seen in any of the studies with volunteers.

In a longer study involving long-term patents in a mental institution, twelve men (group A) were maintained for three years on a daily diet containing 0.4 mg thiamin. Another twelve men (group B) received the same daily diet, together with a yeast extract that raised the total daily intake to 0.8 mg thiamin, for the first two years. They were all the subject of intensive clinical, biochemical, neurological, and psychiatric observation. The development of mental and physical changes in group A was slow but significant, with loss of appetite, slight edema, and loss of interest and sociability. Blood levels of "pyruvic plus

lactic acids" became consistently higher than in group B only when measured after a glucose load followed by mild exercise. (The significance of this test is explained in Appendix B.) Since the men consumed only some 2,000 kcal per day, the researchers concluded that a level of 0.2 mg thiamin/1,000 kcal was below the adult requirement.

Such results have been obtained repeatedly with diets containing 0.22 mg thiamin/1,000 kcal or less.[24] However, one paper stands out in strong contrast to the rest. It was reported in 1943 that four out of nine feeble-minded institutionalized young males who had been receiving less than 0.1 mg thiamin/1,000 kcal for several months and then none at all for another month remained healthy and continued to excrete 0.1 to 0.3 mg per day in their feces. The authors believed that these subjects received all the thiamin they needed from bacterial synthesis in their intestinal tract.[25] No other paper has reported such a phenomenon. But, even if its existence were to be confirmed for some exceptional people, this would not affect the standard designed to meet the needs of the general population.

On the other hand, only one of the experimental diets containing 0.3 mg/1,000 kcal or more has been associated with a problem. In this instance, three of the four medical student volunteers who had been doing regular physical endurance tests became more quickly fatigued after their dietary intake was reduced from 0.5 mg to 0.35 mg/1,000 kcal; they all also had a reduction in appetite within three weeks of the change.[26] There was no control group, and these changes perhaps could have been due, at least in part, to the reduction in intake having been made at the beginning of the hot Chicago summer. Of course, a level at which subjects remained healthy for the duration of the other tests could also possibly have been inadequate over a longer period.

WHAT COULD BE CONCLUDED?

In view of the large number of cases of both "wet" and "dry" beriberi seen in Allied soldiers who were prisoners of war, there seemed no reason to doubt that Westerners were as susceptible to the disease as were Asians, when consuming comparable diets. But were Asians immune from the anorexia and nausea observed in Western volunteers on a thiamine-deficient diet and from "cerebral" beriberi even though all these changes, including those associated with Wernicke's disease, had also been seen in a wide range of animal models?

Platt, who had studied beriberi in China in the 1930s, said later that he had never seen evidence of the condition, but that the beriberi cases he had studied were generally mild.[27] Of course, it would obviously be difficult where conversation between doctor and patient required an interpreter to pick up signs such as mental confusion and lethargy, but nystagmus would have been an obvious sign.

In Japan, cases of beriberi began to reappear during the 1970s, typically among active youths between fifteen and twenty years old, living largely on white rice, instant noodles, and drinks rich in sugar. On examination the patients appeared well nourished and had good muscle development. They had acute polyneuritis, often accompanied by edema and cardiac abnormalities. Although they had vague feelings of fatigue and nausea, neither nystagmus nor ophthalmoplegia was reported in any of nearly four hundred cases.[28]

The findings from the literature as a whole are consistent with Wernicke's disease resulting from thiamin deficiency in a small proportion of people of European origin, but never, apparently, in Asians. It has been noted that even among alcoholics of European descent, living on poorly balanced diets, only some 3 percent develop Wernicke's disease, although they would all appear to be at similar risk.[29]

Evidence to support the idea that susceptible people might have a genetic difference was published in 1977. Workers in Los Angeles reported that the transketolase enzyme preparations obtained from four patients with Wernicke's disease all needed a much higher concentration of thiamin pyrophosphate to become as active as similar enzyme preparations from ten control subjects.[30] If the results reflected the characteristics of thiamin-requiring enzymes in the brains of these subjects, it would be understandable that these people, and others like them, would show a different set of reactions to a low-thiamin diet from those of other people.

We know of other diseases that are a problem only for a genetic minority. For example, a mentally retarded infant was diagnosed as being unable to metabolize branched-chain amino acids that had risen to abnormally high levels in her blood. When she was given a single dose of 10 mg thiamin (i.e., twenty times the normal requirement), the amino acid levels fell to normal. It appeared that a key enzyme for the metabolism of these compounds, which was known to require thiamin pyrophosphate as its coenzyme, was slightly abnormal and required a higher concentration of the coenzyme for the two to be

normally attached and function together.[31] There have also been comparable observations where individuals with a rare genetic abnormality of an enzyme required higher levels of one or another B vitamin in order for it to function normally.[32]

CHOOSING AN "ALLOWANCE" TO RECOMMEND

Another approach to assessing people's need for thiamin was to obtain records of the normal diets of different groups and to estimate their thiamin content, then to rate the diets on whether or not they were associated with any signs of vitamin deficiency. This approach was actually attempted even before thiamin had been isolated, by using the results of animal feeding tests to compare the antineuritic value of different foods. G. R. Cowgill spent many years on this attempt, using his own preparation of yeast extract as his standard.[33] This was later compared, in turn, with the League of Nations' International Unit described in chapter 7, and it was concluded that the protection level for adults lay between 200 and 500 IU per day.[34] With the isolation of thiamin, this was recalculated as 0.6 to 1.5 mg per day.

With the development of chemical analysis for thiamin, much more precise estimates could be obtained for the quantity in different diets. In 1938, R. R. Williams and Thomas Spies had estimated the thiamin contents of one hundred reported dietaries. They ranked them in order of value for "mg thiamin/1,000 kcal" with the results as shown in Table 10.1.

The authors accepted that dietary descriptions were in many cases abbreviated, and that judgment had to be used in categorizing individual items, so that estimates were only approximate. Nevertheless, there seemed to be good support for the idea that diets containing over 0.3 mg thiamin/1,000 kcal kept people free from beriberi, which was in good agreement with the results from the controlled trials described earlier. They also tried calculating "thiamin/carbohydrate calorie," but this did not improve the relationship with beriberi incidence.[35]

From this time on, it became usual to express standards as "mg thiamin/1,000 kcal consumed," regardless of whether calorie consumption was high because of physical activity or physical size, because it was felt that need for thiamin was particularly related to energy metabolism. This was in contrast to the practice with most other nutrients of expressing the requirement per unit of body weight. In

Table 10.1 Experiences with one hundred group diets ranked according to their estimated thiamin content

Thiamin (mg)/ 1,000 kcal	*Number of diets*	*Number associated with beriberi*	*Number with no such association*
Under 0.25	64	61	3
0.25–0.275	4	2	2
More than 0.275	32	3	29

SOURCE: Estimates made by Williams and Spies (1938).

either case, most tables of nutrient "allowances" have given values for "average" people in different classes, with assumptions about their weight and calorie intake.

Finally, there have been attempts to measure requirements using various metabolic tests. One was derived from the observation that although subjects placed on a low intake of thiamin soon ceased to excrete a measurable amount of free thiamin in the urine, they continued to excrete essentially the same quantity of thiamin "metabolites," the two separate ring structures that come from the splitting of the thiamin molecule. The body's long-term daily "need" for thiamin is then, it was suggested, equivalent to the quantity broken down each day—which in this test was approximately 0.9 mg/head/day, or 0.33 mg/1,000 kcal.[36] Since this value is in general agreement with conclusions based on other criteria, it has been considered "supportive" of them. Other biochemical tests that have been used as indicators of status are described in Appendix B.

The recommendation first made by the U.S. Food and Nutrition Board in 1945, and continued until 1989, was that adult diets should contain at least 0.5 mg/1,000 kcal. When transferred to tables of "nutrient needs/head/day," this has become 1.5 mg/day for men fifteen to fifty years old (assuming 3,000 kcal/day) and 1.1 mg/day for women in the same age range (assuming 2,200 kcal/day), with an additional 0.4 mg for pregnancy and 0.5 mg for lactation.[37] A "recommended allowance" is intended to be somewhat higher than a minimum requirement for remaining healthy; it also includes a margin of safety for individual variability and allows for some imprecision in the data on which the estimated is based.

The United Nations and the British recommended allowances were based on essentially the same data as the American ones but have

for many years remained slightly lower at 0.4 mg/1,000 kcal.[38] It is difficult to say that one value is right and the other wrong. In the instance when the allowance for another nutrient was placed higher in the United States, it was argued that "the intention [in the United States] was to provide ample allowances that may be more generous than would be practical for feeding large groups under conditions . . . of economic stringency."[39]

I understand that preliminary recommendations for the next revision of U.S. RDAs include values of 1.2 mg thiamin for men and 1.1 mg for women of average weight, without adjustment for energy intake, but they have not yet been officially published.[40] These values have been calculated to be 20 percent greater than intakes at which one-half of the test subjects had given marginally low values in the biochemical tests discussed in Appendix B.

SUPERPERFORMANCE FROM EXTRA VITAMIN?

Another question of interest has been whether extremely high intakes of thiamin, as of other vitamins, might confer super-strength or extra resistance to fatigue. The results of a test of this idea were published in 1942 from the University of Minnesota. Each day for four to six weeks, groups of soldiers were given pills containing at least 5 mg thiamin, plus three other vitamins. Others received pills that were identical in appearance but contained no vitamins. The participants were then all put to heavy labor under stressful conditions. For a second period the pills were reversed. The men themselves continued to eat standard army rations and did not know what their pills contained. There was no indication of any effect of the vitamins given as supplements to an ordinary, "good" diet.[41]

Two other studies were carried out to investigate whether a thiamin supplement would improve learning in children at an orphanage where the diet was estimated to contribute 0.9 mg/day. Thirty-seven children received a daily pill containing 2 mg thiamin, and thirty-seven others received a placebo. The trial was double-blind—neither the children nor the evaluators knew who was receiving the vitamin until the results had been tabulated. The tests involved primarily mathematical and word games. Initially the scores from all the tests were 3.4 percent higher on average for those who would be receiving the supplement. After forty-five days, with continued testing, the per-

formance of both groups had improved; those receiving extra thiamin had an overall average score 9.4 percent higher than the others, a difference that was statistically significant.[42]

A further test of the same design but lasting nine months gave similar results. In addition, the participants' visual acuity was tested, and some small advantage seen in the supplemented children.[43] One wishes that the results of similar studies with other groups were available to strengthen or confute the findings from this particular group.

THE PROBLEMS OF INFANTS

The question of infants' thiamin requirement has been a troublesome one. They are the group with the highest mortality from a deficiency, and yet it has been judged unethical deliberately to risk inducing a deficiency condition in an infant in order to determine their need. In one series of trials in New York, infants were given a formula made from purified nutrients and the thiamin intake dropped until little or none appeared in the urine. This level, which varied from 0.14 to 0.20 mg/day, was then considered to correspond to each infant's bare requirement.[44] The RDA has been set at 0.3 mg/day, which is equivalent, if the infant consumes a liter of milk contributing 750 kcal, to approximately 0.4 mg/1,000 kcal.[45] Human breast milk, even after a month of lactation, has been found to provide only about 0.3 mg/1,000 kcal, and in the first few weeks no more than 0.2 mg/1,000 kcal.[46] Since the thiamin status of infants breast-fed by well-nourished mothers does not seem to be a problem, another recommendation is that infant formulas also need to contain no more than 0.3 mg/1,000 kcal.[47]

It seems that nature provides little or no margin of safety for the newborn human, and that infants, for their first weeks of life, probably have to rely in part on reserves built up in the womb. Since breast-fed infants between two and four months of age may die within twenty-four hours of first showing definite signs of the disease, there is typically no time for medical attention. Prevention can therefore come only from an improvement of mothers' diet, and overcoming traditions that may make it more limiting than for nonpregnant women.[48]

There have been repeated suggestions that the milk of thiamin-deficient mothers, as well as being low in thiamin, is toxic because the raised levels of pyruvic acid and of other compounds in their blood

have passed into their milk.[49] This seems to have remained only a suspicion, but improving maternal diets should correct both possible problems, as well as providing infants with a higher reserve at birth.

Workers in India have urged that a high death rate among infants between two and four months of age should always be suspected to indicate a problem of thiamin deficiency, and is a sensitive warning sign in the absence of medical attendance in rural communities.[50]

So much for what standards of thiamin intake have been developed. I now will consider the approaches that have been used to assure that they are attained in practice.

CHAPTER 11

How Should the Knowledge Be Used?

From the work described in the previous chapters, it seems clear that, for both prevention and cure of beriberi, the need is to obtain an adequate intake of thiamin. Even before this was understood, however, some empirical procedures had been worked out that achieved this without the correct reason being understood. Thus Kanehiro Takaki, in recommending that Japanese naval diets have some of the white rice replaced by "wheat flour and meat," or later by barley, thought that the important change was an increase in protein intake. And the physicians in Japan who recommended patients move from coastal cities to the rural countryside thought this would allow them to escape toxic miasmas, whereas the really significant change was again to a mixed diet of higher thiamin content.

Adolphe Vorderman's attempts to convert Javanese prisons to the use of brown, rather than white, rice and Hulshof Pol's use of beans to supplement the diets of asylum patients were both stimulated by results from chicken experiments, as described in chapters 3 and 4, although the source of their activity had not yet been discovered.

CHANGING THE PREPARATION OF RICE

After the confirmation of the association of beriberi with white rice in the British colonies in Southeast Asia and then by Americans in the Philippines, attention was concentrated on changing the methods of preparing rice.[1] The American proposal was that fully milled white rice should be either banned entirely or taxed so that it could only be afforded by the relatively rich, who, in any case, ate a variety of foods that supplied enough of the anti-beriberi principle.[2] The phosphorus content of the product was recommended for use as an indicator of how much of the silverskin had been retained by modified milling.

When this policy was applied to troops and government servants

in the Philippines, it immediately ran into trouble, as described in chapter 6. The "no. 2 rice" that was introduced into their rations was found to contain dirt and weevils: it had been machine-milled to remove only the husk and was a grade normally used for feeding to animals, so little trouble was taken to clean it. The army successfully petitioned Washington to have its previous supply of rice restored.

In Thailand, recruits conscripted from the country into a police training school late in 1908 and then fed on white rice had almost all (444 out of 500) developed beriberi by the end of February 1909 and been sent home to recover. At home they were used to eating hand-pounded rice, and from this time on a hand mill was installed at the school and used just to remove the husks of the rice; successive batches of recruits then remained healthy and were happy with this type of staple food to which they had always been accustomed.[3]

However, it seems to have been a universal conclusion that once people in Southeast Asia had gotten used to white rice, they were extremely reluctant to give it up.[4] A scientist with long experience wrote: "Hand-pounding rice is a tedious chore. . . . people will always avoid it if they can. . . . Attempts to restrict or prevent the spread of rice milling are impracticable as a policy."[5]

It was, of course, technically possible for machine mills to produce clean samples of undermilled rice containing the desired proportion of silverskin, as measured indirectly by means of analysis for their phosphorus content.[6] The term "70 percent rice" was, for example, used for milled rice that still retained 30 percent of its silverskin. But, unlike the conditions in a traditional village where rice is freshly hand-pounded each day before consumption, machine milling inevitably entails a period of storage because the product has to be distributed first to wholesalers, then to retailers who always need to have rice ready in stock for their customers. Under conditions of heat and high humidity, the fat in the silverskin becomes rancid, and the rice becomes infested by weevils that thrive on this material, so that the product is rejected, unless the only alternative is hunger: it is not therefore a satisfactory article for international trade.[7]

In Japan, with its cooler climate and with widespread electrification, there were small local mills that could provide fresher samples of undermilled rice to each community so that the problems were less frequent. Batches were also fumigated to kill any weevils and then were stored in airtight bins that prevented their reentry.[8] How-

ever, people generally still preferred white rice. A Japanese physician wrote in 1939: "Since white rice is not toxic, it seems impossible to prohibit it while alcoholic drinks and tobacco are still allowed. . . . war is the only justification for controlling freedom of food choice."[9] It was proposed, therefore, to educate the public's taste gradually by introducing "70 percent rice" into school meals and urging housewives to try boiling "70 percent rice" and then adding a little ground-up white rice to give the grains a white coating.[10] Under World War II rationing restrictions, such rice was the only kind permitted and was accepted as a patriotic necessity; but, as had been predicted, after the war the policy had to be abandoned, and the public returned to white rice.[11]

In Malaya after World War II, the government tried to enforce a law requiring all rice to be undermilled, but apparently a black market for white rice came into being and flourished.[12] In both Shanghai and Hong Kong in the late 1930s, beriberi was a serious problem among refugees sheltering there from the fighting in mainland China, but they were "extremely unwilling to eat anything but polished rice."[13]

GERM RICE IN JAPAN

As noted in chapter 8, although the high antineuritic value of rice germ had been reported in England in 1919, this seemed to have been forgotten by scientists working in the colonial territories during the 1920s and 1930s. But this was not the case in Japan, where it was discovered that rice germ had an attractive flavor, as well as being nutritious.[14] Repeated attempts were then made to modify rice milling machinery so that while the silverskin was removed, at least 80 percent of the germ was retained. This was achieved with certain types of rice, and the product was well accepted, and also found in hospital tests to be protective against beriberi.[15] The armed forces were then apparently willing to make such "germ-rice" their standard purchase, and there was even discussion of having it made compulsory for millers to produce such rice. However, the makers of milling machinery were unable to develop the process further so that it could be applied to the major types of rice, and other approaches had to be used.[16]

Where it seemed impossible to persuade people to give up the use of white rice, Japanese food scientists recommended first that the use

of polishing powders be stopped, since they increased the proportion of germ that was dislodged, and their presence on white rice also provided a reason for washing even a clean batch prior to its cooking, with a further serious loss of the vitamin.[17] Attempts were also made to cook the grains in a minimum of water, or to drink any surplus cooking water.[18] The advantages of these changes have been discussed in chapter 8. It was thought that with these precautions, and taking a moderate quantity of legumes, a diet based on white rice should be adequate.

PARBOILED RICE

It was, of course, realized from about 1910 that the traditional Bengal process of parboiling rice yielded a product that kept its users free from beriberi even when it was fully milled.[19] As explained in chapter 2, the process involved a preliminary soaking and drying of the grain still in its husk before it was subjected to milling. The obvious technical advantage of the procedure was that the husks could then be split and separated more easily than with untreated grains. The nutritional advantage was that much of the thiamin had diffused from the silverskin into the endosperm during the initial soaking, as described in chapter 8.

With hindsight this seems to have been a serendipitous discovery, or development, somewhat analogous to the traditional Central American practice of treating mature corn grains with lime (calcium hydroxide), which made them softer to grind but also made their content of the vitamin "niacin" nutritionally available and so spared the users from pellagra, another deficiency disease.[20]

It was estimated in 1945 that some 20 percent of the world's rice production was being parboiled.[21] Why, then, was the process not recommended for adoption whenever white rice was the staple and beriberi endemic? The first problem was that any staple food for poor people had to be cheap. In the traditional small Indian processing plant, water was reused, and drying relied on sunshine that could be intermittent, so that the product typically tasted "musty" from the presence of molds. People brought up on parboiled rice were used to this flavor, but when attempts were made to spread its use, others found it unacceptable.[22] Aykroyd wrote in 1940 that there was a tendency for its use to decline slightly even where it had been the tradi-

tional staple because the high-caste Brahmin community did not consider it "civilized."[23]

Technologists have developed quicker procedures involving alternate vacuum and high pressure to wet the paddy, followed by forced-air drying. These prevent any mustiness of the product, but the initial steeping and steaming inevitably result in a slightly yellower grain. The gelatinized starch also gives a translucent, "glassy" appearance rather than a "chalky" one to the final polished product, and the flavor after cooking is still different from that of cooked "raw" rice. Unfortunately, the extra cost of this processing more than offsets the gain from a smaller percentage of grains being broken during milling. With a further dry-heat treatment, quick-cooking "converted" rice is obtained.[24] There is a market for this among relatively well-off consumers but not among those who might otherwise be at risk from beriberi.

WORLD WAR II PRISON CAMPS

Chapter 10 has described the appearance of beriberi among prisoners of war of the Japanese in World War II. These prisoners included physicians and, in the civilian camps, even nutritional scientists who had been working on the beriberi problem. What could they do when they suddenly found themselves and their companions at risk from the disease?

A. G. Van Veen, whose work has been mentioned in previous chapters, was one of those interned in Java, and he has described how they prepared dry yeast as a supplementary food. As sources of nitrogen for the growing yeast they used "decayed fish, livers of sick cows and even ammonia out of urine." They also prepared acetic acid by fermentation, because an acidic solution was known to extract thiamin more efficiently from the rice bran that was available. Their main problem, however, was sheer undernutrition, with prisoners sometimes receiving no more than 1,000 kcal per day, so that apathy and sleepiness were more common than specific deficiency diseases.[25] And for this they had no technical solution.

C. R. Burgess was interned in the military camp on Singapore Island. He was able to get a message to his former technician, who was Chinese and still at liberty, to steal a copy of Robert Williams and Thomas Spies's newly published *Vitamin B_1 and Its Use in Medicine*

from the Singapore Medical College and smuggle it to him. This was accomplished, and the book provided him with tables of the thiamin content of a whole range of materials.[26]

Burgess concluded, when looking back on their experiences, that the most important contribution from their efforts probably came from minimizing the washing of their polished rice, and either cooking it so that no surplus water was left or using the cooking water in soups.[27] When rice polishings became available, they were first eaten as such, but more than 2 oz per day were commonly found to precipitate diarrhea (a chronic problem in the camp), and extracts were then made, using a few drops of sulfuric acid ("battery acid") to acidify the solution. Yeasts also were grown but appeared more useful as a source of riboflavin than of thiamin. With hindsight, this may have been because the need for killing the organism in order to make the thiamin available had not yet been recognized. Extracts were also made from leaves, but these too served mainly for the correction of riboflavin deficiency. When some soybeans, which were valued as a source of thiamin, became available, they were fermented to make tempeh, which was found to be better tolerated than plain, boiled beans.[28]

After the Japanese guards had learned of their country's surrender, they offered a large store of polished rice to the prisoners. The Allied medical officers urged restraint in its use, since they feared that a sudden high intake of carbohydrate by people on the margin of thiamin deficiency would precipitate acute beriberi.[29]

THIAMIN-RICH SUPPLEMENTS

As explained in chapters 6 and 7, extracts from rice bran, with partially concentrated anti-beriberi activity, were being used in Japan as early as 1912, and in the Philippines from 1915. Later, yeast extracts were also being marketed by pharmaceutical companies. These preparations were particularly useful for treating infants, whose condition could degenerate quickly.

In the 1920s and 1930s, the marketing of multiple vitamin supplements in the United States, and to a lesser extent in Europe, became a big business despite there being little evidence of any of the classical deficiency diseases in these areas. Medical and governmental opinion tended, in general, to hold that "vitamin pills were a waste of money better spent on healthful foods." The manufacturers responded

by arguing that the expense was small, and the relief of vague feelings of tiredness and being "below par" could make all the difference to one's enjoyment of life and professional success.[30] A company marketing a "rice polishings concentrate" in the United Kingdom claimed that "failure of an apparently ample diet to sustain health and virility could be due to unsuspected loss of vitamin B_1 during the preparation of staple foodstuffs."[31]

As methods for the relatively cheap synthesis of vitamins began to be developed in the late 1930s, opinions again differed over how they could best be used. Pharmaceutical companies were anxious to add them to their product lines, which already included nutritional supplements such as fish liver oils and yeast extracts.[32] Government departments were still concerned that vitamins should not be marketed with unfounded claims that could mislead the public.[33]

A PROBLEM IN WESTERN COUNTRIES?

There were also, particularly in Britain, groups of activists claiming that the Great Depression had left millions of unemployed whose income from government relief was insufficient for their families to receive a balanced diet that included adequate levels of milk, fruit, and vegetables. The height of children growing up in poor families was certainly below that of more privileged children.[34] From a study of the diets of pregnant women at different economic levels, it was estimated that the poorest group received only 0.63 mg thiamin per day on average, while those with higher incomes received twice as much.[35] Activists urged therefore that the level of support be raised. The government's response was that medical surveys of schoolchildren had not shown signs of deterioration in general health, and if the unemployed were eating an unbalanced diet it was because they were making poor food choices as a result of their ignorance.[36] Even setting the standards for individual nutrients became involved in what had become a social and political issue.[37]

There had been several dietary surveys in the United States as well, some conducted by the U.S. Public Health Service, and their authors pointed to the inadequacies of the diets being eaten by low-income groups.[38] For example, in one study of low-income teenagers in New York City, more than half of the participants were estimated to be receiving less than the National Research Council's recommended daily

allowance of 1.5 mg thiamin, and 14 percent were receiving less than two-thirds of the recommended amount. The corresponding percentages for those receiving low levels of vitamin A, riboflavin, and ascorbic acid were all higher.[39] In this instance the recommendation was that free or subsidized school lunches should be redesigned to provide more micronutrients.[40]

THE ENRICHMENT OF FOODS

One obvious way for governments to raise micronutrient intakes was to encourage (or even enforce, if necessary) their addition to specific foods, a procedure called "enrichment." The principle was already accepted—common salt with added iodine (in the form of an iodate or iodide) was available, and milk was fortified with vitamin D. In 1939 the American Medical Association's Council on Foods endorsed a paper setting out reasons for believing that many American diets contained suboptimal levels of thiamin as a consequence of the use of white (rather than whole wheat) flour and an increasing proportion of sugar.[41] The council also decided to encourage "the addition of vitamins or minerals to . . . general purpose foods to recognized high natural levels . . . [where it is] in the interest of public health."[42]

In 1940 the British government, already at war with Germany, announced a policy that required all white flour to be enriched with synthetic thiamin.[43] In the United States the National Research Council recommended similar enrichment for all flour purchased for the armed services.[44] Standards were also developed in 1941 for the voluntary use of enriched bread and flour for sale to the public. To be labeled as "enriched," a pound of flour had to contain no less than 1.66 mg thiamin, 6 mg niacin, and 6 mg iron (in available form).[45] In the case of thiamin this meant in practice the addition of approximately 1.25 mg to meet the standard. Initially, high-vitamin yeast powder was commonly used, until the wholesale price of synthetic thiamin fell to below 30 cents/g in 1943. By that time the cost of enriching 100 lb of white flour with the three nutrients had fallen to 6 cents.[46] Separate standards had to be set for enriched bread, but they corresponded to those for enriched flour after allowing for the higher moisture content of bread.

At the end of 1943 the enrichment standards were changed to include riboflavin, which was then available in sufficient quantity, and

the levels of other nutrients were raised—in the case of thiamin to 2.0 mg/lb. As a consequence, the total cost of enriching 100 lb of white flour was increased to 13 cents, but nutrient prices continued to fall, so that by late 1944 the cost was again below 8 cents.[47] By then, under wartime regulations, all white bread in the United States had to be enriched.

Meanwhile, in Britain, where wheat imports were reduced as a result of heavy shipping losses in the Atlantic, the government enforced an increase in extraction rate for flour production from 70 to 85 percent in 1942. The milling procedure was also adjusted to retain the scutellum, which had been found to contain 60 percent of the thiamin in the whole grain, so that there was no longer a need for enrichment.[48]

It is difficult to estimate what value the introduction of enrichment of flour may have had in either the United States or Britain because so many other changes were occurring as a consequence of World War II. The large numbers of people unemployed as a result of the Great Depression of the 1930s were now able to find work, and could thus afford a better diet. In Britain there was strict food rationing, but nevertheless overall health statistics improved—perhaps because of a more equal distribution of what was available, with highest priority given to pregnant women and young children.[49]

It had been predicted that the greatest effect of enrichment in the United States would be among alcoholics who did not bother to cook or to eat a balanced diet. Indeed, a physician at Bellevue Hospital in New York, where "skid row" subjects were taken, did tell the War Food Administration that he had seen a diminution in signs of B-vitamin deficiency, which he attributed to bread enrichment.[50] After the war the great majority of bread continued to be enriched.[51] Starting in 1946, a group of doctors in Chicago were hoping to study cases of thiamin deficiency in a large general hospital but were unsuccessful. Judging from their earlier experience, they then expected to be able to find cases among a large group of chronic alcoholics, but again without success. From a study of foods eaten in the skid row area of Chicago it was concluded that, on average, enriched flour and bread provided the members of this community with about 0.7 mg thiamin per day, which, combined with the other foods they ate, was sufficient to prevent any obvious deficiency.[52]

ENRICHMENT IN NEWFOUNDLAND

In Newfoundland, as noted in chapter 9, beriberi had been a serious problem in the 1920s in communities that were isolated throughout the long winters. Compulsory enrichment of flour began in Newfoundland in 1944. Two survey teams went there just before enrichment began to obtain baseline data for measuring any benefits that could be observed at a later date.[53] By 1944 there had already been great changes in the area as a result of the war. Newfoundland had become of strategic significance, and a large air base was built there, primarily for planes to refuel on the way from the United States to operational bases in Britain. Labor was in demand, with the numbers on relief having fallen from over ninety thousand in 1933 to less than eight thousand, and fishermen were receiving more for their catches.[54]

The survey teams learned that "florid [fully developed] beriberi has almost disappeared" and found "little evidence of peripheral neuritis." However, they noticed lethargy and apathy together with nervousness in many of the subjects studied, which they felt could have been the result of mild thiamin deficiency. From government statistics it appeared the available food could have supplied an average of 0.9 mg thiamin per head.[55] In a more intensive study of one particular poor community on the west coast of Newfoundland, most appeared to be undernourished, but the most common deficiencies were of vitamin A, riboflavin, and iron.[56]

In 1948 the same types of survey were repeated. In the intervening years Newfoundlanders had been receiving margarine fortified with vitamin A and also further enriched flour and bread, which had been predicted to raise possible daily thiamin intake to 2.3 mg per head.[57] Analyses of urinary thiamin from subjects in the outports showed, on average, more than a fourfold increase since 1944. Excretion of riboflavin, another vitamin used in flour enrichment, had also increased significantly. In contrast, the average excretion of vitamin C had fallen, and the evidence for its deficiency had increased. Since vitamin C was not included in the enrichment programs, this tended to confirm the conclusion that flour enrichment had been an important factor in improving the subjects' B-vitamin status. The teams also had an overall impression of an improved alertness in the adults and especially in the children.[58] They also pointed out that the

relatively high thiamin intake was only achieved by the generally high bread consumption.[59]

THE PROBLEMS OF RICE ENRICHMENT

Since thiamin deficiency had been concentrated mostly among rice eaters, it was of great interest, when peace was restored to Southeast Asia in 1945, to see whether rice enrichment could be adopted there. Adding thiamin to wheat flour had been simple in principle—a matter of mixing one powder with another. For rice there was a problem because trying to add a powder to a bag of rice grains would result in it falling to the bottom or adhering loosely to the grains and being lost when they were washed. Obviously, some other method of enrichment needed to be developed.

In 1946 workers at the Hoffman–La Roche plant in New Jersey, where thiamin was in commercial production, published a new procedure for enriching rice with micronutrients. White rice grains were tumbled in a rotating container while being sprayed with a nutrient solution and then were redried in a current of hot air. The grains were next sprayed again with a coating solution that, after a further drying, formed a water-insoluble layer around the grains, now described as "premix rice." The concentration of thiamin in these grains was such that when 1 part was mixed with 199 parts of ordinary white rice, the final concentration would be 4.4 mg/kg.[60] Further tests showed that after rice was washed three times and cooked in an open boiler, the loss of thiamin was only 14 percent, compared with over 50 percent for undermilled rice.[61] One problem arose with the inclusion of riboflavin as an additional micronutrient. This vitamin has a strong yellow color, and users have tended to pick out the premix grains when they are identifiable by their different color. For this reason riboflavin was sometimes omitted.

Another process, called the "acid-soaking method," was developed at Kyoto University in Japan. White rice grains were soaked in a solution of thiamin, and sometimes other vitamins, acidified with 1 percent acetic acid. After the grains were drained, they were steamed briefly to gelatinize the surface starch and then were dried in a current of hot air.[62] These premix grains could then be blended with 199 parts of ordinary rice as in the previous procedure. Alternatively, consumers could buy them and mix a small quantity with ordinary rice

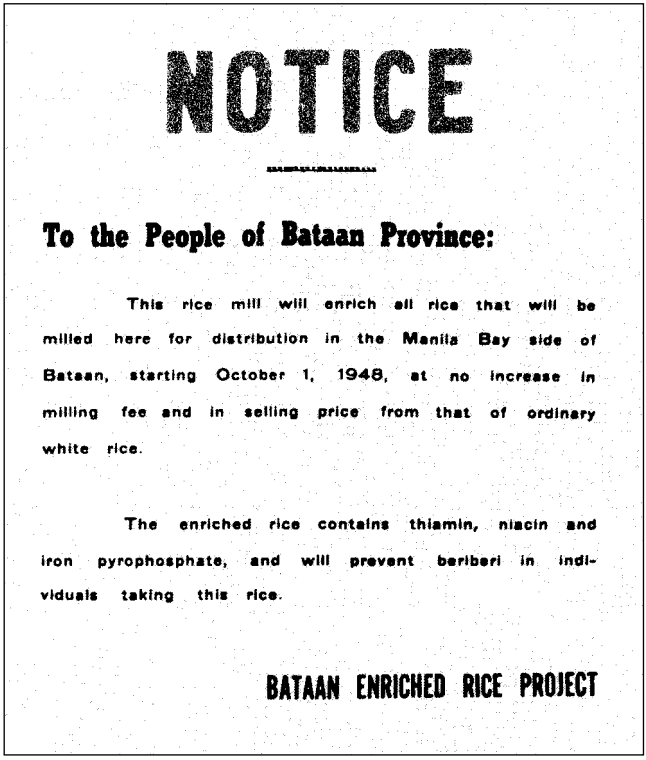
at home when preparing a meal. This, of course, reflected the widespread understanding of the beriberi problem in Japan.[63]

A later development, also in Japan, was to mix vitamins and minerals with powdered starch, then process the mix into granules roughly the size and shape of rice grains, and finally to coat the granules with shellac or some other coating that is insoluble in hot water but digestible when eaten. The manufacturers also used compounds of thiamin that were less water-soluble but still digestible, including thiamin naphthalene sulfonate and dibenzoyl thiamin.[64]

A LARGE TRIAL IN THE PHILIPPINES

R. R. Williams's interest in the anti-beriberi factor in rice polishings began in the Philippines in 1909, when he was a young man. He then, as we saw in chapter 7, went on in the 1930s to lead a team that identified and synthesized thiamin. With the end of World War II, and with the synthetic vitamin now being available in good quantity, he was anxious to complete his nearly forty years of work on the subject by returning to the Philippines and demonstrating how the vitamin could be used to eliminate the beriberi problem there. After their synthesis of thiamin, he and his colleagues had been able to obtain patent rights in the United States, and royalties amounting to some $4 million were to come in over the next ten years. Williams and Waterman arranged that, after relatively small payments to themselves and the other chemists, the main portion should be placed in the Williams-Waterman Fund for the Combat of Dietary Diseases. And, naturally, he had a big say in how the money should be used.[65]

In 1946 Williams was able to travel to the Philippines and to persuade the authorities there to agree to a trial of rice enrichment.[66] The country still faced many problems of restoration from war damage and was experiencing political unrest, but from July 1947 to February 1948 a large baseline survey was conducted in the province of Bataan (spelled *Baatan* in papers published in the Philippines). This area is known to readers of World War II history as the last holdout of U.S. soldiers after the Japanese invasion in 1941. It was chosen for the trial because it was close to Manila but was on a peninsula with access by only one good road, which allowed ready scrutiny of entering rice shipments. Under the leadership of Dr. Juan Salcedo, more than



NOTICE

To the People of Bataan Province:

This rice mill will enrich all rice that will be milled here for distribution in the Manila Bay side of Bataan, starting October 1, 1948, at no increase in milling fee and in selling price from that of ordinary white rice.

The enriched rice contains thiamin, niacin and iron pyrophosphate, and will prevent beriberi in individuals taking this rice.

BATAAN ENRICHED RICE PROJECT

Fig. 11.1. Public notice that rice enrichment in the Bataan area is about to begin (Williams-Waterman Fund, 1950; courtesy of Research Corporation).

twelve thousand people were examined, of whom 2 percent had "frank beriberi" and a further 10 percent had "suggestive or doubtful beriberi." The area had had 166 "deaths per 100,000 population" from the disease in the previous year, a rate that made it second only to tuberculosis in mortality statistics. Over 80 percent of the deaths recorded as being from beriberi occurred in infants.[67]

The eastern portion of the area, containing nearly 70 percent of its population, was chosen to receive enrichment for a year, while the less populated western portion served as a control area (Fig. 11.1). The premix grains were prepared in the United States with thiamin, niacin, and iron, as described earlier.[68] Riboflavin was omitted for fear that people would be put off by any yellow staining of their cooked rice. The twenty-three mills in the test area were each given the premix free

Fig. 11.2. Enriched rice being loaded from a small mill in the Bataan area (Williams-Waterman Fund, 1950; courtesy of Research Corporation).

of cost and also a feeder that would blend it with ordinary white rice at the standard "1 in 200" ratio (Fig. 11.2). Enrichment began in October 1948 and continued for two years. Inspectors were employed to sample and examine the rice on sale at mills and markets. With training it was possible for them to distinguish the premix grains when a standard sample of rice was spread out in a thin layer, and to count the number of these grains present. The results were satisfactory, but a problem developed during the first year with some enriched rice appearing in parts of the control area.[69]

The second, follow-up clinical survey was carried out from July 1949 to February 1950. Nine thousand people were examined in the enriched area, and only seven (i.e., 0.1 percent) showed frank beriberi, compared with 2.1 percent previously in the same area. In the control area twenty-four hundred people were studied, and the incidence of frank beriberi was now 3.5 percent, compared with 1.6 percent previously. If the numbers from the town where enriched rice had been found were omitted, the increased incidence would have been greater.[70] The values, together with the numbers of "suggestive" and "doubtful" cases are set out in Table 11.1. The relatively small change in the overall death rate in the enriched area was explained by an epidemic of infectious diarrhea at that time.

It was concluded that the trial had shown that the enrichment of rice in a poor tropical country was technically possible and that it could greatly reduce deaths and sickness from beriberi. An increase in the mean hemoglobin levels of blood samples from 10.9 to 12.9 g/100 ml over the period of the trial was attributed to the iron added to the pre-

Table 11.1 Results from two areas of the Bataan Peninsula, where one area received enriched rice for two years

	Enrichment area		*Control area*	
A. Survey results				
Times of surveys	(1947)	(1949)	(1947)	(1949)
Number examined	(10,600)	(9,100)	(2,570)	(2,400)
Percent with signs of beriberi:				
a. Frank	2.1	0.1	1.6	3.5
b. Suggestive	4.2	0.6	1.2	3.3
c. Doubtful	8.1	0.9	3.8	1.9
d. Total of a, b, and c	14.3	1.6	6.7	8.7
B. Mortality statistics				
Collection period	(1947–48)	(1948–49)[a]	(1947–48)	(1948–49)
Population of area	(63,500)		(29,400)	
Deaths/1,000 population/year:				
a. From beriberi	2.67	1.17	1.49	1.63
b. From tuberculosis	3.06	2.58	2.53	2.65
c. Diarrhea	0.93	1.76	0.97	1.33
d. All causes	15.27	14.97	14.65	16.77

SOURCE: Data summarized from Salcedo et al. (1948, 1950).

[a]The 1947 survey was conducted from July 1947 to February 1948; the 1949 survey from July 1949 to February 1950. The distribution of enriched rice began in October 1948. The statistics run for the period from October to September of the following year. The 1948–49 period begins, therefore, when enrichment had only just begun, so that it may have had insufficient time to influence health at the beginning of the period.

mix grains and was taken to demonstrate another benefit to be obtained from enrichment.[71]

The idea was that with the end of the experiment, during which the premix had been supplied free to the millers, it would be sold to them at cost; they, in turn, would increase their charge to customers by the same amount. This would correspond to about 12 U.S. cents per 100 lb of rice, or only about 35 cents for the total quantity consumed by one person in a year (at the rate of 12 to 13 oz per day). For people who purchased white rice, rather than having their own rice processed at a local mill, this would amount to a 1 to 2 percent price increase. A law was passed enforcing rice enrichment in Bataan and

Tarlac provinces, and it was "hoped to extend rice enrichment to 1.8 million additional people by the end of 1951."[72]

THE SUBSEQUENT CONTROVERSY

Williams himself visited Bataan in 1951 and has described how the visit became a triumphal tour, with banquets in his honor, and a large parade of schoolchildren in a town square, where both he and Juan Salcedo spoke from a decorated platform to a crowd of many thousands.[73] In 1950 Williams had encouraged the United Nations to send an international team to review the Bataan experiment, so that the results could be brought to the attention of other Asian countries, and he offered financial support from the Williams-Waterman Fund. However, the Philippine government was concerned that political insurgents had made the countryside unsafe at that time, so that the survey could not begin until early 1952.[74] And in the event the report was very different from what Williams had hoped for and expected.

Two of the UN's specialized agencies were concerned with nutritional problems—the Food and Agriculture Organization (FAO) and the World Health Organization (WHO). The team sent out was therefore a joint FAO/WHO delegation. It consisted of W. C. Aalsmeer, a Dutch physician working in Indonesia who had published papers on the clinical treatment of beriberi patients; K. Mitra, who advised the Indian government on nutritional matters; I. A. Simpson, a British chemist working in Malaysia who had published on the distribution of thiamin in the rice grain; and Nestor Obando, an agricultural economist from South America. They were instructed that the results of the experiment in Bataan should be surveyed, and that they should also report on all aspects of enrichment, including its administrative and economic aspects.[75]

The team's own dietary survey in Bataan led it to agree with earlier conclusions that the typical diet without enrichment of the rice was inadequate to provide protection from beriberi, and that with enrichment it would be adequate.[76] The researchers also confirmed that cooking rice in the usual Philippine way, in which all the cooking water was absorbed by the grains, led to little loss of thiamin from the premix grains. They warned, however, that when a large excess of cooking water was used, as in some other parts of Asia, thiamin losses could be quite high.[77]

They reviewed the biochemical data obtained by the Philippine Institute of Nutrition in the two surveys and agreed that the fourfold increase in mean urinary thiamin excretion indicated a considerable increase in thiamin status. But they expressed surprise that there was only a relatively small rise in the mean thiamin level in blood samples (from approximately 3.5 to 4.1 µg/100 ml).[78] They also examined fifty-four people whom local doctors had classified as having "possible beriberi" and agreed that all but three of them were suffering from the condition.

The only actual values for the intensity of beriberi in the postwar period that they listed in their report were the mortality rates, as reproduced here in Table 11.2.[79] There is no reference anywhere in the report to the Bataan province having been divided into an "enriched" and a "control" area, and the values in Table 11.2 refer to the combined total from the two areas.

With regard to the conclusions to be drawn from the trial, the team referred readers to the papers published by Salcedo and his colleagues. They added that, because they had arrived in the Philippines more than a year after the experiment had ended, they were "not in a position to report upon it. Nevertheless . . . it is logical to presume . . . that the greatly increased drop [in beriberi mortality] in Bataan as compared with those recorded in Tarlac Province during the period 1949–51 was due to the introduction of additional thiamine." However, they were puzzled by the mortality rate in Bataan having remained low in 1951, since, after the enrichment experiment had ceased in the fall of 1950, no more than 10 percent of the rice used there had continued to be enriched.[80]

In their tours of the Bataan and Tarlac areas they visited a number of mills and reported that the flow of premix into the stream of milled rice was not always correctly adjusted, and that in some instances the miller had not noticed that the premix feeder was empty. They also commented that millers at larger plants were unhappy at having to purchase premix, since some of their output went to Manila, where it competed with unenriched rice that was still permitted there.[81]

Their final summing up begins as follows: "Great credit is due to those responsible for . . . conducting extensive trials of enriched rice under difficult conditions . . . a pioneer attempt to solve a serious nutritional problem by novel methods." The researchers recognized the important advantages of rice enrichment—that it could be introduced

Table 11.2 Recorded beriberi mortality rates per 100,000 of the population in different areas of the Philippines in successive years[a]

Year	*Philippines as a whole*	*Manila*[a]	*Tarlac Province*	*Bataan Province*	*Means for ten further provinces*[b]
1946	145	87(14)	444	229	—
1947	139	84(12)	438	186	(118)
1948	140	96(14)	346	193	(113)
1949	122	53 (6)	263	82	(101)
1950	116	14	245	20	(103)
1951	—	(12)	130	21	(113)
(1954–57)	—	(4)	(111)	(30)	(113)

NOTE: Rates refer to combined adult and infant deaths, the latter constituting 80 to 90 percent of the total. The values not in parentheses were all given in the FAO report (Aalsmeer et al. 1954).

[a]The values given for mortality in Manila for the years 1946–49 were total number of beriberi deaths in the city. As explained in the text, the second value (in parentheses) against each of these years has been recalculated as a "rate" based on the estimated population of Manila rising steadily from 600,000 in 1946 to 900,000 in 1949.

[b]These are means for the ten provinces, Bulacan-Davao, listed alphabetically (Williams 1961).

fairly rapidly, benefited the whole community, and did not affect the flavor of the rice. However, they noted "serious obstacles to the successful introduction of rice enrichment by the present method into many countries where rice is a staple food." The first obstacle listed was "the considerable expense involved in paying for the import of the vitamins." The remaining points concerned mostly the practical difficulties of ensuring that millers complied with the instructions they received, given that enrichment increased their costs. They then referred to problems in implementing other measures such as the use of undermilled and parboiled rice, and ended with the hope that "the present methods of rice enrichment may be improved so that many of the disadvantages would be overcome."[82]

The published report was preceded by an endorsement from W. R. Aykroyd and R. C. Burgess, who headed the nutrition divisions of FAO and WHO, respectively. Both have been cited already: Aykroyd for his early study of beriberi in Newfoundland, and his later work in India, and Burgess for his work with beriberi patients as a prisoner of war in Singapore. They explain that Salcedo was sent a draft of the report, and that he had prepared a further paper (to be considered

shortly) that is included as an appendix to the published version. They themselves state:

> The observations of the team, together with Dr. Salcedo's contribution, should help to clarify the whole problem of rice enrichment. It is only by trial and error, by careful balancing of the pros and cons, and by objective appraisals such as those made by the team, that various controversial issues can be decided and final conclusions reached, step by step, on a subject which is of great practical importance in many rice-eating countries.[83]

Salcedo pointed out that the cost of importing the vitamins to fortify rice for 3 million people would come to only 1/200th of the total annual cost of foods already imported into the country. It was also expected that Japanese manufacturers would soon be producing vitamins and offering them at competitive prices. This did not seem a significant bar, therefore, to a program that would improve people's health and productivity. There were always difficulties at the beginning of any novel program, and the FAO team saw the situation after only a year of the commercial stage of enrichment in a small part of the country. Salcedo then resummarized the contrasting findings in the enriched and control areas of Bataan and ended with a quotation from another writer: "These results . . . fortify the contention that enrichment of rice is an effective means of eliminating beriberi in rice-eating populations."[84]

Williams was shocked by what he considered to be the ambivalence of the FAO report and "its disregard of scientific objectivity." He was particularly critical of the use of statistics for the neighboring Tarlac province as evidence of a general decline of beriberi in the absence of enrichment. The report had referred to some enrichment having begun in Tarlac in January 1951, but it estimated that the premix taken up there could have enriched only some 7 percent of the total quantity of rice consumed, and that this small amount could not have been responsible for the fall in mortality. Williams, on the other hand, concluded that it showed that families with a beriberi problem were the ones who sought out the enriched product.[85]

He denied the team's claim that data for other provinces were not available, and said that their use would confirm that there was no comparable decline elsewhere.[86] He reprinted the full series of statistics in a later publication, and I have added to Table 11.2 the mean values

for a series of ten provinces (chosen at random) that do confirm his contention.[87]

Williams also pointed out that the apparent striking fall in the incidence of the disease in Manila arose from a misuse of the available statistics. Up to 1949 the numbers listed for the city were *not* rates but total numbers of deaths.[88] To calculate rates we need to know the city's population. In 1940 it was estimated to be 632,000. The next census in 1949 recorded 1.18 million, but it now included adjacent areas of Quezon City and Rizal City.[89] I have assumed, in view of the great destruction of much of the city in World War II, that its population rose steadily from about 600,000 in 1946 to 900,000 in 1949. The new estimates for rates of beriberi, as shown in Table 11.2, no longer indicate such a dramatic fall over the period. The values are, however, strikingly lower than for the remainder of the country. This could be due to the greater use of imported foods there, and also perhaps to medical services being more widely available than in the provinces.

Williams accepted that the visiting team, through no fault of its own, had come at a difficult time for the enrichment program. These researchers were seeing the problems of enforcement on a large scale, with opposition from many millers who were pressing politicians to reverse the new laws. He also suspected that the team had an anti-American bias and were suspicious of any program in which a U.S. company was trying to market its products at a profit.[90]

THE CONTROVERSY IN HINDSIGHT

A modern scholar, Anne Hardy, has recently reviewed in some depth the controversy between Williams and the FAO/WHO scientists. Her first point is that Williams was correct in believing that there had been a British influence at work in these organizations that was antipathetic to "technical fixes" such as rice enrichment in underdeveloped areas. She suggests that Platt and Aykroyd, in particular, had become convinced, from their international experience in the 1930s, that nutrition problems almost always sprang from poverty, and that only "structural solutions" would result in a general improvement in the quality of diets eaten by underprivileged people.[91]

In this context, structural solutions would include encouraging the use of a wider range of crops, of types already familiar in the area, and the general improvement of economic conditions for the less priv-

ileged so that they would have increased purchasing power. These are obviously long-term solutions, but, once in place, they would also provide long-term benefits.[92]

The enrichment of rice with thiamin alone, or with one or two other micronutrients, would require the entry of external materials and ideas into the community. The drawbacks would be of two kinds. First, the addition of these few specific micronutrients might well not make good all the deficiencies that would be corrected by the introduction of more natural foodstuffs into the diet. Second, the necessary governmental effort and encouragement needed to introduce and enforce enrichment, probably with the aid of international organizations, could well peter out after an initial tide of enthusiasm. Where cereal milling is carried out in many widely dispersed units, the problem, even with a strong political will, would be enormous. Hardy quotes Aykroyd's statement that such actions "cannot be taken unless governments are stable, strong and able and ready . . . to promote the welfare of their peoples. . . . these conditions are rarely fulfilled."[93]

My own feeling is that Hardy was right in saying that Williams's idea of white rice being enriched throughout all, or even a large portion, of the Philippines was impractical. The islands are dispersed, and travel at that time was quite slow, so that efficient supply and supervision of hundreds of mills could not have been achieved. However, it seems extreme to dismiss out of hand any project that could be described as a technical fix. I, too, have been a critic of projects to develop sophisticated protein isolates for under-developed areas.[94] On the other hand, the addition of traces of iodine-containing compounds to commercial salt has been of great value in reducing the problem of goiter even in many quite primitive areas. Also, of course, in the Philippines the beriberi problem arose largely because peasant communities had already adopted externally developed milling machinery. The concept of rice enrichment would thus be a technical refinement of an already adopted technology from outside. Whether or not it is applied in a particular area should, it seems, be a matter of cost-benefit considerations and practicality rather than of principle.

LATER EXPERIENCE IN ASIA

Despite Williams's hopes, enrichment of rice did not become national policy in any of the countries in Southeast Asia where beriberi had

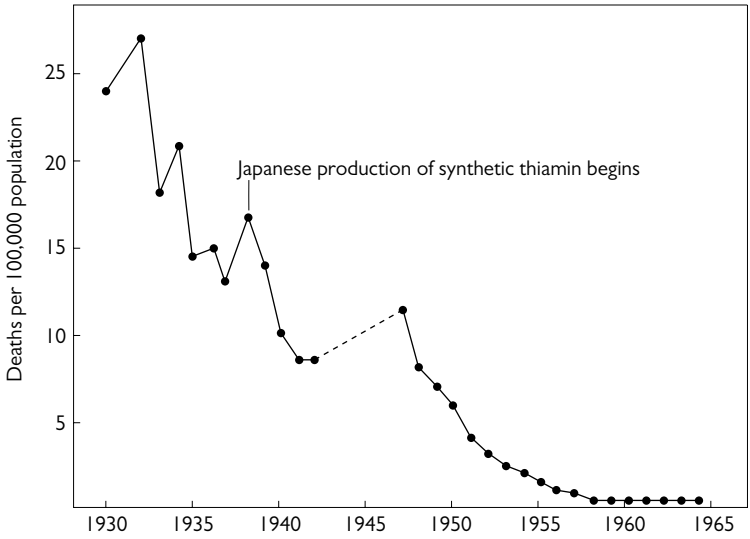


Fig. 11.3. Official statistics for mortality rates from beriberi in Japan, 1930–65 (based on data in Kawasaki, 1965; Mitsuda and Yasumoto, 1974). The dashed section of the line represents the World War II period.

been a constant problem. In 1962 it could only be reported that the armed forces in Taiwan were being issued enriched rice, and that it was available, at customers' choice, in Japan and to a small extent in Thailand.[95]

Even without enrichment, however, it appeared that beriberi was becoming less common. R. R. Williams himself commented, as a result of a visit to Malaya in 1951, that "the disease in full blown form seems largely to have disappeared."[96] R. C. Burgess, who had worked there for many years, has confirmed this and attributed the change, in great part, to education and the availability of thiamin pills.[97] And, from a survey of nutritional problems in Southeast Asia and the South Pacific in 1976, it was concluded that anemia and protein-energy malnutrition in children were the major concerns, and that, among trace nutrient problems, riboflavin and vitamin A deficiencies and also goiter each occurred in nine countries, whereas beriberi was considered to be only a "mild problem" in two (Vietnam and the Philippines).[98]

One writer challenged the "official" view in 1960, writing that, in his experience, beriberi was occurring in many parts of the Thai countryside, wherever milling of rice was replacing hand pounding.[99] Oth-

ers have added to the view that "beriberi does not prevail today as a killing epidemic" because of "slow but steady improvements in the standards of living, increasing awareness of the relationship of food to health and well-being," as well as "the availability at a cheap rate of synthetic thiamine."[100] Both views may be correct in a country where remote peasant life has little or no connection with that in rapidly growing industrial areas.

Japan experienced the most dramatic change, as is seen from the mortality statistics set out in Figure 11.3. Large-scale production of synthetic thiamin began there in the late 1940s, and by 1960 it amounted to 93,000 kg per year. If this amount had been distributed evenly among a population of nearly 100 million, it would have provided 2.6 mg/head/day—that is, more than twice as much as the 1.05 mg that had been calculated to be available in natural form in the national diet.[101]

ANOTHER CONTROVERSY IN AUSTRALIA

When the decision was made in the United Kingdom in 1940 to fortify white flour with thiamin, the flour mill owners in Australia approached their government to determine whether they should do the same. The question was referred to a medical and scientific committee, which recommended against it.[102] In 1958 a further expert committee was set up to reexamine this question, since the practice in Australia still differed from that in both the United Kingdom and the United States. It reviewed calculations indicating that the overall food supply in Australia provided 0.38 mg thiamin/1,000 kcal, and that results from dietary surveys of individuals gave average intakes of 0.35 to 0.36 mg/1,000 kcal. The committee believed the minimal requirement to be 0.2 to 0.3 mg/1,000 kcal, and that the "0.5" RDA value used in the United States was unnecessarily high.[103]

In contrast, for "alcoholics," even between bouts (i.e., while living and working in the community), the mean intake was nearly 0.2 mg/1,000 kcal (including calories from alcohol), and for 20 percent of them it was no more than 0.175 mg/1,000 kcal. The committee concluded that the general population did not need additional thiamin and that "it would be wrong in principle to add a substance to bread in order to treat a minority which is suffering from a disease—alcoholism. Better methods for treating this problem should be sought."[104]

As early as 1960, attention had been drawn to the high incidence in Australia of alcoholic beriberi patients with heart failure.[105] From the present perspective, however, the most worrisome aspect of chronic alcoholism was the high incidence of Wernicke's encephalopathy, leading to Korsakoff's psychosis. In that condition patients were incurable and needed institutional care for the remainder of their lives. In 1978 it was suggested, in a paper from New York, that it would actually be cheaper for all alcoholic beverages to be fortified with thiamin, so that alcoholics would no longer be at risk for thiamin deficiency that would, for some of them, develop into long-term brain disorders.[106]

The idea was quickly taken up in Australia, where the proportion of such cases appeared to be higher than elsewhere; in Queensland in the late 1970s there were over 60 admissions/year/million population, with 170 patients housed in a single hospital.[107] In another paper the situation in the State of Victoria was reviewed, where records showed twenty-one "first admissions for Korsakoff's psychosis"/year/million population. The authors emphasized the importance of studies on the implication of all the proposed means of increasing the thiamin intake of alcoholics.[108]

By 1986 it seemed clear that thiamin added to beer was stable and did not alter the beer's flavor or appearance.[109] Attention was focused on beer because it had traditionally been the prime drink of Australian alcoholics. And it was calculated that adding thiamin to all the beer produced in Australia would cost no more than keeping eight "Korsakoff" patients in the hospital.[110]

It also appeared that the public could be persuaded to accept the idea of "enriched" beer.[111] However, its opponents feared that it would come to be regarded as a "health food" and would "divert attention away from the main issue of high alcohol consumption."[112] It also remained to be proved that such enrichment would reduce the number of "Wernicke" and "Korsakoff cases."[113] Calculations were presented which indicated that enrichment of bread and flour would not be of significant value for most alcoholics in Australia because of their low consumption of these foods.[114]

In 1987 the government's advisory body, the National Health and Medical Research Council, recommended that "thiamin should be added to alcoholic beverages" in order to provide at least 1.25 mg/1,000 kcal. This level, some three times the requirement for a basal diet,

was chosen to allow for losses during storage and possible diminished absorption. But other organizations, including the Dietitian's Association of Australia and the Nutrition Society of Australia, registered their opposition.[115] The brewing industry as well as temperance organizations also lobbied against it, and the value of adding thiamin to wine seemed dubious after it was found to have largely disappeared after "enriched" wines had been stored for twelve months.[116]

The Research Council was forced to withdraw its recommendation and, instead, finally endorsed the enrichment of flour and bread, which was implemented in January 1991.[117] In Sydney hospitals from 1983 to 1990, the number of annual "first admissions" of patients diagnosed with Wernicke-Korsakoff syndrome had ranged from 72 to 104 (average 84); in 1992 and 1993 it was 64 and 70, respectively. This trend would appear to be consistent with enrichment having had some partial protective effect on the development of the condition.[118] By 1998 it appeared that a 40 percent reduction in incidence had been achieved, but that there was no sign of further improvement. Two research teams have now stressed that the fortification of beer in Australia is still required.[119]

CHAPTER 12

Aspects of the Subject in Hindsight

I will try to draw together here some of the main conclusions that were looked at in earlier chapters only in terms of the knowledge at the time.

THE SOCIAL CAUSES OF BERIBERI

In a biochemical sense, the cause of beriberi is a deficiency of thiamin. At the next level, one can generalize that this was because the staple foods of the sufferers contained too little of this vitamin, and that their supplementary foods were not sufficiently rich, or in sufficient quantity to correct the deficiency.

Then, in turn, comes the question of the social circumstances that led to such a choice of diet. There is no one simple answer because the circumstances differed so much from place to place. In Brazil, it was not the slaves but the rich who were at risk, as a result of their preference for plantains and tapioca (refined from cassava) with a lot of sugar, and few vegetables. In Japan, too, it was originally the better-off who seemed to suffer, while the poor rickshaw boys, for example, remained immune. In Japan, hand-powered machines began to be used in about 1700 to produce white rice, as a luxury for the better off; and soon afterward, beriberi began to be seen in its serious forms.[1] It seems clear that we humans, unlike some animals, lack an instinct to select a diet adequate in thiamin. I myself have been amazed to see hungry young chicks refuse to touch a purified diet until we added thiamin, which we discovered to have been accidentally omitted from a published formula.

Asian soldiers were sometimes supplied by the colonial powers with staple foods and given supplementary "ration money" to buy additional foods of their choice. This was done particularly where members of a unit came from groups with differing food customs. In practice, many of the men would send most of this money to their

families, thinking that they could support themselves very well on the plentiful supply of staples that they were given. Even where the official rations were considered to be complete, by the standards of the day, the disease often arose when people were unable to buy "extras" of their choice. Thus, in the Dutch colonial expedition to Atjeh, discussed in chapter 3, beriberi was a serious problem in both army and navy units; with hindsight, this appears to be explained by the men being away from the bazaars beside their home bases, where they could "eat out." For prisoners, who suffered severely from beriberi, there was no possibility of supplementing their official rations.

It is also clear that nineteenth-century authorities were not deliberately issuing inferior diets. They had every reason to want their servicemen, in particular, to be "fighting fit." It was galling, and seemingly inexplicable, to military doctors that their patients should develop beriberi while being kept under the ordinary standards of Western hygiene, and then recover in their own villages where every rule of good hygiene seemed to be flouted. The solution for both prisoners and sailors in Japan was the introduction into their diet of barley in place of much of the rice—which was actually an economy.

Poverty was, of course, an important factor—combined with ignorance—in the appearance of beriberi in the isolated "outposts" of Newfoundland. Having to purchase six months' worth of supplies ahead of time in any case limited choices, but it appears that the problem disappeared when the people were less poverty-stricken and could choose a greater variety of items. This change occurred before the cause of the disease was fully understood.

The introduction of steam-powered machine milling of rice is, of course, agreed to have been the immediate cause of the greatest increase of beriberi in Southeast Asia. It was a Western introduction, akin to the roller milling of wheat to produce white wheaten flour. It was not specifically related to colonialism, however, because its impact was as great in politically independent Japan. There was nothing definitely "bad" about white rice, and it was almost universally preferred to the brown product. The really poor free-living people in the area generally could not afford white rice and had to use either hand-pounded rice or cheaper grains that were all richer in thiamin. Rich people would normally supplement their white rice with a good

variety of flavorful ingredients, but in Japan, they would eat less of these in the heat of summer because of the traditional belief that most foods, other than rice, were "heating." Women also were taught to avoid "heating foods" during the later stages of pregnancy, regardless of the season, and it was at just this time that women were especially susceptible to the disease.[2] Elsewhere in Southeast Asia, pregnant women were afraid that a "rich" diet would result in a large baby, causing a painful and difficult delivery, so they, too, reduced their diet to little other than rice.[3]

The last at-risk group in Asia consisted of civilians in some kind of institutional living. I have already referred to the cases of prisoners and servicemen. But we have also seen the examples of young men who had come to Shanghai from the countryside to work in factories and live in large boardinghouses, and of Thai civil servants living in barracks. It has also been reported that laborers brought from China to work in newly opened tin mines suffered terribly from beriberi, with a shocking death rate. At first, the mines were almost cut off from other parts of the country, but as roads were improved and traders got through to the mines, and then as wives were able to join their husbands and had the time and skill to prepare more complex meals, the problem disappeared.[4] It seems a common observation that men on their own are not very good at feeding themselves, as exemplified in Western countries by the appearance still of cases of "bachelor scurvy."

In some social situations, an increase in affluence could make things worse. Physicians working in this century in rural Indonesia, and also Malaysia, have commented that it was in such times that beriberi cases increased, and that this was because a peasant could then afford to have a miller process his rice, rather than his family having to pound it at home. To be known as a family able to afford white rice conferred a certain social prestige among their neighbors.[5]

The social causes may therefore be said to include the acceptance of technological innovations having unforeseen consequences (the introduction of machine-milled white rice); vanity (showing neighbors that one could afford to buy it); benevolence toward one's family (soldiers sending their ration money home); poverty (isolated Newfoundlanders and young workers living in boardinghouses and unable to afford extra food); alcoholism (with its neglect of ordinary

eating patterns); and, finally, lack of education (where preventives such as thiamin tablets and vitamin-rich supplements were available at an affordable price, but not made use of).

THE DISEASE BEFORE MACHINE MILLING

Someone who has read a little about beriberi in a textbook might summarize his or her impression as follows: "Western colonial powers brought machine milling of rice to Southeast Asia, and their introduction of white rice unbalanced the native diet and caused the tragic appearance of beriberi among the population."

This seems a fairly true statement for the experience in Thailand, as described in chapter 6, but it does not account for the existence of beriberi in China, Japan, and Indonesia prior to any significant Western influence. The Portuguese priests who suffered from beriberi in the Molucca Islands in the 1500s certainly had to rely on bread made from sago meal, and this is always almost totally lacking in thiamin. It may well be that the sufferers whom Bontius saw in Java in the 1600s were also using sago meal, because rice had not yet become the predominant staple there.[6]

There seems at all times to have been a preference for white, rather than brown, rice whenever it was available. And, although the mass production of white rice required the power-driven machinery introduced from the West, the process could also, as mentioned earlier, be carried out with small, labor-intensive hand mills or even with lengthy hand pounding. But it was more expensive because of the extra labor required and the greater breakage of grains that reduced the yield. A rich man, in Japan for example, who "liked his food" could therefore already have what was then the luxury of the fully milled grain. One can imagine that he would also want it to be thoroughly washed to remove any trace of dirt or dust from the rice, which would have further reduced its thiamin content.

THE GERM THEORY

By 1886 the germ theory was explaining so many other diseases that the authorities could have been considered remiss if they had not commissioned studies of whether beriberi might also be explained in this way. As mentioned in chapter 3, this was the basis for Pekel-

haring and his colleague Winkler being sent out by the Dutch government in that year to spend eight months in that country's East Indian colonies. One may be tempted to describe Pekelharing as "the one who got it wrong," in contrast to Eijkman, "who got it right." But a close reading of Pekelharing's report, with its methodical and carefully reported observations, leads one to respect his efforts. He was obviously impressed that, after the disinfection of military housing in Atjeh, the death rate from beriberi had greatly decreased.[7] However, his second recommendation had been that men should be sent away from Atjeh as soon as there was any indication that they were developing the disease, and this, in itself, would clearly reduce the deaths occurring there.

It is to Pekelharing's credit that, at the end of his mission, he recommended that his ideas needed further testing, and that Eijkman should be given time and facilities to continue research into the problem. Also, as described in chapter 3, his emphasis on trying to produce an animal model of the disease was to prove extremely valuable, although, in Eijkman's hands, it led the trail in a quite unexpected direction.[8]

However, it is also clear that Eijkman's work, although it led eventually to his receiving a Nobel Prize, did not immediately cause workers everywhere to see beriberi in a new light as a deficiency disease. To use another phrase, there was no sudden "change of paradigm." Vorderman, and even Eijkman after his first studies back in Holland, thought only of brown rice providing a greater resistance to an infection. As noted in chapter 6, many of the workers assembled at the first international meeting in 1910 (i.e., twenty years later) still regarded the disease as being primarily an infection confined to certain areas of the world.

These workers should not be disparaged just because we now know, with the advantage of hindsight, that they were wrong. The character of the original chicken disease was not identical to that of beriberi, and another generation of human trials was needed to confirm the relevance of the animal work. Even now, it must be accepted that attacks of dysentery, for example, can lead (though we may say "only indirectly") to the appearance of the condition when the diet is marginal. And in recent years two writers, at least, have expressed their belief that outbreaks can be correlated with the growth of toxin-producing fungi on damp, white rice, under conditions where beri-

beri would not otherwise have occurred.[9] It would be unscientific to write off any such claim as inherently impossible.

As pointed out by another writer, it has sometimes been claimed that the discovery of vitamins had to come from work done at U.S. agricultural experiment stations (by McCollum, Mendel, and Osborne) because the ideas of the medical profession were too closely tied to the germ theory.[10] This really does not bear close examination.[11] Holst and Frölich, who carried out the earliest studies of experimental scurvy in guinea pigs, were both physicians, as were Eijkman and Grijns. The latter's conclusion in 1901 (quoted in chapter 4) to the effect that natural foods contain varying amounts of complex, easily disintegrated substances that are essential to the health of nervous tissue, came before any comparable statement from Wisconsin or Connecticut. The earliest statement of rodents' requirement for an unknown essential factor in milk when they were fed on a purified diet also came from a medical man, Cornelis Pekelharing, in 1905. It was unfortunate that both these statements were available only in Dutch for many years and, in practice, unknown in the English-speaking countries.

THE ELEMENT OF LUCK

Looking back, one realizes that it was only through an extraordinary combination of chance circumstances that Eijkman saw a condition with similarities to beriberi in his animal model in the late 1880s. First, we realize now that, if he had continued to work with dogs or rabbits, or even turned to rats or monkeys, a diet of white rice would not have resulted in the more-or-less specific deficiency of thiamin that it did with birds. I know of no explanation for his decision to study another species, except that he needed large numbers of animals, so that they had to be cheap. One would think he would have preferred to continue to use rabbits if they were at all similar in price because, as mammals, they were closer to humans. In practice, they would almost certainly have been fed on green food, but even if they had been fed on white rice their habit of eating "cecal feces" would have protected them from deficiency.[12]

Second, it was an extraordinary coincidence that Eijkman's birds were, without his knowledge, being fed on surplus, cooked white rice. Was the man in charge of feeding the birds given a certain amount of

money to purchase feed, and did he find that it cost him less to give the cook at the adjoining hospital a "gratuity" in exchange for his passing on leftover cooked rice? We know that, with a change of cook, the practice stopped.

As mentioned in chapter 3, if we had been in Eijkman's shoes, with nearly all of his birds getting sick in one period and then none of them doing so in the following period, I believe that most of us would simply have despaired of getting consistent results with chickens and gone back to using rabbits for the inoculation trials. However, as the saying goes, "chance favored the prepared mind," and Eijkman found an explanation for the inconsistencies.

How seriously might the understanding of beriberi have been delayed if the "bird" model of the disease had not been chanced on? We know, as described in chapter 5, that in 1906 a British worker in Malaysia, apparently with no knowledge of the Dutch studies, carried out a controlled human feeding trial in which the type of rice used was the only variable. The results were clear-cut: with ordinary white rice the disease developed, and with parboiled rice it did not. However, it had been hypothesized that the difference was caused by a toxin in the white rice. And this was only sorted out when Fraser and Stanton, now aware of Eijkman and Grijns's work, carried out chicken experiments in which they fed extracts from one type of rice combined with the other.

It is difficult to see how work could have progressed further in that period without Eijkman's animal model. Presumably, progress would have had to wait for the basic research using purified diets with rats that began around 1914, as described in chapter 7, and the gradual discovery of the complex nature of the water-soluble "vitamin B" in the 1920s.

Eijkman was, in one aspect, unlucky. In his first feeding trials his birds fed on uncooked white rice remained healthy after those fed on cooked rice had developed polyneuritis. But, in a later trial, he found that some birds did develop the disease after a long period on uncooked white rice, and he concluded that "removal of silverskin" was the crucial factor. He therefore continued to use uncooked white rice as his basal diet. This rice still contained enough thiamin for his experiments to last many months before the birds developed polyneuritis, with vitamin A deficiency also developing as a confusing factor in many of them. If Eijkman had used cooked rice, he would have ob-

tained more clear-cut results in a shorter time, and been able to run more tests.

AN ETHICAL QUESTION

The use of animal models was essential to the work just described, and for the fractionation of rice bran and the isolation of thiamin. In fact, it is hard to imagine how this work could ever have been accomplished without them. But it has to be accepted that it was at the cost of thousands of animals deliberately being made sick, and suffering as a result.

On the other hand, the suffering of the experimental animals saved the potential future suffering and premature death of thousands of humans—both adult and infant. One claim of animal activists, campaigning to outlaw all experimentation involving animals, has been that humans are so different that results obtained with animals cannot be usefully transferred to ourselves. This was clearly untrue in the present context. In an ideal world there would be no suffering for either humans or animals. In the world as it is, difficult choices have to be made. Most countries permit some types of experimentation using animals, provided that it is for a desirable end and is conducted as humanely as possible, under veterinary supervision.

As we have seen, some experiments were also carried out with "human guinea pigs." Only the one in the Philippine prison, using men under sentence of death, deliberately assigned subjects to diets that were expected to cause disease. In the others, the customary diet was being changed in various ways, in the hope that one at least would improve a particular group's health and then, if that happened, all the subjects would receive the advantage after the trial had finished.

THE TESTING OF HYPOTHESES

As mentioned in chapter 1, Kanehiro Takaki had the idea that the significant difference in the treatment of sailors in the Japanese navy, as compared with those in the British navy, where beriberi was unknown, was that the former were receiving a diet of lower protein content. He was then able to organize a test of the idea by duplicating the long voyage of a training ship in which there had been much beriberi, except that the diet was now redesigned to have a higher protein con-

tent. As we know, the men on the second voyage remained healthy, and Takaki's idea appeared to be confirmed. Nevertheless, it came to be realized later that the important change was that the "higher-protein" ingredients also contained more thiamin.

It is a common saying that it takes only one experiment to prove a theory wrong, while it can never prove it to be correct. Takaki's experience provides a classic example of this idea. A philosopher of science has written recently that, in practice, the originator of an idea usually remains its defender, and it is others who try to topple it; but that "one of the strengths of science is that it does not require scientists to be unbiased, only that they have different biases."[13]

We can see now that it was fortunate that many researchers, from a number of countries, were all working on the problem of beriberi. And there are clear examples of progress arising from differences of view. As described in chapter 5, William Fletcher had been motivated to carry out a trial in the mental hospital where he was the resident physician because he thought that Braddon's claim for the superiority of parboiled rice needed to be discredited; the result was the opposite of his expectation. And after workers started to test extracts from rice bran, and then to report on the value of individual chemicals, every claim was at once scrutinized and retested by others.

One missed opportunity occurred during the Russo-Japanese War when over ninety thousand Japanese soldiers with beriberi were evacuated from Manchuria to hospitals in Japan. This could have proved the occasion for clinical trials to compare the effectiveness of different treatments. However, it seemed that the authorities in these hospitals were so convinced that the disease was an infection that the opportunity was not taken even to test the rival nutritional theory in the expectation of discrediting it. Takaki's reports had apparently been dismissed from their minds because they did not "fit" with their pattern of ideas about the disease. They remain in our minds because they do now fit within our conceptions.

HYPOTHETICAL ENTITIES

Although by 1920 the concept of "vitamin(e) deficiencies" had been put forward to explain a number of diseases including beriberi, skeptics could reasonably claim that they were merely hypothetical entities that no one had actually seen, and therefore in the same class as

"miasmas." This criticism provided one stimulus to the intensive efforts in the 1920s and 1930s to isolate these factors as pure crystals and to demonstrate their activity. As described in chapter 7, Jansen and Donath were the first to achieve this, in 1926, but it proved very difficult, even for the original authors, to obtain further crystalline material for study of its chemistry. Instead, it was the "antiscurvy" vitamin C that was then isolated, and whose simpler structure was the first to be worked out.[14]

The final synthesis of the relatively complex thiamin molecule in 1936 was a considerable scientific achievement. It was helped by the combination of cooperation and intense competition characteristic of research in which several teams were involved. The cooperation came from each team publishing details of its own progress along the way, so that its contribution to the whole would be recognized. Although the ideas about the structure of the molecule could be criticized as being dependent on particular concepts or interpretations, there was no gainsaying the biological activity of the chemists' final synthetic product.

As described in chapters 8 and 9, the overall outcome from the analyses of foods for thiamin, and from examination of the diets eaten where beriberi occurred, was that these diets were all of low thiamin content, and that this appeared to be a sufficient explanation for the appearance of the disease. The one exception was outbreaks in a number of mental hospitals. Possibly some special factor exists in these disturbed patients, but it may also be that they were simply not eating the full diet prescribed by the authorities, so that the outbreaks cannot be considered as disproofs of the generalization.

The next finding, which signaled an important step forward in biochemical understanding in the 1930s, was that thiamin served as part of the enzyme system responsible for obtaining energy from the oxidation of sugars. This work, described in Appendix B, was the first step in linking the clinical effects of a vitamin deficiency with what was described as a "biochemical lesion."

THE BROAD PICTURE

Research that began as a project in colonial medicine, investigating a strange "tropical" disease confined to particular places, has led to findings of much wider interest. Thiamin has now been found to be part

of essential enzyme systems not only in all members of the animal kingdom but also in plants and bacteria. One difference is that plants and most bacteria are capable of synthesizing the molecule.[15]

Presumably the animal kingdom, in the course of evolution, lost that ability because it conferred no advantage. Animals had to eat plants in order to obtain sources of energy that had resulted from photosynthesis, and, in doing this, they automatically obtained the "one part per million" or so of the thiamin that they needed. And, where they lived in some kind of symbiosis with bacteria (as with ruminants or "feces-eaters"), the synthesis of thiamin by these microorganisms provided an additional supply. Carnivores, of course, obtain the nutrients synthesized by plants indirectly—by eating the plant-eaters. Whatever may have been the "natural" diet of humans, with increasing population pressure all but a small minority now have to take most of their food directly from plants, much of it in the form of cereal grains and other seeds, since animal production gives a much smaller calorie yield from the same land area.

With the development of civilization and the geographical separation of food production from the consumers in large city populations and particularly in areas with severe winters, food has to be processed into storable and easily transportable forms. Thus sugarcanes are processed to yield crystalline sugar, vegetable oils are extracted from oil seeds, and so on. As has been described throughout the book, cereal grains are deskinned and degermed, in part to yield a longer shelf life and in part to remove fibrous "bits" that many people dislike eating. Under these circumstances, and with additional cooking losses, those eating only plant fractions no longer automatically receive the necessary trace of thiamin along with their calories, and the risk of deficiency increases when the range of foods eaten is greatly reduced.

The knowledge of thiamin's concentration in different materials is enough in itself to direct us to a choice of more balanced "natural" foods, where these are available—for example, whole grains and beans. But we also have the choice of enriching unbalanced, processed foods with synthetic thiamin and other micronutrients. In the United States, as in many other countries, we now receive synthetic thiamin whenever we eat a food prepared with white flour, and also a large proportion of breakfast cereals. Much of the debate set out in chapter 11 dealt with the choice between these two options. Should a

benevolent government impose enrichment on the grounds that it will help people who lack the education, or motivation, to change their own diet? Or, in nonindustrialized areas, should people be taught and encouraged to grow alternative crops and so avoid the introduction of external "high-tech" innovations into previously self-sufficient communities?

At least we now understand the nature of thiamin deficiency and have alternative means to deal with it. The knowledge, therefore, provides a solution to one of the myriad problems involved in keeping ourselves healthy in enormous numbers in a necessarily artificial civilization.

The investigations of beriberi undoubtedly included mistakes, but this does not negate everything that was achieved. This *is* a success story: the puzzle of "this mysterious disease, with no clear analogy to any other disease known to us" was finally solved, and beriberi was found to result from a lack of something required in seemingly infinitesimal quantities. Our present knowledge required the contributions of people from different specialties: physicians, pathologists, epidemiologists, chemists, physiologists, nutritionists, and biochemists, and also chemical engineers in the pharmaceutical industry. The men and women involved in the work were distributed across the planet and represented many nationalities, and the cost of the work was met in part by foundations and universities, as well as by governments.

Some people have asked why vitamins were not discovered earlier. I like Naomi Aronson's reply that this attitude comes from succumbing to the temptation of explaining past thinking from the vantage point of the present.[16] One possible analogy is being totally puzzled by a magician's trick and then, when it has been explained to us, thinking there really was not much to it. We should, as Aronson suggests, show some "generosity of spirit" and acknowledge and feel gratitude for the work of the many people who, between them, solved what had been the mystery of beriberi, showed how the disease could be prevented, and also added a new dimension to our understanding of the foods on which our lives depend.

APPENDIX A

Thiamin Chemistry

The purpose of this appendix is to go a little further than in the main text in explaining how scientists first studied the chemical structure of the vitamin crystals, then how they reconstructed the same molecule in the laboratory and measured its concentration in foods. Finally, some similar molecules with different properties are illustrated.

ELEMENTARY ANALYSIS

The crystals were first subjected to ordinary elementary analysis. There were some problems in obtaining consistent values because the crystals could still retain a certain amount of moisture unless most carefully dried and because there was variability in analytical values for nitrogen. Ordinary elemental analysis requires that the test material be decomposed by strong heat. For carbon (C) and hydrogen (H) analyses, test materials are combusted at red heat in a stream of oxygen; the carbon dioxide and water vapor are trapped in separate absorption tubes, and their gains in weight are measured. The common "Kjeldahl" procedure for determining nitrogen (N) starts with the test material being boiled in strong sulfuric acid together with a catalyst. This decomposes most organic compounds with the nitrogen atoms being incorporated into ammonium sulfate. The solution can then be made alkaline and the free ammonia distilled off and titrated against an acid. However, not all organic compounds decompose so readily in this way, and alternative procedures have to be used.[1]

After C, H, and N have been analyzed, it is commonly assumed that the remainder of an organic compound is all oxygen (O), so that it is estimated "by difference." As described in the main text, this was assumed to be the case by Jansen and Donath, who first isolated and analyzed the vitamin.[2] Later it was found that the molecule also contained sulfur (S). On combustion, S is oxidized to sulfur trioxide,

Table A.1 How the empirical formula for vitamin B_1 was determined

Element	*Analytical data (%)*	*Atomic weights*	*Relative number of atoms: (2) ÷ (1)*	*Calculated number of atoms per molecule*[a]	*Rounded-off numbers*
	(1)	*(2)*	*(3)*	*(4)*	*(5)*
C	42.75	12.01	3.559	12.00	12
H	5.35	1.01	5.297	17.86	18
N	16.26	14.01	1.116	3.90	4
S	9.51	32.06	0.297	1.00	1
Cl	20.90	35.45	0.590	1.99	2
(O by difference)	(5.23)	16.00	(0.327)	(1.10)	1
Total	100				

SOURCE: Data reported by Wintersteiner et al. (1935).
[a]Calculation made assuming one S atom, the element present in smallest relative number.

which can be absorbed and measured as sulfate by weighing a precipitate of its insoluble barium salt.[3] When the test material is a hydrochloride, obviously chlorine (Cl) has to be estimated in addition.

When all the values have been obtained, the percentage by weight of each element can be divided by its atomic weight to give an estimate of the relative numbers of the different atoms present. Then, if it is assumed that the element present in lowest proportion has only one atom in each molecule, one can estimate the numbers of the other elements by simple proportion. This procedure has been applied to the mean analytical values reported by Wintersteiner and his colleagues in 1935,[4] with the results shown in Table A.1. The calculated values are all, within the known limits of experimental error, whole numbers. The formula for the hydrochloride could therefore be expressed as:

$$C_{12}H_{18}N_4OSCl_2$$

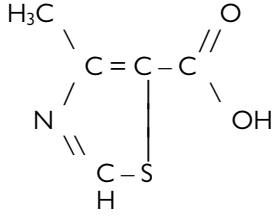
Some of the earlier analyses of the vitamin had indicated that the molecule had only three nitrogen atoms and two oxygen atoms. Underestimation of nitrogen would, of course, lead automatically to an overestimation of "oxygen by difference."

STRUCTURE AND SYNTHESIS

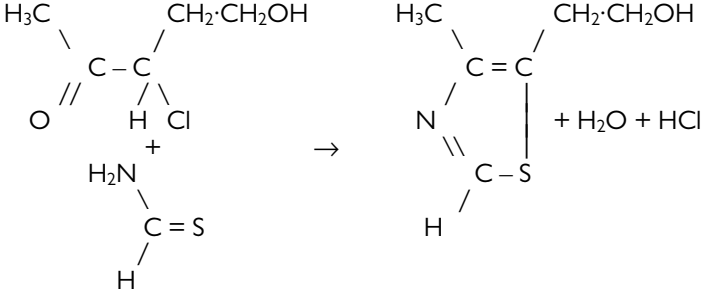
The two compounds obtained after Williams had exposed the vitamin to sodium (Na) sulfite were analyzed in the same ways. Given also the yields of the two products, it appeared that the reaction had been:

$$C_{12}H_{18}N_4OSCl_2 + Na_2SO_3 \rightarrow \underset{\text{(A, soluble)}}{C_6H_9NOS} + \underset{\text{(B, insoluble)}}{C_6H_9N_3O_3S} + 2\,NaCl$$

Product A was the first to be identified. After being boiled with nitric acid, it lost one C and four H, but added an O; the S atom remained. This new compound was now identified by its composition and physical properties with a molecule synthesized over forty years earlier:



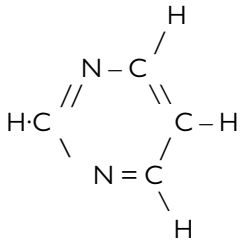
This was a thiazole ring compound, relatively easy to synthesize but not previously known to occur in nature. Chemists guessed that it had originally had a -CH_2·CH_2OH side chain that had been oxidized by nitric acid to -COOH. They then synthesized it by reacting these two compounds:



The product obtained proved to be identical to the one obtained from the vitamin.

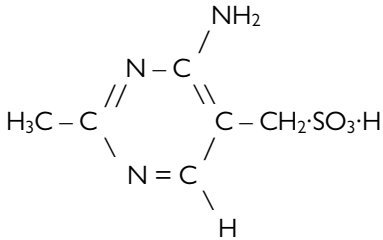
Product B took longer to identify. It failed to react at all with a number of chemicals. It did, however, have an absorption spectrum in ultraviolet light that was characteristic of pyrimidine compounds, long

known to organic chemists, in purines and uric acid. They contain this basic aromatic ring structure:

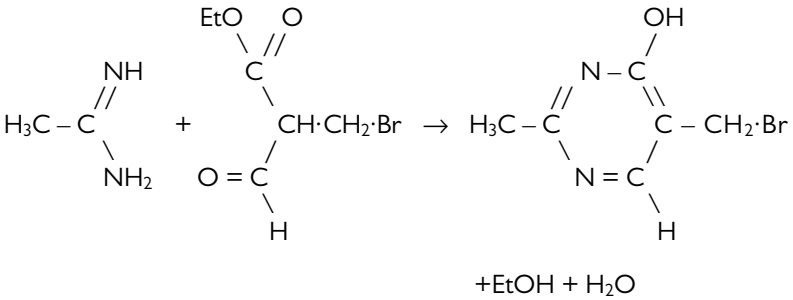


SYNTHESIS

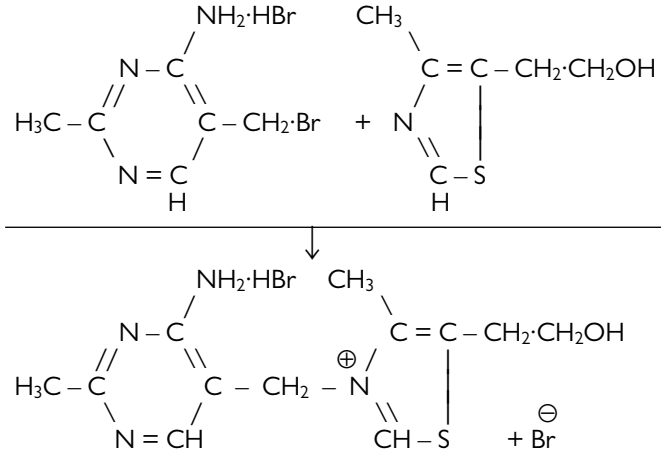
Chemists in both the United States and Germany synthesized a wide range of such compounds having the determined empirical formula. The one that finally matched the properties of the compound isolated after reaction with sulfite was:



Its synthesis, in preparation for constructing the whole vitamin molecule, was obtained by condensing the two molecules (although a few more steps were involved to achieve this):



The -OH group was then replaced by an -NH2 group by treatment with POCl3 followed by ammonia and hydrogen bromide. The two ends of the vitamin could then be joined by heating the two smaller molecules together:



This product proved to be biologically active for rats. It was converted from the hydrobromide to the corresponding hydrochloride with alcoholic silver chloride and then, when crystallized, was found to be identical in physical properties with the crystals isolated from rice polishings and from yeast.

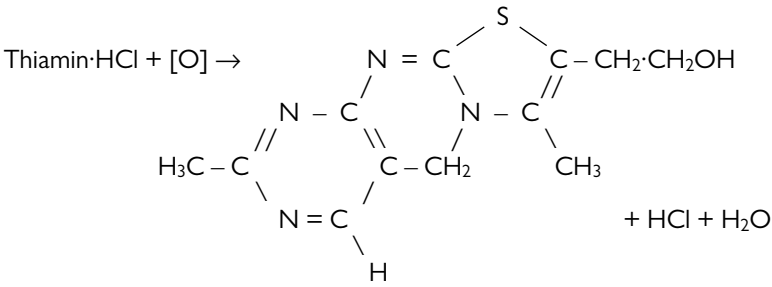
Even this description is a great simplification of the steps and work required for this achievement, and it records only the successful lines of attack. Williams has written that his group tested five hundred different preparations on rats in the course of their work. No doubt the two other groups that made a successful synthesis in the same year did a comparable amount of work.[5] I have not given references for each stage of the work, but an interested reader can get back to the original papers from an excellent review.[6]

CHEMICAL ANALYSIS FOR THE THIAMIN CONTENT OF FOODS

In order to bring thiamin into solution, the food is heated in a dilute acid and then digested with an enzyme preparation that hydrolyzes phosphate esters and also starch. The filtered solution is then passed

through a column of Decalso, a specially prepared silicate that absorbs cations, including thiamin. A hot concentrated solution of potassium chloride is then washed through the column, and the thiamin is displaced and collected in the eluate.

As mentioned in chapter 8, actual measurement became possible with the discovery that mild oxidation of thiamin converted it into a highly fluorescent compound, thiochrome:



This is achieved by adding an alkaline solution of ferricyanide and then shaking with isobutyl alcohol. The less polar thiochrome passes into the alcohol layer, which is separated by centrifugation. An aliquot containing the equivalent of as little as 0.2 mcg thiamin is then placed in a fluorometer and subjected to ultraviolet light in one direction, and the intensity of the blue light emitted in all directions is measured with a sensitive photoelectric cell. The intensity is then compared with that from a standard solution of thiamin passed through the same procedure. A "blank" value is obtained by taking a second extract of the test food through all the stages except for omission of actual ferricyanide, alkali alone being added.

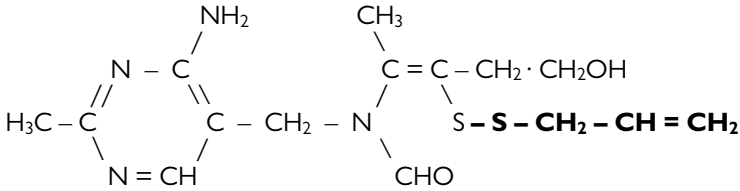
For a compound other than thiamin to produce a misleading value under these conditions it would have to (1) be absorbed as a positively charged molecule on Decalso, (2) lose its charge on treatment with ferricyanide, so as to be preferentially dissolved into the alcohol layer, and (3) fluoresce after oxidation but not before. So far, no such compound has been detected.

Problems that have been encountered relate more to difficulties of complete extraction of thiamin from some foods, and the presence of chemicals in some foods that interfere with the ferricyanide reaction, and of pigments in others that can reduce the measured fluorescence from a given amount of thiochrome. Various modifications can be adopted to get around most of these problems.[7] However, workers

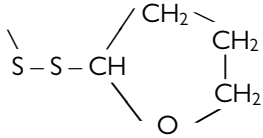
can be misled by the presence of compounds related to thiamin that can be converted to the vitamin itself within animal tissues.

ALLITHIAMINS

It was found in Japan that when thiamin was incubated with garlic extract, it was apparently destroyed, as indicated by chemical analysis, using the thiochrome procedure. However, animal assays showed that the activity remained. Chemists were able to demonstrate that the vitamin had reacted with a compound, "allicin," present in the extract. They found that the thiazole ring had broken open, and the original S atom had linked with the S in the allicin to form a disulfide bond:



The product was named "allithiamin," and it was found that with a reducing agent such as glutathione, thiamin was re-formed.[8] This appeared to happen readily in living tissues. When allithiamin was given either by mouth or by injection, it actually was followed by a greater increase in the level of thiamin in the blood than if the equivalent quantity of thiamin itself had been given.[9] This compound had originally been an accidental product, but chemists in Japan then synthesized a range of compounds with the same disulfide linkage followed by a different side chain. Their properties were then studied for easy digestibility and lack of unwanted side effects. One considered particularly useful was thiamin tetrahydrofurfuryl disulfide (TTFD), with this side chain:



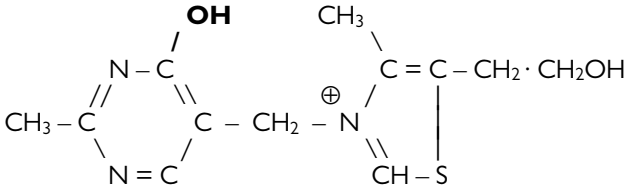
Several allithiamins of this general type have been approved for sale as nutritional supplements in Japan and in some European coun-

tries. Although less water-soluble than thiamin hydrochloride, they have been found to be more readily absorbed through the gut wall.[10] TTFD was used in research in the United States and found to be effective in treating thiamin-deficient alcoholics.[11] It was also calculated that it would be more cost-effective than thiamin for fortifying alcoholic drinks because less would be needed by alcoholics, whose absorption of thiamin itself was often reduced. However, it has not yet been approved for use as an additive in the United States.

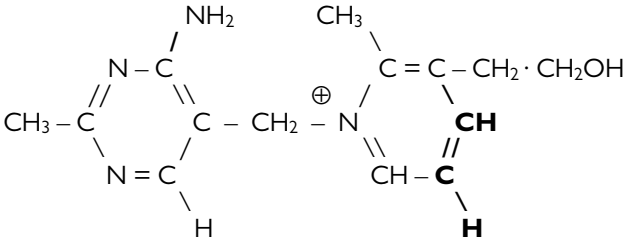
ANTITHIAMINS

Some compounds that differ only very slightly in structure from thiamin itself have been found to block the normal activity of the vitamin.[12] The two that have been most used to hasten the production of thiamin deficiency in animals are shown below. Their points of difference from thiamin itself are shown in boldface.

a. Oxythiamin:



b. Pyrithiamin:



The conditions produced by giving these two antivitamins to animals differ. This is thought to be explained by only pyrithiamin being able to pass the blood-brain barrier and thus to disturb normal brain function.[13]

APPENDIX B

Thiamin Biochemistry

One of the most exciting aspects of the history of thiamin has been that it provided the first evidence for the biochemical function of a vitamin. This was of basic interest, but it has also been of immediate, practical use for the development of more sensitive and quantitative tests of marginal deficiency of the vitamin. The material has been placed in an appendix only because it may be difficult for someone without any background in biochemistry to follow, even in the simplified form presented here.

ACID IN THE BLOOD

As we have seen, pathologists had often pointed to similarities between the neuritis of beriberi and the effects of poisons such as alcohol, arsenic, and the diphtheria toxin. In 1922 a British reviewer insisted that, although the deficiency theory explained many things, the neuritis could still be due to a toxin produced indirectly as a result of the deficiency causing a disordered metabolism.[1] And several workers had argued that the disorder was particularly related to carbohydrates, since their presence at high levels in a diet appeared to speed the appearance of the disease, at any rate in birds.[2]

In 1925 results began to appear that tied in with such an idea. Japanese workers reported that both birds fed on polished rice and patients with beriberi had elevated levels of lactic acid in their blood.[3] This compound was called "lactic" because it had originally been found in soured milk.

It was believed at that time that muscles obtain the energy to contract from the breakdown of molecules of glucose ($C_6H_{12}O_6$) to twice their number of molecules of lactic acid ($C_3H_6O_3$).[4] This reaction required no oxygen. The lactic acid would then be resynthesized to glycogen (similar to starch, and made up of glucose units condensed together), and the energy needed to drive the reaction in this direc-

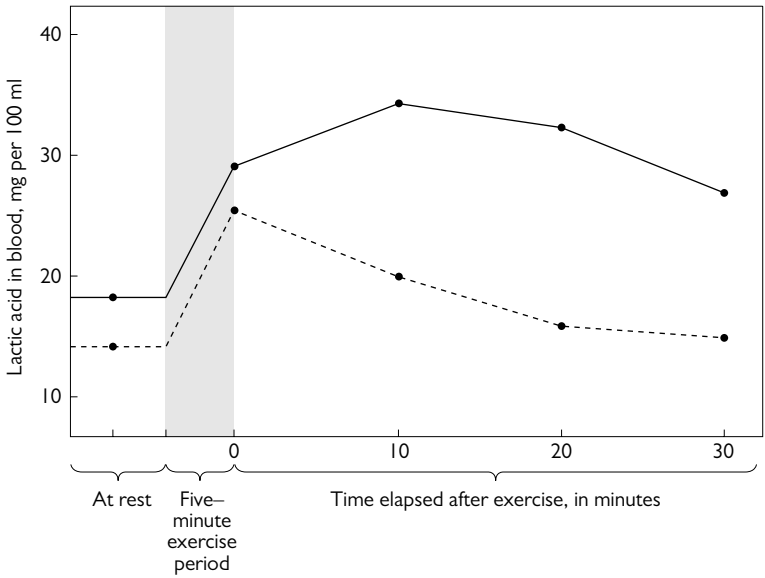


Fig. B.1. Mean values for the lactic acid contents of the blood of patients with beriberi (*solid line*), and the same subjects when cured (*dashed line*), before and after a standard period of exercise (data from Hayasaka, 1929).

tion would come from oxidation of carbohydrate or of lactic acid itself. Some of the reconversion to glycogen would occur within the active muscle, but as exercise became more severe, an increasing portion of the lactic acid would diffuse into the bloodstream and be picked up from there, for reconversion or oxidation either in the liver or in other muscles.[5]

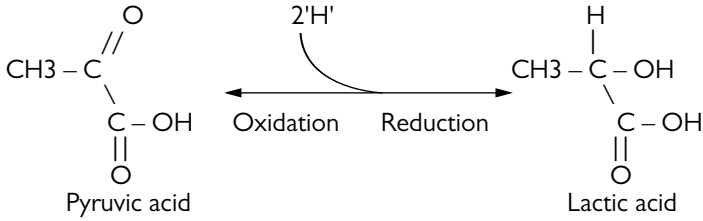
Another group of Japanese workers compared the metabolism of patients with beriberi and of healthy subjects both at rest and after exercise. The oxygen uptake of the patients increased less during the exercise, but the greatest difference between the groups was seen during the subsequent recovery from fifteen minutes of a standard exercise. After thirty minutes, the level of lactic acid in the blood of the beriberi patients was still elevated, whereas that of the healthy subjects had returned to the preexercise values (Fig. B.1).[6] The authors concluded that in beriberi a defect restricted the reconversion and/or oxidation of lactic acid.

Nevertheless, a worker in France had reported that he could find no difference between the rates of oxygen uptake in liver or muscle

taken from deficient or from normal pigeons.[7] Rudolph Peters and his colleagues at Oxford confirmed this finding but went on to study the metabolism of minced tissue from the brains of pigeons. They found particularly high levels of lactic acid in the lower portions of the brain of pigeons killed in a state of "head retraction," and they suggested that this could even be responsible for the abnormalities in these birds.[8] They went on to show that samples of these tissues when minced, with added glucose, also had abnormally low oxygen uptakes and, most important, that the uptakes could be increased, almost to the levels in tissue from normal birds, by the addition of minute quantities of a vitamin B_1 concentrate.[9]

This was an exciting finding because it was the first time that a vitamin preparation had given a measurable response when added to a specific isolated tissue rather than to a whole animal, thus supporting the idea that it should now be possible to discover the role of vitamins in particular biochemical reactions in the body.[10] Finding an effect with brain tissue, but not with either liver or muscle, could also be related to brain tissue being able to utilize only glucose as a source of energy, whereas the other tissues can also utilize fatty acids. As mentioned previously, there had been findings indicating indirectly that thiamin was needed specifically for carbohydrate utilization.

While this work was in progress, it was realized from experiments in normal metabolism that glucose was not metabolized directly to lactic acid, as had been thought, but was oxidized to pyruvic acid ($C_3H_4O_3$), which was then oxidized further to carbon dioxide and water.[11] However, if pyruvic acid accumulated in tissues for any reason, it was then largely converted to lactic acid but could be reconverted when the level of pyruvic acid fell.



Further studies showed that it was primarily pyruvic acid that was accumulating in the blood of thiamin-deficient pigeons and also of

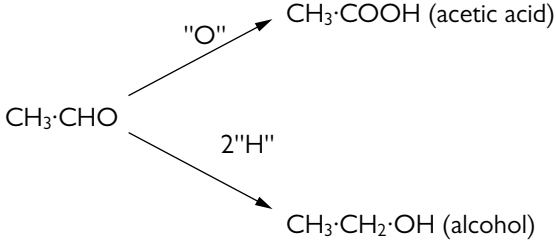
beriberi patients.[12] Some of the analytical procedures for lactic acid in use at that time actually measured pyruvic acid as well, which explains the confusion.

ENZYME ACTIVITY REQUIRING THIAMIN

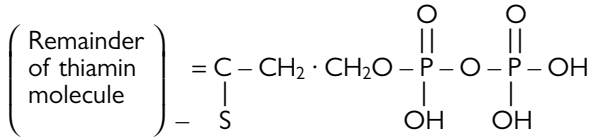
At this point a paper from Germany brought two lines of investigation together. The action of yeast in fermenting sugars to either alcohol (ethanol) or vinegar (acetic acid) had been studied for many years, and it was known that the process would continue even after the intact yeast cells had been broken up. In 1906 British investigators had shown that the process required at least two materials that were present in yeast. One had the ordinary properties of an enzyme, or "ferment," that is, being unable to diffuse through the pores in a parchment sheet and being inactivated by heat. The other necessary fraction did diffuse and was therefore assumed to be composed of small molecules, was not inactivated by moderate heat, and was called a "co-ferment."[13] By 1937 biochemists knew that the fermentation of sugars proceeded in several stages and that the co-ferment was required for the enzyme pyruvate decarboxylase, which broke down the three-carbon pyruvic acid to acetaldehyde and carbon dioxide.

$$CH_3{\cdot}CO{\cdot}COOH \longrightarrow CH_3{\cdot}CHO + CO_2$$

If there was oxygen present, the aldehyde was then converted to acetic acid. If not, it was reduced to ethanol:



Lohmann and Schuster, working at Heidelberg, were able to fractionate a large quantity of yeast from the Löwenbräu brewery and isolate the "co-ferment," now renamed cocarboxylase. They then identified it as thiamin diphosphate or pyrophosphate (TPP).[14] Thiamin itself was inactive, but yeast had the ability gradually to add the phosphate groups to the hydroxyl group of the molecule and so activate it.



So here were some very primitive life forms apparently engaged in reactions very similar to those of higher animals far distant on the evolutionary tree. Indeed, further investigations with animal tissues confirmed that it was thiamin pyrophosphate that acted as an essential cofactor for the animal (and human) enzyme pyruvate dehydrogenase, which both decarboxylated and then oxidized it to an acetyl group. Enzymes were again present to convert absorbed thiamin to TPP. Animals had also developed a further complex system for obtaining more useful energy from the oxidation of the "acetyl" group released by this enzyme, and one enzyme in this system—alpha-ketoglutarate dehydrogenase (KGDH)—has also been found to require TPP to function. A third enzyme—transketolase—requiring TPP is involved in an alternative system for the oxidation of glucose. I will be referring to this enzyme again, in connection with the assessment of thiamin status. The fact that it is present in red blood cells that can easily be sampled makes it convenient for assay. The systems involving these enzymes are described in any biochemistry textbook.

BIOCHEMICAL EXPLANATIONS OF DEFICIENCY SYMPTOMS

There are numerous papers that relate to this topic; here I refer only to a few, and to specialist reviews. Peters, in whose laboratory at Oxford the work on brain metabolism had begun in the 1930s, suggested that the reduced ability to metabolize pyruvate in thiamin-deficient pigeons constituted a "biochemical lesion." He defined this term as "the biochemical change or defect which directly precedes pathological change or dysfunction."[15] Used in this context, the term implied that the reduction in pyruvate metabolism was the cause of the malfunction of the central nervous system, manifesting itself by loss of appetite, neck drop, convulsions, and so forth.

It was postulated that malfunction of nerve cells in the affected parts of the brain could be caused either by a lack of energy or by a poisoning effect from an excess of pyruvate and lactic acids, under

conditions of thiamin deficiency. Doubts have since been expressed regarding whether the changes in enzyme activity were sufficient to account for the effects of deficiency.[16] However, it has been reported that the KGDH enzyme is concentrated in parts of the brain that are known to be damaged in thiamin deficiency.[17] These parts are thought to have especially high energy requirements, since they are constantly monitoring sensory information.

Two other ideas have also been advanced. The first was that thiamin played an essential role in the conduction of an impulse along a nerve fiber, the evidence being that "electrical stimulation of a variety of preparations of nervous tissue caused release of thiamin." It has been suggested that "thiamin plays an important role in the function of the sodium channel" in nerve conduction.[18] The second idea has been that in thiamin deficiency the blood-brain barrier loses its integrity in certain specific areas. Normally this barrier limits entry into the brain of many of the chemicals normally circulating in the blood supply. Results from several studies have indicated that in parts of the brain where there were lesions, the barrier was behaving abnormally, but it is unclear whether this was the cause or a later result of the lesions.[19]

This is obviously an exceedingly difficult research area, and participants at the symposium "Thiamine and Central Nervous System Function" in 1995 seemed to agree that "despite intensive research efforts over the last century, the precise role played by thiamine in CNS function remains much of a mystery."[20] Thus, it is not clear which of thiamin's biochemical functions fails during deficiency, nor why certain activities of the brain continue normally while others, such as eye movements, are particularly affected.

The immediate reasons for heart failure in cardiac beriberi have also been the subject of discussion. It could be caused by the muscles' lack of energy due to the relative inactivity of enzyme systems oxidizing sugars, or possibly to the heart receiving abnormal nervous signals.[21]

ASSESSMENT OF THIAMIN STATUS

There has been an interest in devising simple tests of whether people are in marginal thiamin status even though they have no clinical signs of disease. We have already seen the evidence that beriberi sufferers generally have an abnormally high level of pyruvic and lactic acids

in their blood after exercise and/or after ingesting a large quantity of glucose. However, this procedure has not proved satisfactory when many people must be screened in a short period.[22]

Urinary excretion of thiamin has also been found to relate to intake. The ideal would be to collect an individual's total urine output for twenty-four hours and then, knowing the volume, and analyzing for thiamin concentration, to calculate the total daily output. In practice, it is usually only possible to obtain a sample of urine at the time of examination, and then to measure the concentration of vitamin in the sample. However, there is a method of obtaining a rough estimate of what proportion of the day's output was present in the sample. Throughout the day, everyone excretes a quantity of another compound, creatinine, that is roughly in proportion to their muscle mass. It has been found, in turn, that the level of thiamin expressed in proportion to the level of creatinine does give a reasonably good indication of thiamin status for population groups.[23] A value from 2.7 to 6.6 mg thiamin/100 g creatinine is considered to reflect a marginal deficiency; less than that indicates a definite deficiency.

Another measure that is sometimes used is the concentration of TPP in a subject's red blood cells. Values between 0.024 and 0.030 mg of thiamin equivalent per liter are again considered marginal, with a lower value indicating deficiency. However, it is considered inferior to the transketolase assay.[24] This test has been modified in individual laboratories, but in one of the early demonstrations of its usefulness the procedure, in outline, was as follows. A blood sample was drawn from a subject without special precautions and allowed to hemolyze. Two subsamples were taken, and a quantity of ribose-5-phosphate added to each; thiamin pyrophosphate (TPP) was added just to the second tube. After an hour's incubation, each sample was analyzed for the production of hexose sugars. If the hexose formation in the sample containing added TPP was 15 to 24 percent greater, it was concluded that the subject was marginally thiamin-deficient. A response of 25 percent or more indicated a definite deficiency.[25] Because of variability between subjects, most workers have found the response to added TPP to be a more reliable indicator than the absolute response without this addition.[26]

Notes

A general note on units: Most of the English-speaking countries are still accustomed to the weights of food being expressed in pounds and ounces, and I have retained those units where possible. For those accustomed to the metric system, a pound (lb) is equivalent to 454 grams (g), and an ounce (oz) to about 28 g. Small quantities are all expressed in metric units. A milligram (mg) is one-thousandth of a gram, and a microgram (mcg) is one-millionth. Some authors have used the expression "parts per million"; this is equivalent to "mg/kg," where kilogram (kg) is the term for a thousand grams.

CHAPTER 1. THE NATIONAL DISEASE OF JAPAN (1875–85)

1. Pompe van Meerdervoort (1970), pp. 1–36.
2. Barr (1967), pp. 19–39.
3. Lockheimer (1969), pp. 163–65; Huard, Ohya, and Wong (1974), pp. 219–21.
4. Griffis (1895), p. 571.
5. Bowers (1980), pp. 48, 65–66.
6. Palm (1884), pp. 953–54.
7. Wernich (1878), p. 169; Ashmead (1890–91), p. 168.
8. Maget (1877), pp. 376–77.
9. Hoffman (1873), p. 17.
10. Scheube (1882–83), p. 146.
11. E.g., Hoffman (1873); Anderson (1876).
12. Anderson (1876), p. 5; Wong and Lien-teh (1932), p. 212.
13. Scheube (1882–83), pp. 143–44; Ching-lang (1936), pp. 324–25.
14. Scheube (1882–83), p. 145.
15. Ibid., p. 146.
16. Eldridge (1880), p. 290.
17. Maget (1877), pp. 357, 361.
18. Ibid., p. 362.
19. Ibid., pp. 368–69.
20. Bowers (1970), pp. 5, 35; Pompe van Meerdervoort (1970), p. 97.
21. Huard, Ohya, and Wong (1974), pp. 242–44.
22. Wong and Lien-Teh (1932), p. 29.
23. Copland (1858), 1:166.
24. Bowers (1980), p. 109.

25. Simmons (1880), p. 42; Scheube (1882–83), pp. 149–59; Baelz (1884), p. 330.
26. Winslow (1952), p. 34.
27. Hannaway (1993), p. 295; Worboys (1994).
28. Hoffman (1873); Palm (1884), p. 1008.
29. Eldridge (1880), pp. 339–41.
30. Cited by Scheube (1882–83), pp. 142–43.
31. Wernich (1877), pp. 348–49.
32. Wernich (1878), pp. 193–94.
33. Simoon (1991), pp. 23–24, 495–96.
34. Saneyoshi (1901), p. 73.
35. Baelz (1884), p. 330.
36. Scheube (1882–83), pp. 149–50.
37. Simmons (1880), pp. 45, 75. The adzuki bean should probably be classified as *Phasealus angularis* (Sacks [1977]).
38. Fujikawa (1911), p. 15.
39. Scheube (1882–83), pp. 115–16.
40. Huard and Wong (1959), p. 145. In modern times the cheapest grain in the North was millet, which was also found to keep the poor free from beriberi, according to Snapper (1941), pp. 187–88.
41. Oshima (1905), p. 18; Omori (1925), p. 186; Keizo (1958), pp. 51–58, 271.
42. Palm (1884), p. 996, though the same suggestion was referred to earlier by Maget (1877), p. 377.
43. Anderson (1876), p. 27; Palm (1884), pp. 998–99.
44. Howarth (1983), pp. 10–16.
45. Anderson (1877), p. 247; Takaki (1906c), p. 1370.
46. Bowers (1980), pp. 48, 65–66.
47. Takaki (1906a), p. 421.
48. Takaki (1885), p. 33.
49. Ibid., p. 29.
50. Carpenter (1994), pp. 88–99.
51. Ibid., pp. 150–51.
52. Takaki (1885), pp. 29–30. Further data were supplied by Oshima (1905), pp. 57–59.
53. Takaki (1887); Anonymous (1887).
54. Van Leent (1880a,b); Eijkman (1898a).
55. Takaki (1886). Barley had been recommended for beriberi sufferers as early as the Kyo-ho period (1716–35), according to Fujikawa (1911), p. 15.
56. Takaki (1885), p. 34.
57. Saneyoshi (1901), pp. 59–60; Toki (1911).
58. Miura (1889); Takaki (1906a), p. 426; Itokawa (1976), p. 584.

CHAPTER 2. RICE AS A STAPLE FOOD

1. Hill (1977), p. xv.
2. Hauck, Sudsaneh, and Hanks (1958), p. 33.

3. Crawfurd (1820), p. 40.
4. Ohnuki-Tierney (1993), p. 116; Seligman (1994), p. 167.
5. Lang (1996); Simoon (1991), pp. 69–70.
6. Mikkelsen and De Datta (1991), pp. 108–19.
7. Freeman (1977), p. 147.
8. Schafer (1967), p. 181; Chang (1987), p. 67.
9. Juliano (1993), pp. 3–7.
10. Thorel (1873), pp. 395–96; Aykroyd et al. (1940), p. 11; Cheng (1968), p. 12.
11. Fletcher (1909), p. 130; Aykroyd (1932), p. 184; Gariboldi (1974).
12. Vedder (1913), pp. 82–83.
13. Anderson and Anderson (1977), p. 345.
14. Ohnuki-Tierney (1993), p. 15.
15. Davis (1912), p. 25; Green (1918), pp. 3–5; Cheng (1968), pp. 98–101.
16. Highet (1913), p. 60.
17. Fon (1986).
18. E.g., Salcedo et al. (1949), p. 1.
19. Hauck, Sudsaneh, and Hanks (1958), pp. 33–34.
20. Yang (1938), p. 61.
21. Mote (1977), p. 241.
22. Pavy (1881), p. 145.

CHAPTER 3. STUDIES IN THE COLONIES: A DUTCHMAN'S CHICKENS

1. Wessels (1926), pp. 74–75.
2. Major (1945), pp. 604–5.
3. Bontius (1769) pp. 1–3.
4. Platteuw (1881); Manson and Daniels (1909), p. 615.
5. Le Roy de Méricourt (1868), p. 129.
6. Christie (1804), pp. 77–79.
7. Ibid., pp. 79–82, 86.
8. Ridley (1819), p. 231.
9. Ibid., p. 234.
10. Ibid., pp. 235–37.
11. Ibid., p. 239.
12. Le Roy de Méricourt (1868), p. 131. Malcolmson (1835), who had seen much beriberi in Madras, also makes no suggestion of dietary supplements as a means of treatment.
13. Ibid., pp. 133–34.
14. Ibid., pp. 142–43.
15. Ibid., p. 155.
16. Ibid., pp. 154–56.
17. Ibid., pp. 150–53.
18. Ibid., pp. 159–60.
19. Ibid., p. 162.

20. Van Leent (1880a), pp. 185–88.
21. Ibid., p. 184.
22. Ibid., p. 193.
23. Hirsch (1883, 1885).
24. Hirsch (1885), pp. 577, 591–93.
25. Ibid., p. 597.
26. Ibid., pp. 600–601.
27. Bulloch (1938), pp. 67–125.
28. Ibid., pp. 239–52.
29. Brock (1988), pp. 140–68.
30. Snow (1855).
31. Castiglioni (1947), p. 809.
32. Pekelharing and Winkler (1888), p. i.
33. Ibid., pp. 74–81.
34. Ibid., pp. 17–19.
35. Ibid., p. 95.
36. Ibid., pp. 96–97.
37. Ibid., pp. 99–101.
38. Ibid., pp. 107–10.
39. Ibid., pp. 122–24.
40. Van Eecke (1888); Cornelissen (1886); Pekelharing and Winkler (1888), pp. 126–27.
41. Pekelharing and Winkler (1888), pp. 131–33.
42. Baart de la Faille (1946), p. 304; Knecht-van Eekelen (1989), p. 59.
43. Eijkman (1889), pp. 81–84.
44. Eijkman (1990), pp. 5–10, 18–20, 33.
45. Ibid., pp. 20–23.
46. Eijkman (1929), p. 203.
47. Eijkman (1990), pp. 23–28.
48. Eijkman and Van Eecke (1891), p. 302.
49. Eijkman (1990), pp. 31–37.
50. Ibid., pp. 42–43.
51. Fiebig (1890).
52. Eijkman (1990), p. 43.
53. Ibid., pp. 46–48.
54. Ibid., pp. 49–50.
55. Gelpke (1890), p. 149.
56. Eijkman (1893a,b).
57. Van Leent (1880a,b).
58. Eijkman (1990), pp. 51, 54–55; Voit (1881), pp. 348–49.
59. Eijkman (1990), pp. 59–62.
60. Ibid., pp. 66–75.
61. Bouchard (1894); Hudson (1989). To borrow from the writing of a social historian, Eijkman was searching for a "legitimate pattern in the bewildering universe of clinical phenomena" (Rosenberg, 1991, p. xvii).
62. Bunge (1885); Carpenter (1990).

63. Grijns (1935), p. 141.
64. Jansen (1959), pp. 13–14.
65. Postmus (1954); Luyken (1994).
66. Eijkman was to imply in his Nobel Prize lecture that he was the one who had the original idea, but a modern Dutch scholar has pointed out that Vorderman, in his report on the investigation, wrote at the time that the idea was his (Knecht-van Eekelen, 1984, pp. 65–66).
67. Vorderman (1897), p. 54.
68. Ibid., pp 1–3.
69. Ibid., p. 58.
70. Ibid., pp. 59–64; Vorderman (1898).
71. Vorderman (1897), p. 102.
72. Miura (1889).
73. Vorderman (1897), pp. 104–5.
74. Ibid., pp. 106–7.
75. Ibid., p. 121–23.

CHAPTER 4. THE CHICKEN DISEASE REINTERPRETED

1. Eijkman (1897a), p. 275.
2. Eijkman (1897b,c); Eijkman and Vorderman (1898).
3. Eijkman (1898a), p. 275.
4. Glogner (1898), p. 56.
5. Glogner (1897), p. 136.
6. Quoted by Van der Burg (1898), p. 88.
7. Eijkman (1898b), pp. 291–92.
8. Ibid., p. 292.
9. Van Leent (1880a), p. 183.
10. Ibid., pp. 185–89.
11. Eijkman (1898b), pp. 186–209.
12. Ibid., pp. 233–43, 287, 289. In a recent paper Kamminga (1998) has discussed Eijkman's changing views in more depth.
13. Jansen (1959).
14. Luyken (1990), p. 1661.
15. Van Dieren (1897), pp. 132–34.
16. Baart de la Faille (1946), pp. 315–16.
17. Eijkman (1906), p. 158.
18. Baart de la Faille (1946), pp. 316, 328.
19. Anonymous (1935); Kik (1957a).
20. Grijns (1901).
21. Grijns (1935).
22. Ibid., pp. 2–8.
23. Ibid., pp. 11–12.
24. Ibid., pp. 14–18.
25. Ibid., p. 20.
26. Vorderman (1893), p. 349.

27. Grijns (1935), pp. 18–19.
28. Ibid., pp. 19–22.
29. Ibid., p. 24.
30. Ibid., pp. 24–27.
31. Ibid., pp. 34–38.
32. Roelfsema (1901).
33. Hulshoff Pol (1902), p. 525.
34. Hulshoff Pol (1904), pp. 140–41.
35. Grijns (1909b), in English translation in Grijns (1935), p. 141; Jansen (1959), p. 105.
36. Van Rijnberk (1928), p. 2856. On the anti-beriberi factor alone there had been 1,400 papers published up to 1929 (Stechow, 1943, pp. 18–89), and by 1932 there were 168 in a single year (Harris, 1933, p. 253).
37. Eijkman (1911), p. 700.

CHAPTER 5. THE BRITISH TAKE THEIR TURN

1. Worboys (1988).
2. Durham (1904), p. 113.
3. Braddon (1907), pp. 522–35.
4. Manson (1902), p. 832.
5. Rost (1902).
6. Sambon (1902), p. 836.
7. Ross (1902), p. 837.
8. Wright (1902), p. 1.
9. Ibid., pp. 12–23.
10. Ibid., pp. 45, 83–84.
11. Ibid., p. 45.
12. Ibid., pp. 85–86.
13. Ibid., p. 82.
14. Travers (1902).
15. Wright (1902), pp. 44–45.
16. Ibid., p. 50.
17. Ibid., pp. 58–60.
18. Ibid., pp. 63–68.
19. Wright (1903), pp. 66–67.
20. Durham (1904), pp. 128–31, 153.
21. Wright (1905), p. 133.
22. Travers (1905).
23. Braddon (1907).
24. Ibid., pp. 28–29.
25. Ibid., p. 355.
26. Ibid., pp. 173–93.
27. Vorderman (1897), pp. 14, 21.
28. Braddon (1907), pp. 147–48; Fletcher (1909), pp. 129–30.
29. Braddon (1907), pp. 370–96.

30. Ibid., pp. 368–72.
31. Ibid., pp. 452–53.
32. Daniels (1906), pp. 80, 105.
33. Fletcher (1907), p. 1776.
34. Ibid., p. 1777.
35. Ibid., p. 1778.
36. Fletcher (1909), pp. 131, 133–34.
37. Fraser and Stanton (1909a), pp. 5–6.
38. Anonymous (1938).
39. Fraser and Stanton (1909a), pp. 6–7.
40. Ibid., pp. 13–14, 22.
41. Fraser and Stanton (1909b).
42. Braddon (1911), p. 153.
43. Wylie (1988). D. W. Fraser (1998) has also recently reviewed this controversy.
44. Fraser and Stanton (1909a), unnumbered preface page.
45. Fraser and Stanton (1909b), p. 8.
46. Schaumann (1908), p. 49.
47. Fraser and Stanton (1909b), p. 7.

CHAPTER 6. THE AMERICANS CALL A MEETING

1. Heiser (1910), p. 177.
2. Koeniger (1884), pp. 419–21; Calderon (1914).
3. Kilbourne (1910), pp. 127–29.
4. Fales (1907), p. 779.
5. Kilbourne (1910), pp. 130, 135.
6. De Haan (1910), pp. 69–70.
7. Grijns (1909a).
8. De Haan (1910), p. 69.
9. De Haan and Grijns (1909).
10. Fraser and Stanton (1910b), p. 61.
11. Vedder (1913a), p. 144.
12. Highet (1910).
13. Castellani (1910), p. 138.
14. Shibayama (1910).
15. Clark (1910).
16. Strong and Crowell (1912), pp. 289–90.
17. Fraser and Stanton (1910b), p. 61.
18. Highet (1910), pp. 78–79.
19. Aron and Hocson (1910), p. 112 n. 45.
20. Dangerfield (1905), pp. 3, 180.
21. Dubruel (1905), p. 147.
22. Petit (1903).
23. O'Zoux (1910), p. 131.
24. Hulshoff Pol (1904), p. 1; Angier (1905), p. 592.

25. Cited by Primet (1911), pp. 579–82.
26. Laveran (1910).
27. Primet (1911), pp. 589–91.
28. Ibid., pp. 595–60.
29. Ibid., p. 597.
30. Ibid., pp. 603–4.
31. Saneyoshi (1901), pp. 58–59; Takaki (1906a), p. 428.
32. Herzog (1906a), p. 169; Shibayama (1910), p. 123.
33. Herzog (1906a), pp. 172–79.
34. Takaki (1906b).
35. Miura (1906).
36. Jeanselme (1911), p. 608.
37. Saneyoshi (1901), p. 80.
38. Shibayama (1910).
39. Chamberlain (1911).
40. Strong and Crowell (1912), p. 291.
41. Ibid., p. 295.
42. Ibid., pp. 400–406.
43. Ibid., pp. 406–7.
44. Ibid., p. 408.
45. Campbell (1994), p. 635.
46. Tsuzuki (1912).
47. Musgrave and Richmond (1907); Andrews (1912).
48. Hirota (1898), pp. 387–88.
49. Chamberlain and Vedder (1912).
50. Wells (1921), pp. 69–70.
51. Ibid., p. 73; Albert (1931), pp. 308–9.
52. Davis (1912).
53. Heiser (1912), p. 71.
54. Ibid., pp. 32–33.
55. Fraser and Stanton (1912), p. 68.

CHAPTER 7. THE ISOLATION AND CONSTRUCTION OF A VITAMIN

1. Eijkman (1906), pp. 161–62.
2. Schaumann (1908); Simpson and Edie (1911–12), p. 319.
3. Grijns (1909a); Fraser and Stanton (1910a); Chamberlain and Vedder (1912).
4. Schaumann (1911).
5. Suzuki, Shimamura, and Odake (1912), p. 104.
6. Suzuki (1925), p. 29.
7. Williams (1962).
8. Vedder (1913a).
9. McCollum (1957), p. 223.
10. Baldwin (1975), p. 4.

11. Chamberlain, Vedder, and Williams (1912), pp. 51–52; Vedder and Williams (1913).
12. Funk (1911).
13. Harrow (1955), pp. 3–47.
14. Funk (1912).
15. Goldblith and Joslyn (1964), pp. 145–72.
16. Drummond and Funk (1914).
17. Griminger (1972), p. 1112.
18. Williams (1915).
19. Williams (1916), p. 49.
20. Williams (1953), p. 258.
21. Williams (1916), p. 56.
22. Williams (1917), p. 519.
23. Funk (1922), pp. 20–23; McCollum (1957), pp. 203–12.
24. Hopkins (1930), p. 194.
25. Pekelharing (1905), p. 122.
26. van Leersum (1926).
27. Hopkins (1906), pp. 395–96.
28. Hopkins (1930), p. 194.
29. Hopkins (1912). The thinking behind the criticism has been discussed further by Ihde and Becker (1971).
30. Needham (1962), p. 293.
31. McCollum (1909).
32. Osborne and Mendel (1911).
33. Hopkins and Neville (1913); Osborne and Mendel (1913); Becker (1983).
34. McCollum and Davis (1913, 1915).
35. Apple (1996).
36. E.g., Sherman and Smith (1931); Sebrell and Harris (1954).
37. Funk (1922), p. 18.
38. Williams and Spies (1938), p. 126.
39. McCollum and Kennedy (1916), p. 501; McCollum, Simmonds, and Parsons (1918), p. 413.
40. Mitchell (1919), p. 400.
41. Reviewed by Sherman and Smith (1931), pp. 111–33.
42. Chick and Roscoe (1927); Sherman (1928).
43. Holst and Frölich (1907).
44. Carpenter (1986), pp. 173–79.
45. Eijkman (1990), pp. 71–72.
46. Eijkman (1913), p. 330.
47. Dutcher (1919); Jansen (1921), p. 259; Kon (1927).
48. Williams (1917); Gulland and Peters (1929).
49. Smith (1930).
50. Birch and Harris (1934).
51. Smith (1930), p. 121; Sherman and Smith (1931), p. 104; Dann (1936); Swank and Bessey (1941), p. 87.

52. McCarrison (1928), p. 57.
53. Fridericia et al. (1927–28); Kon and Watchorn (1927–28).
54. Morgan (1960); Kon (1962), pp. 361–63.
55. Review by Wostmann, Knight, and Kan (1962).
56. Jansen and Donath (1926), pp. 1391–92.
57. Harris (1938), pp. 110–12, 135–38.
58. Sherman and Smith (1931), pp. 57–68.
59. Funk (1922), pp. 164–65.
60. Jansen and Donath (1926), pp. 1396–98.
61. Eijkman (1927), pp. 379–82.
62. Williams, Waterman, and Gurin (1930).
63. Williams (1961), p. 118.
64. Jansen and Donath (1926), pp. 1398–400.
65. Sherman and Smith (1931), pp. 47–61; Williams (1961), pp. 117–20.
66. Windaus et al. (1932), p. 126.
67. Williams (1956), pp. 16–19.
68. Wintersteiner, Williams, and Ruehle (1935).
69. Williams (1961), pp. 121–25.
70. Williams (1956), pp. 21–22.
71. Williams and Cline (1936).
72. Andersag and Westphal (1937); Todd and Bergel (1937).
73. Leong and Harris (1937).
74. Hawes, Monteiro, and Smith (1937), pp. 90–93.
75. Hawes (1938), p. 475.
76. Heilbron (1948), p. 386.

CHAPTER 8. CHEMICAL ANALYSES OF FOODS: EXPLANATIONS AND SURPRISES

1. Barger, Bergel, and Todd (1935).
2. Jansen (1936).
3. Ellefson (1985).
4. Leung, Butrum, and Chang (1972).
5. Hogan (1950), pp. 751–52.
6. Jaffé (1980), pp. 92–94.
7. Grijns (1901), translated in Grijns (1935), p. 38.
8. Farrer (1955).
9. Roy (1957). During boiling, the well water went from pH 7.9 to pH 9.4.
10. Dwivedi and Arnold (1973), p. 55.
11. Farrer (1955); Tannenbaum, Young, and Archer (1985).
12. Meredith (1945), p. 443.
13. Tmangraksatve and Srisukh (1955), p. 15; Grewal and Sangha (1990).
14. Kik and Williams (1945), pp. 51–58.
15. Vedder and Feliciano (1927), p. 404.
16. Jansen (1921), p. 272.

17. Kik and Williams (1945), Table 6.
18. E.g., Holst (1911), pp. 76–77.
19. Schaumann (1911), p. 61.
20. Tsuzuki (1912), p. 995; McCarrison and Norris (1924), p. 47.
21. Jansen and Donath (1926), p. 1391.
22. Van Veen (1933), pp. 955–57. Salcedo et al. (1949), pp. 10–11, presented more detailed confirmatory results later.
23. Yang (1938), pp. 61–63.
24. Platt (1939a), pp. 20–22; Platt (1958), pp. 10–11.
25. Platt (1939b), pp. 196–99. Platt wrote that the monks and nuns had been in Hong Kong. However, Heiser (1936, p. 209) recounted a similar experience as having taken place in Saigon and being discussed at a meeting in Hong Kong. This may be what Platt had misremembered.
26. Kik and Williams (1945), Tables 4 and 5.
27. Swaminathan (1942), Table 3.
28. Yang (1938), p. 62; Aykroyd et al. (1940), p. 29; Arimoto et al. (1952); Chen, Ge, and Liu (1984), p. 25.
29. Tmangraksatve and Srisukh (1955), p. 18.
30. Farrer (1955), pp. 264–68.
31. Fletcher (1907).
32. McCarrison and Norris (1924), p. 65; Aykroyd (1932), p. 187.
33. Aykroyd et al. (1940), pp. 25–26.
34. Stanton (1923), p. 174.
35. McCollum and Davis (1915), p. 188.
36. Chick and Hume (1919), p. 59.
37. Chick, Hume, and MacFarlane (1971), pp. 124–26.
38. Carpenter (1986), p. 181.
39. Hopkins, Chick, et al. (1919), p. 31; Jansen (1921), p. 276.
40. Altson and Simpson (1941).
41. Hinton (1948a).
42. Altson and Simpson (1941).
43. Aykroyd et al. (1940), p. 11.
44. Nicholls (1947).
45. Fraser and Stanton (1913), pp. 361–62.
46. Hinton (1948a), p. 239.
47. Kennedy, Schelstraete, and Tamai (1975), p. 183.
48. U.S. Department of Agriculture (1990).
49. Paul and Southgate (1978), pp. 114–21.
50. Hoagland (1924); Christensen, Latzke, and Hopper (1936).
51. Farrer (1955), pp. 275–84.
52. Lane, Johnson, and Williams (1942), pp. 616–17.
53. Parsons, Polisar, and Otto (1947); Kingsley and Parsons (1947).
54. Paul and Southgate (1978), p. 272.
55. Lane, Johnson, and Williams (1942).
56. Leung, Butrum, and Chang (1972).

CHAPTER 9. BERIBERI WITHOUT WHITE RICE

1. Jacobs (1974), pp. 240, 684–85.
2. Cooley (1967), p. 138; Whyte (1974), pp. 259–60; Reid (1988), p. 19.
3. Fiebig (1890), pp. 461–65. However, beriberi is not mentioned as a problem in more recent studies of sago-eaters in the coastal swamp areas of the Moluccas or nearby New Guinea (Oomen, 1971, p. 15; Townsend, 1971; Ruddle et al., 1978, pp. 42–69; Lie, 1980). This may be explained by the ready availability of fresh fish and sweet potatoes (Postmus and Van Veen, 1949, p. 318).
4. McPherson (1966), p. 278.
5. Shattuck (1881); Putnam (1890), pp. 500–501.
6. Ibid., p. 505.
7. Birge (1890).
8. Hirsch (1885), pp. 584, 589–90.
9. Holst (1907), pp. 622–23; Holst (1911), pp. 76–77.
10. Carpenter (1986) pp. 173–78.
11. Holst (1911) pp. 76–77.
12. Simpson and Edie (1911), p. 338; Chick and Hume (1919), pp. 51.
13. Holst (1911), p. 78.
14. Leung, Butrum, and Chang (1972).
15. Hirsch (1885), p. 577; Anonymous (1873).
16. Féris (1881, 1882).
17. Féris (1881), pp. 6–12.
18. Féris (1882), p. 87.
19. Ibid., p. 88.
20. Féris (1881), pp. 11–12.
21. Ibid., pp. 27–30.
22. Freyre (1963), pp. 160–61.
23. Dent (1886), p. 419.
24. Freyre (1963), p. 190.
25. Lovelace (1912).
26. Lovelace (1913).
27. Vedder (1913b).
28. Walcott (1915).
29. Vedder (1913a).
30. Norman (1898), pp. 872–73.
31. Ibid., p. 876.
32. Norman (1899).
33. Norman (1898), p. 876.
34. Bondurant (1897), pp. 728–29.
35. Ibid., pp. 730–31.
36. Vedder (1913a), pp. 273–74.
37. Sprawson (1920), p. 338.
38. Willcox (1923), pp. 431–32, 441–47; Harrison (1996), who quotes also from letters and unpublished reports.

39. Little (1912), p. 2030.
40. Aykroyd (1928).
41. Mitchell (1930).
42. Passmore (1980), p. 245.
43. Aykroyd (1930), p. 367.
44. Holst (1907), p. 627; Copping and Roscoe (1937), p. 1898.
45. Briant and Klosterman (1950); Farrer (1955), pp. 271–73.
46. Aykroyd et al. (1949); Goldsmith et al. (1950).
47. Dalal (1929); Review by Patwardhan (1961), pp. 421–28.
48. Pearse (1908); Megaw (1923), p. 225.
49. Lal and Roy (1937a).
50. Lal and Roy (1937b).
51. Pasricha, Lal, and Banerjee (1940); Sarkar (1948).
52. Review by Yudkin (1949), p. 389.
53. Ibid., p. 390.
54. Owen and Ferrebee (1943).
55. Green, Carlson, and Evans (1941, 1942); Murata (1965), p. 246.
56. Yudkin (1949), pp. 392–93.
57. Jubb, Saunders, and Coates (1956).
58. Evans, Jones, and Evans (1950); review by Evans (1975), pp. 476, 479. Although thiaminases were unlikely to be a practical problem for humans, in one set of unusual circumstances it appears that they were deadly. In 1861 a group exploring the interior of the Australian continent ran out of provisions on the return journey. They lived largely on the sporocarps in the fronds of a fern (*Marsilea drummondii*) that are now known to contain two to three times more thiaminase than bracken ferns; and this thiaminase enzyme is more heat-resistant than that of bracken ferns. All four travelers experienced progressive leg weakness and extreme general lassitude. Three died, and the fourth, even after being rescued and regaining his strength on a normal diet, remained lame. (J. W. Earl and B. V. McCleary, Mystery of the poisoned expedition. *Nature* 368 [1994]:683–84.)
59. Murata (1965), pp. 220–21; Murata (1982), pp. 146–47.
60. Kimura (1965), p. 269.
61. Ibid., p. 270.
62. Bhagvat and Devi (1941); Somogyi (1949); Somogyi (1966), pp. 81–91.
63. Vimokesant et al. (1976).
64. Evans (1975), pp. 481–87; Panijpan et al. (1978), pp. 265–67; Ratanaubolchai, Pikulkarntalert, and Panijpan (1980).
65. Swaminathan et al. (1950).
66. Kuo and Hilker (1973).
67. Alcock, cited by Reynolds (1900), p. 1770.
68. Wright (1901), p. 1610.
69. Manson (1902), p. 830.
70. Shattuck (1928).
71. Ibid., p. 541.
72. Meyer (1932).

73. Minot, Strauss, and Cobb (1933), p. 1249.
74. Strauss (1935).
75. Jolliffe, Colbert, and Joffe (1936), p. 526.
76. Jolliffe and Colbert (1936).
77. Tomasulo, Kater, and Iber (1968); Thomson, Baker, and Leevy (1970); Haas (1988), p. 489.
78. Vorhaus (1939), p. 837.
79. Brown (1941).
80. Weiss and Wilkins (1937), p. 104.
81. Blankenhorn et al. (1946); Burwell and Dexter (1947); Lahey et al. (1953); Blacket and Palmer (1960); Jeffrey and Abelmann (1971).
82. Reviews by McIntyre and Stanley (1971); Zuidema (1980); and Majoor and Hillen (1982).
83. Victor, Adams, and Collins (1971), p. 2.
84. Ibid., pp. 4–8; review by Truswell and Apeagyei (1982).
85. Alexander (1940). ("Hemorrhagic polioencephalitis" was another term used to describe the condition.)
86. Jolliffe et al. (1941).
87. Phillips et al. (1952); Victor and Adams (1961), pp. 385–87; Cole et al. (1969).
88. Blennow (1975).
89. Nadel and Burger (1976); Kramer and Goodwin (1977); Harper (1980); Velez, Myers, and Guber (1985); Anonymous (1989); Klein et al. (1990).
90. Drenick, Joven, and Swendseid (1965).
91. Devathasan and Koh (1982).
92. Frantzen (1966), pp. 429–50.
93. Wechsler (1933).
94. Ecker and Woltman (1939), p. 1796.
95. Campbell and Biggart (1939); Campbell and Russell (1941).
96. Bergener and Gabriel-Jürgens (1967).
97. Evans, Carlson, and Green (1942); Jubb, Saunders, and Coates (1956); Cogan, Witt, and Goldman-Rakic (1985).
98. Prickett (1934), pp. 462–63, 467–68.
99. E.g., Street et al. (1941); Swank and Bessey (1941), p. 87; North and Sinclair (1956).
100. E.g., Walshe (1922), p. 316; Meiklejohn (1940), p. 266.
101. Hawes, Monteiro, and Smith (1937), pp. 90–93.

CHAPTER 10. HOW MUCH THIAMIN DO WE NEED?

1. Scott and Herrman (1928).
2. Fraser and Stanton (1909a), p. 23.
3. Smith and Woodruff (1951), pp. 57–62.
4. Ibid., pp. 79–80.

5. Ibid., pp. 50–53.
6. Ibid., pp. 72, 76–79.
7. Hibbs (1946), pp. 271–73.
8. Ibid., p. 274.
9. Ibid., p. 276.
10. Ibid., pp. 279–81.
11. Cruickshank (1946), pp. 125–27.
12. Spillane (1947), pp. 123–24, 136.
13. Smith and Woodruff (1951), p. 170.
14. Ibid., p. 63.
15. Cruickshank (1946), p. 124; De Wardener and Lennox (1947), p. 11.
16. De Wardener and Lennox (1947), p. 12.
17. Cruickshank (1950), p. 337; Smith and Woodruff (1951), p. 170.
18. De Wardener and Lennox (1947), pp. 14–17.
19. Williams et al (1940), pp. 787–92.
20. Ibid., pp. 795–96.
21. Jolliffe et al. (1939); Elsom et al. (1942).
22. Williams et al. (1943), p. 40. The Mayo Clinic physician was R. *D.* Williams, not to be confused with R. *R.* Williams, the chemist who began work in the Philippines in 1909 and was later a leader in the United States in the characterization and synthesis of thiamin. From 1940 on, both men were active in programs to have the American diet enriched with synthetic thiamin.
23. Ibid., pp. 49–53.
24. Papers listed by Foltz, Barborka, and Ivy (1944), p. 341; Food and Nutrition Board Subcommittee (1989), p. 126.
25. Najjar and Holt (1943). (It was stated later that "zero" thiamin diet was found to contain 0.128 mg/1,000 kcal. Wilder and Williams, 1944, p. 70.)
26. Foltz, Barborka, and Ivy (1944), p. 343.
27. Platt (1958).
28. Takahashi (1981).
29. Review by Wood (1985), pp. 176–79; Haas (1988), p. 504; Martin, McCool, and Singleton (1993), p. 31.
30. Blass and Gibson (1977).
31. Scriver et al. (1971).
32. Review by Mudd (1982).
33. Cowgill (1934).
34. Baker and Wright (1936); Harris (1938), p. 68.
35. Williams and Spies (1938), pp. 95–100.
36. Ziporin et al. (1965).
37. Food and Nutrition Board Subcommittee (1989), pp. 127–29.
38. Panel on Recommended Allowances (1969), p. 17; Passmore, Rao, and Nicol (1974), p. 39).
39. Gordon and Ganzon (1959), p. 503; Carpenter (1994), p. 182.
40. Private communication (1999).
41. Keys and Henschel (1942).

42. Harrell (1943), p. 38.
43. Harrell (1947).
44. Holt et al. (1949), p. 65.
45. Food and Nutrition Board Subcommittee (1989), p. 128; private communication (1998).
46. Nail, Thomas, and Eakin (1980), p. 200.
47. Raiten, Talbot, and Waters (1998), p. 2188S.
48. Postmus (1958), pp. 366–67.
49. E.g., Fehily (1944).
50. Aykroyd and Krishnan (1941), p. 707.

CHAPTER 11. HOW SHOULD THE KNOWLEDGE BE USED?

1. Fraser and Stanton (1909b), p. 7.
2. Heiser (1912).
3. Highet (1913), p. 50.
4. E.g., Van Veen (1940), p. 363.
5. Aykroyd (1958), p. 48.
6. Highet (1913), pp. 51–52.
7. E.g., Bernard and Lambert (1925), p. 129; De Langen (1925), pp. 82–83; Hou (1939), p. 302.
8. Williams (1961), p. 277.
9. Saiki (1939), p. 275.
10. Ibid., p. 276.
11. Anonymous (1950), p. 339; Inouye and Katsura (1965b), p. 4; Mitsuda and Yasumoto (1974), p. 132.
12. Parman (1962), p. 610.
13. Hou (1939), p. 302; similar observations were made by King and Ride (1945), p. 143.
14. Shimazono (1925), p. 60; Kimura (1938), p. 5; Kimm (1938), p. 637.
15. Inouye and Katsura (1965a), pp. 73–74; Kawasaki (1965), p. 293.
16. Saiki (1939), p. 274.
17. Ibid., p. 271.
18. E.g., Tmangraksatve and Srisukh (1955), p. 17.
19. E.g., Fletcher (1909).
20. Carpenter (1981).
21. Gariboldi (1974), p. 1.
22. E.g., Fraser and Stanton (1909a), pp. 5–6; Van Veen (1939), p. 267.
23. Aykroyd (1940), p. 351.
24. Kik and Williams (1945), pp. 61–71; Aalsmeer et al. (1954), p. 5; Bhattacharya and Ali (1985); Luh and Mickus (1991).
25. Van Veen (1947), pp. 281–82.
26. Williams (1951).
27. Burgess (1946), p. 416.
28. Smith and Woodruff (1951), pp. 188–92.

29. Burgess (1946), p. 417.
30. Apple (1996).
31. Horrocks (1995), p. 240.
32. Horrocks (1995); Apple (1996), pp. 13–32.
33. Apple (1996), pp. 102–8.
34. Orr (1937).
35. McCance, Widdowson, and Vernon-Roe (1938), p. 618.
36. Smith and Nicolson (1995), pp. 300–302; Smith (1997), pp. 152–54.
37. Smith (1995).
38. Reviewed by Kruse et al. (1943).
39. Wiehl (1942), p. 71.
40. Stamm and Wiehl (1942).
41. Cowgill (1939b).
42. Council on Foods (1939), p. 681.
43. Moran and Drummond (1940).
44. Wilder and Williams (1944), p. 3.
45. Ibid., p. 22.
46. Ibid., p. 85.
47. Ibid., p. 87.
48. Kent-Jones (1946), p. 15.
49. Magee (1946).
50. Wilder and Williams (1944), p. 7.
51. Bradley (1962), p. 604.
52. Figueroa et al. (1953), pp. 179, 193.
53. Adamson et al. (1945); Metcoff et al. (1945).
54. Aykroyd et al. (1949), pp. 331–32.
55. Adamson et al. (1945), pp. 238, 242.
56. Metcoff et al. (1945), pp. 486–87.
57. Adamson et al. (1945), p. 234.
58. Aykroyd et al. (1949), pp. 347–51; Goldsmith et al. (1950), p. 67.
59. Scobie, Burke, and Stuart (1949), p. 238.
60. Furter et al. (1946), p. 487.
61. Ibid., p. 488.
62. Mitsuda (1969), pp. 210–11.
63. Nutrition Committee for S. and E. Asia (1957), p. 17.
64. Gershoff et al. (1975), p. 172; Yong (1979), pp. 66–68.
65. Williams (1956), pp. 5–10.
66. Williams (1961), pp. 192–94.
67. Salcedo et al. (1948).
68. Furter et al. (1946).
69. Salcedo et al. (1950), pp. 502–6.
70. Ibid., pp. 507–20.
71. Burch et al. (1952), pp. 250–51.
72. Salcedo et al. (1950), pp. 521–22.
73. Williams (1961), p. 200.
74. Ibid., p. 201.

75. Aalsmeer et al. (1954), p. 1.
76. Ibid., p. 20.
77. Ibid., pp. 72–73, 81–82.
78. Ibid., pp. 35–36.
79. Ibid., pp. 12, 40.
80. Ibid., p. 39.
81. Ibid., pp. 48–51.
82. Ibid., pp. 67–68.
83. Aykroyd and Burgess (1954).
84. Salcedo (1954), p. 106.
85. Williams (1954), pp. 289–90.
86. Ibid., p. 289.
87. Williams (1961), p. 209.
88. Ibid., p. 213.
89. Anonymous (1948, 1950).
90. Williams (1961), p. 202.
91. Hardy (1995), pp. 63–67.
92. Ibid., pp. 62–63.
93. Ibid., pp. 73–75; Aykroyd (1953), p. 234.
94. Carpenter (1994), p. 179.
95. Parman (1962), p. 609. Compulsory enrichment of rice had been considered in India and rejected (Indian Council of Medical Research, 1953).
96. Williams (1961), p. 235.
97. Burgess (1958), p. 6.
98. Burgess and Burgess (1976), p. 65.
99. Stahlie (1960), p. 131. The disease was also reported to have been persisting in rural areas of the Philippines (Salcedo, 1962).
100. Bhuvaneswaran and Sreenivasan (1962), pp. 588, 597.
101. Kawasaki (1965), p. 294.
102. Clements (1986), p. 201.
103. Clements et al. (1959), pp. 20–21, 26.
104. Ibid., pp. 22, 32.
105. Blacket and Palmer (1960), p. 483.
106. Centerwall and Criqui (1978, 1979).
107. Price and Theodoros (1979), p. 316.
108. Wood and Breen (1980).
109. Meilgaard (1982); Wood (1985), pp. 198–99.
110. Price and Theodoros (1979), p. 317.
111. Budge and Price (1982).
112. Finlay-Jones (1986), p. 3.
113. Wood (1985), p. 199.
114. Price et al. (1987), p. 563; Connelly and Price (1996).
115. Rouse and Armstrong (1988), p. 605.
116. Skurray (1990).
117. Ma and Truswell (1995), p. 531.

118. Ibid., pp. 532, 534.
119. Harper et al. (1998); Drew and Truswell (1998).

CHAPTER 12. ASPECTS OF THE SUBJECT IN HINDSIGHT

1. Ohnuki-Tierney (1993), p. 15; Scheube (1882–83), p. 145.
2. Manderson and Mathews (1981), p. 4; Manderson (1986), p. 137.
3. Postmus (1958), p. 365; Stahlie (1960), p. 131.
4. Burgess (1958), pp. 4–5.
5. Van Veen (1939), p. 267; Wilcocks (1944), p. 989; Burgess (1958), p. 6.
6. Jacobs (1974), p. 215.
7. Pekelharing and Winkler (1888), pp. 130–31.
8. Carter (1977), p. 131; the *Index Medicus* listed beriberi as an infection in 1913, an intoxication in 1914, and finally as a deficiency disease only in 1915 (Follis, 1960, p. 314).
9. Ueno (1974); Tainsh (1984).
10. E.g., Follis (1960), p. 306; Ihde and Becker (1971), p. 16.
11. Aronson (1986), p. 633. Whether or not the successes of the germ theory and the experimental procedures used to develop animal models were a help or a hindrance to "deficiency" theories is discussed in depth by others (Ihde and Becker, 1971; Carter, 1977), and more recently by Kamminga (1998), p. 235.
12. Reid et al. (1963), p. 384.
13. Hull (1988), pp. 13, 22.
14. Carpenter (1986), pp. 187–97.
15. Wigglesworth (1965), pp. 470–71; Pant and Dang (1972), pp. 318–19; Goodwin and Mercer (1983), pp. 134, 339.
16. Aronson (1989), p. 88.

APPENDIX A. THIAMIN CHEMISTRY

1. Scott (1939), pp. 2475–94.
2. Jansen and Donath (1926).
3. Scott (1939), pp. 2507–10.
4. Wintersteiner, Williams, and Ruehle (1935).
5. E.g., Grewe (1936).
6. Wuest (1962).
7. Freed (1966), pp. 127–45; Leveille (1972); Horwitz (1980), pp. 740–42.
8. Fujiwara (1965), pp. 179–80.
9. Ibid., pp. 191–93.
10. Kawasaki (1965), p. 290.
11. Blass and Gibson (1977), pp. 1367–68.
12. Rogers (1962), p. 413.
13. Gubler (1976), p. 124.

APPENDIX B. THIAMIN BIOCHEMISTRY

1. Walshe (1922), p. 315.
2. Funk and Schönborn (1914); Braddon and Cooper (1914)
3. Tanaka and Endo (1925).
4. Hill, Long, and Lupton (1924), p. 438.
5. Ibid., pp. 458–62.
6. Inawashiro and Hayasaka (1928); Hayasaka (1929), p. 90.
7. Roche (1925), p. 426.
8. Kinnersley and Peters (1930), p. 721.
9. Meiklejohn, Passmore, and Peters (1932), p. 394.
10. Peters (1963), pp. 1–39.
11. Meyerhof (1933).
12. Thompson and Johnson (1935).
13. Harden and Young (1906)
14. Lohmann and Schuster (1937).
15. Peters (1967), p. 1.
16. E.g., Itokawa (1996), p. 4.
17. Calingasan et al. (1994).
18. E.g., Itokawa (1996), p. 5.
19. Review by Harata and Iwasaki (1996).
20. Itokawa and Butterworth (1996), p. 1.
21. Hashimoto (1937); Olson and Schwartz, (1951).
22. Review by Sauberlich (1967), p. 535.
23. Ibid., pp. 532–33.
24. Anderson, Vickery, and Nicol (1986), pp. 87–88.
25. Brin (1962).
26. Sauberlich et al. (1979), pp. 2243–45.

References

Aalsmeer, W. C., K. Mitra, I. A. Simpson, and N. Obando, eds. 1954. *Rice enrichment in the Philippines.* FAO Nutritional Studies, no. 12.

Adamson, J. D., et al. 1945. Medical survey of nutrition in Newfoundland. *Canadian Medical Association Journal* 52:227–50.

Addinall, C. R. 1940. *The story of vitamin B_1.* Rahway, N.J.: Merck.

Albert, J. 1931. Studies on infantile beriberi based on five hundred and fourteen cases. *Philippine Journal of Science* 45:297–318.

Alexander, L. 1940. Wernicke's disease: Identity of lesions produced experimentally by B_1 avitaminosis in pigeons with hemorrhagic polioencephalitis occurring in chronic alcoholism in man. *American Journal of Pathology* 16:61–69.

Altson, R. A., and I. A. Simpson. 1941. A note on the distribution of vitamin B_1 (thiamin) in the rice grain. *Malayan Agricultural Journal* 29:127–28.

Andersag, H., and K. Westphal. 1937. Uber die Synthese des antineuritische Vitamin. *Berichte der Deutschen chemischen Gesellschaft* [*B*]. 70:2035–54.

Anderson, E. N., Jr., and M. L. Anderson. 1977. Modern China: South. In *Food in Chinese culture,* edited by K. C. Chang, 319–82. New Haven, Conn.: Yale University Press.

Anderson, S. H., C. A. Vickery, and A. D. Nicol. 1986. Adult thiamine requirements and the continuing need to fortify processed cereals. *Lancet* ii:85–89.

Anderson, W. 1876. Kakke. *St. Thomas's Hospital Reports* 7, no. 5:5–30.

———. 1877. Further remarks on Kakke. *St. Thomas's Hospital Reports,* n.s., 8:247–50.

Andrews, V. L. 1912. Infantile beriberi. *Philippine Journal of Science* 7B:67–88.

Angier. 1905. Le béribéri. *Annales d'Hygiène et de Médecine Coloniales* 8:591–607.

Anonymous. 1873. Review of Da Silva Lima's essay on beriberi in Brazil. *Edinburgh Medical Journal* 18:832–45.

Anonymous. 1887. Kakké or Japanese beri-beri. *Lancet* ii:189–90.

Anonymous. 1908. *The Russo-Japanese war: Medical and sanitary reports.* London: HMSO.

Anonymous. 1935. Introduction. In *Prof. Dr. G. Grijns' Researches on vitamins, 1900–1911,* edited by W. A. P. Schüffner et al. Gorinchem: Noorduyn en Zoon.

Anonymous. 1938. Obituary: Sir Thomas Stanton. *British Medical Journal* i:312–13.

Anonymous. 1948 and 1950. *Whitaker's Almanac.* London: Whitaker.

Anonymous. 1950. Beriberi in Japan. *Nutrition Reviews* 8:339–41.
Anonymous. 1988. Thiamin and alcoholic beverages: To add or not to add? *Medical Journal of Australia* 148:605–6.
Anonymous. 1989. Deaths associated with thiamine-deficient parenteral nutrition. *Morbidity and Mortality Weekly Report* 38:43–46.
Anonymous. 1998. New dietary reference intakes. *Nutrition Today* 33:257–59.
Apple, R. D. 1996. *Vitamania: Vitamins in American culture.* New Brunswick, N.J.: Rutgers University Press.
Arimoto, K., et al. 1952. The loss of vitamin B_1 through washing and cooking of rice. *Annual Report of the National Institute of Nutrition, Japan,* pp. 32–34. Tokyo: National Institute of Nutrition.
Aron, H., and R. Hocson. 1910. Phosphorus starvation with special reference to beriberi: II. *Philippine Journal of Science* 5B:98–122.
Aronson, N. 1982. Nutrition as a social problem: A case study of entrepreneurial strategy in science. *Social Problems* 29:474–87.
———. 1986. The discovery of resistance: Historical accounts and scientific careers. *Isis* 77:630–46.
———. 1989 Why weren't vitamins discovered earlier? *Knowledge and Society* 8:87–105.
Ashmead, A. S. 1890–81. Some observations on kakké, the national disease of Japan. *University Medical Magazine Philadelphia* 3:168–75.
Aykroyd, W. R. 1928. Vitamin A deficiency in Newfoundland. *Irish Journal of Medical Science* 28:161–65.
———. 1930. Beriberi and other food deficiency diseases in Newfoundland and Labrador. *Journal of Hygiene* 30:357–86.
———. 1932. The effect of parboiling and milling on the antineuritic vitamin (B_1) and phosphate content of rice. *Journal of Hygiene* 32:184–92.
———. 1939. The improvement of the poor rice-eater's diet. *Proceedings of the 6th Pacific Science Congress, California* 6:313–17.
———. 1940. The poor rice-eater's diet. *Bulletin of the Health Organization of the League of Nations* 9:342–56.
———. 1953. FAO. *Nutrition Abstracts and Reviews* 23:229–43.
———. 1958. Beriberi: Rice. *Federation Proceedings* 17(suppl. 2):48–50.
Aykroyd, W. R., and R. C. Burgess. 1954. Note by the Nutrition Division of FAO and the Nutrition Section of WHO. In *Rice enrichment in the Philippines,* edited by W. C. Aalsmeer et al. FAO Nutritional Studies, no. 12:iii.
Aykroyd, W. R., N. Jolliffe, O. H. Lowry, et al. 1949. Medical resurvey of nutrition in Newfoundland. *Canadian Medical Association Journal* 60:329–52.
Aykroyd, W. R., and B. G. Krishnan 1941. Infantile mortality in the beriberi area of the Madras presidency. *Indian Journal of Medical Research* 29:703–8.
Aykroyd, W. R., B. G. Krishnan, R. Passmore, and A. R. Sundararajan. 1940. The rice problem in India. *Indian Medical Research Memoir,* no. 32.
Baart de la Faille, J. M. 1946. Christiaan Eijkman. In *Nederlandsche Helden de Wetenschap,* edited by T. P. Sevensma, 299–333. Amsterdam: Kosmos Publishing.

Baelz, B. 1884. Kakke (béribéri) du Japon. *Archives de Médecine Navale* 41: 330–38.

Baker, A. Z., and M. D. Wright. 1936. Vitamin B_1 in human diets. *Proceedings of the Royal Society of Medicine* 29:1145–54.

Baldwin, R. S. 1975. Robert R. Williams (1886–1965): A biographical sketch. *Journal of Nutrition* 105:1–14.

Barger, G., F. Bergel, and A. R. Todd. 1935. A crystalline fluorescent dehydrogenation product from vitamin B_1. *Nature, London* 136:259.

Barr, P. 1967. *The coming of the barbarians* London: Macmillan.

Becker, S. L. 1983. Will milk make them grow? An episode in the discovery of the vitamins. In *Chemistry and modern society,* edited by J. Parascandela and J. Whorton, 61–83. Washington, D.C.: American Chemical Society.

Bennet, J. 1946. Nutritional conditions in army prison camps in the Far East. *Proceedings of the Nutrition Society* 5:89–94.

Berg, A. 1973. *The nutrition factor.* Washington, D.C.: Brookings Institution.

Bergener, M., and P. Gabriel-Jürgens. 1967. Thiamine excretion and transketolase activity in chronic alcoholism and Wernicke's encephalopathy. *German Medical Monthly* 12:396–97.

Bernard, P. N., and A. Lambert. 1925. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo* 1:91–146.

Bhagvat, K., and P. Devi. 1941. Inactivation of thiamine by certain foodstuffs and oil seeds. *Indian Journal of Medical Research* 32:131–44.

Bhattacharya, K. R., and S. Z. Ali. 1985. Changes in rice during parboiling, and properties of parboiled rice. *Advances in Cereal Science Technology* 7:105–67.

Bhuvaneswaran, C., and A. Sreenivasan. 1962. Problems of thiamine deficiency states and their amelioration. *Annals of the New York Academy of Sciences* 98:576–601.

Birch, T. W., and L. J. Harris. 1934. Bradycardia in the vitamin B_1–deficient rat and its use in vitamin B_1 determinations. *Biochemical Journal* 28:602–21.

Birge, W. S. 1890. Cases of beri-beri occurring in the Provincetown Grand Bank fishing fleet. *Boston Medical and Surgical Journal* 123:464.

Blacket, R. B., and A. J. Palmer. 1960. Haemodynamic studies in high output beri-beri. *British Heart Journal* 22:483–501.

Blankenhorn, M. A., C. F. Vilter, I. M. Scheinker, and R. S. Austin. 1946. Occidental beriberi heart disease. *Journal of the American Medical Association* 131:717–26.

Blass, J. P., and G. E. Gibson. 1977. Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. *New England Journal of Medicine* 297:1367–70.

Blennow, G. 1975. Wernicke's encephalopathy following prolonged artificial nutrition. *American Journal of Diseases of Children* 129:1456.

Bondurant, E. D. 1897. Endemic multiple neuritis (beriberi). *New York Medical Journal* 66:685–91, 728–32.

Bontius, J. 1769. *An account of the diseases, natural history and medicines of the East Indies.* London: Noteman.

Bouchard, C. 1894. *Lectures on auto-intoxication in disease.* Translated by T. Oliver. Philadelphia: Davis.

Bowers, J. Z. 1970. *Western medical pioneers in feudal Japan.* Baltimore: Johns Hopkins University Press.

———. 1980. *When the twain meet: The rise of Western medicine in Japan.* Baltimore: Johns Hopkins University Press.

Braddon, W. L. 1907. *The cause and prevention of beri-beri.* London: Rebman.

———. 1911. Correspondence: Beri-beri. *Journal of Tropical Medicine and Hygiene* 14:153–54.

Braddon, W. L., and E. A. Cooper. 1914. The influence of the total fuel-value of a dietary upon the quantity of vitamine required to prevent beri-beri. *British Medical Journal* i:1348–49.

Bradley, W. B. 1962. Thiamine enrichment in the United States. *Annals of the New York Academy of Sciences* 98:602–6.

Briant, A. M., and A. M. Klosterman. 1950. Influence of ingredients on thiamine and riboflavin retention and quality of plain muffins. *Transactions of the American Association of Cereal Chemists* 8:69–77.

Brin, M. 1962. Erythrocyte transketolase in early thiamin deficiency. *Annals of the New York Academy of Sciences* 98:528–41.

Brock, T. D. 1988. *Robert Koch: A life in medicine and bacteriology.* Madison, Wis. Science Tech.

Brown, E. B., J. C. Hamm, and H. E. Harrison. 1943. Comparison of thiamine values by chemical and bioassay methods. *Journal of Biological Chemistry* 151:153–61.

Brown, M. R. 1941. Alcoholic polyneuritis. *Journal of the American Medical Association* 116:1615–18.

Budge, M., and J. Price. 1982. Public reaction to a proposal to fortify beer with thiamin. *Journal of Food and Nutrition* 39:147–51.

Bulloch, W. 1938. *A history of bacteriology.* London: Oxford University Press.

Bunge, G. 1885. Ueber die Assimiliation des Eisens. *Hoppe-Seyler's Zeitschrift für Physiologische Chemie* 9:49–59.

Burch, H. B., J. Salcedo, E. O. Carrasco, C. L. Intengan, and A. B. Caldwell. 1950. Nutrition survey and tests in Bataan, Philippines. *Journal of Nutrition* 42:9–29.

Burch, H. B., J. Salcedo, E. O. Carrasco, and C. L. Intengan. 1952. Nutrition resurvey in Bataan, Philippines. *Journal of Nutrition* 46:239–54.

Burgess, H. J. L., and A. P. Burgess. 1976. Malnutrition in the Western Pacific region. *WHO Chronicle* 30:64–69.

Burgess, R. C. 1946. Deficiency diseases in prisoners-of-war at Changi, Singapore. *Lancet* ii:411–18.

———. 1958. Epidemiology and infantile beriberi. *Federation Proceedings* 17(suppl. 2):3–7, 39–48.

Burwell, C. S., and L. Dexter. 1947. Beri-beri heart disease. *Transactions of the Association of American Physicians* 60:59–64.

Butterworth, R. F. 1989. Effects of thiamine deficiency on brain metabolism:

Implications for the pathogenesis of the Wernicke-Korsakoff syndrome. *Alcohol and Alcoholism* 24:271–79.

Calderon, F. 1914. Some data concerning the medical geography of the Philippines. *Philippine Journal of Science* 9B:199–218.

Calingasan, N. Y., H. Baker, K.-F. R. Shen, and G. E. Gibson. 1994. Distribution of the a-ketoglutarate dehydrogenase complex in rat brain. *Journal of Comparative Neurology* 346:461–79.

Campbell, A. C. P., and J. H. Biggart. 1939. Wernicke's encephalopathy (polioencephalitis haemorrhagica superior): Its alcoholic and non-alcoholic incidence. *Journal of Pathology and Bacteriology* 48:245–62.

Campbell, A .C. P., and W. R. Russell. 1941. Wernicke's encephalopathy: The clinical features and their probable relationship to vitamin B deficiency. *Quarterly Journal of Medicine,* n.s., 10:41–51.

Campbell, K. A. 1994. Knots in the fabric: Richard Pearson Strong and the Bilibid prison vaccine trials, 1905–1906. *Bulletin of the History of Medicine* 68:600–638.

Cannon, A. 1929. The pathology of beriberi. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 23:263–68.

Carpenter, K. J. 1981. Effects of different methods of processing maize on its pellagragenic activity. *Federation Proceedings* 40:1531–35.

———. 1986. *The history of scurvy and vitamin C.* New York: Cambridge University Press.

———. 1990. The history of a controversy over the role of inorganic iron in the treatment of anemia. *Journal of Nutrition* 120:141–47.

———. 1994. *Protein and energy: A study of changing ideas in nutrition.* New York: Cambridge University Press.

Carpenter, K. J., and W. J. Lewin. 1985. A reexamination of the diets associated with pellagra. *Journal of Nutrition* 115:543–52.

Carpenter, K. J., and B. Sutherland. 1995. Eijkman's contribution to the discovery of vitamins. *Journal of Nutrition* 125:155–63.

Carter, K. C. 1977. The germ theory, and the deficiency theory of disease. *Medical History* 21:119–36.

Castellani, A. 1910. Discussion. *Philippine Journal of Science* 5B:138.

Castiglioni, A. 1947. *A history of medicine.* 2d ed. New York: Knopf.

Centerwall, B. S., and M. H. Criqui. 1978. Prevention of the Wernicke-Korsakoff syndrome. *New England Journal of Medicine* 299:285–89.

———. 1979. Prevention of the Wernicke-Korsakoff syndrome: An updated cost benefit analysis. *New England Journal of Medicine* 300:320–21.

Chamberlain, W. P. 1911. The eradication of beriberi from the Philippine (Native) Scouts by means of a simple change in their dietary. *Philippine Journal of Science* 6B:133–46.

Chamberlain, W. P., H. D. Bloomberg, and E. D. Kilbourne. 1911. A study on the influence of rice diet and of inanition on the production of multiple neuritis of fowls and the bearing thereof on the etiology of beriberi. *Philippine Journal of Science* 6B:177–208.

Chamberlain, W. P., and E. B. Vedder. 1912. The cure of infantile beriberi by the administration to the infant of an extract of rice polishings. *Bulletin of the Manila Medical Society* 4:26–29.

Chamberlain, W. P., E. B. Vedder, and R. R. Williams. 1912. A third contribution to the etiology of beriberi. *Philippine Journal of Science* 7B:39–52.

Chang, T.-T. 1987. The impact of rice on human civilization and population expansion. *Interdisciplinary Science Reviews* 8:63–69.

Chen, X.-C., K.-Y. Ge, and L.-F. Liu. 1984. Studies on beriberi and its prevention. *Journal of Applied Nutrition* 36:20–26.

Cheng, S.-H. 1968. *The rice industry of Burma: 1852–1940.* Kuala Lumpur: University of Malaya Press.

Chick, H., and E. M. Hume. 1919. The distribution in wheat, rice, and maize grains of the substance, the deficiency of which in a diet causes polyneuritis in birds and beri-beri in man. *Proceedings of the Royal Society, Series B* 90:44–60.

Chick, H., E. M. Hume, and M. MacFarlane. 1971. *War on disease: A history of the Lister Institute.* London: Deutsch.

Chick, H., and M. H. Roscoe. 1927. On the composite nature of the water-soluble B vitamin. *Biochemical Journal* 21:698–711.

Ching-lang, K. 1936. Infantile beriberi in Shanghai. *Chinese Medical Journal* 50:324–40.

Christensen, F. W., E. Latzke, and T. H. Hopper. 1936. The influence of cooking and canning on the vitamin B and G content of lean beef and pork. *Journal of Agricultural Research* 53:415–32.

Christie, T. 1804. Letter on beriberi. In *An essay on the diseases incident to Indian seamen,* edited by W. Hunter, 77–87. Calcutta: Honorable East India Company.

Chun, J. W. H., and W. L. Teh. 1926. Beriberi control from an administrative standpoint. *Oriental Journal of Diseases of Infants* 1:25–35.

Clapham, W. C. S. 1872. Brief notes on beri-beri as seen in Java. *Lancet* ii:293.

Clark, F. 1910. Discussion. *Philippine Journal of Science* 5B:144.

Clements, F. W. 1986. *A history of human nutrition in Australia.* Melbourne: Longman Cheshire.

Clements, F. W., et al. 1959. Report of a committee appointed to review the nutritive significance of Australian bread. *National Health Medical Research Council Special Reports,* no. 9.

Cogan, D. G., E. D. Witt, and P. S. Goldman-Rakic. 1985. Ocular signs of thiamine-deficient monkeys and in Wernicke's disease in humans. *Archives of Ophthalmology* 103:1212–20.

Cole, M., et al. 1969. Extraocular palsy and thiamine therapy in Wernicke's encephalopathy. *American Journal of Clinical Nutrition* 22:44–51.

Connelly, L., and J. Price. 1996. Preventing the Wernicke-Korsakoff syndrome in Australia: Cost-effectiveness of thiamin-supplementation alternatives. *Australian and New Zealand Journal of Public Health* 20:181–87.

Cooley, F. L. 1967. Allang: A village on Ambon Island. In *Villages in Indonesia,* edited by Koentjaraningrat, 129–56. Ithaca, N.Y.: Cornell University Press.

Copland, J. 1858. *A dictionary of practical medicine.* 3 vols. London: Longman.
Copping, A. M., and M. H. Roscoe. 1937. The water-soluble B-vitamins in yeast, flour and bread. *Biochemical Journal* 31:1879–902.
Cornelissen, A. H. 1886. Beri-beri. *Nederlands Tijdschrift voor Geneeskunde* 30 II:489–90.
Council on Foods. 1939. Report of annual meeting. *Journal of the American Medical Association* 113:680–81.
Cowgill, G. R. 1934. *The vitamin B requirement of man.* New Haven, Conn.: Yale University Press.
———. 1939a. Human requirements for vitamin B_1. In *The vitamins,* 229–248. Chicago: American Medical Association.
———. 1939b. The need for the addition of vitamin B_1 to staple American foods. *Journal of the American Medical Association* 113:2146–51.
Crawfurd, J. 1820. *History of the Indian archipelago.* 3d ed. Edinburgh: Constable.
Crow, C. 1914. *America and the Philippines.* New York: Doubleday.
Cruickshank, E. K. 1946. Experiences in the military camp at Singapore. *Proceedings of the Nutrition Society* 5:121–27.
———. 1950. Wernicke's encephalopathy. *Quarterly Journal of Medicine,* n.s., 19:327–38.
———. 1952. Dietary neuropathies. *Vitamins and Hormones* 10:1–45.
Dalal, K. R. 1929. Report on the investigation of an outbreak of epidemic dropsy in Rangoon in the year 1924. *Indian Medical Gazette* 64:19–20.
Dangerfield, H. V. 1905. *Le béribéri.* Paris: Maloine.
Daniels, C. W. 1906. Observations in the Federated Malay States on beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* vol. 4, no. 1.
Dann, F. P. 1936. Vitamin B assay using rat curative method and oral administration of addenda. *Journal of Nutrition* 12:461–68.
Davis, C. N. 1912. Observations on beriberi in Shanghai. *Transactions of the 2nd Congress of the Far Eastern Association for Tropical Medicine, Hong Kong,* 23–30.
De Bevoise, K. 1995. *Agents of apocalypse: Epidemic disease in the colonial Philippines.* Princeton, N.J.: Princeton University Press.
De Haan, J. 1910. On the etiology of beriberi. *Philippine Journal of Science* 5B:65–71.
De Haan, J., and G. Grijns. 1909. Over het ontbreken van antigen en zoogenaamde antistoffen bij beri-beri en bij kippenneuritis. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 49:258–73.
De Langen, C. D. 1925. The international control of beri-beri. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo* 1:61–85.
———. 1927. Beri-beri: Een klinische studie van voeding en ziekte in Nederlands-Indië. The Hague: G. Naeff.
De Wardener, H. E., and B. Lennox. 1947. Cerebral beriberi (Wernicke's encephalopathy). *Lancet* i:11–17.
Dent, H. C. 1886. *A year in Brazil.* London: Kegan Paul.

Devathasan, G.. and C. Koh. 1982. Wernicke's encephalopathy in prolonged fasting. *Lancet* ii:1108–9.

Donath, W. F., and J. P. Spruyt. 1936. Het B_1-vitamine gehalte en de voedingswaarde van eenige belangrijke Indische voedingsmiddelen. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 76:642–95.

Drenick, E. J., C. B. Joven, and M. E. Swendseid. 1965. Occurrence of acute Wernicke's encephalopathy during prolonged starvation for the treatment of obesity. *New England Journal of Medicine* 274:937–39.

Drew, L. R., and A. S. Truswell. 1998. Wernicke's encephalopathy and thiamine fortification of food: Time for a new direction? *Medical Journal of Australia* 168:534–35.

Dreyfus, P. M., and M. Victor. 1961. Effects of thiamine deficiency on the nervous system. *American Journal of Clinical Nutrition* 9:414–25.

Drummond, J. C., and C. Funk. 1914. The chemical investigation of the phosphotungstate precipitate from rice polishings. *Biochemical Journal* 8:598–615.

Drummond, J. C., and G. F. Marrian. 1926. The physiological role of vitamin B. Part I. *Biochemical Journal* 20:1229–55.

Dubruel, C. M. E. 1905. *Le béribéri.* Paris: Taffard.

Durham, H. E. 1904. Notes on beriberi in the Malay Peninsula and on Christmas Island. *Journal of Hygiene* 4:112–55.

Dutcher, R. A. 1919. Antineuritic properties of certain physiological stimulants. *Journal of Biological Chemistry* 39:63–68.

Dwivedi, B. K., and R. G. Arnold. 1973. Chemistry of thiamine degradation in food products and model systems: A review. *Journal of Agricultural and Food Chemistry* 21:54–60.

Ecker, A. D., and H. W. Woltman. 1939. Is nutritional deficiency the basis of Wernicke's disease? *Journal of the American Medical Association* 112:1794–96.

Eijkman, C. 1889. Over de oorzaak der Beri-Beri. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 29:76–87.

———. 1893a. Bijdrage tot de kennis van de stofwisseling bij de bewoners der tropen. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 33:163–217.

———. 1893b. Iets over de "Voeding in Garnizoen" van den Europeeschen Soldaat in Nederlandsch-Indië. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 32:336–52.

———. 1893c. Polyneuritis bij hoenderen. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 32:353–62.

———. 1897a. Eine Beri-Beri-ähnliche Krankheit der Hühner. *Virchow's Archiv* 148:523–32.

———. 1897b. Ein Versuch zur Bekämpfung der Beri-Beri. *Virchow's Archiv* 149:187–94.

———. 1897c. Note sur la prophylaxie du béribéri. *Janus* 2:23–29.

———. 1898a. Beri-beri en voeding: Ein kritisch-historische studie. *Nederlands Tijdschrift voor Geneeskunde* 34:186–209, 233–47, 275–303.

———. 1898b. Beri-beri: Zur Abwehr. *Archiv für Schiffs- und Tropen-Hygiene* 2:103.

———. 1906. Über Ernährungspolyneuritis. *Archiv für Hygiene* 58:150–70.

———. 1911. Polyneuritis gallinarum und beriberi. *Archiv für Schiffs- und Tropen-Hygiene* 15:698–712.

———. 1913. Über di Natur und Wirkungsweise der gegen experimentelle Polyneuritis wirksamen Substanzen. *Archiv für Schiffs- und Tropen-Hygiene* 17:328–35.

———. 1927. Experiments with Jansen and Donath's antiberiberi-vitamin. *Koninklijke Akademie van Wetenschappen, Amsterdam, Proceedings* 30:376–82.

———. 1929. Nobel lecture: Antineuritic vitamin and beriberi. In *Nobel Lectures: Physiology or medicine, 1922–1941.* Amsterdam: Elsevier, 1965.

———. 1990. *Polyneuritis in chickens, or the origin of vitamin research.* [D. G. van der Heij, translator of papers originally published in *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 30:295–334 (1890); 32:353–62 (1893); 36:214–69 (1896)]. Basel: Hoffman–La Roche.

Eijkman, C., and J. W. F. J. Van Eecke. 1889. Beri-beri. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 29:74–88.

———. 1891. Verslag over de onderzoekingen gedurende het jaar 1890. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 31:296–303.

Eijkman, C., and C. J. C. van Hoogenhuyze. 1916. The influence of feeding and starvation on the development of *polyneuritis gallinarum. Koninklijke Akademie van Wetenschappen, Amsterdam, Proceedings* 18:1467–80.

Eijkman, C., and A. G. Vorderman. 1898. De bestrijding der beri-beri. *Koninklijke Akademie van Wetenschappen, Amsterdam, Verslag. Wis-en Natuurkundige Afdeeling* 6:6–11.

Eldridge, S. 1880. On beri-beri. *Pacific Medical and Surgical Journal* 23:289–95, 337–47.

Ellefson, W. C. 1985. Thiamin. In *Methods of vitamin assay,* edited by J. Augustin et al., 349–63. 4th ed. New York: Interscience.

Elsom, K. O.., J. G. Reinhold, J. T. L. Nicholson, and C. Chornock. 1942. The normal requirement for thiamine. *American Journal of the Medical Sciences* 203:569–77.

Engel, R. W., and P. H. Phillips. 1938. The lack of nerve degeneration in uncomplicated vitamin B_1 deficiency in the chick and the rat. *Journal of Nutrition* 16:585–95.

Erdman, A. M. 1964. Cornelis Adrianus Pekelharing—a biographical sketch. *Journal of Nutrition* 83:2–9.

Evans, C. A., W. E. Carlson, and R. G. Green. 1942. The pathology of chastek paralysis in foxes. *American Journal of Pathology* 18:79–91.

Evans, W. C. 1975. Thiaminases and their effects on animals. *Vitamins and Hormones* 33:467–504.

Evans, W. C., N. R. Jones, and R. A. Evans. 1950. The mechanism of the antianeurin activity of bracken (*Pteris aquilina*). *Biochemical Journal* 46:xxxviii–xxxix.

Fales, L. H. 1907. Beriberi, its etiology and prevention. *Journal of the American Medical Association* 48:776–81.

Farrer, K. T. H. 1955. The thermal destruction of vitamin B_1 in foods. *Advances in Food Research* 6:257–311.

Fehily, L. 1944. Human-milk intoxication due to B_1 avitaminosis. *British Medical Journal* ii:590–92.

Féris, B. 1881. Le béribéri d'apres les travaux Brésiliens. *Archives de Médecine Navale* 37:1–32.

———. 1882. Etude sur la nature du béribéri. *Archives de Médecine Navale* 38:81–119.

Fiebig, M. 1890. Beriberi onder de dessabevolking in Nederlandsch-Indië. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 30:432–504.

Figueroa, W. G., et al. 1953. Lack of avitaminosis among alcoholics. *American Journal of Clinical Nutrition* 1:179–99.

Finlay-Jones, R. 1986. Should thiamine be added to beer? *Australian and New Zealand Journal of Psychiatry* 20:3–6.

Fletcher, W. 1907. Rice and beri-beri: Preliminary report of an experiment conducted at the Kuala Lumpur lunatic asylum. *Lancet* i:1776–79.

———. 1909. Rice and beri-beri. *Journal of Tropical Medicine and Hygiene* 12:127–35.

Follis, R. H. 1960. Cellular pathology and the development of the deficiency disease concept. *Bulletin of the History of Medicine* 34:291–317.

Foltz, E. E., C. J. Barborka, and A. C. Ivy. 1944. The level of vitamin B–complex in the diet at which detectable symptoms of deficiency occur in man. *Gastroenterology* 2:323–44.

Fon, D. S. 1986. Rice drying. In *Post-harvest prevention of paddy/rice loss,* edited by C. H. Huang, 89–95. Taipei: Council of Agriculture.

Food and Nutrition Board Subcommittee. 1989. *Recommended dietary allowances.* 10th ed. Washington, D.C.: National Academy Press.

Foster, W. D. 1970. *A history of medical bacteriology and immunology.* London: Heinemann.

Frantzen, E. 1966. Wernicke's encephalopathy. *Acta Neurologica Scandinavica* 42:426–41.

Fraser, D. W. 1998. Vitamins and vitriol: W. L. Braddon's epidemiology of beriberi. *American Journal of Epidemiology* 148:519–27.

Fraser, H., and A. T. Stanton. 1909a. An enquiry concerning the etiology of beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* no. 10.

———. 1909b. The etiology of beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* no. 11.

———. 1910a. The etiology of beri-beri. *Lancet* ii:1755–57.

———. 1910b. The etiology of beriberi. *Philippine Journal of Science* 5B:55–63.

———. 1911. The etiology of beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* no. 12.

———. 1912. The etiology and prevention of beriberi. *Transactions of the 2nd Congress of the Far Eastern Association for Tropical Medicine, Hong Kong,* 65–69.

———. 1913. Unpolished rice and the prevention of beriberi. *Transactions of the 3rd Congress of the Far Eastern Association for Tropical Medicine, Saigon,* 359–64.

Freed, M. 1966. *Methods of vitamin assay.* New York: Interscience.

Freeman, M. 1977. Sung. In *Food in Chinese culture,* edited by K. C. Chang, 142–93. New Haven, Conn.: Yale University Press.

Freyre, G. 1963. *The mansions and shanties: The making of modern Brazil.* Translated by H. de Onis. New York: Knopf.

Fridericia, L. S., et al. 1927–28. Refection: A transmissible change in the intestinal content, enabling rats to grow and thrive without vitamin B in the food. *Journal of Hygiene, Cambridge* 27:70–102.

Fujikawa, Y. 1911. Geschicte der Beriberi. In *Mitteilungen der Beriberi-Studien-Kommission,* 10–17. Tokyo: Bureau of Medical Affairs, Ministry of War.

Fujiwara, M. 1965. Absorption, excretion and fate of thiamine and its derivatives in human body. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 179–213. Kyoto: Vitamin B Research Committee of Japan.

Funk, C. 1911. On the chemical nature of the substance which cures polyneuritis in birds, induced by a diet of polished rice. *Journal of Physiology* 43:395–400.

———. 1912. The etiology of the deficiency diseases. *Journal of State Medicine* 20:341–68.

———. 1922. *The vitamines.* 2d ed. Translated by H. E. Dubin. Baltimore: Williams and Wilkins.

Funk, C., and E. V. Schönborn. 1914. The influence of a vitamine-free diet on the carbohydrate metabolism. *Journal of Physiology* 48:328–31.

Furter, M. F., W. M. Lauter, E. De Ritter, and S. H. Rubin. 1946. Enrichment of rice with synthetic vitamins and iron. *Industrial and Engineering Chemistry* 38:486–93.

Gariboldi, F. 1974. Rice parboiling. *FAO Agricultural Development Paper,* no. 97. Rome: United Nations.

Gelpke, C. O. 1890. Ein Beitrag zur Bestreitung der Beriberi. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 30:144–53.

Gershoff, S. N., et al. 1975. Amino acid fortification of rice studies in Thailand. 1. Background and baseline data. *American Journal of Clinical Nutrition* 28:170–82.

Glogner, M. 1897. Neuere Untersuchungen über die Aetiologie und den Klinischen Verlauf der Beri-Beri-Krankheit. *Archiv für Schiffs- und Tropen-Hygiene* 1:46–53, 125–37.

———. 1898. Onderzoek naar het verband tusschen den aard der rystvoeding in de gevangenissen op Java en Madoera. *Archiv für Schiffs- und Tropen-Hygiene* 2:49–56.

Goldblith, S. A., and M. A. Joslyn, eds. 1964. *Milestones in nutrition.* Westport, Conn.: Avi.

Goldsmith, G. A., W. J. Darby, R. C. Steinkamp et al. 1950. Resurvey of nutritional status in Norris Point, Newfoundland. *Journal of Nutrition* 40:41–69.

Goodwin, T. W., and E. I. Mercer. 1983. *Introduction to plant biochemistry.* 2d ed. Oxford: Pergamon Press.

Gordon, H. H., and A. F. Ganzon. 1959. On the protein allowance for young infants. *Journal of Pediatrics* 54:503–28.

Green, L. B. 1918. *The milling of rice in the Madras Presidency.* Madras: Government Press.

Green, R. G., W. E. Carlson, and C. A. Evans. 1941. A deficiency disease of foxes produced by feeding fish. *Journal of Nutrition* 21:243–56.

———. 1942. The inactivation of vitamin B_1 in diets containing whole fish. *Journal of Nutrition* 23:165–74.

Grewal, P. K., and J. K. Sangha. 1990. Effect of processing on thiamin and riboflavin contents of some high-yielding rice varieties of Punjab. *Journal of the Science of Food and Agriculture* 52:387–91.

Grewe, R. 1936. Der Konstitution des Aneurins (vitamin B_1). *Naturwissenschaften* 24:657–62.

Griffis, W. E. 1895. *The Mikado's empire.* New York: Harper and Brothers.

Grijns, G. 1901. Over polyneuritis gallinarum. I. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 41:3–110. [Also in English translation in Grijns (1935), pp. 1–108.]

———. 1909a. Over polyneuritis gallinarum. II. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 49:216–38. [Also in English translation in Grijns (1935), pp. 109–26.]

———. 1909b. Over polyneuritis gallinarum. III. *Mededeelingen uit het Geneeskundig Laboratorium,* 1908 and 1909. [Also in English translation in Grijns (1935), pp. 127–58.]

———. 1935. *Researches on vitamins, 1910–1911.* Gorinchem, Holland: J. Noorduyn en Zoon. [English translations of preceding papers.]

Griminger, P. 1972. Casimir Funk—a biographical sketch. *Journal of Nutrition* 102:1106–13.

Gubler, C. J. 1976. Biochemical changes in thiamine deficiencies. In *Thiamine,* edited by C. J. Gubler, M. Fujiwara, and P. M. Dreyfus, 121–39. New York: Wiley.

Gulland, J. M., and R. A. Peters. 1929. The alleged antineuritic properties of certain quinoline and glyoxaline derivatives. *Biochemical Journal* 23:1122–25.

Haas, R. H. 1988. Thiamin and the brain. *Annual Review of Nutrition* 8:483–515.

Hannaway, C. 1993. Environment and miasmata. In *Companion encyclopedia of the history of medicine,* edited by W. F. Bynum and R. Porter, 1:292–308. London: Routledge.

Harata, N., and Y. Iwasaki. 1996. The blood-brain barrier and selective vulnerability in experimental thiamine-deficiency encephalopathy in the mouse. *Metabolic Brain Disease* 11:55–69.

Harden, A., and W. J. Young. 1906. The alcoholic ferment of yeast-juice. II. The coferment of yeast juice. *Proceedings of the Royal Society of London Biology* 77:369–75.

Harding, T. S. 1943. What about vitamin tablets? *Scientific American* 168:214–15.

Hardy, A. 1995. Beriberi, vitamin B_1 and world food policy. *Medical History* 39:61–77.

Hare, J. H. 1905. *A photographic record of the Russo-Japanese war.* New York: Collier.

Harper, C. G. 1980. Sudden, unexpected death and Wernicke's encephalopa-

thy: A complication of prolonged intravenous feeding. *Australian and New Zealand Journal of Medicine* 10:230–35.

Harper, C. G., et al. 1998. Prevalence of Wernicke-Korsakoff syndrome in Australia: Has thiamine fortification made a difference? *Medical Journal of Australia* 168:542–45.

Harrell, R. F. 1943. Effect of added thiamine on learning. *Contributions to Education,* no. 877. New York: Teachers' College, Columbia University.

———. 1947. Further effects of added thiamine on learning and other processes. *Contributions to Education,* no. 928. New York: Teachers' College, Columbia University.

Harris, L. J. 1933. Vitamins. *Annual Review of Biochemistry* 2:253–98.

———. 1938. *Vitamins and vitamin deficiencies.* Vol. 1. London: Churchill.

Harris, L. J., and Y. L. Wang. 1941. An improved procedure for estimating vitamin B_1 in foodstuffs and biological materials including comparisons with biological assays. *Biochemical Journal* 35:1050–67.

Harris, R. S., and H. Von Loerecke. 1960. *Nutritional evaluation of food processing.* New York: Wiley.

Harrison, M. 1996. The fight against disease in the Mesopotamia campaign. In *Facing Armageddon,* edited by H. Cecil and P. Liddle, 475–89. London: Leo Cooper.

Harrow, B. 1955. *Casimir Funk: Pioneer in vitamins and hormones.* New York: Dodd, Mead.

Hashimoto, H. 1937. Acute pernicious form of Beriberi and its treatment by intravenous administration of vitamin B_1. *American Heart Journal* 13:580–88.

Hathaway, M. L., and J. E. Strom. 1946. A comparison of thiamine synthesis and excretion in human subjects on synthetic and natural diets. *Journal of Nutrition* 32:1–8.

Hauck, H. M., S. Sudsaneh, and J. R. Hanks. 1958. Food habits and nutrient intakes in a Siamese rice village. *Cornell Thailand Project: Interim Report Series,* no. 4. Ithaca, N.Y.: Cornell University.

Hawes, R. B. 1938. The treatment of acute fulminating cardiac beriberi (*shoshin*). *Transactions of the Royal Society of Tropical Medicine and Hygiene* 31:474–82.

Hawes, R. B., E. S. Monteiro, and C. E. Smith. 1937. The treatment of acute cardiac beri-beri or *Shosin* with massive doses of vitamin B_1. *Journal of the Malaya Branch, British Medical Association* 1:87–96.

Hayasaka, E. 1929. Studies on the effect of muscular exercise in beri-beri. V. *Tohoku Journal of Experimental Medicine* 14:85–92.

Heilbron, I. M. 1948. Recent developments in the vitamin A field. *Journal of the Chemical Society,* pp. 386–93.

Heiser, V. G. 1910. Unsolved health problems peculiar to the Philippines. *Philippine Journal of Science* 5B:171–78.

———. 1912. Beriberi, with a suggestion for governmental aid in its eradication. *Transactions of the 2nd Congress of the Far Eastern Association for Tropical Medicine, Hong Kong,* 31–33, 71.

———. 1913. Beriberi: An additional experience at Culion: How can knowledge as to its prevention best be applied from the standpoint of state medicine? *Transactions of the 3rd Congress of the Far Eastern Association for Tropical Medicine, Saigon,* 369–73.
———. 1936. *An American doctor's odyssey.* New York: Norton.
Herzog, M. 1906a. Beri-beri in the Japanese army during the late war: The kakke coccus of Okata-Kokubo. *Philippine Journal of Science* 1:169–79.
———. 1906b. Studies in beriberi. *Philippine Journal of Science* 1:709–64.
Hibbs, R. E. 1946. Beriberi in Japanese prison camp. *Annals of Internal Medicine* 25:270–82.
Highet, H. C. 1910. Beriberi in Siam. *Philippine Journal of Science* 5B:73–79.
———. 1913. Studies on beriberi and its prevention in Siam. *Journal of Tropical Medicine and Hygiene* 16:48–61.
Hill, A. V., C. N. H. Long, and H. Lupton. 1924. Muscular exercise, lactic acid and the supply and utilization of oxygen. *Proceedings of the Royal Society of London, Series B* 66:438–75.
Hill, R. D. 1977. *Rice in Malaya.* Kuala Lumpur: Oxford University Press.
Hinton, J. J. C. 1942. The vitamin B_1 and riboflavin contents of wheat germ. *Journal of the Society of Chemical Industry, London* 61:143–44.
———. 1944. The chemistry of wheat germ with particular reference to the scutellum. *Biochemical Journal* 38:214–17.
———. 1948a. The distribution of vitamin B_1 in the rice grain. *British Journal of Nutrition* 2:237–41.
———. 1948b. Parboiling treatment of rice. *Nature* 162:913–15.
———. 1952. The structure of cereal grains. In *Food Science,* edited by E. C. Bate-Smith and T. N. Morris, 72–87. Cambridge: Cambridge University Press.
Hirota, Z. 1898. Uber die durch die Milch der au Kakke (Beriberi) leidenden Frauen verursachte Krankheit der Säuglinge. *Centralblatt für Innere Medizin* 19:385–92.
Hirsch, A. 1883. *Handbuch der Historisch-Geographischen Pathologie.* 2d ed. Pt. 2. Stuttgart: Ferdinand Enke.
———. 1885. *Handbook of geographical and historical pathology.* 2d ed. Translated by C. Creighton. Pt. 2. London: New Sydenham Society.
Hoagland, R. 1924. Antineuritic value of hog muscle. *American Journal of Physiology* 67:300–308.
Hoffman, T. 1873. Die japanische Kak-ke. *Deutsche Gesellschaft für Natur- und Völkerkunde Ostasiens, Tokyo* 1, no. 2:16–21.
Hogan, A. G. 1950. The vitamin requirements of poultry. *Nutrition Abstracts and Reviews* 19:751–91.
Holst, A. 1907. Experimental studies relating to "ship-beri-beri" and scurvy. *Journal of Hygiene* 7:619–33.
———. 1911. The etiology of beri-beri. *Transactions of the Society of Tropical Medicine and Hygiene* 5:76–80.
Holst, A., and T. Frölich. 1907. On the etiology of scurvy. *Journal of Hygiene, Cambridge* 7:634–71.

Holt, L. E., et al. 1949. The thiamine requirement of the normal infant. *Journal of Nutrition* 37:53–65.

Hopkins, F. G. 1906. The analyst and the medical man. *Analyst* 31:395–403.

———. 1912. Feeding experiments illustrating the importance of accessory factors in normal dietaries. *Journal of Physiology* 44:425–60.

———. 1930. The earlier history of vitamin research. Reprinted in *Hopkins and biochemistry,* edited by J. Needham and A. C. Chibnall, 191–200. Cambridge: Heffer, 1949.

Hopkins, F. G., H. Chick, et al. 1919. Report on the present state of knowledge concerning accessory food factors (vitamines). *Medical Research Council Special Report Series,* no. 38.

Hopkins, F. G., and A. Neville. 1913. A note concerning the influence of diets upon growth. *Biochemical Journal* 7:97–99.

Horrocks, S. M. 1995. The business of vitamins: Nutrition science and the food industry in inter-war Britain. In *The science and culture of nutrition, 1840–1940,* edited by H. Kamminga and A. Cunningham, 235–58. Amsterdam: Rodopi.

Horwitt, M. K., E. Liebert, O. Kreisler, and P. Wittman. 1948. Investigations of human requirements for B-complex vitamins. *Bulletin of the National Research Council* (USA), no. 116.

Horwitz, W., ed. 1980. *Official methods of analysis.* 13th ed. Washington, D.C.: Association of Official Analytical Chemists.

Hou, H. C. 1939. Vitamin B_1 deficiency in the Chinese diet. *Proceedings of the 6th Pacific Science Congress, California* 6:299–311.

Houston, D. F., and G. O. Kohler. 1970. *Nutritional properties of rice.* Washington, D.C.: National Academy of Sciences.

Howarth, S. 1983. *Morning glory: A history of the Imperial Japanese Navy.* London: Hamish Hamilton. [Also published in the United States in 1983 under the title *Fighting ships of the rising sun.* New York: Atheneum.]

Huard, P., Z. Ohya, and M. Wong. 1974. *La médecine Japonaise de origines à nos jours.* Paris: Roger Dacosta.

Huard, P., and M. Wong. 1959. *La médecine Chinoise au cours des siècles.* Paris: Roger Dacosta.

Hudson, R. P. 1989. *Theory and therapy: Ptosis, stasis, and autointoxication. Bulletin of the History of Medicine* 63:392–413.

Hull, D. L. 1988. *Science as a process.* Chicago: University of Chicago Press.

Hulshoff Pol, D. J. 1902. Katjang idjo, un nouveau médicament contre le béribéri. *Janus* 7:524–34, 570–81.

———. 1904. *Beri-beri: Voorkoming en geneezing door toediening van katjang-idjo* (*Phaseolus radiatus* L.). Amsterdam: J. H. de Bussy.

Hume, E. H. 1940. *The Chinese way in medicine.* Baltimore: Johns Hopkins University Press.

Ihde, A. J., and S. L. Becker. 1971. Conflict of concepts in early vitamin studies. *Journal of the History of Biology* 4:1–33.

Inawashiro, R., and E. Hayasaka. 1928. Studies on the effect of muscular exercise in beri-beri. I. *Tohoku Journal of Experimental Medicine* 12:1–27.

Indian Council of Medical Research. 1953. Fortification of foods. *Indian Council of Medical Research Special Report,* no. 27.

Inouye, K., and E. Katsura. 1965a. Diagnosis, prevention and therapy of beriberi. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 64–80. Kyoto: Vitamin B Research Committee of Japan.

———. 1965b. Etiology and pathology of beriberi. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 1–28. Kyoto: Vitamin B Research Committee of Japan.

Itokawa, Y. 1976. Kanehiro Takaki (1849–1920): A biographical sketch. *Journal of Nutrition* 106:581–88.

———. 1996. Thiamine and nervous system function: An historical sketch. *Metabolic Brain Disease* 11:1–7.

Itokawa, Y., and R. F. Butterworth. 1996. Special issue on thiamine and CNS function. *Metabolic Brain Disease* 11: i.

Jacobs, H., ed. 1974. *Documenta Malucensia I (1542–1577).* Rome: Institutum Historicum Societatis Iesu.

Jaffé, W. G. 1980. Hemagglutinins. In *Toxic constituents of plant foodstuffs,* edited by I. E. Liener, 73–102. 2d ed. New York: Academic Press.

Jansen, B. C. P. 1921. On vitamins. *Transactions of the 4th Congress of the Far Eastern Association for Tropical Medicine, Weltevreden,* 258–77.

———. 1936. A chemical determination of aneurin (= vitamin B_1) by the thiochrome reaction. *Recueil des Travaux Chimiques des Pays-Bas* 55:1046–52.

———. 1950. C. Eijkman. *Journal of Nutrition* 42:3–8. [Reprinted in *Founders of Nutrition Science,* edited by W. J. Darby and T. H. Jukes, 1:288–94. Bethesda, Md.: American Institute of Nutrition, 1992.]

———. 1959. *Het levenswerk van Christiaan Eijkman, 1858–1930.* Haarlem: Bohn.

Jansen, B. C. P., and W. F. Donath. 1926. On the isolation of the anti-beri-beri vitamin. *Koninklijke Akademie van Wetenschappen, Amsterdam, Proceedings* 29:1390–400.

Jeanselme, M. E. 1911. Opinions et travaux des médecins japonais sur l'origine du béribéri. *Bulletin de la Société de Pathologie Exotique* 4:604–8.

Jeffrey, F. E., and W. H. Abelmann. 1971. Recovery from proved shoshin beriberi. *American Journal of Medicine* 50:123–28.

Jolliffe, N., and C. N. Colbert. 1936. The etiology of polyneuritis in the alcohol addict. *Journal of the American Medical Association* 107:642–47.

Jolliffe, N., C. N. Colbert, and P. M. Joffe. 1936. Observations on the etiologic relationship of vitamin B (B_1) to polyneuritis in the alcohol addict. *American Journal of the Medical Sciences* 191:515–26.

Jolliffe, N., R. Goodhart, J. Gennis, and J. K. Cline. 1939. The experimental production of vitamin B_1 deficiency in normal subjects. *American Journal of the Medical Sciences* 198:198–211.

Jolliffe, N., H. Wortis, and H. D. Fein. 1944. The Wernicke syndrome. *Archives of Neurology and Psychiatry* 46:569–97.

Jubb, K. V., L. Z. Saunders, and H. V. Coates. 1956. Thiamine deficiency encephalopathy in cats. *Journal of Comparative Pathology* 66:217–27.

Juliano, B. O. 1993. Rice in human nutrition. *FAO Food and Nutrition Series,* no. 26.

Kamminga, H. 1998. Credit and resistance: Eijkman and the transformation of beri-beri into a vitamin deficiency disease. In *From physical theory to biotechnology: A Festschrift for Mikulás Teich,* edited by K. Bayert and R. Porter, 232–54. Amsterdam: Rodopi. [Also referenced as *Clio Medica* 48:232–54.]

Kamminga, H., and A. Cunningham. 1995. Introduction. In *The science and culture of nutrition, 1840–1940,* edited by H. Kamminga and A. Cunningham, 1–14. Amsterdam: Editions Rodopi.

Kawasaki, C. 1965. From natural thiamine to synthetic thiamine: The brief history of thiamine preparations in Japan. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 288–95. Kyoto: Vitamin B Research Committee of Japan.

Keizo, S. 1958. *Japanese life and culture in the Meiji era.* Translated by C. S. Terry. Vol. 5. Tokyo: Obunsha.

Kennedy, B. M., M. Schelstraete, and K. Tamai. 1975. Chemical, physical and nutritional properties of high-protein flours and residual flours from the overmilling of uncoated milled rice. IV. *Cereal Chemistry* 52:182–88.

Kent-Jones, D. W. 1946. Factors influencing the nutritive value of bread as human food: Enrichment. *Proceedings of the Nutrition Society* 4:14–22.

Keys, A., and A. F. Henschel. 1942. Vitamin supplementation of U.S. army rations in relation to fatigue and the ability to do muscular work. *Journal of Nutrition* 23:259–69.

Keys, A., A. Henschel, H. L. Taylor, O. Mickelsen, and J. Brozek. 1945. Experimental studies on man with a restricted intake of the B vitamins. *American Journal of Physiology* 144:5–42.

Kik, M. C. 1957a. Gerrit Grijns. *Journal of Nutrition* 62:1–12.

———. 1957b. The nutritive value of rice and its by-products. *Arkansas Agricultural Experiment Station Bulletin,* no 589.

Kik, M. C., and R. R. Williams. 1945. The nutritional improvement of white rice. *National Research Council Bulletin,* no. 112.

Kilbourne, E. D. 1910. Food salts in relation to beriberi. *Philippine Journal of Science* 5B:127–35.

Kimm, R.-H. 1938. On the chemical constituents of rice-embryo. *Scientific Papers from the Institute for Physical and Chemical Research* 34:637–77.

Kimura, O. 1919. Histologische Degenerations—und Regenerations—vorgänge im peripherischen Nervensystem. *Mitteilungen über allgemeine Pathologie und Pathologische Anatomie* 1:1–160.

Kimura, R. 1965. Thiamine decomposing bacteria. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 255–74. Kyoto: Vitamin B Research Committee of Japan.

Kimura, T. 1938. The problem of abolishing the use of highly milled rice. *Journal of the Public Health Association of Japan* 14 (August):1–8.

King, G., and L. T. Ride. 1945. The relation of vitamin B_1 deficiency to pregnancy toxaemias. *Journal of Obstetrics and Gynaecology of the British Empire* 52:130–47.

Kingsley, H. N., and H. T. Parsons. 1947. The availability of vitamins from yeasts. IV. *Journal of Nutrition* 34:321–31.

Kinnersley, H. W., and R. A. Peters. 1930. Brain location of acidosis in avitaminosis B, and its relation to the origin of symptoms. *Biochemical Journal* 24:711–22.

Klein, G., M. Bohue, S. Probst, R. Dudziak, H. Förster, and F. Asskali. 1990. Lebensbedrohliche Lactacidosen bei totaler parenteraler Ernährung: Therapieerfolg mit Thiamin. *Deutsche Medizinische Wochenschrift* 115:254–56.

Knecht-van Eekelen, A. de. 1984. *Naar een rationele zuigelingenvoeding (1840–1914).* Nijmegen: G. J. Thieme.

———. 1989. The interaction of Western and tropical medicine. In *Dutch medicine in the Malay Archipelago,* edited by G. M. van Heteren, 57–71. Amsterdam: Rodopi.

———. 1997. Geschiedenis van het genezen: beriberi: "Een zeker soort verlamming." *Nederlands Tijkschrift voor Geneeskunde* 141:1199–203.

Koeniger. 1884. Ueber epidemisches Auftreten von Beriberi in Manila 1882/83. *Deutsches Archiv für Klinische Medizin* 34:419–32.

Kon, S. K. 1927. A note on the temporary spontaneous disappearance of typical "beriberi" symptoms in pigeons fed on diets deficient in vitamin B. *Biochemical Journal* 21:834–36.

———. 1962. Vitamins A and B_{12} and some comments on refection. *Proceedings of the Royal Society, Series B* 156:351–65.

Kon, S. K., and J. C. Drummond. 1927. The physiological role of vitamin B. Pt. III. *Biochemical Journal* 21:632–52.

Kon, S. K., and E. Watchorn. 1927–28. Relation between the nature of the carbohydrate in the diet and refection in rats. *Journal of Hygiene, Cambridge* 27:321–27.

Kramer, J., and J. A. Goodwin. 1977. Wernicke's encephalopathy: Complication of intravenous hyperalimentation. *Journal of the American Medical Association* 238:2176–77.

Kruse, H. D., et al. 1943. Inadequate diets and nutritional deficiencies in the United States. *Bulletin of the National Research Council* (USA), no. 109.

Kuo, J. Y.-H., and D. M. Hilker. 1973. A fluorescent thiamine derivative formed by reacting hemin and thiamine: Effect on thiamine-deficient rats. *Nutrition Reports International* 8:169–73.

Labberton, Van H. 1910. *Geïllustreerd handbaek van Insulinde.* Amsterdam: Vivat.

Lahey, W. L., et al. 1953. Physiological observations on a case of beriberi heart disease. *American Journal of Medicine* 14:248–55.

Lal, R. B., S. P. Mukherji, S. C. Roy, and G. Sankaran. 1939. Studies on the nature and origin of certain (? toxic) substances present in the supplies of mustard oil associated with outbreaks of epidemic dropsy. *Indian Journal of Medical Research* 27:207–24.

Lal, R. B., and S. C. Roy. 1937a. Investigations into the epidemiology of epidemic dropsy. I: Introductory notes and historical survey. *Indian Journal of Medical Research* 25:163–213.

———. 1937b. Investigations into the epidemiology of epidemic dropsy. V:

Experiments on human volunteers. *Indian Journal of Medical Research* 25:239–59.
Lane, R. L., E. Johnson, and R. R. Williams. 1942. Studies of the average American diet. I. Thiamine content. *Journal of Nutrition* 23:613–24.
Lang, J. 1996. *Feeding a hungry planet: Rice, research, and development in Asia and Latin America.* Chapel Hill: University of North Carolina Press.
Latham, W. C. 1971. A historical perspective. In *Nutrition, national development, and planning,* edited by A. Berg, N. S. Scrimshaw, and D. L. Call, 313–28. Cambridge, Mass.: MIT Press.
Laveran, A. 1910. Nomination d'une Commission. *Bulletin de la Société de Pathologie Exotique* 3:135.
Le Roy de Méricourt, A. 1868. Beriberi. In *Dictionnaire encyclopédique des sciences médicales,* edited by A. Dechambre, 9:129–65. Paris: Asselin.
Leong, P. C., and L. J. Harris. 1937. Antineuritic potency of synthetic and natural crystalline vitamin B_1. *Biochemical Journal* 31:672–80.
Leung, W.-T. W., R. R. Butrum, and F. H. Chang. 1972. *Food composition table for use in East Asia.* Rome: FAO.
Leveille, G. A. 1972. Modified thiochrome procedure for urinary thiamine. *American Journal of Clinical Nutrition* 25:273–74.
Lie, G. H. 1980. The comparative nutritional roles of sago and cassava in Indonesia. In *Sago: The equatorial swamp as a natural resource,* edited by W. R. Stanton and M. Flach, 43–55. The Hague: Martinus Nijhoff.
Lindeboom, G. A. 1971. Eijkman, Christiaan. In *Dictionary of scientific biography,* edited by C. C. Gillispie, 4:310–12. New York: Scribner.
Little, J. M. 1912. Beriberi caused by fine wheat flour. *Journal of the American Medical Association* 58:2029–30.
Lockheimer, F. R. 1969. Government and the development of science in Japan. In *The social reality of scientific myth,* edited by K. H. Silvert, 154–70. New York: American Universities Field Staff.
Lohmann, K., and P. Schuster. 1937. Untersuchungen über die Cocarboxylase. *Biochemische Zeitschrift* 294:188–214.
Lovelace, C. 1912. The etiology of beriberi. *Journal of the American Medical Association* 59:2134–37.
———. 1913. Some further remarks on beri-beri. *American Journal of Tropical Diseases and Preventive Medicine* 1:140–45.
Luh, B. S., and R. R. Mickus. 1991. Parboiled rice. In *Rice.* Vol. 2, *Utilization,* edited by B. S. Luh, 51–88. 2d ed. New York: Avi.
Luyken, R. 1990. Honderd jaar geleden vitamines door Eijkman. *Nederlands Tijdschrift voor Geneeskunde* 134:1658–62.
———. 1994. A. G. Vorderman (1857–1902): Voedingsonderzoek in het voormalige Nederlands-Indië. *Voeding* 55:10–13.
Ma, J. J., and A. S. Truswell. 1995. Wernicke-Korsakoff syndrome in Sydney hospitals: Before and after thiamine enrichment of flour. *Medical Journal of Australia* 163:531–34.
Magee, H. E. 1946. Application of nutrition to public health: Some lessons of the war. *British Medical Journal* i:475–81.

Maget, G. 1877. Les médecins et la médecine au Japon. *Archives de Médecine Navale* 27:357–80.

Majoor, C. L. H., and H. F. P. Hillen. 1982. Cardiale beriberi met melkzuuracidose en cardiovasculaire collaps (sjosjin), een bij alcoholici niet zeldzaam ziektebeeld. *Nederlands Tijdschrift voor Geneeskunde* 126:749–57.

Major, R. H. 1945. *Classic descriptions of disease.* 3d ed. Springfield, Ill: Charles C. Thomas.

Malakar, M. C., and S. N. Banerjee. 1959. Effect of cooking rice with different volumes of water on the loss of nutrients and on digestibility of rice *in vitro. Food Research* 24:751–56.

Malcolmson, J. G. 1835. *A practical essay on the history and treatment of beriberi.* Madras: Government of Madras.

Manderson, L. 1986. Food classification and restriction in Peninsular Malaysia: Nature, culture, hot and cold? In *Shared wealth and symbol: Food, culture, and society in Oceania and Southeast Asia,* edited by L. Manderson, 127–43. Cambridge: Cambridge University Press.

Manderson, L., and M. Mathews. 1981. Vietnamese behavioral and dietary precautions during pregnancy. *Ecology of Food and Nutrition* 11:1–8.

Manson, P. 1902. The prophylaxis and treatment of beri-beri. *British Medical Journal* ii:830–34.

Manson, P., and C. W. Daniels. 1909. Beriberi. In *A system of medicine,* edited by C. Allbutt and H. D. Rolleston, vol. 2, pt. 2, 615–43. London: Macmillan.

Martin, P. R., B. A. McCool, and C. K. Singleton. 1993. Genetic sensitivity to thiamine deficiency and development of alcoholic organic brain disease. *Alcoholism, Clinical and Experimental Research* 17:31–37.

Matsumuro, H., Y. Hattori, S. Wada, and R. Hayashi. 1951. Studies on vitamin B_1 content of rice endosperm. *Annual Report of the National Institute of Nutrition, Japan,* p. 41. Tokyo: National Institute of Nutrition.

May, J. M., and D. L. McLellan. 1974. *The etiology of malnutrition in eastern South America.* New York: Hafner.

McCance, R. A., E. M. Widdowson, and C. M. Vernon-Roe. 1938. A study of English diets by the individual method. III. Pregnant women at different economic levels. *Journal of Hygiene* 38:596–622.

McCarrison, R. 1921. *Studies in deficiency disease.* London: Hodder and Stoughton.

———. 1928. Beriberi columbarum. *Indian Medical Research Memoirs,* no. 10.

McCarrison, R., and R. V. Norris. 1924. The relationship of rice to beri-beri in India. *Indian Medical Research Memoirs,* no. 2.

McCollum, E. V. 1909. Nuclein synthesis in the animal body. *American Journal of Physiology* 25:120–41.

———. 1957. *A history of nutrition.* Boston: Houghton Mifflin.

McCollum, E. V., and M. Davis. 1913. The necessity of certain lipins in the diet during growth. *Journal of Biological Chemistry* 15:167–75.

———. 1915. The nature of the dietary deficiencies of rice. *Journal of Biological Chemistry* 23:181–230.

McCollum, E. V., and C. Kennedy. 1916. The dietary factors operating in the production of polyneuritis. *Journal of Biological Chemistry* 24:491–502.
McCollum, E. V., N. Simmonds, and H. T. Parsons. 1918. A biological analysis of pellagra-producing diets. V. *Journal of Biological Chemistry* 33:411–23.
McIntyre, N., and N. N. Stanley. 1971. Cardiac beriberi: Two modes of presentation. *British Medical Journal* iii:567–69.
McPherson, C. 1966. The first recognition of beri-beri in Canada? *Canadian Medical Association Journal* 95:278–79.
Megaw, J. W. D. 1923. The beriberi problem. *Transactions of the 5th Congress of the Far Eastern Association for Tropical Medicine, Singapore,* 218–33.
Meiklejohn, A. P. 1940. Is thiamin the antineuritic vitamin? *New England Journal of Medicine* 223:265–73.
Meiklejohn, A. P., R. Passmore, and R. A. Peters. 1932. The independence of vitamin B_1 deficiency and inanition. *Proceedings of the Royal Society of London, Series B* 111:391–95.
Meilgaard, M. C. 1982. Technical aspects of the enrichment of beer with thiamine. *Journal of Studies on Alcohol* 43:427–33.
Melnick, D. 1944. A critique of values suggested as the thiamin requirement of man. *Journal of the American Dietetic Association* 20:516–20.
Meredith, W. O. S. 1945. Analysis of data for A.A.C.C. check sample service. I. Protein and thiamine results. *Cereal Chemistry* 22:437–48.
Metcoff, J., et al. 1945. Nutritional survey in Norris Point, Newfoundland. *Journal of Laboratory and Clinical Medicine* 30:475–87.
Meyer, A. 1932. Ueber das Vorkommen von B-Avitaminose unter den heisigen Lebensbedingungen. *Schweizerische Medizinische Wochenschrift* 62: 243–46.
Meyerhof, O. 1933. Intermediate products and the last stages of carbohydrate breakdown in the metabolism of muscle and in alcoholic fermentation. *Nature, London* 132:337–40, 373–75.
Meyers, F. M. 1941. Possible adaptation to a low vitamin B_1 intake. *American Journal of the Medical Sciences* 201:785–89.
Mickus, R. R., and B. S. Luh. 1991. Rice enrichment with vitamins and amino acids. In *Rice.* Vol. 2, *Utilization,* edited by B. S. Luh, 35–49. 2d ed. New York: Avi.
Mikkelsen, D. S., and S. K. De Datta. 1991. Rice culture. In *Rice.* Vol. 1, *Production,* edited by B. S. Luh, 103–86. 2d ed. New York: Avi.
Minot, G. R., M. B. Strauss, and S. Cobb. 1933. "Alcoholic" polyneuritis: Dietary deficiency as a factor in its production. *New England Journal of Medicine* 208:1244–49.
Mitchell, H. H. 1919. On the identity of the water-soluble growth-promoting vitamine and the antineuritic vitamine. *Journal of Biological Chemistry* 40:399–413.
Mitchell, H. S. 1930. Nutrition survey in Labrador and Northern Newfoundland. *Journal of the American Dietetic Association* 6:29–35.
Mitsuda, H. 1969. New approaches to amino acid and vitamin enrichment in

Japan. In *Protein-enriched cereal foods for world needs,* edited by M. Milner, 208–19. St. Paul, Minn.: American Association of Cereal Chemists.
Mitsuda, H., and K. Yasumoto. 1974. The amino acid fortification of intact cereal grains. In *New Protein Foods,* edited by A. M. Altschul, 1A:121–54. New York: Academic Press.
Miura, K. 1906. Erfahrung uber Beriberi im japanisch-russischen Krieg. *Archiv für Schiffs- und Tropen-Hygiene* 10:646–50.
Miura, M. 1889. Zur Aetiologie der Kakké. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 29:370–72.
Mohnike, O. 1852. Aanteekeningen over de Geneeskunde der Japanezen. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 1:198–300, 325–61.
Moran, T., and J. C. Drummond. 1940. Reinforced white flour. *Nature* 146: 117–18.
Morgan, T. B. 1960. Starch refection: A misnomer. *Proceedings of the Nutrition Society* 19:vi–vii.
Mote, F. W. 1977. Yuan and Ming (1271–1644). In *Food in Chinese culture,* edited by K. C. Change, 195–257. New Haven, Conn.: Yale University Press.
Mudd, S. H. 1982. Vitamin-responsive genetic abnormalities. *Advances in Nutritional Research* 4:1–34.
Murata, K. 1965. Thiaminase. In *Review of Japanese literature on beriberi and thiamine,* edited by N. Shimazono and E. Katsura, 220–54. Kyoto: Vitamin B Research Committee of Japan.
———. 1982. Actions of two types of thiaminase on thiamin and its analogues. *Annals of the New York Academy of Sciences* 378:146–55.
Musgrave, W. E., and G. F. Richmond. 1907. Infant feeding and its influence upon infant mortality in the Philippine Islands. *Philippine Journal of Science* 2B:361–85.
Nadel, A. M., and P. C. Burger. 1976. Wernicke's encephalopathy following prolonged intravenous therapy. *Journal of the American Medical Association* 235:2403–5.
Nail, P. A., M. R. Thomas, and R. Eakin. 1980. The effect of thiamin and riboflavin supplementation on the level of those vitamins in human breast milk and urine. *American Journal of Clinical Nutrition* 33:198–204.
Najjar, V. A., and L. E. Holt. 1943. The biosynthesis of thiamine in man. *Journal of the American Medical Association* 123:683–84.
Needham, J. 1962. Sir Frederick Gowland Hopkins: Opening address. *Proceedings of the Royal Society of London, Series B* 156:289–94.
Nicholls, L. 1947. Thiamine of milled raw and parboiled rice. *Nature, London* 160:298.
Norman, C. 1898. On beri-beri occurring in temperate climates. *British Medical Journal* ii:872–76.
———. 1899. The etiology of beri-beri. *British Medical Journal* ii:686.
North, J. D. K., and H. M. Sinclair. 1956. Nutritional neuropathy: Chronic thiamine deficiency in the rat. *Archives of Pathology* 62:341–53.
Nutrition Committee for S. and E. Asia. 1957. Report of 4th session. *FAO Nutrition Meeting Report Series,* no. 14.

Ogata, T., S. Kawakita, H. Oka, S. Suzuki, and S. Kagoshima. 1924. Kritische Betrachtung über Identität oder Nichtidentität der Vitamin-B-mangelkrankheit mit der menschlichen Kakke. *Deutsche Medizinische Wochenschrift* 50:527–29.

Ohnuki-Tierney, E. 1993. *Rice as self: Japanese identities through time.* Princeton, N.J.: Princeton University Press.

Olson, R. E., and W. B. Schwartz. 1951. Myocardial metabolism in congestive heart failure. *Medicine* 30:21–41.

Omori, K. 1925. Studies on the cause and treatment of beri-beri in Japan. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo,* 183–204.

Oomen, H. A. P. C. 1971. Ecology of human nutrition in New Guinea: Evolution of subsistence patterns. *Ecology of Food and Nutrition* 1:1–16.

Orr, J. B. 1937. *Food, health and income.* 2d ed. London: Macmillan.

Osborne, T. B., and L. B. Mendel. 1911. Feeding experiments with isolated food substances. *Carnegie Institute of Washington Publication,* no. 156.

———. 1913. The relation of growth to the chemical constituents of the diet. *Journal of Biological Chemistry* 15:311–26.

Oshima, K. 1905. A digest of Japanese investigations on the nutrition of man. *Office of Experiment Stations Bulletins,* no. 159.

Owen, P. S., and J. W. Ferrebee. 1943. The anti-thiamine factor in fish. *New England Journal of Medicine* 229:435–36.

O'Zoux. 1910. Notes sur le béribéri á la Réunion. *Bulletin de la Société de Pathologie Exotique* 3:131–35.

Padua, A. B., and B. O. Juliano. 1974. Effect of parboiling on thiamin, protein and fat of rice. *Journal of the Science of Food and Agriculture* 25:697–701.

Palm, T. A. 1884. Kakké: A study of disease in Japan. *Edinburgh Clinical Pathology Journal* 1:953–1008.

Panel on Recommended Allowances. 1969. *Recommended intakes of nutrients for the United Kingdom.* London: HMSO.

Panijpan, B., P. Vilartsakdanon, et al. 1978. Resolution of the initial phase controversy in the thiamine-polyphenol reaction. *International Journal for Vitamin and Nutrition Research* 48:262–67.

Pant, N. C., and K. Dang. 1972. Physiology and elimination of intracellular symbiotes in some stored product beetles. In *Insect and mite nutrition,* edited by J. G. Rodriguez, 311–22. Amsterdam: North Holland.

Parman, G. K. 1962. Vitaminization of food outside the United States. *Annals of the New York Academy of Sciences* 98:607–13.

Parsons, H. T., M. G. Polisar, and D. M. Otto. 1947. Observations on the nature of the interference of live yeast with the availability of thiamine. *Federation Proceedings* 6:417.

Pasricha, C. L., S. Lal, and K. Banerjee. 1940. The effects of oral administration of argemone oil to laboratory animals. *Indian Journal of Medical Research* 27:947–51.

Passmore, R. 1980. Obituary notice: Wallace Ruddell Aykroyd (1899–1979). *British Journal of Nutrition* 43:245–50.

Passmore, R., M. N. Rao, and B. M. Nicol. 1974. Handbook of human nutritional requirements. *FAO Nutritional Studies,* no. 28.

Patwardhan, V. N. 1961. *Nutrition in India.* 2d ed. Bombay: Indian Journal of Medical Sciences.

Paul, A. A., and D. A. T. Southgate. 1978. The composition of foods. *Medical Research Council Special Report,* no. 297. 4th ed. London: HMSO.

Pavy, F. W. 1881. *A treatise on food and dietetics.* 2d ed. New York: William Wood.

Pearse, F. 1908. On the identity of beri-beri and epidemic dropsy. *Journal of Tropical Medicine and Hygiene* 11:69–70.

Pearse, T. F. 1910. The 1909 outbreak of beri-beri or epidemic dropsy in Calcutta. *Journal of Tropical Medicine and Hygiene* 13:354–57.

Pekelharing, C. A. 1905. Over onze kennis van de waarde der voedingsmiddelen uit chemische fabrieken. *Nederlands Tijdschrift voor Geneeskunde,* ser. 2, 2:111–24.

Pekelharing, C. A., and C. Winkler. 1888. *Recherches sur la nature et la cause du béri-béri et sur les moyens de le combattre.* Utrecht: Kemink & Fils. [Also published in English translation by J. Cantlie (1893) London: Bale, Sons and Danielsson.]

Peters, R. A. 1963. *Biochemical lesions and lethal synthesis.* London: Pergamon Press.

———. 1967. The biochemical lesion in thiamine deficiency. In *Thiamine deficiency: Biochemical lesions and their clinical significance,* edited by. R. A. Peters and G. E. W. Wostenholme, 1–8. Boston: Little, Brown.

Peters, R. A., and R. H. S. Thompson. 1934. Pyruvic acid as an intermediary metabolite in the brain tissue of avitaminous and normal pigeons. *Biochemical Journal* 28:916–25.

Petit. 1903. De l'emploie du paddy (riz non décortiqué) dans le béribéri. *Annales d'Hygiène et de Médecine Coloniales* 6:98–100.

Phillips, G. B., M. Victor, R. D. Adams, and C. S. Davidson. 1952. A study of the nutritional defect in Wernicke's syndrome. *Journal of Clinical Investigation* 31:859–71.

Platt, B. S. 1939a. Beriberi. *Henry Lester Institute for Medical Research Annual Report for 1937–38,* 18–25.

———. 1939b. Rice and its importance for human nutrition. In *Nutrition in the colonial empire.* British Parliamentary Command Paper no. 6050: London: HMSO.

———. 1958. Clinical features of endemic beriberi. *Federation Proceedings* 17(suppl. 2):8–18.

———. 1967. Thiamine deficiency in human beriberi and in Wernicke's encephalopathy. In *Thiamine deficiency,* edited by R. A. Peters and G. E. W. Wostenholme, 135–43. Boston: Little, Brown.

Platt, B. S., and S. Y. Gin. 1938. Chinese methods of infant feeding and nursing. *Archives of Disease in Childhood* 13:343–54.

Platt, B. S., and G. D. Lu. 1936. Chemical and clinical findings in beri-beri with special reference to vitamin B_1 deficiency. *Quarterly Journal of Medicine,* n.s., 5:355–73.

Platteuw. 1881. Oorsprong van de benaming der beri beri. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 21:664–66.

Pompe van Meerdervoort, J. L. C. 1970. *Doctor on Desima.* Translated by E. P. Wittermans and J. Z. Bowers. Tokyo: Sophia University.

Postmus, S. 1954. Adolphe Guillaume Vorderman, 1844–1902. *Voeding* 16:185–87.

———. 1958. Beriberi of mother and child in Burma. *Tropical and Geographical Medicine* 10:363–70.

Postmus, S., R. Luyken, and P. J. Van der Rijst. 1955. *Nutrition bibliography of Indonesia.* Honolulu: University of Hawaii Press.

Postmus, S., and A. G. Van Veen. 1949. Dietary surveys in Java and East-Indonesia. *Chronica Naturae* 105:229–36, 261–68, 316–23.

Price, J., R. Kerr, M. Hicks, and P. F. Nixon. 1987. The Wernicke-Korsakoff syndrome: A reappraisal in Queensland with special reference to prevention. *Medical Journal of Australia* 147:561–65.

Price, J., and M. T. Theodoros. 1979. The supplementation of alcoholic beverages with thiamine—a necessary preventive measure in Queensland? *Australian and New Zealand Journal of Psychiatry* 13:315–20.

Prickett, C. O. 1934. The effect of a deficiency of vitamin B_1 upon the central and peripheral nervous systems of the rat. *American Journal of Physiology.* 107:459–70.

Primet, E. 1911. Rapport sur le béribéri. *Bulletin de la Société de Pathologie Exotique* 4:575–604, 656–57.

Putnam, J. J. 1890. A form of poly-neuritis, probably analogous to or identical with beri-beri, occurring in sea-faring men in Northern latitudes. *Journal of Nervous and Mental Disease* 15:495–505.

Raiten, D. J., J. M. Talbot, and J. H. Waters. 1998. Assessment of nutrient requirements for infant formulas. *Journal of Nutrition* 128:2059S–2293S.

Ratanaubolchai, K., S. Pikulkarntalert, and B. Panijpan. 1980. A comparison of three reagents in converting thiamine to thiochrome in the presence of plant extracts and polyphenols. *Experientia* 36:825–26.

Reid, A. 1988. *South East Asia in the age of commerce.* Vol. 1. New Haven, Conn.: Yale University Press.

Reid, J. M., E. L. Hove, P. F. Brancher, and O. Mickelsen. 1963. Thiamine deficiency in rabbits. *Journal of Nutrition* 80:381–85.

Reynolds, E. P. 1900. Further observations on epidemic arsenical peripheral neuritis. *British Medical Journal* ii:1769–71.

Ridley, J. 1819. An account of an endemic disease of Ceylon entitled berri berri. *Dublin Hospital Reports* 2:227–53.

Roche, J. 1925. La respiration des tissus: Avitaminose et inanition. *Archives Internationales de Physiologie* 24:413–27.

Roelfsema, H. E. 1901. Mededeeling omtrent de behandeling van beri-beri met kadjang hidjoe. [Report reprinted in Hulshoff Pol, *Beri-beri*, 214–19, Amsterdam: J. H. de Bussy, 1904.]

Rogers, E. F. 1962. Thiamine antagonists. *Annals of the New York Academy of Sciences* 98:412–29.

Rosenberg, C. E. 1991. Introduction. In *Framing disease: Studies in cultural his-*

tory, edited by C. E. Rosenberg and J. Golden, xiii–xxvi. New Brunswick, N.J.: Rutgers University Press.
Ross, R. 1902. Some more instances of the presence of arsenic in the hair of early cases of beri-beri. *British Medical Journal* ii:837.
Rost, E. R. 1902. The cause of beri-beri. *British Medical Journal* ii:834–35.
Rouse, I. L., and B. K. Armstrong. 1988. Thiamin and alcoholic beverages: To add or not to add? *Medical Journal of Australia* 148:605–7.
Roy, J. K. 1957. Further observations on cooking water and thiamin stability. *Journal of the Indian Chemical Society Industrial and News Edition* 20: 42–43.
Ruddle, K., D. Johnson, P. K. Townsend, and J. D. Rees. 1978. *Palm sago: A tropical starch from marginal lands.* Honolulu: University Press of Hawaii.
Sacks, F. M. 1977. A literature review of *Phasealus angularis*—the adsuki bean. *Economic Botany* 31:9–15.
Saiki, T. 1939. The inadequacies of the polished rice and fish diet and practical means of supplementing it. *Proceedings of the 6th Pacific Science Congress, California* 6:271–77.
Salcedo, J. 1954. Views and comments. In *Rice enrichment in the Philippines,* edited by W. C. Aalsmeer et al., 101–6. FAO Nutritional Studies, no. 12.
———. 1962. Experience in the etiology and prevention of thiamine deficiency in the Philippine Islands. *Annals of the New York Academy of Sciences* 98:568–75.
Salcedo, J., et al. 1950. Artificial enrichment of white rice as a solution to endemic beriberi. *Journal of Nutrition* 42:501–23.
Salcedo, J., E. O. Carrasco, F. R. Jose, and R. C. Valenzuela. 1948. Studies on beriberi in an endemic sub-tropical area. *Journal of Nutrition* 36: 561–78.
Salcedo, J., I. Concepcion, A. F. Guerrero, E. C. Pascual, and R. C. Valenzuela. 1949. Studies of the thiamine content of rice, vegetables and other foods in Bataan Province. *Acta Medica Philippina* 5, no. 4:1–19.
Sambon, L. W. 1902. A discussion on beri-beri. III. *British Medical Journal* ii:835–37.
Sandels, M. R. 1930. Experimental nutritional polyneuritis in the rat. *Journal of Nutrition* 21:409–13.
Sandwith, F. M. 1909. Discussion on beriberi. *Lancet* i:1526.
Saneyoshi, Y. 1901. On kak'ke (beri-beri). *Sei-I-Kwai Medical Journal* 20:55–60, 71–83.
Sarkar, S. L. 1926. Katakar oil poisoning. *Indian Medical Gazette* 61:62–63.
Sarkar, S. N. 1948. Isolation from argemone oil of dihydrosanguinarine and sanguinarine: Toxicity of sanguinarine. *Nature, London* 162:265–66.
Sauberlich, H. E. 1967. Biochemical alterations in thiamine deficiency—their interpretation. *American Journal of Clinical Nutrition* 20:528–42.
Sauberlich, H. E., Y. F. Herman, C. O. Stevens, and R. H. Herman. 1979. Thiamin requirement of the adult human. *American Journal of Clinical Nutrition* 32:2237–48.

Schafer, E. H. 1967. *The vermilion bird: T'ang images of the South.* Berkeley: University of California Press.

Schaumann, H. 1908. Beriberi und Nucleinphosphorsäure in der Nahrung. *Archiv für Schiffs- und Tropen-Hygiene* 12(Beiheft 5):37–57.

———. 1911. Further contributions to the etiology of beriberi. *Transactions of the Society of Tropical Medicine and Hygiene* 5:59–75.

Scheube, B. 1882–83. Die japanische Kak-ke (Beri-beri). *Deutsches Archiv für Klinische Medizin* 31:141–202, 307–48; 32:83–119.

Scobie, K., B. S. Burke, and H. C. Stuart. 1949. Studies of nutrition in Newfoundland children. *Canadian Medical Association Journal* 60:233–41.

Scott, L. C., and G. R. Herrman. 1928. Beriberi ("maladie des jambes") in Louisiana. *Journal of the American Medical Association* 90:2083–90.

Scott, W. F. 1939. *Standard methods of chemical analysis.* 5th ed. New York: Van Nostrand.

Scriver, C. R., S. Mackenzie, C. L. Clow, and E. Delvin. 1971. Thiamine-responsive maple-syrup urine disease. *Lancet* i:310–12.

Sebrell, W. H. 1931. Observations on the assay of the antineuritic vitamin. *Public Health Reports* 46:917–25.

Sebrell, W. H., and R. S. Harris. 1954. *The vitamins.* 3 vols. New York: Academic Press.

Seligman, L. 1994. The history of Japanese cuisine. *Japan Quarterly* 41:165–79.

Shattuck, F. C. 1881. A curious endemic. *Boston Medical and Surgical Journal* 105:400.

Shattuck, G. C. 1928. The relation of beri-beri to polyneuritis from other causes. *American Journal of Tropical Medicine* 8:539–43.

Sherman, H. C. 1928. Nutritional significance of our present knowledge of the multiple nature of vitamin B. *Journal of Nutrition* 1:191–99.

Sherman, H. C., and S. L. Smith. 1931. *The vitamins.* 2d ed. New York: Chemical Catalog Company.

Shibayama, G. 1910. Some observations concerning beriberi. *Philippine Journal of Science* 5B:123–25, 140.

Shimazono, J. 1925. On the etiology of beri-beri. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo* 1:37–60.

Shimazono, N., and E. Katsura, eds. 1965. *Review of Japanese literature on beriberi and thiamine.* Kyoto: Vitamin B Research Committee of Japan.

Simmons, D. B. 1880. Beriberi or the kakké of Japan. *China Imperial Maritime Customs, Medical Reports* 19:38–76.

Simoon, F. J. 1991. *Food in China: A cultural and historical inquiry.* Boston: CRC Press.

Simpson, G. C. E., and E. S. Edie. 1911–12. On the relation of the organic phosphorus content of various diets to diseases of nutrition, particularly beriberi. *Annals of Tropical Medicine and Parasitology* 5:313–45.

Simpson, I. A. 1951. A study of the nutritional value of some varieties of Malayan rice. *Bulletin of the Institute for Medical Research, Federation of Malaya,* n.s., no 5.

Skurray, G. R. 1990. Fortification of wine with thiamine (vitamin B_1). *Australian Grapegrower and Winemaker* April:16.

Smith, D. A. 1947. Nutritional conditions and diseases in the civilian internment camp, Hong Kong. *Proceedings of the Nutrition Society* 5:95–107.

Smith, D. A., and M. A. Woodruff. 1951. Deficiency diseases in Japanese prison camps. *Medical Research Council Special Report Series,* no. 274. London: HMSO.

Smith, D. F. 1995. The social construction of dietary standards: The British Medical Association—Ministry of Health Advisory Committee on Nutrition report of 1934. In *Eating agendas,* edited by J. Sobal and D. Maurer, 279–303. New York: Aldine de Gruyter.

———. 1997. Nutrition science in the two world wars. In *Nutrition in Britain: Science, scientists and politics in the twentieth century,* edited by D. F. Smith, 142–65. London: Routledge.

Smith, D. F., and M. Nicolson. 1995. Nutrition, education and ignorance: A twentieth-century debate. In *The science and culture of nutrition, 1840–1940,* edited by H. Kamminga and A. Cunningham, 288–318. Amsterdam: Rodopi.

Smith, M. I. 1930. A new method of evaluating the potency of antineuritic concentrates. *Public Health Reports* 45:116–29.

Snapper, I. 1941. *Chinese lessons to Western medicine.* New York: Interscience.

Snow, J. 1855. *On the mode of communication of cholera.* London: Churchill. [Reprinted in W. H. Frost, ed. *Snow on cholera.* New York: Commonwealth Fund, 1936.]

Sobal, J., and D. Maurer. 1995. Food, eating and nutrition as social problems. In *Eating agendas,* edited by J. Sobal and D. Maurer, 3–7. New York: Aldine de Gruyter.

Somogyi, J. C. 1949. Inactivation of aneurin by extracts of animal and plant tissues. *Internationale Zeitschrift für Vitaminforschung* 21:341–46.

———. 1966. Biochemical aspects of the antimetabolites of thiamin. *Bibliotheca "Nutritio et Dieta,"* 8:74–96. Basel: Karger.

Spillane, J. D. 1947. *Nutritional disorders of the nervous system.* Baltimore: Williams and Wilkins.

Sprawson, C. A. 1920. Beri-beri in the Mesopotamian force. *Quarterly Journal of Medicine* 13:337–55.

Stahlie, T. D. 1960. The natural history of pregnancy and childbirth in Thailand. *Tropical and Geographical Medicine* 2:127–37.

Stamm, E. K., and D. G. Wiehl. 1942. Medical evaluation of nutritional status: The school lunch as a method of improving diets of high school students. *Milbank Memorial Fund Quarterly* 20:83–96.

Stanton, A. T. 1923. The control of beriberi in the Far East. *Transactions of the 5th Congress of the Far Eastern Association for Tropical Medicine, Singapore,* 172–82.

Stechow, M. 1943. *Register der Weltliteratur über Vitamine.* Band I (von 1890–1929). Leipzig: Helingsche Verlagsanstalt.

Strauss, M. B. 1935. The etiology of "alcoholic" polyneuritis. *American Journal of the Medical Sciences* 189:378–82.

Street, H. R., H. M. Zimmerman, G. R. Cowgill, H. E. Hoff, and J. C. Fox. 1941. Some effects produced by long-continued subminimal intakes of vitamin B_1. *Yale Journal of Biological Medicine* 13:293–308.

Strong, R. P., and B. C. Crowell. 1912. The etiology of beriberi. *Philippine Journal of Science* 7B:271–413.

Suzuki, U. 1925. Chemical studies of vitamin B in Japan. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo* 1:27–35.

Suzuki, U., T. Shimamura, and S. Odake. 1912. Über Oryzanin, ein Bestandteil der Reisklei und seine physiologische Bedeutung. *Biochemische Zeitschrift* 43:89–153.

Swaminathan, M. 1942. The effect of washing and cooking on the vitamin B_1 content of raw and parboiled milled rice. *Indian Journal of Medical Research* 30:409–16.

Swaminathan, M., S. B. Dhungat, H. B. N. Murthy, and V. Subrahmanyan. 1950. Interference by certain substances present in ragi (*Eleucine Coracana*) in the determination of thiamine by the thiochrome method. *Journal of Scientific and Industrial Research* 9B:210–12.

Swank, R. L., and O. A. Bessey. 1941. Avian thiamine deficiency: Characteristic symptoms and their pathogenesis. *Journal of Nutrition* 22:77–87.

Tainsh, A. R. 1984. Beriberi and mycotoxicosis: An historical account. *Nutrition and Health* 3:189–93.

Takahashi, K. 1981. Thiamine deficiency neuropathy. *International Journal of Neurology* 15:245–53.

Takaki, K. 1885. On the cause and prevention of kak'ke. *Sei-I-Kwai Medical Journal* 4(suppl. 4):29–37.

———. 1886. Results of the preventive measures taken against the occurrence of kakke (beri-beri) among the Japanese marine prisoners. *Sei-I-Kwai Medical Journal* 5:41–43.

———. 1887. Special report of the kakke patients in the Imperial Japanese navy from 1878 to 1886. *Sei-I-Kwai Medical Journal* 6:73–74.

———. 1906a. Japanese navy and army sanitation. *Surgery, Gynecology and Obstetrics* 2:421–40.

———. 1906b. The preservation of health amongst the personnel of the Japanese army. *Journal of the Royal Army Corps* 7:54–62.

———. 1906c. The preservation of health amongst the personnel of the Japanese army and navy. *Lancet* i:1369–74.

Tanaka, S., and M. Endo. 1925. Über den Stoffumsatz bei Kakke und Geflügerberiberi. *Transactions of the 6th Congress of the Far Eastern Association for Tropical Medicine, Tokyo* 1:149–51.

Tanaka, T. 1934. So-called breast milk intoxication. *American Journal of Diseases of Children* 47:1286–98.

Tannenbaum, S. R., V. R. Young, and M. C. Archer. 1985. Vitamins and minerals. In *Food chemistry,* edited by O. R. Fennema, 478–544. 2d ed. New York: Marcel Dekker.

Thanangkul, O., and J. A. Whitaker. 1966. Childhood thiamine deficiency in northern Thailand. *American Journal of Clinical Nutrition* 18:275–77.

Thompson, R. H. S., and R. E. Johnson. 1935. Blood pyruvate in vitamin B_1 deficiency. *Biochemical Journal* 29:694–700.

Thomson, A., H. Baker, and C. M. Leevy. 1968. Thiamine absorption in alcoholism. *American Journal of Clinical Nutrition* 21:537–38.

Thorel. 1873. Agriculture et horticulture de l'Indo-Chine. In *Voyager d'exploration en Indo-Chine,* edited by F. Garnier, 2:343–491. Paris: Hachette.

Tmangraksatve, S., and S. Srisukh. 1955. Thiamine in Thai rice. *Journal of the Pharmaceutical Association of Thailand* 8:8–23.

Todd, A. R., and F. Bergel. 1937. A synthesis of aneurin. *Journal of the Chemical Society,* pp. 364–67.

Toki, Y. 1911. Resultate der Vorbeugung der Kakkekrankenheit bei der Gardedivision. In Bureau of Medical Affairs, *Mitteilungen der Beriberi-Studien-Kommission,* 47–54. Tokyo: Ministry of War.

Tomasulo, P. A., R. M. H. Kater, and F. L. Iber. 1968. Impairment of thiamine absorption in alcoholism. *American Journal of Clinical Nutrition* 21:1341–44.

Townsend, P. K. 1971. New Guinea sago gatherers: A study of demography in relation to subsistence. *Ecology of Food and Nutrition* 1:19–24.

Travers, G. A. O. 1902. The theory of the causation of beri-beri by a toxin conveyed by rice considered in the light of local experience of the disease. *Journal of Tropical Medicine* 5:231–33.

———. 1905. Relating to the paper entitled "The successful application of preventive measures against beri-beri" by Dr. Hamilton Wright. *Journal of Hygiene* 5:356–59.

Truswell, A. S., and F. Apeagyei. 1982. Alcohol and cerebral thiamin deficiency. In *Adverse effects of foods,* edited by E. F. P. Jelliffe and D. B. Jelliffe, 253–58. New York: Plenum.

Tsuzuki, J. 1912. Die Behandlung der Beriberikrankheit mit Antiberiberin. *Deutsche Medizinische Wochenschrift* 38:995–97.

Ueno, Y. 1974. Citreoviridin from *Penicillium citreo-viride* Biourge. In *Mycotoxins,* edited by I. F. H. Purchase, 283–302. Amsterdam: Elsevier.

U.S. Department of Agriculture. 1990. Composition of foods. *Agricultural Handbook,* no. 8. Washington, D.C.: Government Printing Office.

Van der Burg, C. L. 1898. Le béri-béri et l'alimentation avec du riz. *Janus* 3:83–89, 185–89.

Van Dieren, E. 1897. *Kantteekeningen op Dr. Vorderman's Beri-beri-rapport en Nog Iets.* Amsterdam: Scheltema and Holkema.

Van Eecke, J. W. F. J. 1888. Eenige bijdragen tot de keenis van der oorzaken en den aard der beri-beri. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 27:71–83.

Van Gorkom, W. J. 1898. Beri-beri in de gevangenissen op Java: Critiek op Vorderman's enquête-verslag. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 38:709–74.

Van Leent, F. J. 1880a. Communication sur le béri-béri, *Congrès Périodique International des Sciences Médicales* 6:170–94.

———. 1880b. Mededeelingen over beri-beri. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 20:272–310.

Van Leersum, E. H. 1926. The discovery of vitamines. *Science* 64:357–58.
Van Rijnberk, G. 1928. Christiaan Eijkman. *Nederlands Tijdschrift voor Geneeskunde* 72:2852–56.
Van Veen, A. G. 1933. Die invloed van wasschen en stoemen op het B_1-vitaminegehalt van rijstsoorten van verschillenden slijpgraad. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 73:945–57.
———. 1939. On diets consisting principally of milled rice and dried salted fish. *Proceedings of the 6th Pacific Science Congress, California* 6:265–69.
———. 1940. The rice problem. *Bulletin of the Health Organization of the League of Nations* 9:357–65.
———. 1947. Malnutrition in Java during the Japanese occupation. *Proceedings of the Nutrition Society* 5:280–82.
Vaughn, M., and H. S. Mitchell. 1933. A continuation of the nutrition project in northern Newfoundland. *Journal of the American Dietetic Association* 8:526–31.
Vedder, E. B. 1913a. *Beriberi.* New York: William Wood.
———. 1913b. Some further remarks on beri-beri. *American Journal of Tropical Diseases and Preventive Medicine* 1:826–47.
Vedder, E. B., and E. Clark. 1912. A study of *Polyneuritis Gallinarum* V. *Philippine Journal of Science* 7B:423–58.
Vedder, E. B., and R. T. Feliciano. 1927. An investigation to determine a satisfactory standard for beriberi-preventive rices. *Transactions of the 7th Congress of the Far Eastern Association for Tropical Medicine, British India,* 375–408.
Vedder, E. B., and R. R. Williams. 1913. Concerning the beriberi-preventing substances or vitamines contained in rice polishings. *Philippine Journal of Science* 8B:175–95.
Velez, R. J., B. Myers, and M. S. Guber. 1985. Severe acute metabolic acidosis (acute beriberi): An avoidable complication of total parenteral nutrition. *Journal of Parenteral and Enteral Nutrition* 9:216–19.
Victor, M., and R. D. Adams. 1961. On the etiology of the alcoholic neurologic diseases. *American Journal of Clinical Nutrition* 9:379–96.
Victor, M., R. D. Adams, and G. H. Collins. 1971. *The Wernicke-Korsakoff syndrome.* Philadelphia: F. A. Davis.
Vimokesant, S., S. Nakornchai, et al. 1976. Food habits causing thiamine deficiency in humans. *Journal of Nutrition Science and Vitaminology* 22(suppl.): 1–2.
Voit, C. 1881. Physiologie des allgemeines Stoffwechsels und der Ernährung. In *Handbuch der Physiologie,* edited by L. Hermann, vol. 6, pt. 1, pp. 1–575. Leipzig: Vogel.
Vorderman, A. G. 1893. Analecta op bromatologisch Gebied. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 33:343–97.
———. 1897. *Onderzoek naar het gevangenissen op Java en Madoera en het voorkomen van beri-beri onder de geïnterneerden.* Batavia: Jav. Boekh. & Drukkerij.
———. 1898. Toelichting op min beri-beri-verslag. *Geneeskundig Tijdschrift voor Nederlandsch-Indië* 38:47–68.

Vorhaus, M. G. 1939. Evaluation of vitamin B_1 (thiamin chloride) in the treatment of polyneuritis. *American Journal of Medical Science*198:837–44.
Walcott, A. M. 1915. Beriberi in the Amazon basin. *Journal of the American Medical Association* 65:2143–47.
Walshe, F. M. R. 1922. Some recent observations on the nervous lesion in experimentally produced avian polyneuritis. *Medical Science Abstracts and Reviews* 5:314–19.
Wechsler, I. S. 1933. Etiology of polyneuritis. *Archives of Neurology and Psychiatry* 29:813–27.
Weiss, S., and R. W. Wilkins. 1937. The nature of the cardiovascular disturbances in nutritional deficiency states (beriberi). *Annals of Internal Medicine* 11:104–48.
Wells, A. H. 1921. The preparation of tikitiki extract for the treatment of beriberi. *Philippine Journal of Science* 19:67–73.
Welsch, D., et al. 1979. Case study: Thailand. In *Global malnutrition and cereal fortification,* edited by J. E. Austin, 237–68. Cambridge, Mass.: Ballinger.
Wernich, A. 1877. Klinische Untersuchungen über die japanische Varietät der Beriberi—Krankheit. *Virchow's Archiv* 71:290–363.
———. 1878. *Geographisch-medicinische Studien.* Berlin: August Hirschwald.
Wessels, C. 1926. *De Geschiedenis der R.K. missie in Amboina, 1546–1605.* Nijmegen: Dekker & Van de Vegt.
Whyte, R. O. 1974. *Rural nutrition in monsoon Asia.* London: Oxford University Press.
Wiehl, D. G. 1942. Medical evaluation of nutritional status. *Milbank Memorial Fund Quarterly* 19:61–82.
Wigglesworth, V. B. 1965. *The principles of insect physiology.* London: Methuen.
Wilcocks, C. 1944. Medical organization and diseases of the Netherlands East Indies. *Tropical Diseases Bulletin* 41:983–96.
Wilder, R. M., and R. R. Williams. 1944. Enrichment of flour and bread: A history of the movement. *Bulletin of the National Research Council,* no. 110.
Willcox, W. H. 1923. Beri-beri. In *History of the Great War: Medical services,* edited by W. G. Macpherson, 1:430–49. London: HMSO.
Williams, R. D., H. L. Mason, M. H. Power, and R. M. Wilder. 1943. Induced thiamine (vitamin B_1) deficiency in man. *Archives of Internal Medicine* 71:38–53.
Williams, R. D., H. L. Mason, B. F. Smith, and R. M. Wilder. 1942. Induced thiamine (vitamin B_1) deficiency and the thiamine requirement of man. *Archives of Internal Medicine* 69:721–38.
Williams, R. D., H. L. Mason, and R. M. Wilder. 1943. Evaluation of nutritive contribution of enriched white flour. *Journal of the American Medical Association* 121:943–45.
Williams, R. D., H. L. Mason, R. M. Wilder, and B. F. Smith. 1940. Observations on induced thiamine (vitamin B_1) deficiency in man. *Archives of Internal Medicine* 66:785–99.
Williams, R. J. 1973. *Biochemical individuality.* Austin: University of Texas Press.

Williams, R. R. 1915. Editorial. *Philippine Journal of Science* 10B:95.
———. 1916. The chemistry of the vitamines. *Philippine Journal of Science* 11A:49–57.
———. 1917. The chemical nature of the "vitamines." III. The structure of the curative modifications of the hydroxypyridine compounds. *Journal of Biological Chemistry* 29:495–520.
———. 1951. Travel letter no. 13 (Singapore), Box 11, Papers of R. R. Williams. Collection no. 47241, Library of Congress, Washington, D.C.
———. 1953. Recollections of the "beriberi-preventing substance." *Nutritional Reviews* 11:257–59.
———. 1954. Food fortification in the Orient. *Nutritional Reviews* 12:289–91.
———. 1956. *Williams-Waterman Fund for the combat of dietary diseases.* New York: Research Corporation.
———. 1961. *Toward the conquest of beriberi.* Cambridge, Mass.: Harvard University Press.
———. 1962. Edward Bright Vedder: A biographical sketch. *Journal of Nutrition* 77:1–6.
Williams, R. R., and J. K. Cline. 1936. Synthesis of vitamin B_1. *Journal of the American Chemical Society* 58:1504–5.
Williams, R. R., and T. D. Spies. 1938. *Vitamin B_1 (thiamin) and its use in medicine.* New York: Macmillan.
Williams, R. R., R. E. Waterman, and S. Gurin. 1930. The Jansen and Donath procedure for the isolation of antineuritic vitamin. *Journal of Biological Chemistry* 87:559–79.
Williams-Waterman Fund. 1950. *Better health through better rice.* New York: Williams-Waterman Fund.
Windaus, A., R. Tschesche, H. Ruhkopf, F. Laquer, and F. Schultz. 1932. Die Darstellung von krystallisiertem antineuritischem Vitamin aus Hefe. *Hoppe-Seyler's Zeitschrift für Physiologische Chemie* 204:123–28.
Winslow, C.-E. A. 1952. *Man and epidemics.* Princeton, N.J.: Princeton University Press.
Wintersteiner, O., R. R. Williams, and A. E. Ruehle. 1935. Studies of crystalline vitamin B_1. II. Elementary composition and ultraviolet absorption. *Journal of the American Chemical Society* 57:517–20.
Wong, K. C., and W. Lien-Teh. 1932. *History of Chinese medicine.* Tientsin, China: Tientsin Press.
Wood, B. 1985. Thiamin status in Australia. *World Review of Nutrition and Dietetics* 46:148–218.
Wood, B., and K. J. Breen. 1980. Clinical thiamine deficiency in Australia: The size of the problem and approaches to prevention. *Medical Journal of Australia* 1:461–64.
Woollard, H. H. 1927. The nature of the structural changes in nerve endings in starvation and in beri-beri. *Journal of Anatomy* 61:283–97.
Worboys, M. 1976. The emergence of tropical medicine. In *Perspectives on the emergence of scientific disciplines,* edited by G. Lemaine, R. McLeod, M. Mulkay, and P. Weingart, 75–98. Paris: Mouton.

———. 1988. Manson, Ross, and colonial medicine policy. In *Disease, medicine and empire,* edited by R. Macleod and M. Lewis, 21–37. London: Routledge.

———. 1989. British colonial medicine and tropical imperialism: A comparative perspective. In *Dutch medicine in the Malay Archipelago, 1816–1942,* edited by A. M. Luyendijk-Elshout, 153–67. Amsterdam: Rodopi.

———. 1994. From miasmas to germs: Malaria, 1850–1879. *Parassitologia* 36:61–68.

Wostmann, B. S., P. L. Knight, and D. F. Kan. 1962. Thiamine in germfree and conventional animals: Effect of the intestinal microflora on thiamine metabolism in the rat. *Annals of the New York Academy of Sciences* 98:516–27.

Wright, H. 1901. Changes in the neuronal centres in beri-beric neuritis. *British Medical Journal* i:1610–16.

———. 1902. An enquiry into the etiology and pathology of beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* vol. 2, no. 1.

———. 1903. On the classification and pathology of beri-beri. *Studies from the Institute for Medical Research, Federated Malay States,* vol. 2, no. 2.

———. 1905. The successful application of preventive measures against beriberi. *Journal of Hygiene* 5:129–33.

Wuest, H. M. 1962. The history of thiamine. *Annals of the New York Academy of Sciences* 98:385–400.

Wylie, E. 1988. The search for the cause of *beriberi* in the Malay Peninsula. *Journal of the Malaysian Branch of the Royal Asiatic Society* 61:93–122.

Yang, C.-S., and K. H. Huang. 1934. Beri-beri in Nanking. *Chinese Medical Journal* 48:20–36.

Yang, E. F. 1938. Effect of method of preparation on the vitamin B_1 content of rice. *Journal of the Chinese Chemical Society* 6:55–65.

Yong, S. H. 1979. Fortification technology. In *Global malnutrition and cereal fortification,* edited by J. E. Austin, 43–80. Cambridge, Mass.: Ballinger.

Yudkin, W. H. 1949. Thiaminase, the Chastek paralysis factor. *Physiological Reviews* 29:389–402.

Ziporin, Z. Z., W. T. Nunes, R. C. Powell, P. P. Waring, and H. E. Sauberlich. 1965. Thiamine requirement of the adult human as measured by urinary excretion of thiamine metabolites. *Journal of Nutrition* 85:297–304.

Zuidema, P. J. 1980. Beriberi. *Tropical and Geographical Medicine* 32:195–205.

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