

Special Article :**Eijkman's Discovery of the Vitamins and Some History of Nutrition Research in Indonesia***

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It was a happy coincidence that preparations for this course started in 1990. In this year, it was exactly 100 years ago since Eijkman's first publication appeared, leading to this discovery of vitamins. This famous research was carried out in Indonesia. Today everybody is familiar with vitamins, those miraculous substances, in extremely small quantities essential to life. Indonesia may be considered the native country of vitamins. This has gradually been forgotten by the younger generation. To commemorate this Centenary, 1990 was declared 'The Eijkman Year'. Two entirely independent symposia were organized. One in Jakarta by Dr. Marzuki from the Monash University, Melbourne and one in Utrecht by the Netherlands Society of Tropical Medicine, initiated by myself. Remarkably the organizers of both symposia were not acquainted with each other's activities until late 1989. The symposium in Indonesia was entitled: 'Biochemistry in the tropics: from vitamins to molecular biology'. Its name already indicated that the subjects mainly concerned basic biochemistry. The Utrecht symposium, 'Eijkman centennial international symposium' was epidemiologically and clinically orientated.

At the root of the discovery of the vitamins were the beriberi epidemics sweeping East Asia at the end of the 19th century. In military hospitals, deaths from beriberi amounted to 50 percent of total deaths. Transports of troops demanded on average 10 deaths per ship. The literature reads like a novel. Some investigators held it to be a cosmic disease resembling typhoid fever. Others compared it to rheumatoid arthritis. Some considered the possibility of an inflammation of the spinal cord or presumed an identity with pernicious anaemia or with infectious diseases.

The history of the discovery of the vitamins is well-known to nutritionists as being inherent to rice polishing. As often with revolutionary discoveries, it was the result of a series of sudden unexpected and obviously inexplicable events. On the contrary, Eijkman's keen observation made him discover the

cause. Eijkman's small laboratory consisted of two rooms in the, at that time, military hospital in the capital. The first casual event occurred as chicken in the yard suddenly developed a disease which in many respects resembled beriberi. Newly purchased chicken became ill after 20-30 days and died 30-50 days after the onset of the disease. The clinical signs symptoms were described by Eijkman^{1,2} as follows :

Clinical signs and symptoms

Newly purchased animals became ill on days 20-30. The beginning of the disease is characterized by an unsteady gait. On the following days toes cannot be stretched any more as a result of paresis of the calf muscles. The animal walks straddling, stumbling over its toes, and falling backwards. In this phase of the disease the animal is still quite lively, eats eagerly, is still cackling and crowing, flapping its wings, and appears full of fight. Soon afterwards, however, the animal is falling to one side, unable to rise. Lifting of the head becomes increasingly difficult. Furthermore, the respiratory movements are difficult, indicating paresis of the respiratory muscles. Probably the activity of the heart is also changing. However, it was difficult to obtain definite data on this. The location of the small heart, hidden totally behind the sternum, makes palpation and percussion impossible. Nor did we succeed in feeling the pulse.

The conditions influencing recovery will be discussed under 'etiology'. Here we will mention only that these conditions consisted mainly of changing the diet and careful nursing. *End of quote.*

Postmortem examinations

Pages 299-319 contain detailed description of 25 postmortem examinations, emphasizing neuropathology. Two-thirds of the animals died within a week of showing the first symptoms of the disease, others in the second week. According to the classification of Pekelharing and Winkler, as described by van Eecke, most neural pathology ranged from stages "stand. 1" to

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stad.4". A classic example as it appears in the original manuscript is given in case 1.

Case 1

A big cock died three days after onset of the disease. Microscopic study was made of the nerve tissue, treated with osmic acid, and disaggregated.

Findings

1. Stem of the left n.intercostalis (nr 2): many fibers in "stad. 1-2"
2. Branch for right m.glutaeus maj.: doubtful degeneration
3. Branch for right m.gastrocnemius: many fibers in "stad.1-2"
4. Branch for right m.extensor digitor pedis: many fibers in "stad. 1-2".
5. Branch for right m.peroneus longus: many fibers in "stad. 1-2" *End of quote.*

Briefly summarized, the postmortems showed the following: macroscopically, the most striking observations were: hydropericardium and emaciation. Muscles and fatty tissues were affected. Microscopically, degenerative changes in the peripheral nerves were observed, most frequently in the spinal cord nerves. The cranial nerves were affected less often.

It was the era of bacteriology, and all efforts were aimed at finding the 'responsible microorganism'. Eijkman organized his studies according to the basic laws of bacteriology. He tried to infect healthy chicken with material (blood, faeces, and mucous) of men or chicken suffering from beriberi. And now the second serendipitous event occurred. Let us quote Eijkman again:

"The preliminary results led us to inject blood of expired chickens into a larger number of newly bought chickens. These injected chickens were placed in one cage with six control chickens.

A few days later another five chicken were given injections of blood from a human patient with beriberi. These animals were placed, together with a control chicken, in pairs in bamboo cages. The first signs of the diseases were observed 18 days later. Within a few days thereafter, not a single animal survived, including the controls (which supposedly were not 'infected').

To exclude infection as much as possible, another series of 20 chicken was started. All animals were housed in individual cages. Ten animals were injected with blood or intestinal contents from birds that had died recently. One month later 10 chicken were dead, *including a number of the controls". End of quote.*

This, and a third sudden event made Eijkman abandon the infection idea and brought him to the diet. To continue Eijkman:

"Suddenly an unforeseen event occurred: the disease came to a standstill. At the same time, our attention was drawn by something that, until now, had escaped notice: the diet. For some time the chickens had been fed with (cooked) rice from the military hospital kitchen, instead of the raw rice bought on the market. There was a striking coincidence between the outbreak of the disease and the feeding of the hospital rice.

In the next experiment six chickens were fed raw from our stock, and four received cooked rice from the hospital. The first six remained healthy. The four animals fed with hospital rice became ill. These four animals were not killed for autopsy but were given the ordinary chicken feed-raw rice. They recovered.

From the day the chickens were fed the ordinary chicken feed (raw rice) instead of the cooked rice from the hospital, they improved. After some time they were totally cured". *End of quote.*

These observations were brilliant and revolutionary. The idea that diet could have something to do with diseases was quite new. However Eijkman's initial interpretation was not quite correct. He concluded: "Consequently there is no doubt that feeding cooked rice is the cause of the disease". In his second publication, from 1886^{3,2} Eijkman had to correct this interpretation as follows:

"Before continuing our reporting we have to correct an earlier statement. In 1890 we reported that the feeding of raw hospital rice was not followed by an outbreak of the disease. This statement was based on a feeding experiment lasting three months, which had to be stopped because of unforeseen circumstances.

We describe now some experiments from which it can be concluded that raw hospital rice, in contradiction with earlier statements, can cause the disease (Experiment III).

Consequently, we see that milled rice of different origin can always cause the disease. It is of no importance whether it was fed cooked or uncooked, milled recently, or long ago.

Already in our first publication we mentioned that animals never became ill when they were given the ordinary chicken feed, and that affected animals even recovered with it. However, this ordinary chicken feed was *unhusked or lightly milled/undermilled red rice*. This fact, however, is no proof of the harmlessness of unhusked table rice. The objection remains that the experiments were not conducted for a long enough time. We were of the opinion that we would be able to take away the still-existing doubt by trying to cure the already-ill animals with lightly milled/undermilled rice or unhusked rice. This trial was successful indeed, as was shown in subsequent experiments. "*End of quote.*

The second publication by Eijkman ends with a very important 'Editorial Note':

Editorial Note to the 1896 Publication

In the meantime, health inspector Vorderman made an inspection tour of all the prisons on Java and Madura. During 1895 and 1896 precise data were obtained on the prevalence of beriberi, and samples were taken from the rice used as staple food. The results strongly support Eijkman's idea that the results of the chicken experiments 'may have' practical usefulness. While not prejudging the report of Mr. Vorderman, which is in many respects extremely interesting, we mention, with his permission, the following data.

In only one out of 37 prisons where the inmates were fed undermilled rice did beriberi occur. In 71 % of 52 prisons where fully milled rice was fed beriberi was rampant. *End of quote.*

Eijkman continued to be convinced that amylum contained a toxic substance or produced toxic material in the intestine by chemical or microbiologic processes. He thought that the silverskin of the rice would contain a substance that neutralizes the toxic material.

In 1896 Eijkman returned to The Netherlands because of health problems. In 1898 he was appointed Professor of Public Health at the University of Utrecht. His work was continued by his successor Grijns and by many others in Indonesia. In 1929 Eijkman was awarded the Nobel prize.

In 1911 Casimir Funk proposed to call these obscure but protecting substances 'vitamin'.² Another 15 years elapsed until 1926, when Jansen and Donath, also in Indonesia, succeeded in isolating thiamine in crystalline form.²

If I am rightly informed, the instruments with which Jansen and Donath carried out the chemical isolation of thiamin are preserved in Dr. Latu's small museum in the former 'Eijkman Institute', where my wife and I had the pleasure to work in the period 1945-1949. An interesting anecdote from the time we entered the Institute after the Japanese occupation, is worth mentioning. We came upon the 'Jansen room'. Jansen repatriated in 1929. The room was preserved by Jansen's co-worker, I think his name was Sudarsono, in the original arrangement as Jansen had left behind. You will realize that we are looking forward, to visiting the familiar environment again.

Nutritional studies in Indonesia were not restricted to thiamin research. On the contrary. In the period 1850-1950 all imaginable subjects in the field of nutrition were studied. An excellent overview was published by Van Veen in 1950.⁴ This resulted in more than 400 publications between 1890 and 1950. Abstracts in the English language of these publications

were published in 1955.⁵ Substantial funds for nutrition research were made available. The Government was well aware of the importance of nutrition research for the improvement of health of the population of the Archipelago. In 1915 the newly built 'Medical Laboratory' was opened, housing also the nutritional laboratories. In 1938 the building was renamed Eijkman Institute.⁶ In 1934 the Nutrition Institute (*Instituut voor Volksvoeding*) was founded. About 1940 its staff consisted of some 40 persons. Whether or not the world wide fame of Eijkman's and Jansen and Donath's discoveries had inspired this development is unknown.

Indonesia was far ahead of the Netherlands, where nutrition research was restricted to the hobby of a single person. It was and still is not an official Department of our Universities, with the exception of Maastricht. In Amsterdam nutrition research flourished in the period of the B.C.P. Jansen (1929-1954). As mentioned before, in 1926 Jansen and Donath crowned Eijkman's discovery by the chemical crystalline isolation of thiamin. In this way they proved that vitamins were no vague imaginations but scientific realities. His Indonesian period had raised Jansen's interest in nutrition research. In 1929, he accepted the chair of Physiological Chemistry at the University of Amsterdam. It was self-evident that the research work in his laboratory was directed on nutrition. But the Amsterdam laboratory must have been a great disillusion to Jansen. As with most of the University laboratories at that time, it was housed in a couple of old building, declared unfit for any other purpose. This formed a great contrast with the Eijkman Institute, being built as Laboratory, according to the wishes of the scientists. Nevertheless Jansen succeeded to create a nutrition research center of world renown. It was a great honour for me to specialize in nutrition in Jansen's laboratory. However, as Jansen retired in 1954, nutrition research vanished from the University of Amsterdam. Jansen's successor was an eminent biochemist, Prof. E.C. Slater. It was self-evident that modern, basic biochemistry determined the direction of research for the next decennia. An extraordinary chair of nutrition, founded in 1947, was all that remained.

Back to nutrition research in Indonesia. In the first period beriberi stood central. However the erroneous idea that white, polished rice, was better than husked undermilled or handpounded rice slowed down the development. Even after Eijkman's discovery progress seemed very slow. His studies met with much opposition and criticism. Often they deteriorated in personal abuses. Critics were always based on theoretical considerations, personal ideas, misinterpreted observations, but never on experiments. The only way to

unravel the beriberi problem was to carry out irrefutable experiments as were conducted by Eijkman and successors. Of course investigators in the tropics had to conquer much more and greater technical difficulties than in Western countries.

In 1896 Grijns continued Eijkman's work and determined the beriberi preventing activity of different foods. E.g. *kacang ijo* proved to be very active.

The period between 1918-1932 was dominated by the crystalline isolation of thiamin by Jansen and Donath. As mentioned before this was the first result of its kind, the importance of which can hardly be overrated. It was followed by the isolation of many other vitamins, hormones and enzymes by other scientists. Jansen used to speak of a long, Santa Claus evening.

As far as other subjects only a very incomplete overview can be given. Many analyses of local foods were carried out in order to compile food composition tables. An important observation concerned cassava. Already with routine estimation the protein content proved to be very small. But the routine method, the Kjeldahl method, estimates only total nitrogen, including non-protein-nitrogen. Van Veen⁷ showed that only 50 percent of nitrogen originated from protein. Consequently many data of food composition tables concerning cassava (and other tubers) have to be reduced by 50 percent.

Already in the early twenties Jansen started animal experiments to study the nutritional value of different proteins. He demonstrated that combinations of vegetarian proteins had the same nutritional value as animal protein. This was of great importance to an overpopulated country like Indonesia, where animal protein is extremely scarce and expensive. Specific Indonesian combinations are, a.o.,: rice with *tempe*, rice with *kacang ijo*. Or, more generally: combinations of cereals with pulses, later called 'double mixes' by Jelliffe. This was long before the determination of the 'biological value' of proteins became common property in western laboratories. Even today, it is not generally accepted that combinations of vegetarian proteins can replace meat, fish, eggs.

Different aspects of metabolism of inhabitants of the tropics were studied, a.o., by Radsma. Serum cholesterol in blood of the Javanese people was already studied by De Langen in 1918. It was found to be extremely low. For us, Europeans, something to be jealous about!

Many other Biochemists and physiologists joined the staff of the Nutrition Institute and other laboratories. In the thirties the economic depression also hit Indonesia. As mentioned before, the Govern-

ment was convinced of the importance of good nutrition research for optimal health. The civil servants were urged to concentrate research on practical problems. Results had to benefit the health of the population as much as possible.

As soon as chemical analyses of vitamins became available, these methods were introduced in Indonesia. These methods were used to analyse foods, but also the vitamin status of population groups. These vitamins included vitamin A and provitamin A: the carotenoids, thiamin, riboflavin (vitamin B₂), nicotinic acid and ascorbic acid (vitamin C). These methods were rather complicated and were seriously hampered by the hot, humid, climate. Of course there was no question of air conditioning.

Vitamin A deficiency was, and still is, another scourge of rice eating countries, where it can have dramatic consequences. If not treated in an early stage, it leads to total blindness of children (xerophthalmia, keratomalacia). The estimation of vitamin A in blood could detect vitamin A deficiency in a very early stage, early enough to take measures. It was also demonstrated that the vitamin A level of breastmilk of mothers of children, suffering from vitamin A deficiency, was very low. De Haas expressed it very strongly: "These mothers feed their children blind with breast milk". This could have been prevented by eating sufficient food, rich in vitamin A or provitamin A (carotenoids), such as yellow and orange fruits and leafy vegetables often neglected by the rural population. Poverty was not always the cause of deficiency. Ignorance often was. De Haas also started a very aggressive campaign against the importation of fat free milk in which vitamin A was not present at all. It was also possible to estimate the daily vitamin A requirement, long before this was done by more sophisticated methods in western countries. This could be done with the aid of the 'natural experiment'. There were regions with ample vitamin A deficiency and others without. The vitamin A content of the diet of the latter can be considered to be the daily requirement. The resulting figures agreed very well with the daily allowance of today.

The goitre problem was attacked. Goitre was, and still is, a problem of mountainous areas. Again the base for attack was the chemical laboratory⁸. The western method of fortification of salt with iodine was unsuitable because of the hot, and humid climate. Special methods had to be applied to protect iodine, added to the salt.

Toxicological research was another topic. Many Indonesian foods are toxic. It was possible to isolate

toxic substance from *bongkrek*, *jengkol* and *kawakawa*.

In 1940 the first Indonesian food composition table was published.

Quite new and, again, pioneering were nutritional surveys among population groups, started in 1934. They were started much earlier than in most western countries and organization and methods were often more extensive. These surveys included many disciplines, e.g.: a medical examination, biochemical analyses of blood and urine, estimation of the composition of the daily diet and calculation of the nutritional value with the use of food composition tables, economic, agricultural and social studies. Evidence of the broad view was the addition of an agriculturist to the staff of the Nutrition Institute.

Some 35 surveys were conducted between 1934 and 1942.⁹ Some well-known include:

- Kutawinangun, the first complete study
- Segalaherang and Rengasdengklok, both areas with ample vitamin A deficiency
- Pulusari and Gunung Kidul, because of endemic 'hunger edema'
- Pacet, a rather prosperous area, nevertheless with a low vitamin A intake.

After the war, in 1945, the Netherlands Red Cross sent a nutrition team to Java, consisting of two medical doctors, two biochemists, a biologist, four laboratory workers and ample laboratory equipment. They studied the nutritional status of internees from Japanese prisoner-of-war camps, of rural population groups having lived under very abnormal conditions under the Japanese occupation, of homeless children. My wife and I had the honour of being members of this team. The Nutrition Institute and the chemical department of the Eijkman Institute started work again, together with the Red Cross team. Other groups which were studied included: school children, personnel of Governmental Institutions like administrative services hospitals, all of which were in a state of undernutrition but nevertheless had to start work again. The results of

these studies constituted the basis of optimal refeeding procedures.

I have come to the end of this brief summary of nutritional studies in Indonesia in the period 1850-1950. It may be clear that many problems have been tackled. Often with great success. Sometimes rewarded with discoveries of world-wide importance. On the other hand, there are a number of challenging problems, which have escaped notice. E.g.: the calcium puzzle, hypertension, nutrition and cancer, secular trends of anthropometric data such as height and weight of children. A number of western degenerative or metabolic diseases such as atherosclerosis, hypertension, stroke diabetes, gall-bladder diseases seem to be rare in Indonesia. Will their prevalence increase when nutrition habits get a more western character? We hope to discuss some of these items in the next few days.

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