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Publication/Creation

1910-1927

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HIS EXCELLENCY THE GOVERNOR

OF THE STRAITS SETTLEMENTS

AND SCIENTIFIC POACHERS.

1911

The Discovery of the Cause of Beri-Beri

A Disease which has cost $9,000,000 and 100,000 lives!

ITS SUCCESSFUL PREVENTION.

It still costs a quarter-of-a-Million annually, but may be prevented for nothing!

A Great Sanitary Reform needed *and a little Justice.*

BY

W. LEONARD BRADDON, M.B.,B.S., Lond., F.R.C.S., Eng.

AUTHOR OF

"The cause and prevention of Beri-beri." *

* Rebmans, London.

RIBEIRO & CO., LTD., SINGAPORE.

HIS EXCELLENCY the Governor of the Straits Settlements, in a recent Budget Speech made a statement the effect of which is to do serious injustice to at least one humble individual—the present writer.

His Excellency's remarks dealt with the question of beri-beri, the severe mortality it causes in the Colony, and the prospect of legislation being shortly introduced whereby the evil might be combated. That possibility—the possibility (if Government so choose) of complete eradicating a terribly frequent and fatal malady from our midst was due, said H. E.—was "the result" I think was the exact phrase—of work done at the Pathological Institute, Kuala Lumpur. Herein lies the burden of my complaint.

The implication that the discovery, whether of the cause of beri-beri, or of the means of preventing it, is the achievement of workers at the Institute is incorrect, and ill-founded—to put it bluntly, is

untrue.

A statement of the kind made by one in the exalted position of H. E.—the Governor of the S. S., and in regard to an important public service (such as all will admit the discovery of the means of prevention of a serious cause of mortality to be) could only have been due either to ignorance of the facts, or to a woeful want of candour in dealing with them, such as I should be loth to suggest.

But the misconception once engendered, the mistaken attribution once made, and thus unfortunately advertised by H. E.—perhaps not unsedulously fostered by those to whom maintenance of the illusion brings vicarious fame—unless early dispelled is likely to remain. I therefore propose to place the public in possession of the truth about a discovery of real public importance, and H. E. the Governor in a position to make amends for the no doubt unintentional injustice which he has committed.

Beri-beri

is not a matter of little or merely academic interest to this country. On the contrary, it has long been and yet indeed remains, through the amount of loss of life and work which it entails, a matter of very great economic as well as humanitarian importance to the Colony, and the Federated Malay States, and indeed all Eastern regions.

Last year, as Sir John mentioned in the speech referred to, over sixteen hundred deaths were registered as due to this cause in the Colony alone. In 1908 there were nineteen hundred deaths. In earlier years there were even more, the proportion being

one-fifth

of all the deaths registered, or about eight per thousand living annually—a rate of death from a single disorder which exceeds the average rate of deaths in England, for instance, from all the infectious diseases put together! A significant fact is, that the disease almost exclusively affects Chinese, whose proportionate mortality from it is thus far higher and more lamentable. The statement may hardly be credited, but is nevertheless well-founded, that of every thousand Chinese living 120 suffer from beri-beri in some degree, 80 are severely attacked, and 16 die of it annually. Most of these victims are young adults, otherwise healthy and vigorous and in the prime of life.

The experienced Medical Officer alone known how appalling are the the ravages of beri-beri. All over the country it steadily claims its victims, sometimes in holocausts. The writer has seen, at a mine, 200 healthy young labourers imported,

all

of whom were dead of beri-beri within a year. On an estate there were imported 80 Banjoerese from Southern Borneo,

Four were sent back

to Borneo less than a year later—the only survivors—the rest had died of beri-beri. On Christmas Island, which was the scene of an important commission of enquiry into the disease, with a population of only 700 individuals, there were in 1902 six hundred and ninety three cases (89 deaths), in 1903 five hundred and ninety one cases (60 deaths), in 1904 nine hundred and-seventy-three cases (91 deaths). During twelve years 1893 to 1904 there were treated in the Selangor State Hospitals alone 35,697 cases (deaths 6,624). In the Colony some 2,000 cases are treated in hospital every year. There have been treated in Government Institutions alone, during the last three decades, over

a quarter of a million cases of beri-beri

of whom **45,000 died.**

The total tribute of deaths during that period from this single disease in the Straits Settlements and Federated Malay States has been probably not less than 150,000.

Not only does beri-beri form thus the severest plague among the population at large, but continually in the past it has been a scourge of our public institutions, decimating or worse than decimating the unhappy inmates, supposed to be peculiarly under the public care, in the Asylums and the Gaols.

Thus in the

Singapore prison

from 1869 to 1882 the disease was never absent. The attack rate on the prisoners was enormous. Thousands suffered from it, hundreds died. The deathrate from it per thousand of the gaol population was never under, and often exceeded 24 per thousand. In 1879 it was 128 per thousand! During those 12 years the deaths of 463 individuals were ascribed and many more probably were actually due to beri-beri. Again in the 7 years following 1897 there were 1,582 such cases—83 deaths.

Remember, these unfortunates were inmates of a Government Institution, admitted able-bodied and healthy, only to acquire and perhaps die of an agonising malady. No doubt everything was done that could be done for them, *after* they had acquired the disease: but Government—Medical Science—was impotent to check the onset or hinder the course of the disorder—

for the cause of beri-beri was then not known.

In this Institution the malady continued its ravages till the end of 1904, when

a means of prevention

the only means of prevention—a single, simple remedy, profoundly simple, and even costless—the

writer's remedy,

had been discovered and applied.

The Singapore Lunatic Asylum

was from its beginning an even worse hotbed of the disease, and furnishes a still more painful history. Although the inmates averaged less than 200 in number between 1896 and 1901, for instance, the cases of beri-beri (and this includes only first attacks and not relapses, which were incessant) numbered 931 ; the deaths numbered 231 ! In one year, 1898, the population being 208 individuals, 201 of them were treated for beri-beri, 55 dying ! The deaths from the horrible disorder in this Government Institution averaged 200 per thousand annually, or in other words the

whole population was destroyed

by it every 5 years. Here again everything that could be thought of was tried to check the spread of the disease, and relieve the unhappy inmates. But the efficiency of these attempts was *nil*—

the cause was still unknown.

Every endeavour to cope with the disease on the lines of infection (as it was then believed by the Superintendent and all other authorities to be) proved futile.

From 1902 onwards some amelioration took place. This followed the adoption, at first irregularly, but later in an efficient manner, of again the only remedy,—the single, simple, costless, but wholly efficient remedy, *the means of prevention devised by the present writer.*

In the Selangor Gaol (Pudu) and the Selangor Lunatic Asylum

the incidence of the disease had been hardly less disastrous. In the former, in the 8 years following its occupation in 1895, there were not less than 2,334 cases, many fatal. In the latter it was worse even than in the Singapore Asylum. Thus in the half year ending December 1898, 66 *per cent.* of the inmates were attacked ; in 1899, 94 *per cent*; and in 1905,

130 per cent !

Here once more the application of the remedy caused

instantaneous

and complete cessation of the disease, the Asylum becoming then freed from it for the first time in all the lamentable years of its history.

Of what nature was this remedy?

Placed by the present writer in the hands of Government, at a time when no other means of prevention of beri-beri was known, or even hinted at, when prevention seemed impossible and treatment hopeless; immediately utilised by them, with a success as instant and complete, as it has been (up to this moment) wholly

unacknowledged,

the remedy flowed naturally from the determination of the cause of the disorder, made and published by the present writer, before even the advent on the scene of those workers at the Institute of Research, to whom H. E. the Governor of the S. S., would now attribute the merits of its discovery.

Simple, inexpensive, claimed (and since demonstrated) to be a complete means of preventing a terrible and widely spread malady, and so long unknown!—it may interest the public to learn something of the steps of

the discovery of the remedy.

THE CAUSE of beri-beri (and equally of the means of preventing it) had long been the special medical mystery of the East, over which it has brooded immemorially like a cloud, sullen, fateful, fascinating, but insoluble.

Numerous Government Commissions, specially paid Expert Investigators had from time to time given labour to the research, in vain. Very many explanations, some entirely fantastic, had been offered as to the origin of the disease: and among them two chiefly found adherents. One was, that beri-beri rose from some sort of infection: the other, that it was the result in some way of bad food in general, or in particular of bad rice. Most investigators (all the supposed experts) favoured the former theory, and in the camp of its adherents were ranged all those who, having written books, were accepted as authorities on tropical disease. The advocates of the food—including rice-theories had always been few, and perhaps never very clamant. Their views, and the data by which they supported their conclusions, more or less carefully examined by those who led medical opinion (or formed it in the schools) had been weighed and found (by those authorities) wanting. I need not now go far back in the medical history or cite many names. There have been at least

a thousand monographs

written about beri-beri! But I will content myself with stating the pronouncements of the two best known living authorities on tropical medicine as stated in their publications. Professor SCHEUBE, the author of the most complete monograph of beri-beri, and also of one of the best known text books on Tropical Diseases generally, states dogmatically (Ed. 1900) "*beri-beri is an infectious disease.*"

SIR PATRICK MANSON, an original investigator of deserved repute, Medical Adviser to the Colonial Office, and author of the best known British text book on Tropical Diseases, after lengthy discussion of all the theories of beri-beri in various publications 1900 to 1903 rejected the food,—including rice-theories entirely. He plumped for infection—of some sort. These were the pronouncements of the authorities in 1900, and I see that in their most recent editions their opinions remain unaltered.

But in 1901 the writer published *facts* which made it practically certain, and in 1904 an accumulation of evidence which made it

absolutely certain

that, contrary to the views of the experts, beri-beri was not in any sense an infection, but a form of

food poisoning,

of which the cause lay in the nature of the grain, the cereal food eaten, the source in this country being the staple food *i. e.*,

rice.

It was shown—

1. That in places and in communities where rice-eaters* and non-rice-eaters lived side by side, sharing in common the chances of supposable infection,

beri-beri attacked invariably only the rice-eaters, never the non-rice-eaters.

2. That *among rice-eaters*, otherwise equally exposed to infection, *beri-beri again attacked those only who ate certain sorts of rice*, or rather rice

in a certain condition.

Those who ate fresh rice (as prepared by the Malays *i. e.*, hand pounded daily for their own use) and those who ate rice prepared by the parboiling process (as customarily used by Tamils, which I called "cured" rice) never got beri-beri.

It attacked those only whose staple diet was the common commercial white rice of the shops, the so-called Rangoon, or Siam rice—sorts which, in contradistinction to the other varieties, I designated "uncured."

3. That *the severity of the disease* and its extent (the number of attacks) in communities *was directly proportional to the quantity of rice consumed.* Its progress, whether as a malady of the individual, or as an epidemic in communities becoming greater when the rice was increased, diminished when this was lessened, and ceasing altogether when the noxious rice was withdrawn, without change of any other circumstance.

Let the reader carefully weigh these statements and consider whether, if true, they could be explained away by any conceivable form of infection? Or whether any conclusion can be drawn from them, other than the writer's conclusion, *i. e.*, that it is to the consumption of the incriminated rice that the disorder is due?

* A rice-eater in this connection meaning not any one who at any time eats a little rice, but one whose staple diet is of that grain: conversily a non-rice-eater is one whose staple is usually of some other sort.

Accepting the data, it is demonstrated that beri-beri attacks only the users of a certain sort of rice; those who eat no rice, those who eat only cured rice, or fresh rice, are absolutely exempt. In other words ***uncured rice is the cause of beri-beri; and there is no escape from this conclusion, unless it can be shown that the data, the statements upon which it is based are untrue.***

The weight to be attached to a conclusion such as this depends largely on the ***extent*** of the evidence by which it is supported.

Had the demonstration been made in regard to one instance, one place, or one time, or in respect to a few persons only, it would have been remarkable. But the facts—the records proving them—referred not to one place or one country only, but to

every part of the country

every state, every town, village and hamlet, every mine, plantation or settlement, throughout the Native States and Colony, wherever the material, the native races, thus subject to or exempt from the disease, lived beside each other and were under observation. They were noted not in one year only, nor at one particular season, but throughout

every season of every year,

and during all the thirty or more years that the country has been under medical observation.

They referred neither to few communities, nor to small numbers of individuals, but to

every community

every one of the thousands of communities into which the population is divided, and to numbers of persons aggregating hundreds of thousands.

The records comprised not only the writer's personal observations, but those of his colleagues in charge of the forty or more Medical Institutions in the country, many of them originally of views on the subject opposed to his own. Yet in all the records so made the results were

invariable,

uniformly in accord.

The weight of the statistical evidence given in the writer's book on the subject may be judged by some examples.

For instance, in regard to the first statement, showing that in mixed communities rice-eaters only suffer, others being exempt. This was proved by records of epidemics all over the world.

In the Malay Peninsula in particular, in a given year, 1901, statistics carefully collected showed, that of 45,022 *rice-eaters* treated in various Government Hospitals, no less than 8,159 or nearly *20 per cent. had beri-beri.* But of 3,566 admissions of races customarily not rice-but *flour-eaters*, only 16 had beri-beri, or *less than ½ per cent.* The exceptions making up this fraction were Sikh or Bengali paupers, some of whom were proved, and the others may reasonably be supposed to have been reduced to eating rice instead of their national diet of flour. Another, larger series of patients showed when analysed

83,719 eaters of uncured rice, of whom 16,325 or again 20 per cent. had beri-beri.

With these were treated *6,903 of the non-rice-eating races, of whom again one half per cent only had beri-beri,* this fraction including as before individuals who in every *investigated* instance proved to have been subsisting on rice instead of their customary flour.

In the last three decades no less than 1,500,000 rice-eaters have been in-patients in the various Government institutions, of whom 300,000 had beri-beri; and ***100,000 natives certainly not rice-eaters, of whom NONE had beri-beri.***

As regards the differences among the rice-eaters, one of the tables given in my book showed among

Tamils,

customarily eaters only of cured rice, 45,135 admissions, of whom less than ½ per cent had beri-beri, the fractional exceptions (which "prove" the rule) including all those Tamils who for one reason or another had given up their cured for other sorts. Uncured rice-eaters admitted with these were the 83,719 named above, of whom 16,325, or 20 per cent. had beri-beri.

Of the 1,500,000 rice-eaters treated in the hospitals, at least 500,000 were Tamils. *No authenticated case of a Tamil known to be subsisting only on cured rice was recorded in all this vast series :* nor has one indeed been since discovered.

The use of "*fresh*" rice is almost entirely confined to

Malays.

The fact is well established (and may be confirmed by whoever chooses to enquire) that natives of this race living in their own Kampongs, and subsisting only on rice of this kind

never get beri-beri.

But in the prisons, the barracks, the towns, on mines, estates, on ships, on journeys, in short wherever he has to use uncured shop rice, the Malay is peculiarly apt to get beri-beri. Accordingly in a series of 4,748 admissions of Malays to hospital, a proportion of 3 per cent was for beri-beri incurred under circumstances such as described.

The vast majority, or to be exact, 97½ per cent, of all the cases of beri-beri was furnished by the

Chinese,

all users of uncured rice. Figures compiled by the writer showed that between 1881 to 1892 there were 466,693 admissions of Chinese to 32 hospitals which had accurate records. Of these 123,639 had beri-beri, and

19,459 died

of it in the hospitals ! All this in a population averaging under 500,000 !

The evidence for the truth of the contention made, it will be seen, was enormous. It may be accepted as demonstrated—as having been then demonstrated—for the first time and completely by the present writer's work,—that the cause of beri-beri is the consumption of uncured, or as others call it, "white" or "scoured" or "polished" rice. It is a conclusion indeed which all but the wilfully blind must see. It stares out of the facts, naked, adamantine, unassailable,—a proposition, a discovery as completely proved, as securely founded as any ever before brought forward in medicine.

More important even than the discovery of the cause of the disease, was

the recognition of its remedy.

It might have been irremediable!

But it became obvious that if in a country, throughout every corner of which beri-beri was rife, the only class of native that was absolutely exempt from its ravages was the cured-rice-eating Tamil, himself in every other respect far more sickly than any other race, then the adoption of cured rice by other natives should secure to them equal immunity, its adoption in Government Institutions should mean the absolute prevention of beri-beri in those Institutions.

This was the remedy, the simple, inexpensive, but completely efficient remedy, placed by the writer in the Government's hands, and

used by them

(with a success as to which I shall presently give some details) before—this is a point to emphasise—any worker at the Institute had contributed a single iota to the issue.

THE ATTACK upon the camp of the infectionists was vigorously but not critically opposed, for their defences were weak, and their retreat became a rout, which has lately been made complete.

My conclusions, first put forward in a paper, read at a Congress in 1901, were received by my colleagues with polite but uniform incredulity. My friend

Dr. Travers

opposed them with an account (in 1901) of an experiment which he had made at the two Selangor Gaols *in 1895*, which he claimed completely disproved all possibility of beri-beri being dependent in any way upon food.

Sir Patrick Manson

hailed this observation as "completely refuting" the rice-theory, declaring at a meeting of the British Medical Association at Oxford in 1902, that it "proved up to the hilt" that between food and beri-beri, rice and beri-beri, there was *no connection whatever!*

My friend,

Dr. W. Gilmore Ellis,

the present accomplished Principal Medical Officer, S. S. in his official report to Government on the Asylum for 1902, wrote :— "as to the cause of the disease [beri-beri] I regret being unable to report any progress. I am convinced and have been for many years that the consumption of mouldy microbic or otherwise diseased rice is *not* the cause." And he went on to narrate an experiment made by himself some *13 years before*, which he claimed completely disproved any connection between beri-beri and food.

Writing in the British Medical Journal of November 14th 1903, Dr. Ellis repeated this statement, and gave an account of another observation "entirely" as he thought "putting Siam rice out of the question as a cause of beri-beri."

It soon appeared that there was an unobserved source of error in Dr. Travers' observation, which entirely vitiated his conclusions.

And Dr. Ellis, after long coquetting with the rice-theory, has since announced his comp.ete conversion—although I have not had the gratification of learning that he attributes any share in the production of this happy result to the evidence adduced by me!

Sir Patrick Manson, to whom my larger work was submitted in manuscript in 1904 before publication, whose attitude against rice had been so emphatic, was as naturally might be expected, not easy to convince. But he recognised at once the formidable nature of the new arguments, and it was to his recommendation that I owed the opportunity afforded me later by the local Government (at the suggestion of the Colonial Office) of conducting

an experiment specially designed

to test the truth (or untruth) of my theory in a manner which would afford demonstration even to the dull.

Sir Patrick's expectation was, that the experiment would overthrow my views, and although the event was on the contrary to confirm them, I have not yet heard that Sir Patrick has recanted his own.

Another redoubtable opponent of the rice-theory was

Dr. Durham

who sent out on a Commission (for which was paid a thousand pounds) to investigate the disorder on Christmas Island, published in January 1904 conclusions absolutely opposed to food theories in general and the rice-theory in particular.

It is evidently not given to all to understand evidence!

Among those who, even after reading my work, required "yet a sign," was

Dr. William Fletcher,

who was in charge of the Selangor Lunatic Asylum, an Institution as we have seen little better than a beri-beri death trap.

Dr. Fletcher decided to try the matter for himself by direct experiment in the Asylum. He stated, in the published account of his results, that at the commencement of the experiment, he held the opinion "that rice was neither directly nor indirectly the cause of beri-beri. His experiment consisted in placing half the inmates on the best rice of a par-boiled variety which was obtainable, the other half on good Siamese rice. No other change of any kind was made in the conditions of the patients, who mixed together freely by day and used alternately the same dormitories.

The experiment lasted from December 5th, 1905, to June 1908. The result was that

in the uncured rice-party, in 1906, 115 per cent. were attacked

(38 cases in a daily average population of 33—the population is of course a changing one): *in 1907, the attack rate on the uncured-rice-eaters was 77 per cent*: in 1908, (six months only) it was 19 per cent.

Among 120 patients on uncured rice there were 41 cases, and 18 deaths from beri-beri.

Among the equal party

on cured rice

there arose throughout the 2½ years

not a single case

and there were no deaths.

"*Contrary to expectation*, the *result of the experiment as far as it goes*," says Dr. Fletcher, "*Is to prove the truth of Dr. Braddon's contention that uncured rice is the cause of beri-beri.*"

This observation of Dr. Fletcher's, with its clear and unambiguous result, was the sole positive addition made (outside the writer's researches) to our knowledge of the cause of beri-beri up to that time. Although itself wholly unnecessary, a mere drop added to the ocean of evidence already presented by me. Dr. Fletcher's observation had at least the merit of convincing himself, and thereby relieving the unhappy inmates of his

Asylum, who were thenceforth dieted on cured rice only, with the result that from that day to this

no more cases

of beri-beri have appeared among them.

We come now to the part played to

the Institute of Medical Research

(or as it is now called the Pathological Institute) in the elucidation of the disorder.

The Institute was originally founded on the recommendation of a Congress of Medical Officers in 1897. For a long time a brass tablet in the entrance hall of the building bore the legend that it was "suggested" by Sir Frank Swettenham and erected under the 'direction' of Dr. Hamilton Wright—whence it may be inferred that all the brass was not used up in the tablet. The chief object of Government seems to have been to provide an establishment in which highly-paid experts might be enable to devote their whole time to the investigation of the diseases of the country, assisted by all the resources which Government could place at their disposal.

The

first Director

of the Institute, DR. HAMILTON WRIGHT, after spending a year or more in proving the existence of Malaria in the Native States (a discovery which however had been anticipated) proceeded to investigate the question of beri-beri. Dr. Hamilton Wright published four extensive monographs on the subject. His principal conclusion was that the existing professional notions about beri-beri were a complete muddle, which he fortunately was able to set right! As the result of a prolonged experimental investigation into the disease at Pudu Gaol 1901-1902, *during which all the prisoners were fed on uncured rice*, he announced that the rice could not in any way be considered to be the cause of the disorder *because it had been boiled* before it was eaten! Any opinion to the contrary Dr. Hamilton Wright derided, as that of a

"bold and badly informed theoriser."

The next Director of the Institute,

Dr. C. W. Daniels,

also published a work on beri-beri, in 1906. In this work, after quoting at length most of the evidence provided by the present writer as proving the orgin of the disease from uncured rice,—proofs, the cogency of which the reader has already realised—Dr. Daniels asserted that "*the hypothesis that diet, or any article of diet sound or unsound can originate the disease has in my opinion* **no facts** to support it"!

(My italics.)

The establishment of the rice theory—almost universally accepted as it is by scientific observers in the East to-day—owes, then, nothing to these two observers; and it is clearly not to their work that His Excellency the Governor of the Straits Settlements can have referred when he sought to attribute the present proved possibility of eradicating beri-beri—the discovery of its cause, and the means of preventing it—to work done at the Institute.

The successor of these experts at the Institute was the present Director,

Dr. H. Fraser,

whose contributions to the subject will next be considered.

I have mentioned that the Government had consented to grant me an opportunity to demonstrate by direct experiment the truth of the views as to the cause of beri-beri which, in season and out of season, both in printed and published, and written official communications, I had ever since 1901 urged upon them.

The Official Medical Adviser of the Resident-General was (by virtue of his office!) the Director of the Institute of Medical Research. We have seen how both the first occupants of this post had failed to understand the evidence by which the origin of beri-beri was indeed already completely proved before they came upon the scene. It is not surprising therefore that their successor Dr. Fraser should have proved equally unillumined, and should have advised Government that my views could not be accepted until demonstrated by further experiment, to be made preferably by himself, or at least under his own control.

After much search the conditions necessary for a suitable observation were found in Jelebu, at

Durian Tipus.

Here my friend

Mr. T. R. Hubback,

of big-game-shooting fame, was engaged in making a road through the wilderness, on which three or four hundred Javanese labourers were employed. The interference with work entailed by daily medical inspection of coolies, for the purposes of an experiment, means loss of time and money, and will not willingly be allowed by many employers merely for the sake of science, or humanity. But Mr. Hubback already knew and had benefited by the application of my views about beri-beri, an epidemic which had appeared among his labourers formerly, having been arrested by the use of my remedy—cured rice. Both as my friend, and scientifically, he was interested in seeing the official test of my views made successful. With great generosity and public spirit he placed the whole of his labour force at my disposal for the experiment, and became the Mæcenas of the enquiry.

I received the official permission of Government

to conduct the enquiry

early in 1907. It was intimated that Dr. Fraser, as Director of the Institute and representing the Government, would be *associated* with me to check and report on the results of the enquiry, the conditions of which were left to us jointly to arrange.

The experiment was designed to ascertain whether in a body of labourers kept free from chances of outside infection, beri-beri would occur in those using uncured rice, at a place and time when a similar number of the same labourers, equally circumstanced in all other respects except that their diet was to be of cured rice, should remain exempt from the disorder. Supposing that this happened, supposing that all the circumstances had been made equal for two suitably large parties (except for the difference in rice) then if beri-beri occurred, and if on its occurrence it attacked exclusively the uncured rice-eaters, it was to be held that the rice-theory would be

officially confirmed.

Well, the experiment was made. To assist Dr. Fraser, and in order that everything might be thoroughly controlled, Dr. A. T. Stanton was appointed as his assistant, to reside at the scene of operations, 60 miles beyond Seremban.

The event, into the details of which I need not now enter, was to completely confirm my theory. All chances of infection

were ruled out. The conditions as to food, labour, housing, clothing were alike for both lots of coolies. But at every station wherever a gang of men was *on uncured rice* (and first and last no less than six stations were occupied by them)

beri-beri broke out.

On the other hand, among the cured rice-eaters, whether they occupied the same stations before, after, or simultaneously with the others,

no case

of beri-beri at any time occurred.

The work of the investigation was conducted *jointly* by Dr. Fraser, Dr. Stanton and myself—and it is fair to add that by far the greater part of it, all the arduous labour of keeping the records, as well as the constant medical supervision of the coolies was the share of Dr. Stanton, and was admirably done by him. The experiment was officially

my experiment.

It was the opportunity granted me by the local Government (on the recommendation of the Colonial Office) to prove the truth of the views of which I had been the first, and then still was

the only exponent,

the demonstration of which was held, and rightly held by Government (at that time at least) to be of the greatest importance to the country. Not only was it thus my experiment *officially*, but the means, the material, the opportunity was—through Mr. Hubback's generosity to me personally—of my providing. The actual observations, the noting of the results obtained, was as I have said, made jointly by the three observers.

Now it will hardly be credited, but is none the less true, that in no less than *five successive communications* made by them to the Government, and the Medical Press, dealing with the enquiry, and its resultant proof of the correctness of the rice-theory of the beri-beri, Drs. Fraser and Stanton put forward the actual observations,

appropriated the results

gained, *as entirely their own*!

Nowhere in the text of any one of these papers is the present writer (whose the investigation really was) anywhere referred to as having either initiated, or organised, or contributed to the research !

There is plagiarism in literature, there is piracy in music (and on the high seas), there is poaching on game preserves, and pilfering in every walk of life—but what is to be said of the brasen appropriation of other workers' results by your scientific egoists,

pirates of research ?

Their *share*—Dr. Fraser and Stanton's *share* in the above investigation—the result of which was, after all, but to bring one brick more to an edifice already built—forms

the sole contribution

which has so far been made to our knowledge of the cause of human beri-beri by workers at the Pathological Institute,—those workers to whom H. E. the Governor of the S. S. has chosen to attribute the merit of having at last made possible the prevention of the disease !

THE CAUSE of beri-beri, then, is the consumption of uncured, "scoured" or "white" rice. That, in this country, is the sole effective cause of a disease which, as we have shown,

yearly kills thousands

of the young and able-bodied.

It may be

prevented absolutely

by the use of rice prepared by a process already in commercial use—the parboiling process.

These facts, unknown, or at least unrealized, before the writer pointed them out, form a definite and practical, an economic as well as scientific discovery, which it is now surely the duty of the Government

to apply

for the benefit of the population at large.

All that is necessary is for them to discourage (if they cannot prevent) the importation and use of rice of the kind which has been proved to be noxious: to make the sale of such rice if not illegal, at least unprofitable.

It will be no hardship for the rice mills to turn out rice which will be harmless, for this will actually save them labour, in the omission of the "scouring" of the grain, which removes from it the essential nutrient portions, the preservation of which in parboiled rice constitutes the sole difference whereby the latter remains fit for human food.

A tax

of a dollar or two on every bag of such rice imported would effectually restrict its use among those who now consume and suffer from it:— and would incidentally bring in much needed grist to the mills of the local exchequer of the Straits Settlements.

OF THE actual working efficiency of the remedy made known by the writer in the prevention of beri-beri in Public Institutions, (namely, the substitution of cured for uncured rice in the diets) the Governor is well aware. My views and recommendations were placed in His Excellency's hands in November 1904. The adoption of cured rice in all the Public Institutions of the Colony was made

by His Excellency's order

immediately after that date.

The results were as immediate and gratifying as they were extraordinary.

In the Singapore Prison, as we have seen, this simple change brought about freedom from the disorder for the first time since 1898.

In the Lunatic Asylum, according to Dr. Ellis (see British Medical Journal, October 1909,) the same result was secured. That pest-hole of beri-beri became freed of it

for the first time in its history

only when cured rice was wholly substituted for the uncured. We have seen the same result in the Selangor Lunatic Asylum.

Not only was the disease thus stamped out of Institutions in which it had long been practically permanent, but

in the hospitals

the mortality among cases *admitted for beri-beri* fell in marvellous degree, everywhere, immediately on the substitution of cured for the uncured grain. Thus in the Tan Tock Seng Hospital, Singapore, where cured rice was introduced in 1905,

the mortality fell at once from 48 to 18 per cent.

In Province Wellesley there was reduction from 44 to *15 per cent* : at the Malacca Hospital from 28 to 7½ per cent : at Jasin from 41 to 9 per cent, and so on.

At Christmas Island, where the Medical Officer had acted on my advice earlier, it was reported that the result was "most marvellous and immediate"—instead of *95 deaths in ten* months, there were only *12 in the next fourteen.*

In the Native States (owing to the obstinacy of my colleagues !) cured rice diet was only adopted, (and then at the instance of Government) much later : but here too, similar results were gained.

At Batu Gajah,

for instance, the death rate fell from *50 per cent* in 1907 to *11 per cent* in 1908 : at Kampar, it was reduced from 37 to 9½ per cent—and so on.

As some 10,000 cases are treated annually in all the hospitals of the Colony and Federated Malay States, the reduction of the death rate from the

frightful figures

formerly prevailing means an enormous saving of life. If only 10 per cent die now where 30 or 40 per cent died before, the number of

lives saved

is two or three thousands *annually.*

Of this achievement, this one fruit of his labours, no one has (so far) sought to deprive the writer.

* * * * *

THERE is another side to the beri-beri question, of great scientific interest. What exactly is the difference between the rice which produces beri-beri and the rice which does not? In what way does that difference operate to produce the disease?

If you swallow something, and the result of swallowing that something is that you become diseased, the matter you have taken may rightly be described as poisonous. It will not alter the correctness of the description to know that if you take something else—an *antidote*—with the poison, it will render the latter inactive. Now uncured rice, *used in the only way in which it ever is used* by the native, namely, as a staple food, produces beri-beri. The ignorant public therefore ought to be protected against its use, as against that of any other poisonous commodity —but that is another story.

On the academic question, whether beri-beri results in the uncured rice-eater because he has taken something *more* than is wholesome, or *less* than is wholesome, there is division among the scientists. The writer's view is that uncured rice is poisonous

in itself;

a position not contradicted by the fact that to restore to such rice the part removed artificially (the bran, etc., which in cured rice is retained) will antagonise or prevent the poisonous action. A simple proof of this is, that if you deprive a fowl (which easily gets beri-beri) of everything except air and water, it dies certainly, but slowly, after perhaps twenty days or more, of starvation—*no paralysis* is produced. But if in addition to the air and water, you give a fowl *uncured rice*, it will die much more rapidly, and with all the paralytic symptoms of *acute beri-beri*.

It is in this field, of the chemical differences between the poisonous and non-poisonous rices, that the workers of the Institute have added

a little

to our knowledge—in confirmation of facts for the most part already well ascertained.

Thus the chemist of the Institute, Mr. R. J. Eaton, made determinations of the compositions of various foodstuffs and rices in local use. He also specially determined for Dr. Fraser the phosphorus content of the rices, finding it more plentiful in fresh than in uncured, and in cured rice than either.

Dr. Fraser confirmed (though he barely acknowledged) an observation long previously made, and subsequently (though he seems not to have been aware of this) greatly extended by Eijkman, showing that fowls fed on white (uncured) rice get a form of paralysis like beri-beri, which is prevented by restoring to such rice the bran, etc., previously taken from it in milling.

Observing that the capacity of rices to produce this beri-beri of fowls varied inversely with their content of phosphorus, Dr. Fraser was led to associate the deficiency of the element with the causation of the disease. This idea again (although he seems not to have known it) had already been anticipated by others, and

disproved.

Beri-beri is not a "phosporus starvation."

A single contribution to

the practical side—

the prevention of beri-beri—was made by Dr. Fraser.

As a remedy against beri-beri, alternative, or to be preferred to the simple course suggested by the writer (which is to avoid wholly the use of uncured or spoiled rice, substituting for it always the cured sort, which being already on the market is easily obtained) Dr. Fraser would have users of white rice buy and keep beside them a little of

the "polishings,"

to be added separately in due quantum to the daily meal!

These "polishings" consist of the bran and fine offals (sharps) removed from rice in the milling process of "scouring" (not "polishing") which renders it white. Mixed with the grit of the millstones, the dirt of the machinery, and the floor-sweepings, the "polishings" are sold to natives and used by them as cattle food ("dedek.")

The exact amount of "polishings" to be added to each meal by the consumer is not indicated. But in Mines and places where the proposal was put into practice, no doubt the cooks and kepalas would be enabled easily to ascertain this, from an analytical table (to be furnished by the Institute of Medical Research) which would be

hung up in the Kongsis

for reference.

The simple hen, uneclectic in its dietetic ways, accepts the "polishings" no doubt readily enough. But imagine the Chinese coolie, already exacting enough, asked to supplement his rice with "*dedek.*" The high phosphorus-content of it would never appeal to him! A question the practical mind, pondering on this quaint proposal of Dr. Fraser's, is moved to ask, is:—If the "polishings" are so essential to the diet, that they must be restored again to white rice whenever this is eaten, why allow them to be removed at all? Why indeed? But it was incumbent on the Institute of Research to contribute something

something practical

to a practical issue—if possible not the same as anything proposed before—and this is it—a suggestion which could not have been bettered by the Wise Men of Gotham.

But perhaps we are taking Dr. Fraser too seriously. He is nothing if not humorous and in this matter of the "po-lishings" he may be only poking fun at us—a pawky

LITTLE JOKE?

THERE is one more side of the beri-beri question—the dollar side.

The 150,000 young labourers who have died of beri-beri in the 30 years of the past represent, at their usual cost of importation per head, a direct loss of about

nine millions of dollars.

The 10,000 cases of beri-beri treated *annually* in our hospitals (each on an average for a month) cost Government *annually* $100,000. The loss of the labour of these patients before they reach hospital, and of the many more who never reach hospital at all, costs the public, it may be estimated, far more. Not less than

a quarter of a million dollars,

probably, represents

the yearly cost

to the community of this one disease.

All this loss will go on recurring year after year, until Government adopt the one efficient remedy, which is simple and practical—and may even be made profitable—of prohibiting absolutely the sale of spoilt rice as food. *Spoilt rice*, in the most exact sense of the word, these uncured commercial white rices are—rendered through the deprivation of their essential nutrient portions in milling worse than useless as food, a not merely deleterious, but definitely

dangerous article.

Not long since the Government engaged at considerable expense the services of a Sanitarian of great experience to report on the causes of the scandalously high death rate of the Colony (40 per mille) and to suggest remedies.

made many suggestions, one and all requiring great sums of money to carry out. He was unaware that the death rate could be reduced, almost at a stroke, by nearly a quarter, by any means so simple as that by which, I have shown, beri-beri may be not only exterminated but even made to pay for its own extinction.

The great (like the Syrian of old) are often averse, as we know from counsels of simplicity. But here obviously there is lying at hand a great sanitary reform, which it is the instant

duty of Government

(or if they will not, then of the community) to have carried out.

I HAVE perhaps now made evident something of the significance of the beri-beri question, of the importance to the country of the discovery which has been made (after so many centuries) of its cause, and the means of preventing it.

As a public service that discovery has

a value—

the exact measure of which is the enormous annual losses which may now, by its application, be prevented. It is surely fitting that those who have rendered this service should receive the recognition of their achievement : and equally as unfitting that the Government, representing the public, should bestow that recognition where it is not due.

It is always invidious to be the advocate of one's own claims, but it is not part even of the scientist's duty to stand idle while the fruits of his labours are appropriated by, or even on behalf of others ; and by the consent of silence to acquiesce in his own effacement.

I do not claim, I trust that I have nowhere implied, that I am the first or the only medical observer who ever attributed to rice the causation of beri-beri. There is nothing new under the sun—and certain—not many—others have in other countries been led before me to the same conclusion, which some—notably Van Dieren—have supported with very striking evidence. The labours of all such of my predecessors in the field have, so far as I have been able by diligence to make myself acquainted with them, been duly recorded in my work.

But I do claim that in this part of the world, in the Straits Settlements and Federated Malay States, among British Investigators I stood first and

alone

for the now accepted theory, and maintained it with evidence,—maintained it moreover against the opposition of all my colleagues, and in particular of the reputed experts on the subject, and the official advisers of Government. I claim that in the evidence, the *facts* laid by me before the Colonial Office in 1904, and published later,—the truth of which has never been impugned—

proofs were given of the origin of beri-beri from rice, for the first time, which were complete and incontrovertible.

Nor have they since in any essential been controverted.

I thus claim to have *demonstrated* what had previously only been *surmised*, and nothing which has been effected since has done more than add a confirmation to my theory.

I may assert (without, I think, any fear of contradiction) that the remedy for beri-beri (which so naturally flowed from the observation of the cause) which was suggested by me, was *first* suggested by me,—was moreover,

the first efficient means ever suggested by anybody for the prevention of the disease.

That remedy was placed by me in the hands of Government, and

was utilised by them,

before any communication by any other observer had been made to them, even confirmatory of my theory.

The result

of its application was (as has been seen) to bring about the immediate and complete cessation of the disease, for the first time in their history, in the Gaols and Asylums in which it was used. By it, moreover, the mortality of cases of beri-beri, against which nothing had ever previously availed, was brought down from appallingly high to very low figures, and the saving of several thousands of lives effected annually.

To the achievement of these results the workers of the Institute of Research, after a long period of active and ill-reasoned opposition, contributed, towards the end,—

what ?

A *share* in one solitary (confirmatory) observation—an observation of which they nevertheless thought so well as to claim the whole.

Yet it is to work done at the Institute that H. E. the Governor of the S. S., would alone attribute the credit of the conquest of beri-beri. !

Surely it is not too much to ask H. E. the Governor of the S. S., now placed in possession of *the facts*, to correct an attribution so unjust, and to manifest his appreciation of a public service by public recognition of its real author.

W. LEONARD BRADDON,
M.B.,B.S., LOND., F.R.C.S., ENG.

SEREMBAN,
January 20th, 1911.

Reprinted from the BRITISH MEDICAL JOURNAL, *June 20th, 1914.*

THE INFLUENCE OF THE TOTAL FUEL-VALUE OF A DIETARY UPON THE QUANTITY OF VITAMINE REQUIRED TO PREVENT BERI-BERI.

BY

W. L. BRADDON, M.B., F.R.C.S. AND E. A. COOPER, D.Sc.

(From the Lister Institute.)

(*Preliminary Communication.*)

IT is now taken as settled that beri-beri is essentially privatory in origin, resulting from the deficiency in the food supply of a substance the precise nature of which has not yet been ascertained.

If this simple explanation were complete, it would follow that the more thorough the withdrawal of the active substance, the speedier would be the onset of the disease and the more severe its effects. Several investigators, however (Maurer,[5] 1907; Cooper,[3] 1913; Caspari and Moszkowski,[2] 1913, and Funk,[4] 1914), have shown that the onset of polyneuritis in birds can be hastened by increasing the ration of polished rice. From this it appears that when the food ration is increased by the addition of carbohydrate material, for example, polished rice, with a very low content of antineuritic substance, although the daily allowance of the essential substance is slightly increased, the development of polyneuritis is actually accelerated.

Analogous observations have been made in the course of the epidemiological studies of human beri-beri. Thus it has been found by nearly all observers[1] that in epidemics of beri-beri the well nourished are the first to succumb, and are actually more liable to the disease than the underfed. Similarly, under natural conditions men, owing to their larger energy output, partake of polished rice more freely than women, and are more liable to beri-beri. In institutions, however, where men and women have the same fixed ration they are equally susceptible to the disease. Again, in prisons and asylums, in which the dietary has been varied from time to time, every increase in the polished rice component of the diet, the ration of other foodstuffs remaining constant, has been followed by increased beri-beri.

From these observations Braddon drew the conclusion that in rice-eating communities the extent and severity of beri-beri vary directly with the quantity absolute or relative of polished rice consumed.

Admitting, then, that in the production of beri-beri a deficiency in the diet of a certain substance is an essential factor, it is evidently of practical importance to ascertain the part played by the substance in metabolism, and, if possible, to determine the quantitative relations which the intake of active material must bear to that of the other components of the dietary, in order that the requirements of the organism can be covered.

With this object in view a study has been made of the effect upon the onset of polyneuritis in birds of increasing the carbohydrate ration of the dietary, and the main experimental results are briefly summarized in this preliminary communication, and will be shortly published *in extenso* in the *Journal of Hygiene*. The observations were made at Seremban, Federated Malay States, during the years 1909–11, and at the Lister Institute during 1913–14.

It is now a well-established observation that chickens fed on $\frac{1}{20}$ their body-weight of polished rice develop polyneuritis in twenty to seventy days, whereas those fed on the same daily ration of unpolished rice (padi), "cured" or parboiled rice, and "fresh" rice (partly polished) remain free from the disease. Braddon found, however, that birds when fed on $\frac{1}{20}$ their body-weight of parboiled rice, which has been soaked for twenty-four hours in water and then strained off, develop polyneuritis just as when fed on ordinary polished rice, and epidemics of beri-beri have been traced to the practice of soaking unpolished rice prior to cooking, and discarding the water.

The effect of adding carbohydrate to a diet which itself was adequate to maintain birds in health was first studied, and experiments made on forty birds showed that, while chickens fed on $\frac{1}{20}$ their body-weight of padi remained free from polyneuritis for at least sixty to a hundred days, when this ration was supplemented by $\frac{1}{3}$ the body-weight of washed parboiled rice or by $\frac{1}{10}$ the body-weight of polished rice the birds contracted the disease in twenty to thirty days.

Experiments were next carried out with the object of ascertaining more precisely what effect increasing the carbohydrate component of a dietary had upon the *rate* of onset of polyneuritis. In these experiments altogether thirty birds (chickens and pigeons) were employed.

It was found that:

1. Whereas pigeons fed on $\frac{1}{20}$ their body-weight of polished rice and $\frac{1}{350}$ of dry yeast daily developed polyneuritis in from thirty-nine to ninety-five days, when the ration of rice was increased to $\frac{1}{5}$ the body-weight the birds fell ill in twenty-two to forty-six days.

2. While pigeons fed on $\frac{1}{20}$ their body-weight of polished rice and $\frac{1}{350}$ of yeast developed polyneuritis in from thirty-two to forty-four days, they became affected with the disease in from fifteen to twenty-two days when the polished rice ration was increased to $\frac{1}{10}$ the body-weight.

3. Whereas chickens fed on $\frac{1}{10}$ their body-weight of polished rice and $\frac{1}{350}$ of yeast did not fall ill with polyneuritis until from sixty-five to one hundred days had elapsed, when this dietary was supplemented by $\frac{1}{10}$ the body-weight of sago the birds contracted the disease in from thirteen to thirty days.

By doubling the carbohydrate ration of the dietary the rate of onset of polyneuritis was thus actually increased as much as from two- to four-fold.

The results so far obtained demonstrated that the amount of antineuritic substance required by the organism increases with the quantity of carbohydrate ingested.

There are at least two possible explanations of this phenomenon. First, the view already advanced by Funk (1914) that the active substance participates in some way in carbohydrate metabolism, and thus the more metabolic work the organism is called upon to undertake the greater its demand in respect of this essential substance. Secondly, that when large rations of starch are ingested the absorption of the antineuritic material is interfered with owing to the presence in the alimentary canal of excess of undigested carbohydrate.

Experiments were therefore next carried out to ascertain which of these was the true interpretation, and it was found that even when daily rations of polished rice as great as $\frac{1}{10}$ the body-weight were fed to chickens together with varying amounts of yeast, 93 to 98 per cent. of the starch was digested and absorbed, and the excreta were free from the antineuritic substance. It was also observed that *in vitro* starch did not absorb the substance from aqueous solution. Furthermore, pigeons fed exclusively on glucose, which is rapidly absorbed, developed polyneuritis. These observations exclude the physical factor, and show that the antineuritic substance is utilized in some way during carbohydrate metabolism.

Whatever be the mechanism involved, it is clear that for the maintenance of health the intake of active substance must be adjusted in relation to the ration of carbohydrate supplied, and it is when this necessary balance is not maintained in the dietary that beri-beri results.

The precise relation which must subsist between the supply of antineuritic substance and the amount of carbohydrate ingested has not yet been ascertained, nor has the corresponding relation for each of the other normal components of a dietary (protein and fat) been determined. Funk (1914), however, has made some experiments which indicate that protein and carbohydrate can be interchanged in a dietary without materially affecting the rate of onset of polyneuritis, whereas if these food materials be replaced by fat the disease develops less readily.

The fact that attention must be paid not merely to the absolute amount of antineuritic foodstuff incorporated in

the dietary but also to the proportion which this bears to its total calorific value is of great practical importance in framing a dietary for the prevention of beri-beri.

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CABLE ADDRESS:
BRADDON, SEREMBAN.
TELEPHONE No. 41 SEREMBAN.

Braddon

MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

Oct 6/1910

Dear Martin

Will you render me your powerful aid in clearing up present the final point in the etiology of beri-beri?

I had proved as you know that beri-beri (as we see it here) depends on the consumption of rice: (1) in a certain state, (2) for a certain time, (3) in a certain quantity or proportion to the rest of the diet.

I have recently found out something on the question.

If you take a "cured" rice which, fed to animals (hens) does not produce it, & soak in cold water 1 or 2 hrs, then the residue, the rice, loses its cold-water-soluble content, it is very active in producing beri-beri. Hens fed on this (they have to be after a week fed artificially) get completely paralysed, ~~with~~ & die in 2 or 3 days - without much wasting. ~~I propose to call the Rice, loss~~ its cold water soluble content, therefore I call evidence beri-beri. ~~that~~ or in the wound birds fed on water only - complete starvation, do not

CABLE ADDRESS:
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TELEPHONE NO. 41 SEREMBAN.

MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

fat or under exercise. They only waste & live much longer without any food at all, whereas they do a walk + rice as above.

It seems the residue on the rice after soaking is likewise a poison. What is in the residue? chiefly starch + some cellulose. Now birds fed on pure starch only + water (Colman's starch) also (& terriers) die paralysed. Hence one must doubt pure starch as a poison — & terriers & be a starch-poisoning.

I am sending a paper shortly to the J. of Hygiene developing this theme. Between I would venture to help is to ascertain what exactly the water soluble content of the rice may be. The solution is acid (gives Millon's reaction readily, but none of the other reducing proteid tests.

If one could isolate & even

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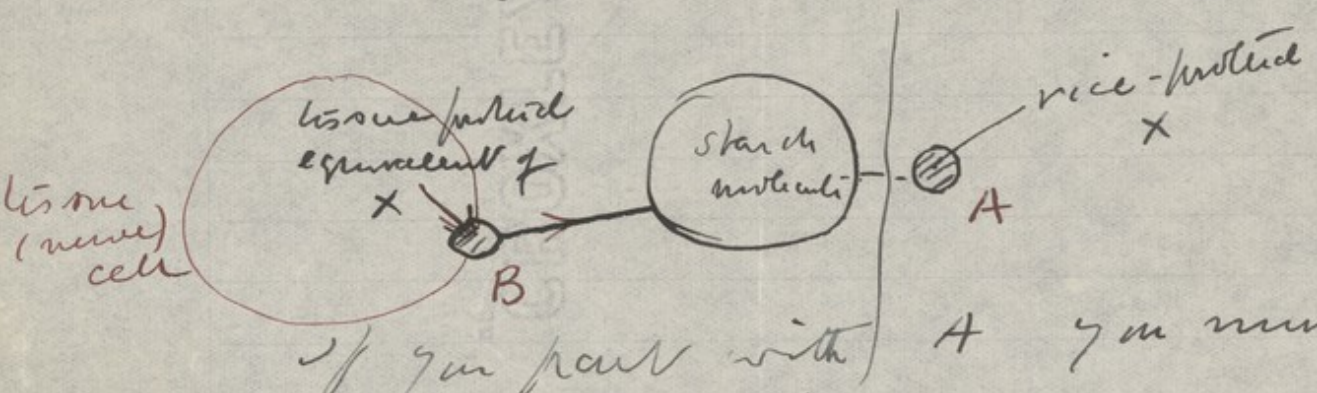
MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

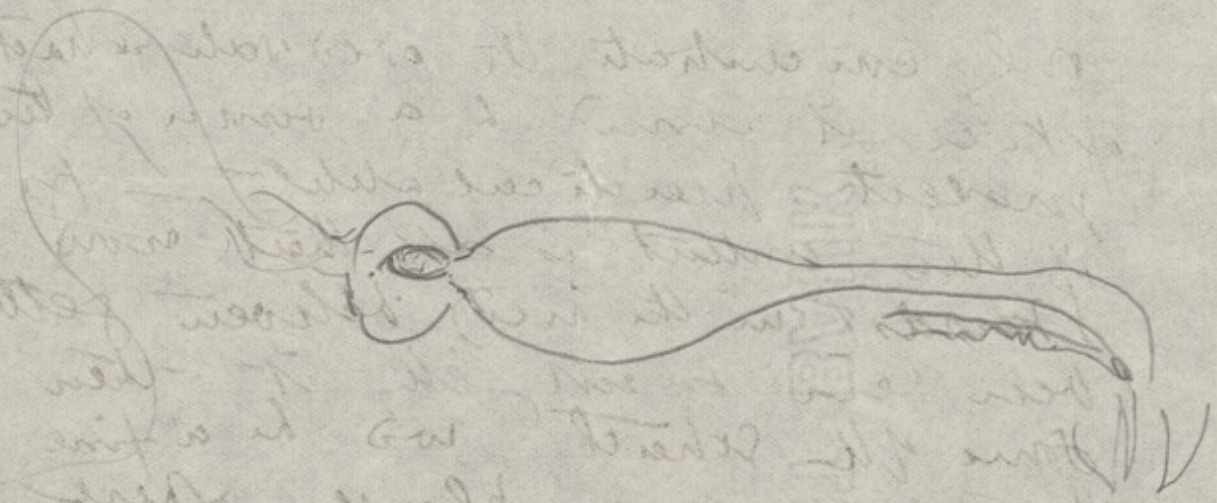
only concentrate the cooked solid & heat of rice it would be a source of the greatest practical utility — for if this content is all that now stands (in the way) between getting beri-beri & not getting it — then some of the starch would be a fine thing to use in places where proper rice cannot be got or other proper foods containing the necessary starch-poisoning-antagonist.

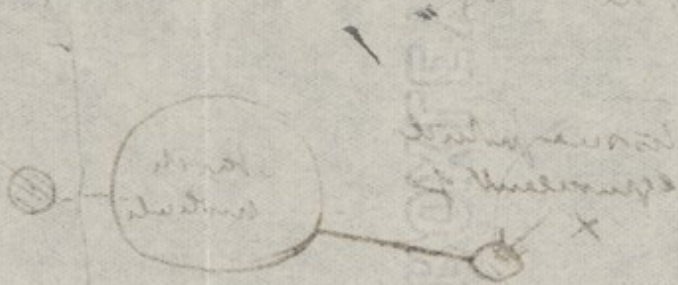
The thing would may be



If you part with A you must
freeze on to B!

I have noticed a
fern fiddle & do not like
bend





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BRADDON, SEREMBAN.
TELEPHONE NO. 41 SEREMBAN.

MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

Mr Institute 2 bags (about 105# each) of "cured" asahan rice.

If you will feed fowls on this dry, ~~soaked~~ put so much water as the grains will take up themselves during 24 hrs - the birds will remain well if you soak in 10 times the bulk of cold water for 12-24 hrs & throw the water away. Birds fed on this rice become paralysed in 10-14 days.

The 'Protect-X' ought to dissolve all immediately on addition of cold water to the grains.

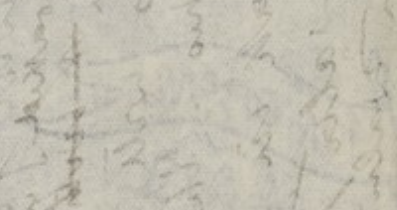
Please give my kind regards to Boycott if he is there with you — also Mac Conkey.

Yours sincerely,

W. Leonard Braddon

Braddon → CJM

Oct 11. 1910



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TELEPHONE NO. 41 SEREMBAN.

MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

23.2.11

Dear Merlin

I got the jars before the bill, the cable arriving [illegible] the day before yesterday. I at once told Sutton to send you 3 bags padi, & 3 bags ordinary rice for shipment. He later agreed to give you a considerable amount of the unknown "x".

I do not know if I sent you the result of my last experiment.

A. 10 chickens, each on ¾ oz (25 gms) padi + about 600 gms each daily

B. do do do on same quantity padi

+ Washed rice 50 gms each daily.

This rice was soaked 24 hrs in 2% HCl (large excess of water) then thoroughly washed with plain water.

They eat the padi up quickly then leave the [illegible] & hound with the rice afterwards, but crops are disinclined.

Results: of A series none got BD they kept as stable weight & looked fit all the time.

CABLE ADDRESS:
BRADDON, SEREMBAN.
TELEPHONE NO. 41 SEREMBAN.

MOUNT BERYL,
SEREMBAN,
FEDERATED MALAY STATES.

B. Series - 9/- Beriberi - 1- in 20 days
1- 24 "
real delight - acute 1- 25 "
attacks. This was 1- 27
then evidently attitude!:- 1- 28
2- 29
3- 30
10

Shew them 9/- the necessary quantum of mixture so to keep them whole (according to Fraser) but the addition of rice (= starch) in excess by feed them.

Do they any chemical reaction between C_2H_6O + Starch
? $C_6H_{10}O_5$ - ?

I have just compiled a scream (for local consumption) entitled "H.E. the Governor of the Straits Settlements & Scientific Teachers" etc etc 9/- is a send-off boy friend Fraser who is just going home on leave I will send you one

Yours ever

H Mowbray

How Ukrainians came to the Lesters

Letters from Brandon 1910, 1911

Brandon → Chin
Feb 28, 1911

Isolation of Anti-beriberi-vitamin

by

Dr. B. C. P. Jansen

and

Dr. W. F. Donath

Reprint from the Mededeelingen van den Dienst der Volksgezondheid in Ned.-Indië Anno 1927, Part 1

G. Kolff & Co., Weltevreden, Batavia

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(*From the Medical Laboratory Weltevreden, Java, Dutch East Indies*).

ISOLATION OF ANTI-BERIBERI-VITAMIN, *)

by

DR. B. C. P. JANSEN and DR. W. F. DONATH.

The first attempts at isolating the substance, which according to EIJKMAN'S [1]) fundamental researches protects against beriberi, were made by GRIJNS [2]), but without success. However EIJKMAN [3]) and GRIJNS found a number of chemical properties of this substance, among which the very important property, that it dissolves very easily in water and in alcohol, and that it readily dialyzes. This is therefore of so great importance because it shows that this substance has a relatively small molecule, and consequently does not belong to the proteins, the nucleoproteids and similar substances. So it is probable, with regard to the great physiological influence, that it belongs to the group, which BARGER has gathered under the name "the simpler natural bases" and which GUGGENHEIM calls "*die biogenen Amine*".

In 1911 C. FUNK [4]) published his first researches about this substance, to which he gave the name "vitamine". Therein he described a compound, which in a quantity of 20 — 40 mgr. could heal a pigeon, which had contracted polyneuritis by being fed on polished rice. Afterwards this substance appeared not to be the "vitamine" looked for; and besides the results observed when feeding the test-animals on protein + fats + carbohydrates + salts purified as far as possible, obliged us to suppose the existence of several suchlike "vitamines", which were discerned by the name of A- and B-, and later on also of C-, D-, E- etc. vitamines [6]). It is still a question which however, as may be expected, soon will be solved now, whether the B-vitamin, described by the American and English authors, which was characterised chiefly by its influence on the growth of young rats, is identical with the anti-beriberi- or antineuritic vitamin, which protects man from beri-beri and birds from polyneuritis [7]). Authors such as EIJKMAN [8]), MENDEL [9]) and

*) In an abridged form this paper has been published in the Proceedings of the Royal Academy of Sciences, Amsterdam, from te Session of 25 Sept. 1926.

1) C. EYKMAN, *Geneesk. Tijdschr. voor Ned. Indië.* **36**, p. 214 (1896).
2) G. GRIJNS, *Geneesk. Tijdschr. voor Ned. Indië.* **41**, p. 1 (1901).
3) C. EYKMAN, *Arch. f. Hygiene.* **58** p. 150 (1906).
4) C. FUNK, *Journ. Physiology.* **43**, p. 395 (1911).
5) J. C. DRUMMOND, *bioch. Jl.* **14** p. 660 (1920).
6) Afterwards DRUMMOND 5) suggested the final "e" from "vitamine" to be dropped, so at this word shall carry no implication as to the chemical constitution of the substance.
th 7) Comp. H. H. MITCHELL, *Jl. biol. Chem.* **40**, p 399 (1919) and A. D. EMMETT and G. O. LUROS, Ibid. **43**, p. 265 (1920).
8) C. EYKMAN, C. J. C. v. HOOGENHUYZE and T. J. G. DERKS, *Jl. biol. Chem.* **50**, p. 311 (1922).
9) CROLL and L. B. MENDEL, *Americ. Jl. Physiol.* **74**, p. 675 (1925).

LEVENE [1]) doubt this identity very much; whilst HAUGE and CARRICK's [2]) experiments make it rather very probable, that we have to deal with two different substances. After FUNK a great many authors tried to isolate the B-vitamin and especially the anti-beriberi-vitamin, but as far as we know they have not succeeded in doing so. A summary of their work may be found in the more recent books on vitamins, see for instance "*The vitamins*" by H. C. SHERMAN and S. L. SMITH. New York 1922, p. 18-48.

When one of us, now more than 9 years ago, came to the Indies, in the same laboratory, where EIJKMAN and GRIJNS worked, he fortwith commenced his attempts at the isolation of the anti-beriberi-vitamin. As basic material rice polishings containing the pericarp and the germ (Mal. *dedek*) were used, which in the Indies are very cheap. Since in the literature on the subject very different methods are described to extract the vitamin from the rice-polishings, it was ascertained first which method was to be preferred [3]). It was found then, that the vitamin was wellnigh quantitatively dissolved by extracting with acidulated water during 48 hours. However of no less importance was the fact, which came to evidence during the investigation, that the technique urgently needed improvement, especially with regard to the duration. For this investigation cocks were used as test-animals, as EIJKMAN, GRIJNS, FRASER and STANTON and others also had done. These animals however, also when fed on polished rice, often show signs of polyneuritis only after several months. One might think, that the method might be considerably accelerated by ascertaining, as was done by FUNK, whether an extract, to be examined as to its vitamin-content, can heal diseased animals. When we inject a polyneuritic pigeon with extract of polishings, recovery actually sets in surprisingly quick: an animal, showing sings of a severe polyneuritis often being apparently normal again some hours after the injection. This wonderful recovery however is no proof for the presence of vitamin in the extract, for EIJKMAN and VAN HOOGENHUIJZE found [4]), that injection of a solution of chloride of potassium and of sodium brings about an as prompt recovery, at least in pigeons. THEILER [5]) even found that injection of distilled water had the same effect. We were able to confirm entirely both observations.

Now it may be expected that an animal, that for a long time has had a deficiency of anti-beriberi-vitamin in its food and has or has not already shown the clinical signs of polyneuritis, will probably also undergo changes in its metabolism; and it would not be impossible that these changes were in a more specific way influenced by the vitamin. In co-operation with DR. MANGKOEWINOTO [6]) we tested the correctness of RAMOINO's [7]) assertion,

1) P. A. LEVENE and M. MUHLFELD, *Jl. biol. Chem.* **57**, p. 341 (1923).
2) S. M. HAUGE and C.H. CARRICK, *Jl. biol. Chem.* **69**, p. 403 (1926).
3) B. C P. JANSEN, *Mededeelingen B. G. D.* 1920, I, p. 22.
4) C. EIJKMAN *Arch. f. Schiffs. u. Trop. Hyg.* **17**, p. 328 (1913).
5) *Third and fourth reports of the Director of Veterinary Research. Pretoria,* March 1915.
6) B. C. P. JANSEN, and R. M. MANGKOEWINOTO, *Meded. B. G. D.* 1920. I. p. 50.
7) P. RAMOINO, *Pathologica.* **7**, p. 101 (1915): Ref. *Trop. Dis. Bull.* **6**. p. 153.

that vitamine-deficiency would bring down the respiratory quotient. Later DR. TEDING VAN BERKHOUT [1]) investigated the changes of several constituents of the blood and of the gaseous metabolism eventually caused by deficiency of anti-beriberi-vitamin in the food. And though these investigations by themselves have yielded important results, yet they did not help us to find a method for estimating more rapidly the vitamin-percentage of extracts.

Better results were obtained by using other, smaller birds as test-animals instead of fowls. First we experimented upon pigeons, the incubation-period of which is already considerably shorter, viz. about one month, then with still smaller birds. *Perkututs* (*Geopelia striata*) appeared to have about the same incubation-period as pigeons. The common rice-birds or *glatiks* (*Padda oryzivora*) used by OTTOW, appeared to be very little suitable on account of their great individual differences: when fed on washed polished rice some contracted polyneuritis already after about a fortnight, others were still in good health after 6 or 7 weeks.

However another kind of ricebirds, the „nuns" or *bondols* (*Munia maja*) appeared to give very satisfactory results: when fed on washed polished rice all *bondols*, a very few only excepted (not more than 1 or 2% of the total number) contract polyneuritis in from 9 to 12 days (Fig. 1 and 2 [2]). When 5% of a definite kind of polishings is added, polyneuritis appears in from 15 to 23 days. If the quantity of polishings is doubled, none of the birds, practically spoken, contracts polyneuritis within 4 weeks. Another kind of ricebirds, the so-called *emprits* appeared exactly equally susceptible, a third kind, the *pekings* being a little less susceptible: the latter birds, fed on washed polished rice contracted polyneuritis in from 14 to 18 days.

The *bondols* being easiest available, we worked at first exclusively with these birds; later on we occasionally used *emprits* as well. In order to estimate the vitamin-percentage of the different fractions, which we obtained when fractionating an extract from rice-polishings, 10 *bondols* every time were put together into a cage and were fed on polished rice, to which a known quantity of the fraction to be examined was added. The polished rice had been washed first during 48 hours in running water, and the shortage of mineral salts and of A-vitamin was compensated for by adding about 2% of a salt-mixture, more or less like that of OSBORNE and MENDEL, and ¼% of codliveroil.

Of the different fractions we estimated every time the quantity which had to be added to the washed polished rice, so as to make the 10 bondols, which were fed on this mixture, contract polyneuritis in from 15 — 23 days. Whereas we found that a *bondol* on an average eats 2 grams of rice daily, we could calculate how many milligrams per *bondol* per day of a definite fraction had to be added to the rice, in order to protect the birds against polyneuritis

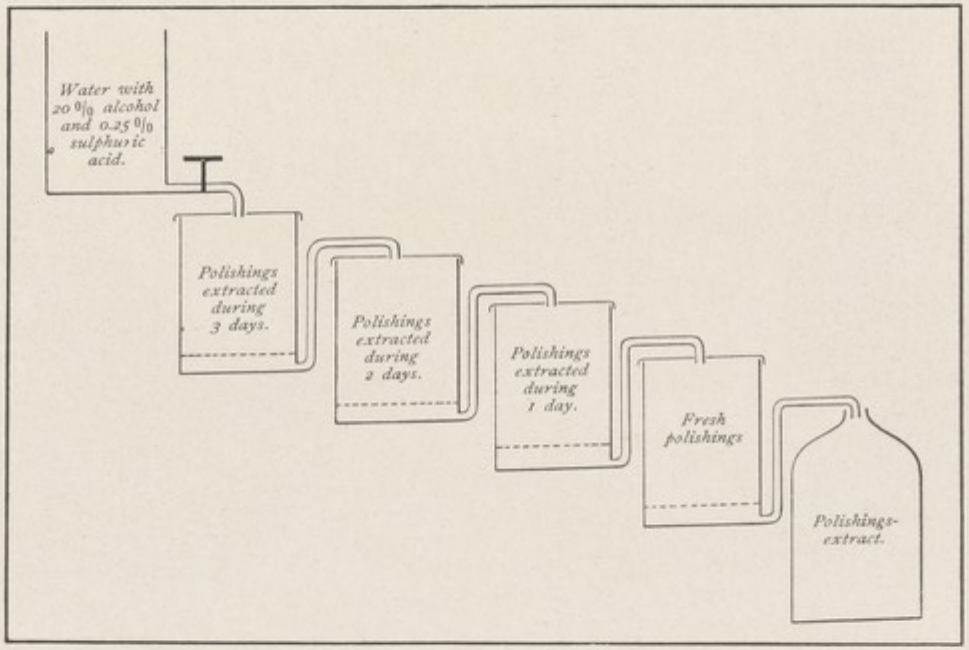
1) P. J. TEDING van BERKHOUT, *Meded. B. G. D.* 1924, p. 343 en 1926, p. 432.
2) For these figures we are indebted to Mrs. Dr. H. MENGERT — PRESSER and Dr. A.J.F. OUDENDAL of the pathological Department of the Medical School, Weltevreden.

Figuur 1. Bondol of nonnetje (Munia maja) met beginnende polyneuritis-verschijnselen. Natuurlijke grootte.

Bondol *(Munia maja)* showing initial signs of polyneuritis. Natural size.

Figuur 2. Bondol of nonnetje (Munia maja) met heftige polyneuritis-verschijnselen. Natuurlijke grootte.

Bondol *(Munia maja)*, showing violent signs of polyneuritis. Natural size.



Extraction of the rice-polishings.

during from 15 to 23 days. For some kinds of polishings a quantity of 100 mgr. per *bondol* per day was sufficient; of most kinds of polishings from the market however this quantity amounted to 140 mgr.

Then fine rice-polishings were extracted with water from the Batavian drinking-water-supply, which water only contains ± 130 mgr. of dissolved salts per Litre. To one Litre of this water we added 2.5 cc. of sulphuric acid, in order to obtain the correct degree of acidity (finally $p_H = \pm 4.5$), and 200 cc. of spiritus fortior to counteract the influence of micro-organisms. The extraction was performed in a row of 4 wooden casks, each containing ± 40 L. In the bottom and in the cover of each cask was an opening for the afflux and the efflux of the liquid. Above the bottom a second loose bottom was constructed, for the greater part consisiting of copper wire gauze. Upon this gauze is a layer of fine gravel, and upon this gravel are the polishings (16 Kg. in each cask). Every day the polishings in one of the casks were renewed and the casks were shifted one place so that the new polishings came into contact with the liquid which has extracted already the polishings from the three other casks, and that the most thoroughly extracted polishings were extracted again with the fresh water-alcohol-sulphuric-acid-mixture. In this way nearly 100 Kg. of polishings could be extracted weekly. The extract obtained in this way from 100 Kg. of polishings, contains about 20 K.G. of solid matter, and nearly all the vitamin present in the polishings. SEIDELL [1]) showed in 1916 that vitamin is selectively adsorbed by LLOYD's reagens, a certain kind of fuller's-earth. After a long search we succeeded in finding in the "acid clay", brought upon the market by the Firm BUNING at Cheribon, a kind of fuller's earth, possessing the same adsorbing properties with regard to vitamin as the above mentioned LLOYD's reagens.

The extract from 100 Kg. of polishings was then diluted to 300 L. (if necessary the p_H was brought to 4.5) and mixed with 3 Kg. of very finely ground acid clay. This mixture was stirred for some hours by means of an electromotor. Then we allowed the acid clay to precipitate and siphoned off the liquid above it. Finally this activated acid clay was drawn off upon a suction-filter of a surface of 45 × 60 cm., and washed repeatedly with small quantities of water acidulated to $p_H = 4{,}5$. The residue was taken from the filter and treated with baryta until a paper strip soaked with tropaeolin 0 is stained intensely reddish-brown by immersing it in the liquid; then the p_H amounts to ± 12 or 13. This baryta-extract, which contains the vitamin, was sucked off again on the suction-filter, and washed first with baryta, afterwards with distilled water; to the filtrate sulphuric acid was added until the reaction is acid with regard to congo paper. The treatment with baryta has to be made as quick as possible, because the vitamin is not quite stable in alkaline solution. However the solution acidulated with sulphuric acid may be safely kept; after 2 or 3 days the barium sulphate has

1) A. SEIDELL. *U. S. Public Health Reports.* **31**, p. 364 (1916).

precipitated. The supernatant liquid then is decanted for the greater part and the remainder is filtered through a hardened filter. This filtrate still contains ± 100 grams of solid matter, and ± 80% of the vitamin, originally present in the polishings. The acid clay extract was further fractionated according to KOSSEL and KUTSCHER's method [1]) with sulphate of silver and baryta, the method however being made more subtile by estimating the p_H of the liquid. To this purpose the quantity of acid clay extract obtained from 100 Kg. of polishings was evaporated in a large porcelain dish upon a warmed waterbath. A very strong current of air was blown over the liquid by means of an exhauster, so as to evaporate about 1½ or 2 L. of water per hour at a temperature of from 30° to 40°C. The liquid was evaporated unto a volume of ± 4 L. This was transferred into a large thick walled beaker of Pyrexglass of ± 10 L. contents, and then treated with sulphate or with nitrate of silver. In our first experiments we used sulphate of silver partly in solution partly solid. However since it lasted some days, before, by continual stirring by means of an electromotor, a sufficient quantity of sulphate of silver had been dissolved, we used nitrate of silver later on. As a rule a quantity of ± 50 gram of nitrate of silver was needed. Whether enough has been added appears, as may be known, from the fact that a sample of the liquid when mixed with a surplus of baryta instantly gives a brown precipitate. When adding the nitrate of silver to the sour acid clay extract a thick precipitate is formed, which does not contain any vitamin. Now we slowly added baryta from a buret or a pipet, whilst the liquid was vehemently stirred by means of an electromotor. The p_H of the liquid, which in the beginning amounts to 2 or 3, then rises slowly. The p_H estimation in most cases was performed by means of the "capillator", brought on the market by the British Drug Houses, which instrument gave very satisfactory results.

Now we can add so much baryta until the p_H amounts to ± 4.5. The voluminous precipitate formed then, contains only a slight quantity of vitamin. The liquid was then filtered off and to the filtrate baryta was added again until the p_H amounted to ± 6.5. In this second silver fraction more than 50% of the vitamin, present in the acid-clay-extract is contained. After the liquid had been filtered off the precipitate baryta was added again until the p_H amounts to ± 8.0. This 3rd silverfraction still contains a considerable quantity of vitamin, mixed however, with a relatively much greater quantity of inactive substances than in the 2nd silverfraction. Therefore this 3rd silverfraction was not further treated directly, but the 3 fractions from different preparations together were, after having been decomposed by hydrochloric acid, anew fractioned again with nitrate of silver and baryta. The filtrate of the third silverfraction still contains a large quantity of solid matter, but practically spoken, no more vitamin.

The 2nd silverfraction was decomposed by a surplus of hydrochloric

1) A. KOSSEL and P. KUTSCHER, *Zeitschr. f. Physiol. Chem.* **31**, p. 165 (1900).

acid and filtered off the silverchlorid formed. This filtrate still contained ± 20 gram of solid matter. The quantity needed per *bondol* per day is ± 0.080 mgr. = 80 γ. As a rule the solution was coloured very darkly and was freed from the greater part of the colouring matter by treating it with "norite" (a proprietary vegetable charcoal), no vitamin being lost by this treatment. In a sample of the filtrate the surplus of hydrochloric acid was estimated by titration with sodiumhydroxid, and then so much sulphuric acid was added, that the total acid-concentration, calculated as to sulphuric acid amounts to 5%. Now a solution of phosphotungstic acid in 5% sulphuric acid was added, until continued addition does not cause a precipitate to form any more. The phosphotungstic acid was purified first according to WINTERSTEIN [1]) by shaking the watery solution with sulphuric acid and ether; thereby the phosphotungstic acid passes into the latter liquid. The results are equally good if the treatment with phosphotungstic acid is made prior to the fractionating with silver and baryta. In this case however much more phosphotungstic acid is needed. If first the fractionating with silver and baryta, and then the treatment with phosphotungstic acid is made, then of the latter substance no more than ± 40 gram per 100 Kg. of polishings are needed. We let the precipitate of phosphotungstic acid settle down for 24 hours, then it was filtered off upon a suction-filter and washed with 5% sulphuric acid. The residue was then sucked off very accurately and, for further purification, dissolved in acetone and water. This acetone-solution was filtered if necessary and then poured into a large surplus of 5% sulphuric acid. Thereby the greater part of the phosphotungstate precipitates. A part however remains dissolved, but this does not contain any more a quantity of vitamin worth mentioning.

The phosphotungstate precipitated anew was, after having been filtered off, decomposed with baryta. Once we tried the dissociation with ether and hydrochloric acid according to WINTERSTEIN. However we did not obtain any better results thereby, whilst the process took up much more time.

In case the decomposition has been made with baryta, the precipitate was first dissolved again in acetone and water, and to this solution concentrated baryta was added, until, also after having been stirred for a long time, phenolphthaleïn-paper was coloured intensely red by the solution. Now the liquid was rapidly filtered off the barium-phosphotungstate and to the filtrate so much sulphuric acid was added that the entire surplus of baryta had precipitated. An eventual surplus of sulphuric acid was removed by chloride of barium. Finally the liquid was acidulated with hydrochloric acid. The solution still contains ± 5 gram of dry-residue, whilst ± 30 γ. per *bondol* per day is necessary to protect the birds from polyneuritis during from 15 to 23 days. This hydrochloric acid solution was evaporated until dry, first on the waterbath and then in vacuo over unslaked lime. The treacly residue

1) E. WINTERSTEIN. *Chemiker Zeitung.* 1898 p. 539.

was mixed with absolute alcohol, in which it almost entirely dissolves. The liquid was filtered off the small quantity of insoluble matter, and an alcoholic solution of platinic chlorid was added to the filtrate. Thereby a thick, orangecoloured precipitate forms. This precipitate, practically spoken, contains all the vitamin, and only about ¼ of the solid matter present in the original alcoholic solution.

After 24 hours the platinum precipitate was filtered off, washed with absolute alcohol, mixed with water and hydrochloric acid, and then decomposed with hydrogen sulphide. Also after a surplus of hydrogen sulphide has been lead through the liquid, one has to wait at least 24 hours before all the platinum sulphide has precipitated. The filtrate of platinum sulphide, if necessary after decoloration with norite, was evaporated, first upon the waterbath, then in vacuo over lime. The dry residue thereby obtained is crystalline for a considerable part. Of the original quantity of 100 Kg. of polishings, still ± 1.4 gram of solid matter has remained. As a rule the vitamine-percentage of the polishings used was such, that ± 7% of polishings had to be added to the washed, polished rice in order to protect the *bondols* during from 15 — 23 days from polyneuritis. So for 2 gram of rice, i.e. the daily quantity eaten by a *bondol*, 140 mgr. of polishings are needed. Consequently in 100 Kg. of polishings there is sufficient vitamin for ± 700.000 *bondols* for one day. Of the platinum-precipitate decomposed with hydrogen sulphide 8 γ. per day per *bondol* is needed. Consequently in the 1.4 gram there is sufficient for ± 175.000 *bondols* for one day. So we see that after all the above mentioned processes ± ¼ of the vitamin originally present in the polishings has been left.

Though it has cost much time before we had worked out this so far, now that we have obtained this knowledge, it is very easy to come unto this stage. The substance obtained in this way is relatively pure. For we will see below that of the pure vitamin ± 2 γ. per *bondol* per day is needed to protect birds during from 15 — 23 days from polyneuritis. Since of the decomposed platinum-precipitate ± 8 γ. per *bondol* per day is needed, this precipitate consists for about one quarter of the vitamin searched for. However further purification takes up very much time, and is performed only at a great loss. For in this decomposed platinum-precipitate two more substances at least besides the vitamin are present. This appears from the following: If the solution obtained by treating the platinum-precipitate with hydrogen sulphide after the platinum-sulphid having been filtered off first, is evaporated, finally over lime until dry, and if this residue is dissolved in alcohol, then a part remains unsolved. From the animal experiment this part appears not to be the vitamin searched for. If now we treat the alcoholic solution with acetone, then a milky opaqueness is brought about, from which after one or more days a partly treacly, partly crystalline precipitate settles down on the bottom and the walls of the vessel. This precipitate contains much more vitamin than the solution, which latter still contains a great part of the solid

Table of yield.

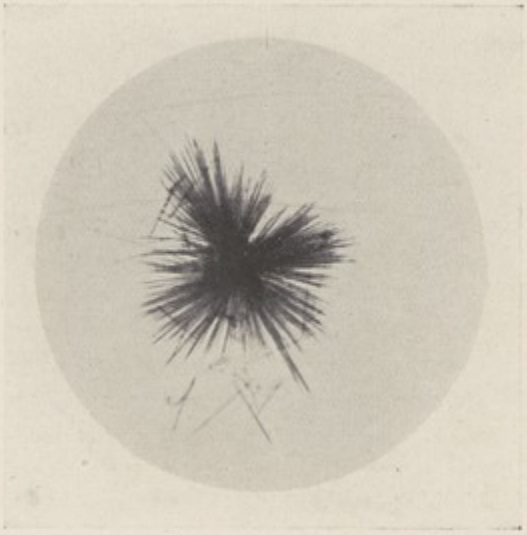
		Bound of daily dose	No doses bondol	Lots
9 p.s. 300 Kg rice polishings		·14 g	2,700,000	
1st. decoupage of 14 sacks Pl. soet- from 100 Kg.	= 1400 mg	·000· 8γ = ·008 mg =~~000~~.	175,000	3/4
p.g. Final pure crystals hydrochloride ~~300 Kg.~~	0·100 g	2μ·00 mg	50,000	13/14
From 100 Kg	0·033	2μ·002 mg	17,000	39/40

Figuur 3. Kristallen van vitamine=hydrochloride. Vergrooting 120 ×.

Crystals of vitamin hydrochlorid.
Magnification 120 ×.

Figuur 4. Kristallen van het goud=dubbelzout. Vergrooting 120 ×.

Crystals of the gold=double=salt.
Magnification 120 ×.



Figuur 5. Kristallen van vitamine=picrolonaat. Vergrooting 120 ×.

Crystals of vitamin picrolonate.
Magnification 120 ×.

matter. So in the platinum-precipitate are present at least: 1st a substance insoluble in absolute alcohol; 2nd a substance, dissolving in absolute alcohol, but insoluble in acetone (this substance appeared to be the vitamin); 3th a substance, soluble in absolute alcohol as well as in acetone. When we dissolve in alcohol the precipitate caused by the acetone, then again a part remains unsolved; this is the substance insoluble in alcohol, which at the first treatment with alcohol had been kept dissolved by the large quantity of the substances soluble in alcohol, which were present. Now we can let crystallize fractionally by dissolving the dissociated platinum-salt, as far as it dissolves, in absolute alcohol. To this we add a small quantity of acetone; the liquid is decanted from the deposit, which settles against the wall of the flask, and acetone is again added to it. Again a deposit settles against the wall, and again the liquid is decanted, etc. Each deposit is dissolved in absolute alcohol, filtered off the unsolved part, precipitated with every time new quantities of acetone etc. By repeating this process several times, we finally obtain the pure vitamine as the hydrochloride (Fig. 3). However since after the addition of acetone, it usually lasts 24 hours, or even two or three times that term, before the opaqueness, milky in the beginning has completely settled, the whole process may last for months. When the vitamin is nearly pure, then the process goes quicker, because a crystalline deposit forms as soon as the alcoholic solution is treated with acetone, which deposit does not settle any more against the wall.

We tried to improve this lengthy and little producing process, but up till now we have not been successful therein. With picrolonic acid a yellow coloured precipitate forms, chiefly consisting of picrolonate of the substance insoluble in alcohol, which picrolonate is hardly soluble in water, and of vitamine picrolonate. Fractioning may be obtained here as well by recrystallization from diluted alcohol, but not much easier than by the alcohol-acetone fractioning, described above. In case of this picrolonic acid fractioning, the fractions can be recognised by their melting-point. The picrolonate of the substance insoluble in alcohol melts above 240° C; the vitamine-picrolonate at 165° C (not corrected) (Fig. 5). When filtering off the different picrolonic acid fractions, as a rule amounting only to some tens of milligrams, we made a profitable use of the GOOCH's crucibles with fritted glass filter disk: from this bottom the precipitate can almost quantitatively be scraped with a small platinum spatula, without getting mixed with paper-fibres. By treatment with ether or acetas aethylicus and hydrochloric acid, the hydrochloride can be easily obtained again from the picrolonate. Via the picrolonic acid as well as through the fractioning with alcohol and acetone we finally obtained from 300 Kg. of bran + 100 mgr. of a crystalline substance, which after recrystallization, had a melting-point of 250°C, determined by means of an ANSCHÜTZ-thermometer, consequently so called corrected melting-point. Already at 200° C the substance shows a brown colour, but yet it melts rather

1 g dose .002 mg pour 300 kg rice

sharply at 250°C. By means of chloride of gold a portion of this substance was transferred into a double-salt, which formed beautiful crystals (Fig. 4).

And now the proof that these crystals actually are the anti-beriberi-vitamin-hydrochloride, searched for:

Of some hundreds of groups, each of ten *bondols*, which in the course of our investigation were fed on washed polished rice mixed with inactive fractions, there has not been one single group, all *bondols* of which or also even a great part of them, remained in good health for longer than 12 days, whilst only a very few individuals held out longer than a fortnight. Now the following experiments — besides a number of preliminary experiments, which all had the same result as the definite ones — were made with the vitamin-hydrochloride: Ten *bondols* every time, during ± 3 weeks were fed on washed polished rice to which varying quantities of the vitamin-hydrochloride had been added:

A. With vitamine-hydrochloride purified by recrystallization from absolute alcohol and acetone:

Cage I: 1 part of vitamin-hydrochloride to one million parts of washed polished rice; since a *bondol* eats an average of 2 gram of rice daily, this corresponds to 2 γ. per *bondol* per day. One *bondol* contracts polyneuritis after 18 days, and two after 23 days: the others are still in good health after 23 days.

Cage II: 1½ part of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 3 γ. per *bondol* per day. After 3 weeks all the birds are in good health.

B. With vitamin-hydrochloride purified via picrolonate:

Cage III: 1 part of vitamin-hydrochloride to one million parts of washed, polished rice, corresponding to 2 γ. per *bondol* per day, three *bondols* contract polyneuritis after 13, 18 and 20 days respectively. The others are still in good health after 3 weeks.

Cage IV: 1½ part of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 3 γ. per *bondol* per day. After 3 weeks all are in good health.

C. With vitamin-hydrochloride obtained by decomposing the gold-double-salt with hydrogen sulphide.

Cage V: 1 part of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 2 γ. per *bondol* per day. One *bondol* contracts polyneuritis after 16 days, two others after 17 days; the others are still in good health after 23 days.

Cage VI: 2 parts of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 4 γ. per *bondol* per day. After 3 weeks all birds are in good health.

So we see that the critical limit, accepted by us, is found at 2 γ. per *bondol* per day: of 30 *bondols*, which are fed on this dose, only one contracts

polyneuritis within 15 days, the majority even remain in good health for longer than 3 weeks. Of the *bondols* which were fed on 3 or 4 γ. of hydrochloride per day, none contracted polyneuritis.

We repeated these experiments also with pigeons.

A. With the hydrochloride purified via the picrolonate.

Pigeons Nos. 1 and 2: 2½ parts of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 30 γ. daily for a pigeon, eating about 12 grams daily. After 6 weeks the food was finished; the pigeons looked absolutely healthy, but their weight had gone down a little, viz. from 267 and 270 to 222 and 235 grams respectively.

Pigeons No. 3 and 4: 5 parts of vitamin-hydrochloride to one million parts of washed polished rice, corresponding to 60 γ. per pigeon per day. After 6 weeks the food was finished. The pigeons looked absolutely healthy. Of one pigeon the weight had remained constant; of the other it had gone down from 270 to 213 grams.

In these experiments with pigeons the proportion of vitamin and rice was made a little more favorable than in the experiments with *bondols*, because we could not know beforehand whether *bondols* and pigeons need a proportionately equal daily quantity of vitamin. The result however being so favorable we made later on with the preparation purified by means of absolute alcohol and acetone the proportion absolutely equal to that in the experiments with *bondols*.

B. Pigeons Nos. 5 and 6: 1 part of vitamin-hydrochloride purified with alcohol and acetone to one million parts of washed polished rice, corresponding to ± 12 γ. per pigeon per day. After a little more than 6 weeks the food was finished: the birds looked healthy; only the weight had gone down from 271 and 292 to 221 and 220 grams respectively.

Pigeons Nos. 7 and 8: 2 parts of vitamin-hydrochloride purified by alcohol and acetone to one million parts of washed polished, rice, corresponding to ± 24 γ. per pigeon per day. After 6 weeks the food was finished: the birds looked healthy, whilst the weight had not or hardly gone down, viz. from 322 and 302 to 325 and 273 grams. Since by washing the polished rice for 48 hours ± 10% of the proteins are lost, it is not excluded, that the decrease of weight, which was observed in some of the birds, is due to protein-shortage. Therefore in the last two experiments 2½% of meat-powder, repeatedly extracted with boiling water, in which, as appeared from experiments purposely made, no perceptible quantity of antineuritic vitamine was present any more, was added to the rice.

Now if we consider that pigeons, which are fed on washed polished rice only, as a rule contract polyneuritis in from 2 to 4 weeks, accompanied by a strong decrease in weight, if the rice is not introduced artificially into the crop, then the great influence appears of the slight addition of vitamin-hydrochloride. To make sure we also fed 2 pigeons on the same washed

polished rice, to which, as had been done in the experiment with the last mentioned pigeons, 2% of salts + ¼% of cod-liver-oil + 2½% extracted meat-powder had been added. One pigeon contracted polyneuritis after 24, the other after 25 days, the weights in that short time going down from 312 and 289 to 207 and 207 grams respectively. Also the behaviour of the pigeons, which get vitamin-hydrochloride added to their food, is entirely different from that of the pigeons, which are fed only on washed polished rice. Already after a few days the latter pigeons almost entirely stop eating spontaneously, they eat very sluttishly, and make the impression of picking only the grains to which traces of pericarp are still adhering, and of throwing away the other grains; the former pigeons however, also those which only get one part of vitamin-hydrochloride to one million parts of washed polished rice, eat greedily and finish their portion altogether.

So from these experiments we are allowed to conclude, that the isolated hydrochloride with a melting-point of 250° C, has a very great power of preventing polyneuritis. But one might ask, whether this salt is actually the vitamin-hydrochloride or whether it is perhaps mixed with a small quantity of a much more powerful substance, which, if this might prove true, would be the vitamin searched for. In our opinion however we may exclude this, considering that the salt has been purified by recrystallization, the mother liquor appearing to be much less powerful. In this case we would have to suppose, that the crystals would have selectively adsorbed the active principle from the liquid, and had retained it during the process of recrystallization and of transference into gold-salt or picrolonate and back again into hydrochloride. And this is rather excluded.

Consequently, according to the proportion of from 1 to 2 parts of vitamin to one million parts of rice, a man, eating about 500 gram of rice a day, needs a daily dose of from ½ to 1 milligram of vitamin. This quantity is in the same scale as that of the daily dose of other physiologically very powerful substances such as thyroxin, adrenalin etc.

As long as it is not yet absolutely pure, the vitamin-hydrochloride crystallizes into bundles of needles. The pure salt consists of small bars joined into rosettes. The hydrochloride in pure condition is not hygroscopic; however it is solved readily in very little water; it is also readily soluble in methyl-alcohol, less readily in aethyl-alcohol; the solution in methyl-alcohol gives a precipatate, when mixed with amyl-alcohol, acetone, ether, chloroform, benzol, petroleum ether or acetas ethylicus.

A 2% solution of the hydrochloride in water gives the following reactions: with mercuric chlorid a scanty precipitate forms which increases through addition of sodium acetate; with a solution of sulfate of mercury in diluted sulphuric acid a thick precipitate forms; with iodine-potassium-iodide a fine black precipitate forms; addition of picric acid causes opaqueness; with styphninic acid a precipitate forms; DRAGENDORFF's reagens, a solution of

iodide of bismuth in potassium-iodide-solution, causes a thick red coloured precipitate; no precipitate forms with zinc chloride, cadmium chloride, acetas plumbi, acetas cupri, chromate of potassium, potassium sulphocyanate and perchloric acid. As has appeared already from the preparation also phosphotungstic acid, picrolonic acid and gold chloride cause a precipitate, the latter two consisting of needle-shaped crystals. The watery solution does not give a precipitate with platinum chloride, however in the solution in absolute alcohol a precipitate forms through addition of an alcoholic platinum chloride solution. By treatment with sulphanilic acid and nitrous acid and afterwards with soda an intensive red colour appears (PAULY's diazo-reaction).

In the hydrochloride no other elements appeared to be present than C, N, H, O and Cl. After the hydrochloride had been transferred into the nitrate, we could ascertain that no halogens formed part of the vitamin itself.

We made some elementary analyses of the hydrochloride and of the gold double-salt by means of the micro-apparatus of PREGLL-MÜLLER-WILLENBERG, with quartz-tube and absorption-tubes ground to fit. In the beginning the results of the carbon-estimations were a little too low. However, after we had filled, as is advised by WREDE [1]), the carbonic acid tube with glasswool soaked in strong caustic potash solution instead of with soda-lime, the results were very good, as appears below:

a. Analysis of the hydrochloride:

5.823 mgr.	yield	9.427 mgr. CO_2	and 3.553 mgr. H_2O.
7.236 „	„	11.989 mgr. CO_2	and 4.316 mgr. H_2O.
4.056 „	„	0.65 cc. N of 30° C	and 731 mm.
4.004 „	„	0.635 cc. N of 30° C	and 730 mm.
4.192 „	„	3.669 mgr. AgCl.	
2.880 „	„	2.548 mgr. AgCl.	

Calculated for $C_6H_{10}ON_2.HCl$	Found:
44.31% C	44.15% C; 45.18% C
6.77% H	6.77% H; 6.62% H
17.23% N	17.34% N; 17.16% N
21.84% Cl	21.64% Cl; 21.88% Cl.

b. Analysis of the gold doble-salt:

12.354 mgr.	yield	5.237 mgr. Au, 6.976 mgr. CO_2 and 2.480 mgr. H_2O.
13.112	„	5.548 mgr. Au, 7.565 mgr. CO_2 and 2.658 mgr. H_2O.
10.178	„	0.57 cc. N of 30° C and 729 mm.
8.991	„	0.507 cc. N (measured over water) of 32°C and 760 mm.
7.293	„	(after decomposition with Mg) 8.901 mgr. AgCl.
5.602	„	(after decomposition with Mg) 6.896 mgr. AgCl.

1) F. WREDE. *Ber. d. Chem. Ges.* **55**, p. 557 (1922).

Calculated for $C_6 H_{10} ON_2 HCl. AuCl_3$	Found:
15.45% C.	15.40% C; 15.73% C.
2.36% H.	2.24% H; 2.25% H.
6.01% N.	6.05% N; 6.00% N.
42.28% Au.	42.39% Au; 42.31% Au.
30.47% Cl.	30.19% Cl; 30.45% Cl.

Consequently these analyses correspond very well to the formula $C_6H_{10}ON_2$ for the vitamin. With regard to the structural formula we may make the following remark:

Mc COLLUM and SIMONDS [1]) as well as PETERS [2]) found that the vitamin is not impaired by treating it with nitrous acid. This points towards the probability that the molecule does not contain primary or secundary amino-groups, but that both nitrogen-atoms are fixed in the nucleus. Now there are only two rings, with 2 nitrogen-atoms, of which we know physiologically important compounds; these are the imidazol (or glyoxaline) ring and the pyrimidin-ring. To the first group substances belong such as histidin, histamin and carnosin, to the second cytosin, uracil and thymin. So it is very probable that in the vitamin either an imidazol- or a pyrimidin-ring is present. We hope soon to be able, to ascertain this more accurately.

In this place we thank our analysts, and particularly Raden SOEDARSONO for their untiring assistance at the experiments.

Postcript.

It is rather clear from the above publication that for the time being the preparation of vitamin from polishings is a much too expensive process, to use the vitamin obtained in this way for the practical control of beri-beri. Matters are different, if we might succeed in ascertaining the structural formula and in building up the substance synthetically. The formula being comparatively simple, it is by no means excluded that we might be able to prepare the vitamine in a little expensive way. And since the daily dose is so small, the price might yet be relatively high without the practical application being thereby prevented. For even if the price of one Kg. should be *f* 1000.—, the amount to spend per person per day, would not be more than 1/10 cent. However it will probably last a long time before we have attained that end, and before we know that this pure material is also the only substance, the presence of which in the food in sufficient quantity prevents also human beri-beri. Therefore for the time being the Medical Laboratory will bring already on the market one of the intermediate products of our isolation experiment, namely the acid clay which has been activated by having adsorbed the vitamine from the extract of polishings. As appears from experiments on ani-

1) E. V. Mc. COLLUM and N. SIMONDS. *Jl. Biol. Chem.* **33**, p. 55 (1918).
2) R. A PETERS. *Biochem. Jl.* **18**, p. 858 (1924).

mals, and also according to the experience, when taken per os by beriberi-patients this preparation, one gram of which contains the vitamin from 30 gram of polishings, cedes its vitamin to the organism, probably in the intestine, with its alkaline reaction. It is not decomposed by the air: a sample, which we kept for nearly a year in a PETRI-scale, appeared to be as active as the fresh prepared substance. If we suppose that an adult eats 500 gram of rice daily, which contains about 7% pericarp, he would consume the vitamin of 35 gram of pericarp, if the rice had been unpolished. However in the native villages the rice is always pounded to a greater or lesser extent, a considerable part of the pericarp being lost in this way, without any cases of beriberi appearing. Consequently we may accept that a daily dose of 1 gram of the above preparation, corresponding to 30 gram of bran, will protect a person, whose chief nourishment consists in polished rice, from beriberi, and that ½ gram will be sufficient for a person, who with his polished rice eats a moderate quantity of other food.

Further we will prepare, especially for the treatment of the infantile beri-beri, an extract from the activated acid clay. This extract contains in 1 cc. the vitamin from ± 300 gram of polishings. Therefore 0.1 cc. is needed per adult daily. This extract may be mixed with the cooked rice, or for babies, with the milk.

Finally the Medical Laboratory will deliver soon sterilised ampules with the solution of the decomposed platinum precipitate, made isotonic by sodiumchloride. One ampule of 2 cc. contains 4 mgr. of decomposed platinum precipitate, therefore 1 mgr. of vitamin, i.e. the daily dose for an adult. These ampules are destined for peracute cases of beriberi.