THE CADUCEUS

JOURNAL OF THE HONG KONG UNIVERSITY MEDICAL SOCIETY.

VOL. 19. MAY, 1940. NO. 2.

All medical papers and other scientific contributions intended for the journal, and all books for review and magazines in exchange, should be addressed to the Editor, "*Caduceus*," Hong Kong University, Hong Kong.

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AN INVESTIGATION INTO THE CAUSATION OF LEUCOPENIA IN TYPHOID FEVER,

by

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The leucopenia which is a very characteristic and constant feature of typhoid fever is marked by a diminution in the numbers of polynuclear cells, whilst the large mononuclear cells are relatively increased. A low leucocyte count may be said to be the rule when the typical lesions produced by the typhoid bacillus are limited to the intestinal canal. During a typhoid septicaemia and in cases where one obtains a positive blood culture, we may obtain at first a moderate neutrophil leucocytosis.

During the actual febrile course of the disease there is undoubtedly a marked diminution or even absence of eosinophils. When convalescence sets in these cells increase in relative proportions.

The actual cause of the leucopenia of typhoid fever is somewhat obscure though various plausible suggestions have been advanced to explain this phenomenon. Naegeli and his co-workers seem to favour a functional paralysis of the haematopoetic organs as being the main causative factor. They found they could induce leucopenia in normal rabbits by infecting them intravenously with graduated amounts of typhoid toxic substances. Other workers give a different explanation: Goldscheider and Jacob claim that the leucopenia is brought about by a different distribution of the white blood cells and that the neutrophils are attracted to the capillaries of the internal organs, especially the lungs. Gallagher (1933), recorded filament and non-filament neutrophil counts of seventeen cases of typhoid fever and found that in practically every instance there had been a striking increase in the

number of non-filamentous forms. He suggested that the leucopenia of typhoid fever was due to a destruction of neutrophils, as there was insufficient evidence of the suppression of blood-forming organs. Anti-leucocytic serum has been produced by Ledingham and Bedson (1915), Bedson (1921), Matsumo (1932) and others. Recently Chew and his co-workers (1936) prepared anti-leucocytic serum relatively free from haemolytic antibodies. They found that when the anti-serum was injected intracardially into guinea pigs, there was an immediate drop in the number of white blood cells in the peripheral blood, the neutrophils being affected more than any of the other cells. These cells almost completely disappeared from the peripheral blood during the first 5 minutes.

It is interesting to note that Bauer (1928) could produce no abscess by injecting turpentine subcutaneously during the height of typhoid fever, although when the fever disappeared in convalescence, the belated abscess appeared at the site of injection.

Recently during some experiments with the toxic filtrates of *B. typhosus* it seemed to be desirable to reinvestigate the effects of the typhoid toxic substances on the leucocytes of rabbits which are very susceptible to the toxins of *B. typhosus*. Our initial experiments (Robertson and Yu 1938) were designed to produce toxic filtrates from a variety of strains of *B. typhosus* of various degrees of virulence. The minimum lethal dose was established in each case and a large series of typhoid strains were examined which had been obtained from patients in the Lester Chinese Hospital, Shanghai. These were grouped as they affected mice and rabbits. The M.L.D. of the organism was determined by a series of toxicity tests. In order to study the effects of *B. typhosus* toxic substances upon the leucocytes of rabbits, we gave predetermined sub-lethal doses of the toxic filtrates intravenously. Total white cell and differential counts were made at intervals. Toxic filtrates of *staphylococcus, scarlatinal streptococcus* and *Diphtheria Bacillus* were used as controls. We found that the administration of a small amount of *B. typhosus* culture filtrate intravenously in rabbits produced a marked leucopenia within one hour. An increase in the number of neutrophils was usually present by the end of 24 hours. The leucocytosis persisted for about 2 days and returned to normal. From the differential count we found that in every case the leucopenia was due to a sharp drop in the proportion of neutrophils. We also injected a small amount of *B. typhosus* toxic filtrate intraperitoneally into rabbits, and the results were essentially the same as in those receiving intravenous injections. It may be mentioned that as a control, rabbits were given intravenous injections of plain sterile meat infusion broth. When this was done an increase in leucocytes resulted. The blood picture of rabbits inoculated with typhoid bacillary toxic substances is similar to that of the same animals when they receive staphylococcus filtrates. Rabbits injected with diphtheria and

streptococcus toxin also showed a moderate drop in the leucocyte count but not to the extent shown by the *staphylococcus* and *B. typhosus* culture filtrates; again there is not much alteration in the production of neutrophils and lymphocytes. It is well known that in the case of *staphylococcus* the destruction of leucocytes is due to a substance called leucocidin, formed by the organism. With the *streptococcus*, the leucocidin has been studied by a number of workers; the more recent studies of Channon and McLeod (1929) and Evans (1931), (1932) on the cytolytic effect of streptococcal filtrates, showed the presence of a thermo-labile toxin which has a marked lytic action on the leucocytes. The leucocidin of *staphylococcus* and *streptococcus* is thermolabile, and is easily destroyed by heat 58°-60°C. Leucocidin is therefore different from the corresponding toxin which is heat-stable. In the case of B. typhosus, experiment shows that culture filtrates of this organism, heated at 60°C. for one hour, still produced marked leucopenia in the same way as unheated filtrates when injected intravenously into a series of rabbits.

Recently Dr. H. Yu my colleague of the Lester Institute of Medical Research, has pursued the investigation further and has produced evidence from the study of a series of typhoid cultures in the General Hospital, Singapore, that the toxic factors and leucopenia producing factors of *B. typhosus* are not identical. The argument is brought forward that both non-toxic and toxic strains of *B. typhosus* have been found to be equally effective in producing leucopenia.

Broth cultures incubated for 24 hours give the same results as cultures which have been incubated for one or two weeks.

The following table indicates the toxic properties and leucopenic effects of a series of *B. typhosus* culture filtrates.

Cultures	*Type of Culture*	*Leucocyte Counts*	
		Before injection	*1 hour after*
		per cu. mm.	*per cu. mm.*
5815	Non-toxic	8100	2400
6001	Toxic	6300	2500
6042	Non-toxic	8200	2200
6087	Non-toxic	12500	2600
6088	Toxic	9500	2200
Ty 2 Lister	Toxic	12900	2400

It has also been found that the leucopenia producing factor of *B. typhosus* is very unstable and when toxic filtrates of the organism are stored for a period in the ice box the potency very markedly falls off. The following table presents the experimental evidence supporting this observation.

Table 2. The result of storage of typhoid culture filtrates in the ice box and their effects on the leucocyte count of rabbits.

Period of storage of filtrate of culture 6088	*Leucocyte Count Before and after injection of 0.01cc. of filtrate*		*Leucocyte Count Before and after injection of 0.4cc. of filtrate*	
	Before	After	Before	After
	per cu. mm.	*per cu. mm.*	*per cu. mm.*	*per cu. mm.*
Immediately after filtration	12900	2500	9600	died
Two days in ice box	8400	7300	10800	3400
Four days in ice box	8200	9300	7600	4700
Seven days in ice box	11500	9900	11000	3600

We have also conducted a series of experiments using previously immunised animals and find that whilst an anti-toxin immunity is conferred that there is no anti-leucopenic immunity produced.

THE IN VITRO EXPERIMENTS.

We attempted to mix rabbits blood with *B. typhosus* culture filtrates *in vitro* in order that the cells might be brought in contact with a greater concentration of toxic filtrates than was possible in experiments on living animals. We desired to see whether there was a reduction in the number, or an actual destruction of the leucocytes. The results showed that there was no alteration either in the total number or the morphology of the leucocytes.

The leucopenia produced by the toxic substances of *B. typhosus* is not due in our opinion to the actual destruction of the leucocytes.

From the Schilling haemogram for rabbits injected with typhoid toxic substances in comparison with that of normal controls, we found that the percentage of segmenters in relation to juveniles is altered. There is an increase in the number of juveniles in the typhoid bloods. This suggested to us that the leucopenia is due to certain factors other than the suppression of the blood forming organs.

PATHOLOGY.

Histological examinations of the tissues were conducted with the assistance of my colleague Dr. L. S. Kau with the object of observing whether the neutrophils had been immobilised in the organs or whether they were absent from the tissues as well as from the peripheral blood. Our conclusions were, that the leucopenia in rabbits following the injection of B. typhosus toxic filtrates is due to the immobilisation of the neutrophils from the peripheral blood in the internal organs. The chief organs showing increased leucocytic immigration were the lungs, spleen, mesentery, lymph nodes, bone marrow.

DISCUSSION.

The transitory leucopenia in the peripheral blood of rabbits following injection of *B. typhosus* toxic substances seems to be due to the temporary accumulation of neutrophils in the reticuloendothelial organs. We deduce from this that the phenomenon of leucopenia in the typhoid fever of man is due to the constant liberation of *B. typhosus* toxic substances in the circulation during the course of the disease. We also think that the leucopenic factor of *B. typhosus* is one of the toxic properties of the organism and differs in antigenic eliciting power from the other *antigens* of the organism. It seems to be a property of *B. typhosus* irrespective of degrees of virulence and toxicity and probably has nothing to do with the "Vi" factor, which we have from other work proven to be more connected with virulence and to be a suitable antigen to use to produce anti-bacterial immunity. Our present concept of the antigenic structure of *B. typhosus* is that we have "H" antigen flagellar, "O" antigen, bacterial body, both of which produce agglutinins; "Vi" antigen associated with virulence and the production of anti-bacterial immunity. The "O" antigen produces anti-toxic immunity. We had best refer to the "L" factor at the present juncture as a "property" rather than an antigen as we have not up to the present demonstrated anti-leucopenic anti-body.

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INFANTILE BERI-BERI IN HONG KONG,*

by

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Soon after assuming my duties as Infant Welfare Officer in Hong Kong I observed that many infants brought to the Centre were showing a complex of symptoms which could not be identified with any infantile disease seen by me in Europe or the United States. A most striking feature of this disease was that such physical signs as were present did not seem to account for the high mortality of infants so affected. Colleagues working in the same field attributed this disease and high mortality rate to malnutrition due either to undernourishment or to faulty feeding.

However, it soon became apparent to me that this theory would have to be discarded in view of the fact that the disease manifested itself in its most acute form in overweight babies, who were strictly breastfed.

Shortly afterwards I noticed a peculiar coincidence: many of the mothers of such infants came into my office with unsure, hesitating steps and when undressing the babies, started to fumble with their hands. Upon enquiry I was told that these mothers had either numbness, weakness of extremeties or oedema of the feet, i.e. they had symptoms that are associated with adult beri-beri. The term "infantile beri-beri" was known to me, but in common with many physicians, I was under the impression that this disease is similar to that of adults, but on a small scale. In the infants, however, I never observed the so-called dry type, i.e., polyneuritis with subsequent atrophy; nor the extensive oedema associated with wet beri-beri.

However, the connection with maternal beri-beri was unmistakable; the acute symptoms disappeared within 24 to 48 hours after cessation of maternal feeding, as well as after administration of therapeutic doses of vitamin B_1.

Knowing that infantile beri-beri was once a problem in the Philippines and that extensive research work has been done in that country to eliminate the disease, I asked the Medical Authorities in Manila to supply me with the literature published on the subject.

In consequence I could definitely identify the symptoms observed by me as those of infantile beri-beri, a disease first observed by Hirota in Tokio in 1888.

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* *Read before the Hong Kong Chinese Medical Association on the 16th May, 1940.*

This great Japanese scientist observed in some breastfed infants the symptoms of obstinate vomiting, restlessness, dyspnoea, oedema, aphonia, oliguria, accelerated but clear heart beats, absence of albumin in the urine, and negative lung findings, and he ascribed them to the ingestion of milk from beri-beric women. At that time the prevailing theory of adult beri-beri was intoxication by toxins contained in polished rice and Prof. Hirota explained the occurrence of infantile beri-beri by the transmission of such toxins in the breast milk. Consequently he recommended the suppression of maternal feeding as the only effective and rational method of treatment.

The discovery of Prof. Hirota created a great sensation at that time, but was soon forgotten. In 1904, however, Dr. Manuel Guerrero of Manila recognised that Taon, the infantile scourge of the Philippine Islands, was identical with Hirota's infantile beri-beri.

By this achievement Dr. Guerrero laid the corner-stone of infant welfare work in the Philippine Islands, as the disease then claimed an average of 16,500 infants yearly. The result of this discovery was also to revive the interest of physicians in the Far East, in this malady. Consequently soon afterwards infantile beri-beri was recognised as a cause of high infantile mortality, first in the Dutch East Indies, then in Indo-China.

In 1912, at the first meeting of the Far Eastern Association of Tropical Medicine, a paper was read by McLaughlin and Andrews (1912) in which they confirmed the identity of Taon with Hirota's infantile beri-beri and supported their finding with the results of necropsies performed on 219 infants of whom 124, i.e., 56.6% showed pathological findings characteristic of infantile beri-beri. In the discussion of this paper, some members of the delegation expressed their scepticism about the identity of Taon with infantile beri-beri. Amongst them was Dr. Hans Aron who claimed that Taon was similar to carbohydrate intoxication (Szerny's Mehlnährschaden) and Dr. F. Clark of Hong Kong, who regarded Taon as nutritional in origin and due to faulty feeding.

However, in the light of subsequent events the assertions of McLaughlin and Andrews were fully confirmed.

Since the recognition of adult beri-beri as a deficiency disease attempts were undertaken to add the deficient factor in the form of rice polishings to the diet of beri-beries. In the case of infantile beri-beri this treatment presented great difficulties in view of the impossibility of administering rice polishings to breastfed infants. This problem was solved, however, by Chamberlain and Vedder, who, in 1912, produced an extract of rice polishings (extract of tiki-tiki) which they successfully administered to infants suffering from Taon without having recourse to cessation of maternal feeding.

In fact, the success of such treatment was so striking that in 1914 at the second district meeting of the Philippine Medical & Pharmaceutical Society, a resolution was presented to the Philippine Legislature which was converted into the Angeles Act, appropriating a certain sum of money for the preparation and free distribution of tiki-tiki extract to the poorer classes.

As a result of this step the infantile mortality in the Philippines which was 346.39 in 1914 fell to 160.24 per mille in 1930 and the mortality rate from infantile beri-beri which was 93.66% in 1914 was reduced to 19.12% in 1930. In fact according to Prof. Jose Albert (1931) it is unusual to see a case of Taon on the Islands now and the native population, which was facing extermination, is now steadily increasing.

After introduction of treatment with extract of tiki-tiki, the theory of intoxication in infantile beri-beri was definitely abandoned in favour of deficiency; one of the reasons was the assertion that this extract does not contain any antitoxins to neutralise the toxins, which were presumed to be present in the milk.

After the isolation of vitamin B_1 by Seidell (1926), Jansen & Donath (1927) and others, extensive studies could be made upon its properties and characteristics. Above all, its intimate connection with carbohydrate metabolism and oxidation in the human body was discovered. It was found that vitamin B_1, as pyrophosphoric ester is a co-enzyme of carboxylase, i.e., its presence is essential for complete oxidation of carbohydrates. In the absence of this vitamin the intermediate products of carbohydrate metabolism, which are known as B.B.S. (bisulphate binding substances) were found in B_1 avitaminosis in increased quantities in such body fluids as blood, urine, cerebrospinal fluid (Kauffman, Cosla and Roche (1927); Palladin and Utewski (1928); Vogt Moller (1931); Platt and Lu (1936) and in human milk Platt and Lu (1939).

In 1931 Vogt Moller was able to find one product of the B.B.S. group—methyl glyoxal in the body fluids of avitaminotic animals. Methyl glyoxal is a toxic substance, as was shown by Szolleme & Seecles (1926); Fishler (1927); Kermak, Lambie & Slatter (1927), and a number of other workers. Since methyl glyoxal was found by Platt & Lu (1936) in the cerebrospinal fluid, blood and urine of avitaminotic human beings.

Prof. J. Albert (1931) of Manila writes: "It is a singular fact, unparalleled in the history of medicine, that human milk as a food appears to be a scourge to the Filipino infant, an inverse phenomenon to the experience of other nations, where human milk is the strongest

bulwark of child hygiene, the 'magic liquor' that guarantees the life of the infant.'" After observing the infants in Hong Kong, I could not but agree that this statement also applies to the local Chinese infants; moreover I gained the impression that the infants of beri-beric mothers were actually intoxicated.

In a few cases of infantile beri-beri I advised the mother to wean the infant; the alternative feeding in such cases was always condensed milk, which in a dilution of 1 in 16 contains only traces of B_1, the amount being hardly sufficient to cover the existing deficiency; but in spite of that, the acute symptoms disappeared within one to two days. In one case the weaned child progressed satisfactorily for a few days, only to be brought to me again with the symptoms of acute beri-beri. On questioning the mother she admitted, after repeated denials, that the previous night she had been too lazy to get up to prepare the infant's food and had consequently breastfed him.

In their monograph "Beri-Beri in Breast-Fed Infants" Guerrero & Quintos (1910) report an interesting case; one of them, Quintos, was called to see a five month old child which was found to have all the symptoms of hyperacute beri-beri. The mother was asked about its feeding and Dr. Quintos heard with surprise that the baby was bottle-fed. It was hard to believe this because it was in opposition to his daily experience; but inasmuch as the mother swore that the food of the child consisted solely of condensed milk and nothing else, there was nothing to do but believe it and to record it in his memoranda as the first case of beri-beri acquired other than by maternal feeding. The child died. A few days later the same physician went to visit a child in the contiguous house who was nursed by the mother and was attacked also by beri-beri. Upon hearing this diagnosis the mother exclaimed: "Therefore the sickness of my child is the same as the one that killed the child of my neighbour!" "How do you know it, madam?" asked the doctor. "Why not, since I gave my breast to that child twice one night when it was left to my care?"

It is hard to believe that vitamin B_1 deficiency could be transmitted by nursing the infant twice only, just as it is hard to explain why infants brought up on rice flour, which is deficient in vitamin B_1, do not present symptoms similar to those of infantile beri-beri. These facts, in conjunction with my other observations, convinced me that in infantile beri-beri the symptoms are due to the presence of toxic substances rather than to vitamin B_1 deficiency alone.

To prove my conviction I undertook a series of chemical analyses on normal and beri-beric milk as well as their comparative estimation of vitamin B_1 content.

In the middle of my investigations I came across the reports from the Tohoku Imperial University at Sendai (Dept. of Paediatrics), where in the last decade extensive studies have been undertaken on the milk of avitaminotic women. The results of these studies were that not only has its toxicity been proved, but a toxic substance has been isolated and in addition an easy method for identification of toxic milk has been discovered and reported.

Toxic milk is identified by means of the peroxidase reaction. Peroxidase is an enzyme found in plants and in the blood and milk of human beings and animals. The reaction is based on the oxidation of substances of a phenolic nature to coloured compounds by a peroxide in the presence of the ferment peroxidase, which catalyses the reaction.

As this ferment is destroyed by heat, the reaction has been used in dairy science to differentiate between pasteurised and raw milk. The reagents used for cow's milk were not sufficiently sensitive for application to human milk until Professor Arakawa, in 1930, modified them. In examining human milk he found that while a positive reaction was given in most cases, there was a group of women whose milk was peroxidase negative. He suspected some connection between a negative peroxidase reaction and maternal B_1 avitaminosis, and in consequence he administered to such women large doses of this vitamin, with the result that within a few days they commenced to secrete peroxidase positive milk. The results of animal experiments by K. Zusuki ond T. Arakawa (1930) have proved definitely that the avitaminotic organism produces peroxidase negative milk and that, in such cases, the peroxidase negativeness of the milk is the first sign of avitaminois.

Further studies have shown that a peroxidase negative milk is specific for B_1 avitaminosis provided the following conditions are excluded :—

(1) The puerperium. (Y. Uga, 1935).

(2) Menstruation. (Arakawa & Abe, 1930 (A), Matsuda (1932) et al).

(3 Pregnancy. (M. Yamagishi, 1935).

(4) Syphilis in the mother. (Arakawa & Abe, 1930 (B), Matsuda, 1931, M. Ishiu, 1935, et al).

In the last case the peroxidase negativeness is explained by dysfunction of the liver and the milk becomes peroxidase positive by antiluetic treatment alone.

By mixing peroxidase positive with peroxidase negative milk one of the authors (Takamatsu, 1934) observed that instead of a weak positive reaction a complete negative was obtained. Thus the peroxidase reaction indicates not the presence or absence of this ferment but the following formula:

$$\textit{Peroxidase reaction} = \frac{\textit{Peroxidase content}}{\textit{Inhibiting substance or substances.}}$$

The inhibiting substances in avitaminotic women disappear after administration of vitamin B_1.

With the exception of syphilis, the other known causes of a peroxidase negative reaction can be ascertained by simple enquiry, hence the reaction provides a method of considerable diagnostic value and is, consequently, in daily use in Japan.

Prompted by the statements of several Japanese paediatricians that the milk of avitaminotic mothers is toxic and to prove its toxicity Asakura (1932) undertook a series of experiments, two of which will be related here: he divided a number of mice which were fed on a vitamin B_1-free diet into two groups. Into the first group he injected daily peroxidase positive milk: of 10 mice one died; into the second group he injected peroxidase negative milk; all the 7 mice thus treated died within 7 days. To prove that death of the mice was not due to vitamin B_1 deficiency, he and one of his co-workers (Asakura & Ohsako, 1933) undertook another experiment; to the first group of mice fed on vitamin B_1-free food previously autoclaved (i.e. with vitamin B_1 destroyed) peroxidase positive milk and into the second group peroxidase negative milk was injected, with the result that the mice of the first group remained alive whereas all the mice of the second group died within 5 days.

In 1934, Takamatsu succeeded in extracting the toxic substance from peroxidase negative milk. This substance, which he was unable to find in peroxidase positive milk, is similar to methyl-glyoxal and is referred to as methyl-gloxal-like substance.

Methyl-glyoxal-like substance and methyl-glyoxal itself both cause death in experimental animals with identical pathological findings, for example cardiac enlargement. Both substances also when added

to peroxidase positive milk causes it to become peroxidase negative. (Takamatsu, 1935).

Methyl-glyoxal-like substance which is the inhibiting factor in the peroxidase negative milk, disappears within a few days after administration of vitamin B_1 to lactating women.

Since Takamatsu's work methyl-glyoxal-like substance has been isolated by a number of other investigators; amongst them Orimo (1939), who identified it in large amounts in the urine of lactating women whose milk was peroxidase negative. Furthermore, this methyl-glyoxal-like substance disappeared from the urine after administration of vitamin B_1. Another worker, S. Sato (1939), after a number of analysis came to the conclusion that methyl-glyoxal-like substance consisted largely of methyl-glyoxal itself.

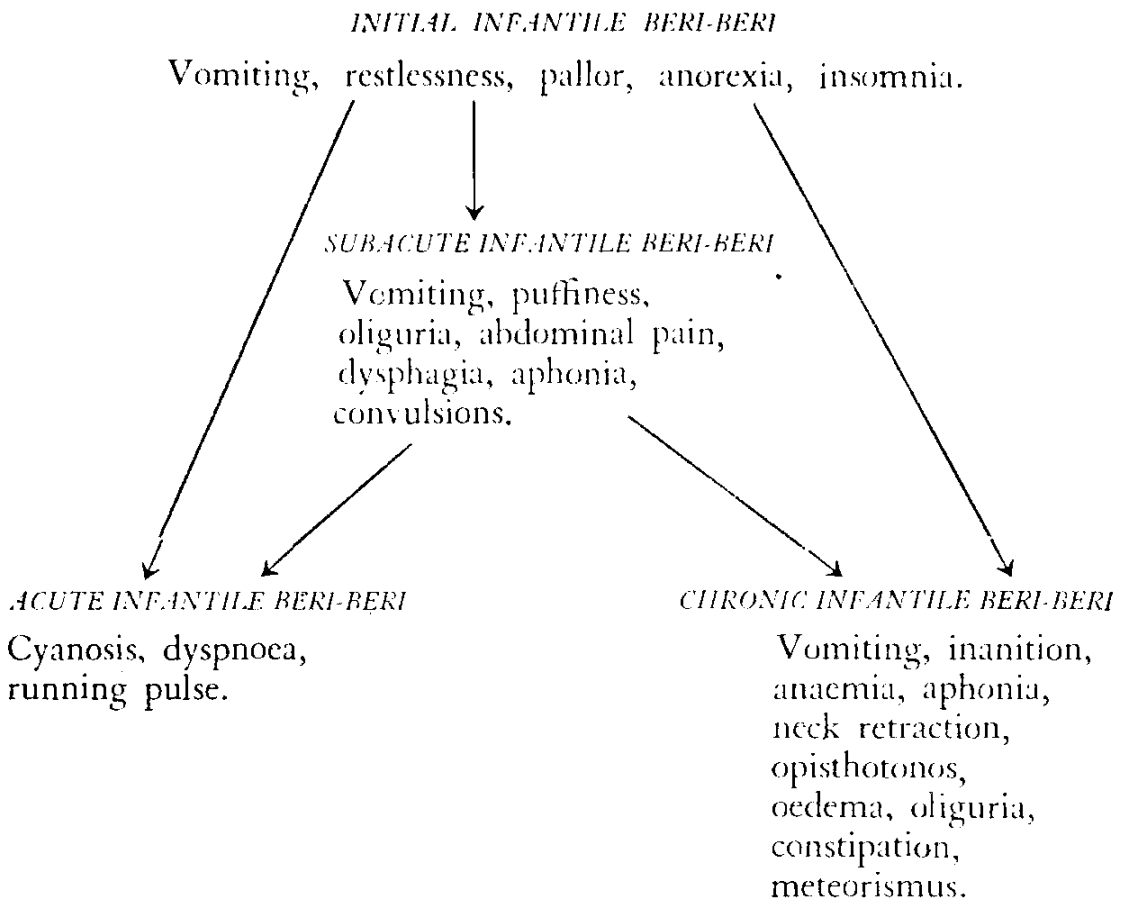
Thus the milk from avitaminotic women has been proven to be toxic as well as vitamin deficient.

It appears therefore that the original authors on infantile beri-beri were right when they regarded this disease as an intoxication. However, the cause is not the external toxins in the diet, but the products of a disordered maternal carbohydrate metabolism.

After ingestion of toxic milk, it is to be assumed that the infantile organism tries to get rid of toxic substances partly by excretion in the urine and possibly in the faeces, but mostly by their further oxidation to non-toxic end products, provided of course, vitamin B_1 is available. As every infant born alive will probably have a reserve, however small, of this vitamin, the toxic action of methyl-glyoxal-like substance is delayed until this reserve is depleted. The toxic action is, however, immediate when the organism is already avitaminotic. On this basis, the case from Guerrero and Quintos' monograph cited earlier in this paper can be explained; this five month old child brought up, since birth, on condensed milk, which, in the dilution given to infants is vitamin B_1 deficient, was already avitaminotic.

After several months of investigation at the infant welfare centre it was found that 18% of the infants on first admission showed clinical signs of beri-beri; consequently the incidence of this disease in the list of diseases in order of frequency was recorded immediately after respiratory and skin disorders.

According to symptoms and the course I divided infantile beri-beri into the following groups:



As can be seen from this diagram, the most common symptom in all stages of infantile beri-beri is vomiting, which is one of the earliest symptoms of an intoxication.

Infants in the initial stage of infantile beri-beri can be recognised sometimes by their appearance :—they are overweight, pale and flabby—a picture similar to that of status lymphaticus. The transition into the acute stage is either sudden or via the subacute stage, in the latter case the cyanosis of the extremeties and around the mouth is a sign of imminent danger.

In the subacute stage puffiness of the face and oliguria is met with in a certain proportion of cases, but in contradistinction to nephritis albumin is absent from the urine and a profuse excretion of urine follows administration of vitamin B_1.

The picture of infants in the acute stage (which corresponds to fulminating adult beri-beri) is similar to that of a cardiac attack or

broncho-pneumonia, the latter being excluded by the fact that the temperature is normal or even subnormal.

The most marked symptom in chronic infantile beri-beri is inanition, which is due to inability to assimilate food owing to depression of gastric and pancreatic secretion, accompanied by reduced enzymatic activity (Farmer & Redenbaugh, 1925; Sure, Kirk & Buchanan, 1935).

Mild cases of chronic beri-beri result in arrest of growth; more severe cases in loss of weight, often ending in marasmus. Symptoms of chronic infantile beri-beri may persist for weeks or months, even after cessation of maternal feeding, especially if artificial feeding is used with foods like rice-flour or condensed milk which are deficient in vitamin B_1. It is important to note, however, that not all marasmic infants with oedema are suffering from chronic beri-beri. Oedema as a result of inanition may appear in every wasting disease.

Infantile beri-beri is often complicated by other diseases; Hirota (1888) reports that sixteen out of his early thirty cases were complicated with intercurrent diseases such as bronchitis, broncho-pneumonia and intestinal catarrh.

The severity of symptoms in infantile beri-beri depends on the amount of toxic substances ingested by the infants: firstly from the amount of toxic milk ingested and secondly from the concentration of toxic substances in it. With the advance of maternal avitaminosis, milk secretion diminishes and eventually stops entirely. Women with advanced avitaminosis and with manifest signs of beri-beri secrete milk which is greater in toxicity but much smaller in quantity than those with early avitaminosis. This is the explanation why overfed babies are attacked by acute infantile beri-beri more often than those normally fed, whereas underfed babies suffer usually from the subacute or chronic type (in the latter case the infants are always on mixed feeding). The amount of milk secreted by women can be found out by test feeds or by pumping and measuring it at regular intervals, whereas the toxicity can be estimated by the peroxidase reaction.

The intensity of this reaction is inversely proportional to the amount of methyl-glyoxal-like substance; in acute cases of infantile beri-beri I often found the reaction chemically weakly positive (= clinically negative), whereas in chronic cases it is almost always completely negative.

In view of the fact that in chronic cases of infantile beri-beri the maternal milk secretion is greatly diminished (often ½-1 oz. in 4 hourly intervals) I advised in such cases that the child be weaned immediately.

The mortality in infantile beri-beri is extremely high; according to the Manila Health Authorities, the mortality rate from this disease was, before introduction of extract of tiki-tiki, 93.66%!

Death may occur in any stage of the disease, and most unexpectedly in infants in the initial stage, who show only one symptom, vomiting of not alarming quantities of milk and mucus (the so-called infantile pre-beri-beri of the Japanese authors). Acute infantile beri-beri if untreated always ends fatally, sometimes, however, only after the second or third attack. Death in chronic beri-beri is mostly due to such complications as broncho-pneumonia, tuberculosis and gastro-enteritis.

Infantile beri-beri begins usually between the first and third months of the infant's life (between 30-100 days) and consequently deaths in the initial and acute stages occur during this period whereas deaths from subacute and chronic beri-beri occur later. The occurrence of this time limit can be easily explained as an average of one month is required for depletion of the infants' vitamin reserve. On the other hand, if women do not become avitaminotic during the last few months of pregnancy and first two months of lactation, they are less likely to become avitaminotic after that time.

According to Miura (1898) and Andrews (1912) pathological findings in infants who had died of beri-beri were (1) cardiac dilatation and hypertrophy, (2) congestion of the viscera, (3) slight effusions in the pericardial, pleural and abdominal cavities, (4) absence of any other findings to account for the death. This applies, however, only in cases of "pure" beri-beri, in complicated cases the picture may be entirely obscured.

As I mentioned earlier in this paper, I found, according to clinical symptoms, that 18% of infants on their first visit to the Centre were suffering from infantile beri-beri of various degrees. To prove these clinical findings I examined the milk of every nursing mother, on her first visit to the Centre, for its peroxidase reaction.

Of 129 women who entered during two weeks only 87 were able to nurse their babies; out of 42 non-nursing mothers a great proportion complained of lack of secretion and upon enquiry confirmed that they had either numbness, weakness or oedema of the feet. Two of the mothers ceased to nurse because their milk was "not good," as all of their breastfed babies died.

Four of the nursing mothers had to be eliminated from the count as 3 of them were in the puerperium and one had a positive Kahn test for syphilis. Out of the remaining 83 nursing mothers 32 were secreting peroxidase negative, i.e. toxic milk.

The result of these examinations fully confirmed my statement founded on clinical diagnosis alone: it means that 38.5% of nursing mothers (out of 83), or 24.8% of the total number (out of 129) on their first visit to the Centre secreted peroxidase negative milk. Consequently it is to be expected that approximately the same percentage

of infants is apt to develop infantile beri-beri. Actually out of 32 infants fed on peroxidase negative milk 26, i.e. 81%, showed various degrees of intoxication:

Initial stage (including infantile pre-beri-beri).....	19
Acute stage	3
Subacute stage	1
Chronic stage	3
Total	26

Of 32 mothers secreting peroxidase negative milk 14 complained of numbness, weakness or oedema of the legs: however it happens sometimes, that women with no subjective or objective symptoms of avitaminosis on their first visit, complain of them some time afterwards. Hirota (1898) mentioned three cases in which manifestation of beri-beri in the mother were retarded fourteen, twenty-nine and thirty-two days after its appearance in the infant. Albert (1931) observed the beginning symptoms of beri-beri in mothers some time after their children died of infantile beri-beri.

The history of previous pregnancies in women secreting peroxidase negative milk is similar to that of syphilitic women, but rather in the reverse order: usually the first living child is followed by deaths in infancy, abortions, miscarriages and still-births.

Herewith are some of the examples (in all these cases Kahn test was negative):—

Card No.	*Age of the Mother*	*No. of Pregnancies*	*No. of Abortions, Miscarriages or Stillbirths*	*Deaths in infancy (under 1 year)*	*Deaths over 1 year*
570/40	32	5	1	2	1
671/40	21	4	1	1	—
674/40	25	4	1	1	—

As can be seen from this table, three women with an average age of 26 had, out of 13 pregnancies, only 5 children alive (one of them was brought to the Centre suffering from infantile beri-beri).

The detoxication of peroxidase negative milk follows within a few days after administration of vitamin B_1, the amount of vitamin given should be not less than 500 I.U. per diem.

Underneath is the record of the peroxidase reaction of two cases:—

Card No.	*Age of Infant*	*Diagnosis*	*Date & Peroxidase Reaction*	*Date & Peroxidase Reaction*	*Date & Peroxidase Reaction*
661/40	2.6/30	Infantile beri-beri	15.4.40 0′ 1′ 5′ — — — Vibixin tabs: 6 daily given from that date	17.4.40 0′ 1′ 5′ — ± +	23.4.40 0′ 1′ 5′ + + + + +
671/40	17/30	Infantile beri-beri	16.4.40 0′ 1′ 5′ — — — Vibixin tabs. 6 daily given from that date	20.4.40 0′ 1′ 5′ — — — Anti-beri-beri tabs: 6 daily, given from that date	23.4.40 0′ 1′ 5′ — ± +

In cases when mothers secrete peroxidase negative milk, infants should be given vitamin B_1 (50-500 I.U. per diem, according to the severity of the symptoms) until it has been found, by repeated tests that maternal milk is persistently peroxidase positive.

It is of interest that the average family income of women secreting peroxidase negative milk is H.K.$18.00 and the maximum H.K.$60.00 per month.

As already mentioned, vitamin B_1 is essential for complete oxidation of carbohydrates; it would follow that persons whose diet consists mostly of carbohydrates require more of this vitamin than those whose diet is mixed. In countries where the staple food is polished rice, vitamin B_1 requirements of the body must be derived from supplementary food. If the supplementary diet is quantitatively insufficient or deficient in vitamin B_1, adult beri-beri must result as a consequence, for example as in Japan, the Philippines, Indo-China, Malaya, India, South China and the Dutch East Indies.

In pregnancy and lactation the requirements are about 3-5 times greater (Macy, 1927) and consequently in places where adult beri-beri is present, this disease occurs more frequently among pregnant and lactating women. Maternal beri-beri or avitaminosis must result in infantile beri-beri with its high mortality rate.

Hong Kong, without being an exception, has the situation aggravated by the fact that people of the poorer classes are victims of food

customs and prejudices, amongst them one which regards fruit and vegetables as "cooling" food because they cause "Fung" (wind). Consequently they believe that such food should be enjoyed in perfect health only and be abstained from when in sickness, invariably during the first month and often during the whole time of lactation.

Inquiries made of 14 women (new entrants at the Centre) revealed the fact that only two of them were eating vegetables and fruit unrestricted and the explanations given are most interesting:

Card No. 607/40. Male infant of 1.15/30. Mother does not eat vegetables and fruit because baby is too young.

Card No. 608/40. Male infant of 1.23/30. Mother does not eat vegetables and fruit beacuse she is afraid baby may get green diarrhoea.

Card No. 609/40. Female infant of 2/12. Mother does not eat fruit and vegetables because she is on a special diet on account of breast abcess.

Card No. 610/40. Male infant of 3.2/30. Mother does not eat fruit and vegetables because people told her it was not good for baby.

Card No. 611/40. Female infant of 1.16/30. Mother eats vegetables but very little, because they are "cooling."

Card No. 612/46. Female infant of 3.20/30. Mother partakes freely of fruit and vegetables.

Card No. 613/40. Male infant 3.9/30. Mother does not eat vegetables because baby vomits after she eats them.

Card No. 614/40. Female infant of 5.15/30. Mother does not eat vegetables because she has "weak legs" (literal Chinese translation for beri-beri). She stopped nursing a few months ago because of lack of secretion.

Card No. 615/40. Male infant of 12/365. Mother does not eat vegetables because she has "weak legs" and oedema. Stopped nursing through lack of secretion.

Card No. 616/40. Female infant of 4.6/30. Mother does not eat vegetables because baby has "wind" and is vomiting.

Card No. 617/40. Male infant of 12/365. Mother does not eat vegetables because it is too early after delivery.

Card No. 618/40. Male infant of 1.5/30. Mother eats fruit and vegetables.

Card No. 619/40. Male infant of 2.9/30. Mother does not eat vegetables because she has cough and vegetables are "cooling."

Card No. 620/40. Male infant of 1.16/30. Mother does not eat vegetables and fruit because baby could not stand them. They are "cooling."

From such enquiries I gained the impression that women with a family income of H.K.$100.00 per month adhere rarely to such food prejudices; however, the explanation is, in my opinion, the higher standard of education. Another impression I received was that mothers of female infants are less "careful" about "cooling" food in their diet. This fact, and the fact that male infants tend to be overfed by their mothers, explains why male infants are more affected by infantile beri-beri than the females.

After having completed my investigations on infantile beri-beri I tried to substantiate my findings by observation of people of the lower strata of society and I was amply rewarded.

Owing to the high infantile mortality in Hong Kong (343 per mille in 1938) the survival of infants, especially over the first 100 days of life, is regarded by these people as a game of chance dependent entirely upon the benevolence of evil spirits. These spirits from whom mothers protect their infants with dozens of talismans and by disguising them as animals, are believed to lurk around and snatch the babies, especially boys, at any unguarded hour.

Upon enquiring about symptoms of disease prior to death, I was usually told that the infants died suddenly and in perfect health. However the mother often admitted that vomiting was present for a few days or that the infants were restless and cried at night. As can be seen, the above-mentioned symptoms would be consistent with those of the initial stage of beri-beri. In some cases I was told that their infants died of "Fung Taam" and upon enquiry I found that this disease is the dreaded infantile scourge, in which babies become suddenly cyanotic and dyspnoeic and die within a few hours. The translation of "Fung Taam" is "Wind-mucus" and the people explain the symptoms by "Wind driving mucus into baby's throat and thus causing suffocation." It seems that to "Fung" (Wind) are attributed most of the symptoms of adult and infantile beri-beri and hence the aversion to "cooling" food. In the case of lactating women, they firmly believe that they can transmit "Fung" through their milk.

Undoubtedly "Fung Taam" is nothing else but acute infantile beri-beri and is identical with Taon in the Philippines.

Chronic infantile beri-beri associated with marasmus is called by the people "Malau gam" or monkey disease.

SUMMARY.

1. 18% of the infants brought to an Infant Welfare Centre were suffering from a disease, which was identified as infantile beri-beri.

2. Previous workers have demonstrated that milk secreted by B_1 avitaminotic women is peroxidase negative. Of 83 nursing mothers examined, at the Centre 32, i.e. 38.5%, were secreting peroxidase negative milk. Of the 32 women whose milk was peroxidase negative, 14 i.e. about 44%, were complaining of symptoms suggestive of adult beri-beri.

3. 81% of infants, breast-fed by mothers whose milk was peroxidase negative, were found to be showing signs of infantile beri-beri of varying severity.

4. Animal experiments by investigators whose work has already been cited, have demonstrated that the milk of B_1 avitaminotic women is not only deficient in vitamin B_1 but is also actively toxic.

5. From the milk and urine of B_1 avitaminotic women, a substance or substances resembling methyl-glyoxal (an intermediate toxic product of carbohydrate metabolism) have been isolated by Takamatsu, Orima and others. S. Sato has shown that the above-mentioned substance consists, in actual fact, chiefly of methyl-glyoxal itself.

ACKNOWLEDGMENTS.

I wish to express my thanks to Dr. E. Q. Lim of the University of Hong Kong, for his valued help in estimating B.B.S.; to Mr. K. T. Liu, also of the University of Hong Kong, for his work in estimating vitamin B_1; to Dr. Howard Smith, Chief Quarantine Officer in Manila, for supplying me with literature on infantile beri-beri to the Bureau of Science, Manila, for supplying extract of tiki tiki and instructions concerning its preparation; to the Henry Lester Institute for Medical Research, Shanghai, for supplying references and above all to my husband, Dr. J. P. Fehily, without whose faith and encouragement this work would not have been possible.

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TWO CASES OF DISTURBANCE OF MOTILITY OF THE UPPER OESOPHAGUS,

by

Dr. E. Vio,

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A report on the following two cases may be of interest, especially from the radiological viewpoint.

CASE I.

An Indian male aged 32 was suddenly seized by violent giddiness and vomiting. These symptoms continued unabated for three days, during which he was absolutely unable to swallow, any attempt being followed immediately by the bringing up of small amounts of blood. On examination there was only some ataxia of the left upper and lower extremities and nystagmus. No fever. A barium paste swallow (Figures 1 and 2) showed filling of pharynx down to the pyriform recesses without active movement; in other words, a paralysis of deglutition. Some barium passed into the oesophagus and some into the trachea. This finding was constant on repeated observations. A sound could easily be passed into the stomach, which contained some partly digested blood. The patient died on the fourth day. Autopsy showed a recent endocarditis which had not been detected clinically and an embolism in the left inferior posterior cerebellar artery. In such cases (Wallenberg's syndrome) there is always some partial involvement of the medulla and a paralysis of the pharyngeal plexus may occur.

CASE II.

A woman aged seventy inadvertently swallowed a big piece of meat. Immediately afterwards she felt that this remained lodged in the gullet producing inability to swallow and unsuccessful attempts to vomit. The condition lasted for one day. A sound could be passed but there was no relief after it was withdrawn. Any attempt to swallow was followed by a severe cough. X-Ray examination (Figure 3) showed that immediately below the level of the pyriform recesses there was a narrow but smooth canal which led into a saccular dilatation, showing several filling defects due to contents. At first this was thought to be a diverticulum. It was soon noticed however, that it was exactly in the line of the oesophagus and that occasionally a thin drop of barium passed on from the lower posterior part of the dilatation exactly along the line of the narrow upper passage which led into it. The whole thing was therefore a pseudodiverticulum of the upper oesophagus itself. Most of the barium passed into the trachea down to the bifurcation. Subsequent observation showed that the size and

SKIAGRAM OF CASE I.

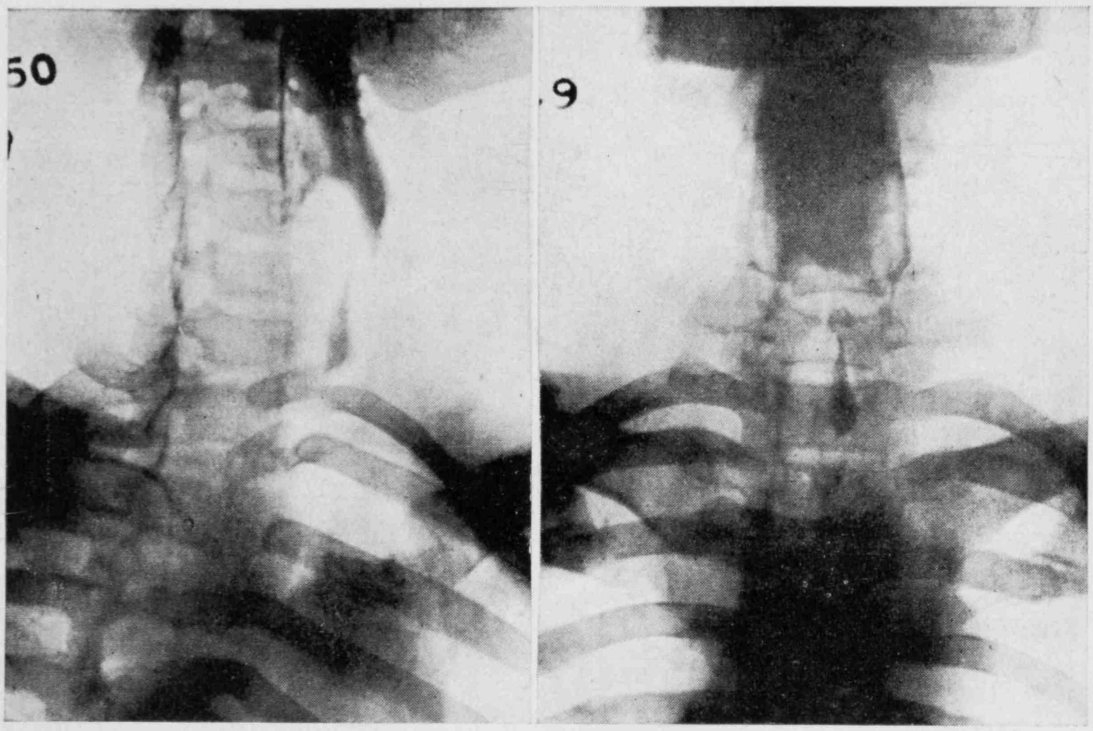

Fig. 1. *Fig. 2.*

To show filling of oesophagus as low as pyriform recesses.

SKIAGRAM OF CASE II.

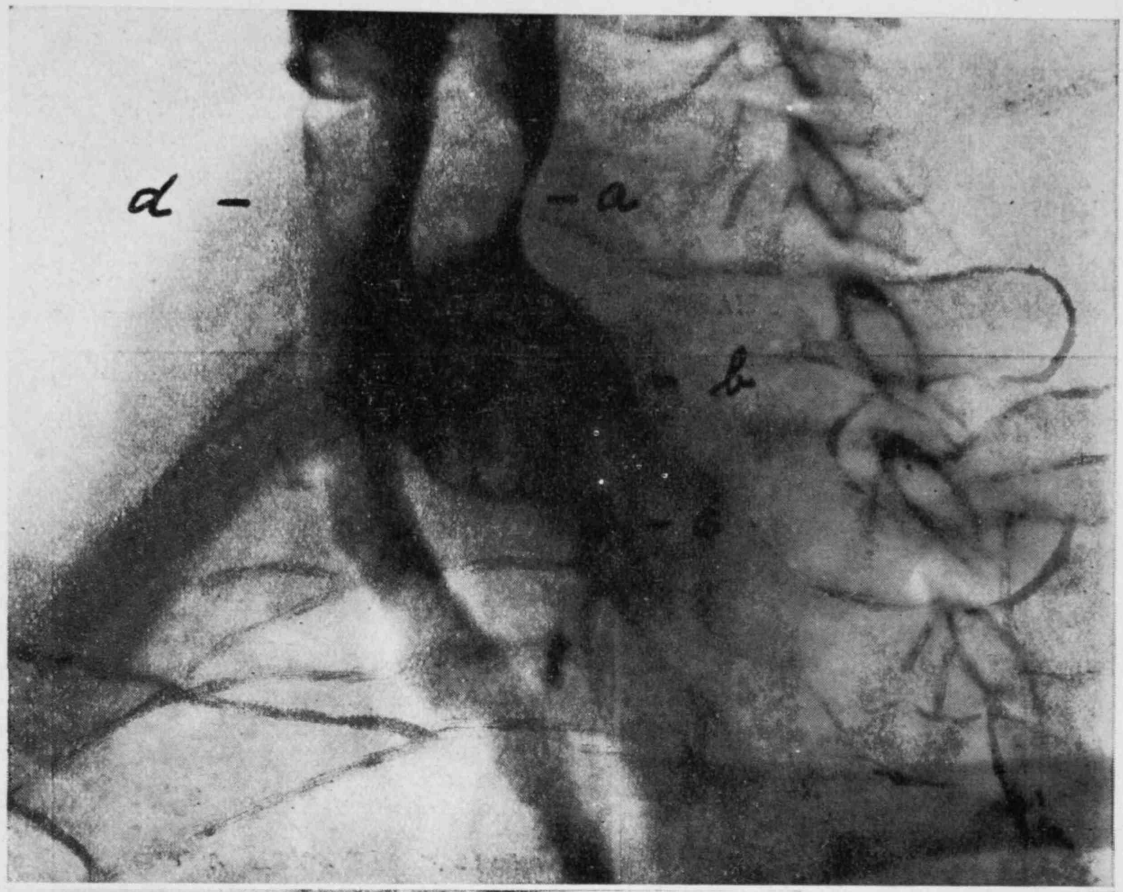

Fig. 3.

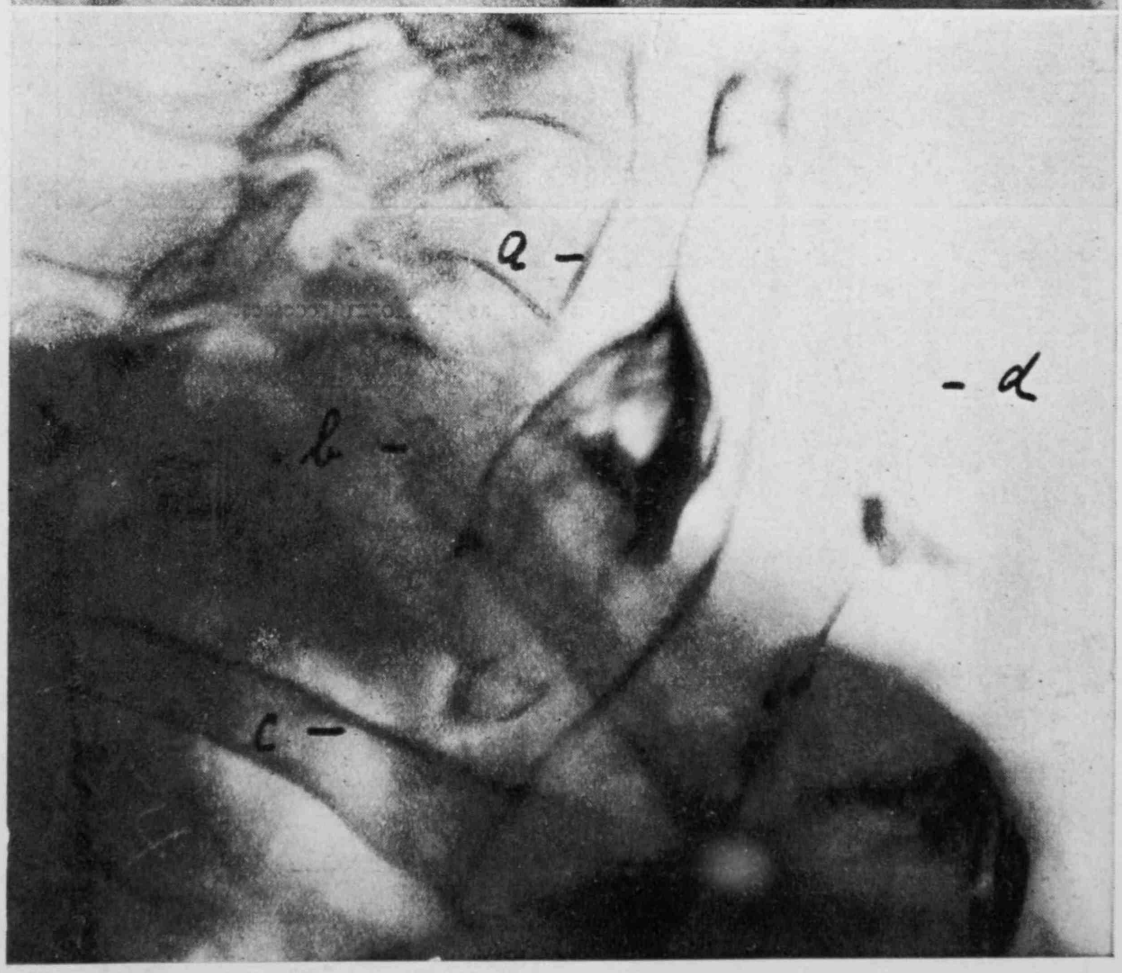

Fig. 4.

Fig. 3. Left semi-lateral; a—upper spasm, b—pseudodiverticulum, c—lower spasm, d—trachea.

Fig 4. Right semi-lateral; a, b, c, d—the same as in Fig. 3.

shape of the pseudodiverticulum were not constant, sometimes it was round, and sometimes elongated (Figure 4) whereas the two narrow passages above and below remained constant. A diagnosis of double spasm of the upper oesophagus with formation of a pseudodiverticulum between them, probably due to a foreign body, was made. A few hours later the patient brought up a piece of meat and a barium swallow given immediately afterwards showed a perfectly normal oesophagus without any indication of diverticula. The patient has remained well ever since. The mechanism which led to these unusual radiological finding may have been the following:

As soon as the piece of meat entered the upper oesophagus it was stopped by a double spasm which prevented it from being swallowed further or brought up. A sound could easily force the spasm, without relieving it so that the piece of meat had to remain where it was as soon as the sound was withdrawn. Eventually the upper spasm was overcome and the foreign body could be ejected. Such double spasms are similar to those which take place in the intestine in cases of obstruction due to gall-stones; their occurrence is well known, but I believe that they are not often demonstrated radiologically.

CLINICAL REPORT OF TWO CASES OF BLACKWATER FEVER FROM CHUN WAN, NEW TERRITORIES. (HONG KONG),

by

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The extreme rarity of blackwater fever in Hong Kong, even among the malaria infested population of the New Territories, justifies the report of the following two cases admitted into this hospital within a period of less than three weeks.

CASE REPORT, No. I.

P. C. K. Chinese male, age 21, was admitted into this hospital on April 16, 1940 with history of rigor and fever two nights previous to admission and the passage of 'bloody urine' for the last 12 hours. Patient was an immigrant from Shanghai and for the last one year had been employed as a mechanic at a factory at Chun Wan, New Territories.

Past History—Patient had had eight attacks of 'malaria' since September 1939. He took quinine for each of these attacks and had never noticed any abnormal colouration of his urine.

Present History—On the night of April 14, 1940 patient had an attack of rigor, fever and sweating. He was given quinine and the next morning he carried on his usual work. But in the afternoon he experienced great prostration and severe frontal haedache when he had another attack of rigor, fever and sweating accompanied by vomiting. The vomiting soon became so severe that he could not even take fluids. On the same night patient noticed that his urine was 'bloody' and there was increased frequency of micturition. There were also increased salivation and a feeling of distension in the abdomen. He was admitted the next morning into this hospital and diagnosed as a case of blackwater fever.

Physical Examination—Patient appeared anaemic and prostrated. The pallor of the lips and skin was so marked that it reminded one of a moribund case of ruptured ectopic gestation Sclerae: slightly icteric. Temperature 97.8 F. Pulse Rate 120/min. Respiration Rate 28/min. Liver: not enlarged. Spleen: 1½cm. below costal margin.

Blood Examination—

R.B.C.	2,400,000
W.B.C.	8,000
Hb% (Tallqvist)	40%

Differential Count:—

Polymorph:	78%
Lymphocytes	21%
Eosinophils	1%

Blood smear :—Plasmodium falciparum present.
(Merozoites—ring forms, intracorpuscular and marginal).

Blood Wasserman Reaction :—negative.

Urine Examination—

Port wine colour. Acid. Specific gravity—1018.

Blood—postive.

Albumin—trace.

Sugar—negative.

Bile—negative.

Microscopical examination :—No red blood corpuscles, a few epithelial cells, amorphous urates, no casts.

Spectroscopic examination showed the presence of oxyhaemoglobin and methaemoglobin.

Treatment and Progress—

The patient was given atebrin gr. 1½ three times a day after food for five days and an alkaline mixture containing potassium citrate gr. 30 and sodium bicarbonate gr. 15 four hourly for one week. Continuous rectal saline was given for the first 48 hours, during which period patient received 9½ pints. His urine was clear of blood about 40 hours after admission and there was never any suppression of urine. He was discharged on April 28, 1940 after 12 days in hospital.

CASE REPORT, No. II.

S. K. S. Chinese boy, age 17 was admitted into this hospital on May 3, 1940 with history of passing 'red urine' for 12 hours following quinine injection. He was a native of Shun Tack, a city on the outskirts of Canton and had been employed as a coolie in a factory at Chun Wan in the New Territories for eight months.

Past History—Patient had ten attacks of 'malaria' in the last six months for each of which he was given quinine and recovered. In one of these attacks which occurred about one month ago he noticed he passed 'red urine' for about six hours. There were no other alarming symptoms and the attack passed off by itself without any special treatment.

Present History—Patient was given an intramuscular injection of quinine, of unknown dosage, on May 2, 1940 at about 9 p.m. for 'prophylactic purposes' in the town, though he had been free from attacks of rigor and fever for 10 days. About one hour after injection, patient felt dizzy and cold and complained

of dimness of vision. He then had an attack of rigor, fever and sweating accompanied by vomiting, severe frontal headache and prostration. Shortly afterwards he noticed his urine was 'blood red' in colour. He was admitted the next morning into this hospital as a case of blackwaer fever.

Physical Examination—Patient appeared sick and prostrated. The pallor of the lips and face was not unlike a neglected case of ruptured ectopic gestation. Temperature 104.2 F. Pulse rate 124/min. Respiration Rate 20/min. Liver: not enlarged. Spleen: 2 cm. below costal margin. Sclerae:—slightly icteric.

Blood Examination—May 3, 1940.

R.B.C. 2,900,000 per cu. mm.
W.B.C. 12,000 per cu. mm.
Hb% (Tallqvist) 45%

Differential Count:—
Polymorph: 63%
Lymphocytes 35%
Monocyte 1%
Eosinophils 1%

Blood smear examination showed the presence of Plasmodium falciparum and Plasmodium vivax. (Merozoites). Some of the red cells were enlarged and had Schüffner's dots.

Urine Examination—

Dark red. Acid. Specific gravity—1014.

Blood—positive (benzidine test).

Albumin—trace.

Bile—negative.

Sugar—negative.

Microscopic examination showed the presence of a few crenated red blood corpuscles, epithelial cells, and amorphous urates.

Spectroscopic examination showed the absorption bands of oxyhaemoglobin and methaemoglobin.

Treatment and Progress—

The patient was given atebrin gr. 1½ three times a day after food for five days and an alkaline mixture containing potassium citrate gr. 30 and potassium bicarbonate gr. 20 four hourly for one week. 60 c.c. of 50% glucose intravenously were also given on admission. Continuous rectal saline was administered for the first 48 hours, during which period patient received 8 pints. Other symptomatic treatment included iron and liver extract. On the morning of May 5, 1940, that is, the next day after admission, the temperature was normal, the urine clear of blood, patient looked well and felt

comfortable. He was discharged on May 14, 1940, after nine days in hospital.

May 14, 1940.

R.B.C. 3,140,000 per cu. mm.
W.B.C. 11,200 per cu. mm.
Hb% 50%

Differential Count :—
Polymorph : 54%
Lymphocytes 45%
Monocytes 1%

Blood smear examination showed enlargement of some of the red cells with the presence of Schüffner's dots, but no parasites were seen.

COMMENTS.

Both our patients were immigrants and not natives of the district and both had had repeated attacks of malaria in a district where malignant tertian infection is endemic and rampant. It is interesting to recall that Chiu (1939) stressed the point that his case of blackwater fever also occurred in an immigrant, whereas Seaton (1935) working in Hainan reported 7 cases belonging to two native families. Both our patients had had inadequate and irregular quinine treatment, and in both malarial parasites were found in the blood smears on admission to hospital. It is to be noted that malarial parasites were not found in Chiu and Seaton's cases.

In the first case the haemoglobinuria occurred about 4 hours after the oral administration of quinine; in the second case it occurred one hour after an intramuscular injection of quinine. There is a similar time relationship between quinine administration and haemoglobinuria in Chiu's case and in one of Seaton's. In both our cases severe frontal headache, persistent vomiting and marked prostration were prominent features. It is noteworthy that the second patient gave a history of passing " red urine " one month previous to admission, thus illustrating the recurrent tendency of the disease. In view of the recent occurrence of these two cases of blackwater fever, a condition which is considered rare in Hong Kong, special care is urged in prescribing quinine to patients suffering from chronic malaria, particularly among immigrants. Attention is drawn also to the necessity of taking every step to ensure the adequate quinine treatment of all malarial patients controlled, where possible, by blood smear examinations.

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HUMAN BLACK TONGUE TREATED WITH NICOTINIC ACID,

by

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Human black tongue is an uncommon condition the main features of which are a hypertrophy of the filiform papillae of the dorsum of the tongue associated with pigmentation which varies from greyish brown to black. Its onset is usually insidious, it is not as a rule attributable to any specific cause, it is asymptomatic and is characterised by chronicity. The condition may persist for years and may be resistant to all forms of treatment.

Swabs taken from the affected papillae usually yield a luxuriant and mixed growth of organisms as the failure of normal cellular exfoliation affords opportunity for the growth of bacteria in the abnormal papillary tufts. The black pigmentation characteristic of the condition is thought to be due to the growth of a pigment—producing Penicillium such as Mucor niger. The aetiology of the condition is unknown. Some cases have been ascribed to general causes such as gastritis with or without hyperacidity, others to local causes such as the use of irritating mouth washes or lotions containing oxidising agents such as sodium perborate or hydrogen peroxide. Isolated cases have been attributed to the use of drugs such as silver nitrate and tannic acid, but in many cases it is impossible to find any aetiological factor. As far as is known there is no aetiological connection with canine black tongue.

The case reported here is of interest because the empiric use of nicotinic acid by mouth appeared to bring about a speedy cure of the condition in a patient showing no signs of pellagra or a pre-pellagrous condition.

Mrs. A. J., a European woman of 36, complained in February this year that "the back of her tongue had turned black." She said that this change had come on in the course of the last two or three weeks and she emphatically denied that any symptoms had accompanied it. Her sole reason for consulting a doctor was that the thought of food passing over this "black fur" made her feel nauseated.

On examination the posterior third of the tongue was seen to be thickly coated with a layer of black fur. On closer examination the fur was found to consist of hypertrophied filiform papillae which had turned black. The circumvallate papillae were not involved in this pigmentation. The tongue was not sore or painful. The taking of

swabs from the affected portion showed that the pigment could be partially removed by rubbing, as the swabs came away brownish-black in colour. Direct smears and culture yielded a mixed growth of staphylococci, streptococci and yeasts, but no Penicillium could be isolated.

The patient, apart from her tongue condition, showed no abnormalities. Her colour was good, her mucosae were not pale and her blood picture was normal. The cardiovascular, pulmonary and nervous systems showed no abnormality. Her teeth were in excellent condition and there were no symptoms referable to the gastrointestinal track apart from some loss of appetite since the tongue became black. This was not more than could be accounted for by the nausea induced by the tongue condition. She was not constipated nor had she noted any menstrual irregularity or abnormality. Her urine contained neither albumen nor sugar.

It is worth emphasising that although the patient had been living for several years in the Far East she showed no symptoms whatever of the pre-pellagrous state. There was no trace of perlèche, angular stomatitis, sore tongue or skin involvement and her diet, which was carefully investigated, proved to be a full and well balanced one.

She was reassured about the harmlessness of the condition and a small dose of nicotinic acid, 50 mgm. night and morning by mouth, was ordered for one week. At the same time she was told that there was no known connection between canine black tongue and human black tongue, and it was pointed out that the drug would probably have no effect.

To everyone's surprise the effect was immediate, and within 72 hours of the first dose of nicotinic acid she reported that the tongue was "almost clean." She continued to take the drug in this dosage night and morning for one week, and thereafter 20 mgm. a day for two weeks until she had taken 980 mgm. in all. At this point she had a sharp reaction shortly after taking her morning tablet; she be came flushed and giddy and had severe palpitation for some minutes. Her symptoms rapidly passed off, the drug was discontinued and her tongue has remained normal from that time.

It is interesting to note that the discovery that she had been using a sodium perborate mouth wash for some weeks was only made after nicotinic acid had been given for four days. By this time the tongue condition had practically cleared up, but the perborate mouth wash was nevertheless discontinued, and no other local treatment was ordered.

I am entirely at a loss to account for this response to treatment with nicotinic acid. There was no rationale for the treatment, and

this was carefully explained to the patient beforehand, and yet it seemed to be dramatic in its effectiveness. The picture of mild grades of B_2 deficiency is well known in Hong Kong and classical pellagra is occasionally seen here. It is quite clear that the woman was not suffering from either of these conditions. It is equally clear that for some unknown reason her black tongue responded immediately to treatment with small doses of nicotinic acid.

SUMMARY.

1. A description is given of a case of human black tongue.
2. Treatment with small doses of nicotinic acid by mouth appeared to produce prompt and lasting cure of the condition. No local treatment was employed.
3. The drug produced a mild reaction after 980 mgm. had been taken.

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