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Nobel Lecture*

Beriberi is a disease prevalent, epidemically, in tropical and subtropical regions of Eastern Asia, where rice is the staple food of the natives; it is found elsewhere among sago-eating peoples (Molucca Islands), as well as in South America, in places where rice or cassava meal is the staple diet, as in certain parts of Brazil. However, the disease also occurs sporadically – here and there even with abundant frequency – in the temperate zone and, in some circumstances, in the frigid zone.

The symptoms of the disease are paralysis and numbness starting from the lower limbs, as well as cardiac and respiratory disorders accompanied by dropsy. These latter symptoms rapidly come to the fore, and we then speak of “wet beriberi”. Soon the motility and sensitivity disturbances, eventually accompanied by severe muscular atrophy, become more pronounced (“dry beriberi”). Mixed and transitional forms, however, are not rare. Where the paralysis is fairly advanced, the peculiar gait of the patient is noticeable. As the extensors of the foot are paralysed, the patient has to raise the knee up and swing the foot forward in order to avoid stumbling over the downhanging toes.

It is mostly young men in full vigour who are stricken by the acute form of the disease; they not infrequently die suddenly, in terrible distress through inability to breathe. This fatal issue, even in the more chronic cases, is often due to intercurrent causes, e.g. physical strain, or diseases such as malaria, dysentery, etc.

Although beriberi was described as long ago as in the first half of the 17th century

by the Dutch specialist in tropical medicine Bontius, it has only shown itself as a really devastating disease in the Malay Archipelago since about the sixties of last century, and then generally speaking not so much among the free population as among people living to some extent under constraint, such as soldiers, sailors, prisoners, imported coolies in the mines and plantations, and so forth. It was particularly common in the native prisons; even detainees awaiting trial, sometimes died of the disease. And in the native hospitals it claimed many a victim among people admitted for a relatively minor ailment, such as gonorrhoea or a fractured bone.

During the protracted war – a true guerilla war – which we had to wage with the Achin sultanate, both army and navy suffered very severely from the disease. Newly drafted native troops were often unfit for service after about six weeks and the pitiful remnant had to be evacuated as quickly as possible. For instance, a man might apparently be in good health in the morning, and even gave proof of his skill during target practice, and then fell victim to the disease by evening. An army doctor of that time mentions that at his hospital 18 soldier died of beriberi on one day.

European troops also suffered from the disease in Achin, though to a lesser extent than the native troops.

Faced with this serious situation, the Home Government decided in 1886 to send out a commission to investigate the nature of beriberi and its cause. Pekelharing, Professor of Pathology, and Winkler, reader in neurology, both of the Medical Faculty of the University of Utrecht, were in charge, and I was seconded to the commission as an assistant. Winkler immediately established that the disease was essentially a form of polyneuritis (more accurately: multiple neuratrophy), a finding which agreed with results obtained by Bälz and von Scheube from investigations conducted by them in Japan. The clinical symptoms were also consistent with this pathological-anatomical diagnosis, which moreover could be confirmed in the living subject by electrical examination (reaction of degeneration, etc.).

At that time there were naturally many different theories as to the cause of beriberi. Two of these were based on the fact that the disease was particularly prevalent among rice-eating populations, although -as already mentioned – this is

not always the case. On the one hand, rice poisoning was suspected; on the other, a deficiency of the rice diet, but not in the same sense as we now understand it.

With regard to the first theory, the disease was found to occur all too often where the rice was of excellent quality from the culinary point of view. Neither was any actual proof of a preexisting poison in the rice diet found, or even sought. This also applies to other poison-theories, e.g. that the disease was due to rotten fish or to "mephitic" gases emanating from the soil.

The second theory was formulated by Van Leent in 1879 in the light of his experience with the East Indies Navy. He considered that an one-sided rice diet resulted in malnutrition owing to its very low content of protein and fat, and that this condition would promote beriberi. He found that the incidence of the disease among native sailors fell considerably when they were put on to a European diet.

There were weighty arguments against this theory, in particular the fact that people with great muscular strength and a welldeveloped *panniculus adiposus* were often attacked by the disease; and also that European crews, on a diet containing sufficient protein and fat, were not immune, even when they were given virtually no rice at all. In the report made after its return to Holland, the commission rejected this theory because it could not be assumed that malnutrition in itself would result in destruction of peripheral nerves. For this a directly injurious effect on the nerves or their centers would be necessary. In the light of our knowledge today, however, we see that there was a very large grain of truth in Van Leent's theory, and it can scarcely be doubted that a lasting improvement in the health of the native crews could have been achieved if it were possible to introduce the Dutch navy food and persuade the men to take it. It is however a very delicate matter to alter the diet to which people have been accustomed from their youth, and consequently with few exceptions the native sailors soon forsook pea soup with sausage and bacon, potatoes, bread with cheese, etc. and went back to the monotonous and poor rice diet, which they were usually able to procure.

Takaki, who – for reasons similar to those of Van Leent – a few years later changed the diet of the Japanese Navy to the European style, thereby – it is reported – achieving lasting success in the fight against beriberi, also had to admit that this measure was difficult to put into effect. "By last year's experience," he said, "we have found that most of the men dislike meat as well as bread and we do

not know what we shall do next."

However this may be, we failed to check the disease permanently, although at first it did seem to subside a little. But this diminution does not prove much since in any case beriberi was subject to considerable periodic fluctuations, apart from the fact that the statistics on the disease were not very reliable. For instance it was quite obvious that these statistics frequently included cases of palpitations of the heart, oedema of the feet, as well as a new cause of death described as "hydraemia perniciosa tropica" – conditions which should obviously have been ascribed to beriberi. In those days diagnosis of beriberi was clearly taboo.

In the limited time which the commission, for official reasons, had at its disposal it was unable to carry out experimental investigations in every conceivable direction, and it is not surprising that at a time when bacteriology was all-triumphant under the leadership of Pasteur and Koch, the commission should have decided first of all to apply the methods of these two men to the problem in hand. It had all the more reason to take this line since beriberi is a disease with pronounced local and periodic tendencies (as defined by von Pettenkofer). The periodic fluctuations, the prevalence under certain climatic and weather conditions, the epidemic occurrence in certain countries and places, the association with buildings, and finally the cases of transmission of the disease described in the literature – all this pointed to an infection. True, under these circumstances a parasitic disease might have been considered -in particular hookworm, widely spread in the tropics, has been accused of being the main cause of beriberi – but the commission was able to establish that anaemia of any severity is not one of the characteristics of this disease.

I shall not dwell on the results of the bacteriological investigations because they have long since ceased to have any significance, although at that time they were apparently of fundamental importance. Polymorphic bacteria were found in the blood of patients, although not regularly, and degeneration of the nerves could be induced in animals by repeated injections of a coccus culture from them. In its report, following its return to Holland, the commission suggested very tentatively that the cause of beriberi had thus been discovered. The commission succeeded in isolating a coccus, which it considered identical with the above-mentioned one, from the air in barracks which, from its point of view, could be regarded as infected.

Following the departure of the commission I was entrusted with the task of continuing its investigations, but at frost I failed to get any further. The disinfection measures which, as is logical, were recommended had not the hoped-for success. Then a chance happening put me on the right track.

A disease, in many respects strikingly similar to beriberi in man, suddenly broke out in the chicken-house at the laboratory in Batavia, and this called for a thorough study. The symptoms of this disease are as follows: The initial stages, following defective evacuation of the crop some days earlier, are characterized by an unsteady gait. The bird has difficulty in perching and has to exert itself in order not to fall; the legs are spread through weakness, and the knee and ankle joint are bent. The bird frequently collapses and falls over when walking. Finally it remains lying on its side and paresis of the wing muscles now becomes obvious from its vain efforts to get up. Paralysis of the body muscles advances rapidly from below. Within a few days the condition of the bird has so deteriorated that it can no longer eat anything without assistance; although swallowing movements are still produced, the bird is unable to lift its head. Symptoms indicating the onset of paresis of the respiratory muscles then appear. Respiration is slowed down, the beak opens, comb and skin become cyanotic, the neck is bent back and the head drawn in. The bird now becomes more and more soporific, the eyes are covered by the nictitating membrane and the body temperature falls a degree or two centigrade below normal.

This was a case of polyneuritis, as indicated by the symptoms and course of the disease and proved beyond question by a microscopic examination.

With regard to the etiology, our original supposition was not confirmed, i.e. that in the case of the strikingly epizootic occurrence of the disease an infection was involved. Attempts to induce the infection with material from affected birds or from birds which had died of the disease were inconclusive since all the chickens, even those kept separate as controls, were affected. No specific micro-organism or any higher parasite was found.

Then suddenly the disease cleared up and we were unable to continue our investigations. The affected chickens recovered and there were no new cases. Fortunately suspicion fell on the food, and rightly so, as it very soon turned out.

The laboratory was still housed provisionally and in a very makeshift manner at the military hospital, although it was administered by the civilian authorities. The laboratory keeper – as I afterwards discovered – had for the sake of economy fed the chickens on cooked rice which he had obtained from the hospital kitchen. Then the cook was replaced and his successor refused to allow military rice to be taken for civilian chickens. Thus, the chickens were fed on polished rice from 17th June to 27th November only. And the disease broke out on 10th July and cleared up during the last days of November.

Deliberate feeding experiments were then conducted in order to check more thoroughly whether or not the propable connection between diet and the disease actually existed. It was found for certain that the polyneuritis was due to the diet of cooked rice. The chickens were attacked by the disease after 3-4 weeks, and in many cases somewhat later, whereas the controls which were fed on unpolished rice remained healthy. In many cases, birds suffering from the disease could be cured by a suitable alteration in diet.

This difference between polished and whole rice did not lie in the fact that the former had not kept so well during storage, since cooked rice which had been freshly prepared from the whole kernel would also cause the disease. In addition to this, rough rice, i.e. rice with only the coarse husk removed, which deteriorates much more easily (being attacked by mites, mould fungi, etc.), proved harmless during the feeding experiments. This rice, as obtained simply by stamping, still has its inner hull – known as its “silver skin” (pericarpium) – and germ wholly or largely intact. We were then able to conclude from a series of highly varied experiments that the antineuritic principle is situated mainly in these parts of the rice kernel, and indeed of any cereal grain. It can easily be extracted with water or strong alcohol and is dialysable. I also established that it can be used medicinally either through the mouth or parenterally.

Feeding with other Amylaceae, such as sago and tapioca, had exactly the same results as cooking rice. Since these contain only traces of primary nutrients other than starch, it was impossible to dismiss out of hand the suspicion that the disease was due to simple inanition, especially as it was accompanied by considerable emaciation. And at that time – when the effectiveness of minute doses of the antineuritic principle had not yet been established – the fact that the affected birds recovered when fed on a diet consisting only of meat, could be regarded as

being tantamount to the result of an experimentum crucis. On the other hand, by adding meat to the starch-rich diet it was possible to prevent the emaciation but not outbreaks of the disease, even though these were somewhat delayed. Thus, inanition in itself could not be the main cause of the disease (any more than "protein" or "salt" deficiency), even though it promoted it. I also concluded from this that an antineuritic principle must have been present in the meat, i:e. in the animal organism, but that this principle was gradually used up while the chickens were being fed on a starch diet. And finally the outcome of these experiments was encouraging for me in that one apparent difference as compared with human beriberi had thus been eliminated, for, as already stated, beriberi not infrequently attacks well-fed, strong individuals. Starvation experiments which I conducted at that time also produced a negative result. This was confirmed many times over (Holst, Shiga, & Kusama; Fraser & Stanton, et al.) before I resumed these experiments (in Holland) in view of a communication from Chamberlain et al. (1911) that they had observed in 3 out of 8 cases, polyneuritis among chickens which had been given drinking water without any solid food. This time I obtained a positive result in no less than six out of eight cases. However, it could not be concluded from this alone that the cause of the disease was general inanition, for, apart from the fact that total starvation includes partial starvation, we were able to show that the starved birds which were suffering from the disease, just as birds which had been fed on an unbalanced diet, recovered again, despite continuing loss of weight, when given 8-10 g vitamin-rich yeast per day.

Investigations with other animal species on the East Indies showed that birds such as pigeons and the Indian rice bird can also be used with success. In contrast, results of experiments with mammals were almost entirely negative. This disappointment could, of course, not prevent me from testing whether and to what extent the discovery which had been made as a result of the study of polyneuritis in birds could be used in the fight against human beriberi, although at that time there was still reason enough to doubt the identity of the two diseases. I was therefore accused of not being logical, a reproach which I am happy to pass over without comment.

The obvious thing to do was to test the preventive and curative effect of rough rice in the case of beriberi by means of experiments and controls. Rough rice is the staple diet wherever the rural population in the Indies grows rice for its own use and shelled it by primitive methods. White, or polished, rice is processed mechanically and is one of the blessings of European civilization, of our improved

techniques which, for instance, have also changed the colour of bread here in Europe from brown to white. Thought-provoking too was the fact, already referred to, that the free population, which fed itself, was much less subject to beriberi than the population whose freedom was restricted, and which was often dependent on imported and therefore mechanically processed, polished, rice. (As already noted, rough rice is unsuitable for prolonged storage.)

When the projected nutritional experiments on man had just begun, an observation was made by Vorderman which had almost the value of a check experiment. As civilian medical inspector for the island of Java he knew that, in accordance with local custom, the native prisoners were given polished rice in some areas, but rough rice in others. The question, therefore, was to ascertain whether there was a connection between the nature of the staple diet and the incidence of beriberi at the prisons. This on-the-spot investigation was carried out by Vorderman at my request, on behalf of the East Indies Government, and at the same time attention was paid to other factors – apart from diet – with a bearing on the subject. As a result of this research, conducted with admirable proficiency and perseverance, my theory based on the chicken experiments was proved correct. The enquiry covered no less than 101 prisons with almost 300,000 inmates. In brief, the proportion of cases of beriberi in the prisons where polished rice was used as staple diet was some 300 times greater than in those where rough rice was used.

Vorderman's remarkable results did not at once find recognition and were received with scepticism and adverse criticism in some quarters. For me, who had meanwhile been repatriated, the results agreed so unequivocally with those of the chicken experiments that the possibility of coincidence could not seriously be considered. However, the nutritional experiments on which I had already embarked were discontinued, and the alteration in the catering regulations for prisoners, suggested after my departure by Vorderman and Grijns, in the long run did not meet with the necessary cooperation of the authorities. Only when Grijns, who continued' my investigations, discovered that a certain bean, the "katjang idju" (*Phaseolus radiatus*), has the protective and curative action in the case of chickens, successful experiments – with this bean – were made on man (Roelfsema, Hulshoff Pol, and Kiewiet de Jonge). It is, however, obvious that this bean is of far less value as a staple food than a suitable rice diet.

New encouragement then came from British India (Braddon, Ellis, Fletcher, and

Fraser & Stanton), on the strength of which in 1910 the following resolution was drawn up by the Far Eastern Association of Tropical Medicine meeting in Manila:

"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 that the Association accordingly desires to bring this matter to the notice of the various Governments concerned."

And in Hong Kong, 1912:

"That the accuracy of the opinion of the Association, recorded in 1910, has received further and more complete confirmation by investigators in Japan, China, French Indo-China, the Philippine Islands, Siam, Netherlands India, the Straits Settlements and the Federated Malay States, namely that beriberi…"

Experiments on animals were naturally also used in order to trace the distribution of the antineuritic principle in living organisms. Numerous animal and vegetable foodstuffs which are more or less rich in this principle are listed in the literature on the subject. In practice this is of the greatest importance, since here too it has been found that the vitamin-rich foodstuffs can be used successfully to combat human beriberi. Concentrated extracts of these have also been prepared and these likewise have a pronounced curative action both against polyneuritis in birds and against beriberi.

Until a short while ago, however, no one had succeeded in extracting the active principle reliably and in pure form from these initial materials, although indeed efforts to do so were not wanting. And I was particularly delighted when a few years ago Jansen and Donath were able to report from the laboratory in Batavia – now a splendid improvement on my old workshop – that they had isolated the antineuritic vitamin from rice bran. It is a crystalline substance, obtained in the form of a hydrochloride, an analysis of which gives approximately the formula.

With this substance they conducted experiments in preventive feeding with rice birds and pigeons, and they found that an addition of 2 mg per 1 kg polished rice, i.e. in the ratio of 1:500,000, is sufficient to give protection against polyneuritis.

They sent me approximately 40 mg, sufficient to carry out not only preventive but also curative experiments on pigeons and young cocks. I was able to confirm that such a minute addition gives protection and – which, indeed, could not have been expected otherwise – also has curative power.

Accordingly the human requirement of antineuritic vitamin can be estimated at 1-2 mg per day.

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* As Professor Eijkman has been prevented by ill health from coming to Stockholm to deliver his Nobel Lecture, he has very kindly sent the text to the Editor of *Les Prix Nobel* for publication.

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