

NOTES ON CASES OF FEVER FREQUENTLY CONFUSED WITH TYPHOID AND MALARIA IN THE TROPICS.

By ALDO CASTELLANI, M.D.,

*Director of the Clinic for Tropical Diseases, Colombo (Ceylon).*

EVERY practitioner in Tropical Countries knows how frequently cases of fever occur in which it is impossible to arrive at a definite diagnosis.

Much light has been thrown on the subject of long-continued fevers by the researches of Leishman, Donovan, Manson, Rogers, etc., especially with regard to Kala-azar. Moreover, the work of Wright, Lamb, and others, has shown that some other forms of long-continued tropical fevers represent cases of Malta fever.

Tropical Fevers of short duration have been recently investigated by Rogers, who has defined a very interesting influenza-like type which he names "seven days' fever."

I desire to call attention to yet other forms of fever lasting two to three weeks, or at times much longer, and characterized by the following symptoms: Temperature generally irregular; pulse frequently very slow; spleen not sensibly enlarged; no roseola; slight intestinal symptoms occasionally present; Widal test constantly negative; malarial parasites absent. Such cases, in Ceylon at least, are of frequent occurrence and are generally diagnosed as malaria, or typhoid, or, since I demonstrated the presence of the latter disease in the Island, as paratyphoid<sup>1</sup>.

While admitting that typhoid fever, especially in tropical climates, may run a most atypical clinical course, I am convinced that a certain proportion of the cases referred to are neither typhoid nor paratyphoid,

<sup>1</sup> Four cases of paratyphoid have come under my observation in Ceylon: three were due to *B. paratyphosus* A and one to *B. paratyphosus* B.

*Fever in the Tropics*

and certainly not malaria, though occasionally a malaria infection may be present at the same time.

I give very briefly the history of four such cases—in which a bacteriological investigation was made.

CASE 1. Austrian gentleman, 23 years of age. Was in Ceylon for two months (January and February, 1905), visiting various places in the interior. On returning to Colombo from the hills he began to feel unwell while in the train, experiencing severe frontal headache and slight rheumatoid pains all over the body. He had no shivering, and no intestinal symptoms. In the evening he took his temperature and found it to be 102·4°. Believing that he was suffering from malaria he swallowed a large dose of quinine (20 grs.) which caused very severe ringing of the ears. In the morning the temperature was much lower (99·4°) and the patient, after having taken five grains more of quinine, drove to Mount Lavinia, a place near Colombo. Coming back in the afternoon he complained again of great malaise and headache ; he again took quinine—10 grains. When he asked me the same evening

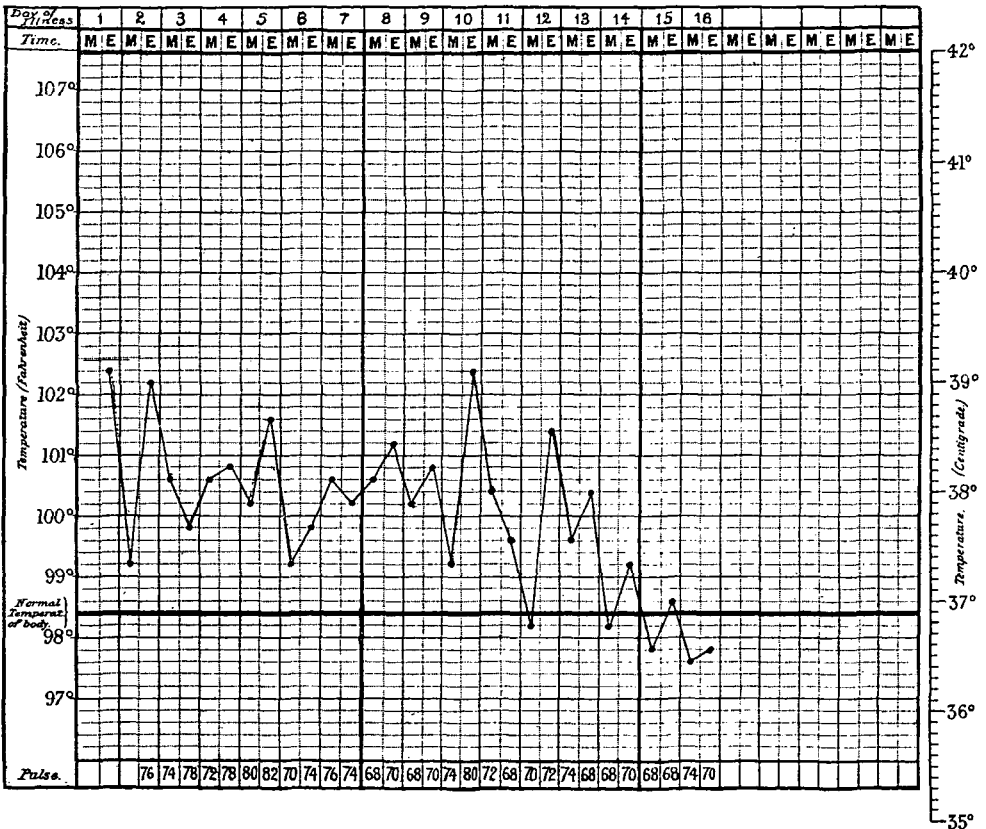


Chart 1.

to examine him his temperature was 102·2°, pulse 76. The tongue was slightly furred ; the spleen could not be felt ; and no roseola spots or any other rash were seen. There was no diarrhoea and the analysis of urine was negative. The fever continued for 12 days longer and was very irregular in its course as shown by temperature chart No 1. The pulse always remained slow ; this want of correspondence between pulse-rate and temperature was observed by me in several other similar cases, though it cannot be said to be a constant symptom. The spleen could never be palpated ; roseolae did not appear ; Widal was negative. As regards intestinal symptoms, there was nothing to be noted with the exception of a tendency to constipation which, however, was never severe. The patient never complained of serious subjective symptoms and the headache left him after the first few days ; his mind always remained clear. He got gradually better and convalescence was rapid.

It may be noted that during convalescence, and also afterwards, the pulse-rate remained about the same viz : 70 to 74 per minute.

CASE 2. Strongly-built man, 50 years of age—a retired officer from the German Army. No previous disease of any kind. Began to feel ill while on board a

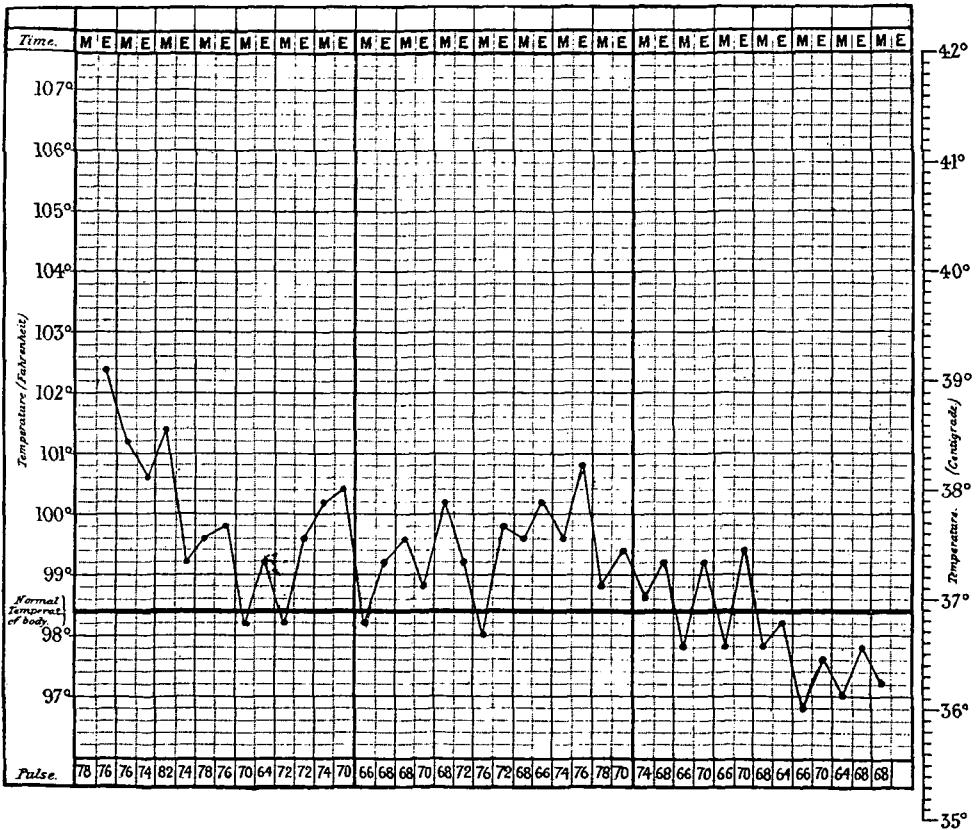


Chart 2.

German steamer during the voyage from Aden to Colombo with malaise, continuous headache, rheumatoid pains all over the body, irregular rises of temperature, slight diarrhoea. He never felt so ill as to have to remain in his cabin. As there was a case of enteric on board, the same disease was suspected in this patient and he was accordingly advised to land at Colombo. During the first three days after landing in Colombo he felt quite well and was getting ready to go up country when suddenly, in the afternoon, his temperature rose to  $103.2^{\circ}$ . There was slight shivering, and severe headache, diarrhoea becoming a prominent symptom, ten or twelve liquid motions being passed in a few hours. I saw the patient in the evening: temperature  $102.4^{\circ}$ , pulse 78; no roseola or any other rash; examination of the chest negative; spleen not enlarged; no pain on palpation of abdomen; the stools which were liquid and yellowish did not contain blood or muco-pus. The fever lasted sixteen days longer and its course was very irregular as shown by temperature chart No. 2. The pulse always remained slow. The spleen could never be palpated and roseola spots never appeared. The diarrhoea lasted for three days only, and the stools never contained blood. The analysis of the urine was negative. Excepting during the first four days the patient did not complain of headache or any serious subjective symptom.

Treatment consisted in the exhibition of the usual intestinal antiseptics and in keeping the patient on liquid diet.

CASE 3. An English civilian, 32 years of age, who had been in the island many years. No previous disease of importance with the exception of two slight attacks of malaria. In the first week of June 1904 he began to feel unwell with lassitude, loss of appetite, and at times feverishness. Being very anxious to go on working, he refused to rest and continued to attend to his duties. When I examined him some days later his temperature was  $103.4^{\circ}$ ; pulse 74 (his pulse rate in health varies from 68 to 72). Spleen could not be felt; no roseola or other rash present. No intestinal symptoms; analysis of urine negative. The examination of the blood showed a few parasites of benign tertian. Quinine was given in large doses for three consecutive days. The malaria parasites disappeared from the peripheral circulation but the temperature was very little affected. The patient was therefore sent to the general hospital. The fever lasted nearly three weeks, presenting a very irregular type. No roseola appeared and the spleen could never be palpated; no diarrhoea. Widal test always negative. During the last days of the illness the inguinal glands, particularly those of the left side, became swollen and slightly painful. This adenitis lasted for several days. The patient gradually improved and shortly afterwards left the hospital. Being fond of physical exercise he did much rowing and fencing. He soon noticed again (about three weeks after having left the hospital) an enlargement of the inguinal glands of the left side, one of which showed signs of suppuration. An incision was made in the gland and the pus collected in a sterile Petri dish with all aseptic precautions. From the pus a germ, to be described presently, was grown in pure culture. Several other inguinal glands became enlarged but they did not suppurate; with rest and local iodine applications the glandular swelling slowly subsided.

CASE 4. Austrian medical man, 24 years of age, arrived from China in April 1905. A week before reaching Colombo he began to feel ill with lassitude, headache,

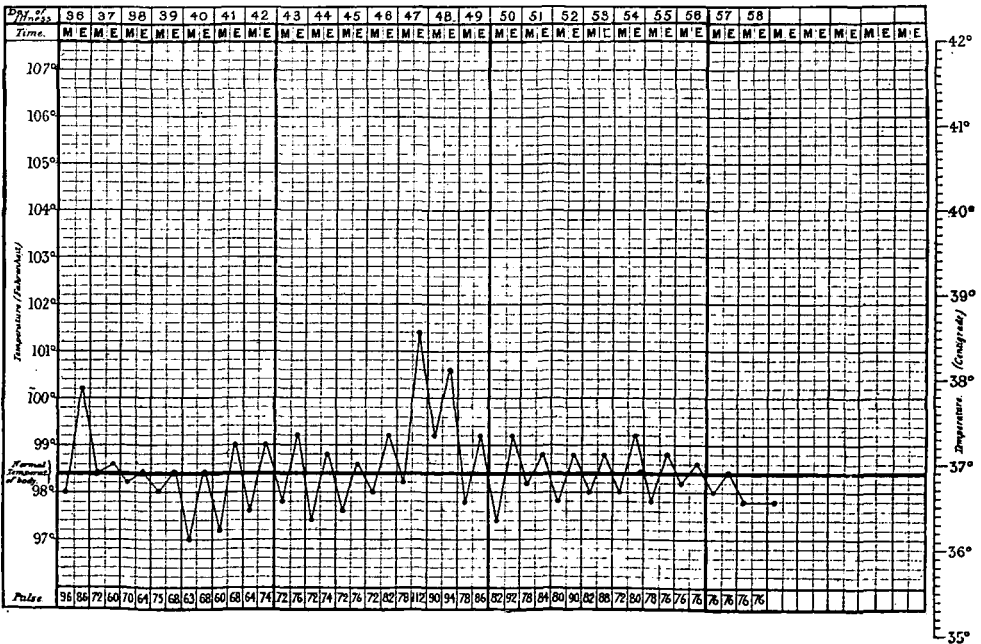
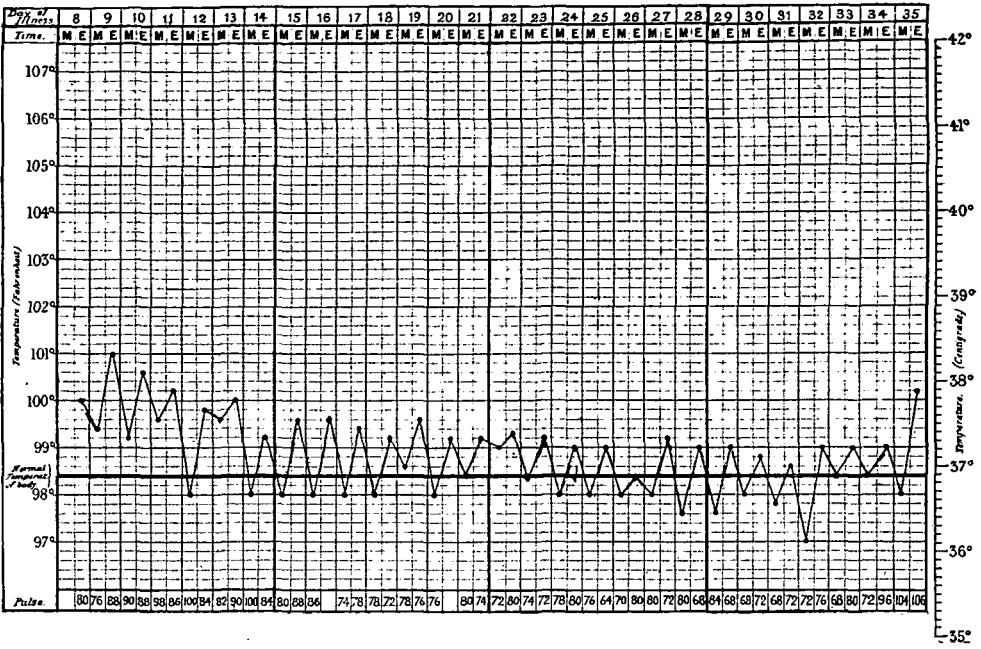


Chart 3.

diarrhoea (10 to 15 motions daily without muco-pus or blood), irregular fever. The patient was landed at Colombo and entered a private nursing home. The disease lasted about two months. The course of the temperature is shown in Chart 3, the diarrhoea ceased very soon and was followed by a long period of constipation. The tongue was generally very little furred; the spleen was very slightly enlarged at the end of the second week; roseola spots were never seen. The convalescence was very prolonged, the patient suffering repeatedly from attacks of nervous tachycardia, a condition to which he had been subject for several years before this illness.

*Microscopical and Bacteriological Examination of the foregoing cases.*

*Case 1.* Malaria parasites constantly absent, even several days after the quinine administration had been discontinued. The relative number of large mononuclear leucocytes was not increased, the count being large mononuclear 8%; polymorphonuclear 65%; small mononuclear 20%; transition forms 5%; eosinophiles 2%. Number of leucocytes per c.mm. 11,000.

The Widal test was negative; it was applied five times, three times during the course of the disease and twice during convalescence—the dilutions of the blood being 1 in 60; 1 in 40; and 1 in 20; time of observation 2 hours.

The blood was tested with two strains of *B. paratyphosus* A; one strain of *B. paratyphosus* B; and three strains of the paradysentery bacillus: none of these germs were agglutinated.

Having obtained the patient's permission on the 5th day of the disease, I drew a few cubic centimetres of blood from an arm-vein by means of a sterile syringe, using the ordinary aseptic precautions. The blood was inoculated at once into several large flasks containing each 300 c.c. of ordinary beef broth according to the "dilution method" introduced by me for typhoid<sup>1</sup>. The flasks were inoculated at 37° C. After two days, three out of six flasks showed a general turbidity, due to the growth in pure culture of a germ to be described below.

The microscopical examination of the stools of the patient did not show anything worth noting with the exception of a very few eggs of *Tricocephalus dispar*. The stools were investigated bacteriologically, using Drigalsky's medium; germs of the coli group only were found. The urine, twice examined bacteriologically, proved sterile.

*Case 2.* The blood was examined for malaria six times; malarial parasites and pigment constantly absent. Number of large mononuclear leucocytes 12%; polymorphonuclear 62%; small mononuclear 18%;

<sup>1</sup> See *Settimana Medica*, 1899, No. 3; *Riforma Medica*, 1900, Nos. 8 and 9.

eosinophiles 8%. Widal, repeated six times, negative. Serum reaction using various paratyphoid and paradysentery strains also negative. The patient having no objection, a few c.c. of blood were taken from a vein and examined as in case 1. In one of the six flasks the medium became turbid after 24 hours and showed the presence of a bacillus identical with that found in case 1. Some colonies of the same germ could be grown from the stools plated, using MacConkey's medium. The urine was sterile.

*Case 3.* The blood, as stated in the short history given above, showed a few benign tertian parasites which soon disappeared after the administration of quinine; the fever however continued its course, showing that it was not due solely to the malarial infection. Widal test repeated many times during the course of the disease, during convalescence, and afterwards, always gave negative results. Serum tests using various strains of paratyphoid bacilli also gave negative results.

The pus from the inguinal gland which had been collected aseptically was plated. All the plates after 24 to 36 hours showed colonies of one germ only which was identical with that cultivated from the blood of cases 1 and 3. Part of the pus was inoculated subcutaneously into a guinea-pig, which remained healthy<sup>1</sup>.

*Case 4.* Malaria parasites or pigment were never found. Plate cultures from the stools yielded many colonies of a germ different to that found in cases 1, 2, and 3. The germ encountered in the stools was also found during convalescence in the urine on two occasions. The blood was not examined for the presence of bacteria, but it was found to agglutinate the bacillus grown from the stools and urine, using a dilution of 1 in 300.

<sup>1</sup> *Note.* Since this paper was written—some months ago—a patient presenting symptoms similar to case 3 has come under my observation. This patient also, after several days of irregular fever, developed an inguinal adenitis, which came to suppuration. From the pus the *B. ceylanensis* A. was grown. These cases cannot, however, in my opinion have anything to do with so-called climatic bubos, which as a rule do not suppurate.

*Description of "Bacillus ceylanensis A" found in cases 1, 2, and 3.*

A rather short rod 2 to 4  $\mu$  in length, resembling closely the typhoid and dysentery bacillus. It is easily stained by the ordinary aniline dyes, but not by Gram. It is non-motile and I have never been able to demonstrate flagella, using various methods of flagella-staining. Brownian movement not very marked.

*Cultural characters. Broth*:—Growth fairly abundant with general turbidity of the medium. After two to four days a pellicle is noticeable on the surface of the medium. The pellicle is more or less marked according to the composition of the medium. In the broth as made up in the Colombo Laboratory<sup>1</sup>, the pellicle appears generally after 36 hours' incubation at 37° C. and is well marked. After a few days a certain amount of sediment is present. Gas bubbles are never observed.

*Peptone Water*:—Diffuse cloudiness, no formation of pellicle.

After some days some whitish sediment is present.

*Gelatin*:—No liquefaction. Colonies roundish, delicate, closely resembling the colonies of the dysentery bacillus (Kruse-Shiga type).

*Agar*:—Growth very similar to that of the typhoid or Kruse-Shiga bacillus. Surface colonies roundish and very delicate; much more delicate than those of many strains of coli.

*Action on the various sugar media*:—

*Saccharose*:—No production of acid; no gas.

*Glucose*:—Slight production of acid; no gas.

*Mannite*:—No formation of acid or gas.

*Dulcite, Maltose, Lactose*:—No formation of acid; no gas.

*Milk*:—Slowly acidified and clotted.

*MacConkey's neutral-red agar*:—Colonies roundish, delicate, do not take up the red stain.

*Serum, Serum-agar, Blood-agar*:—The growth in these media does not show anything characteristic.

*Indol formation*:—None.

*Pathogenicity*:—The intra-peritoneal inoculation of one c.c. of broth culture kills guinea-pigs in 24 to 36 hours. The subcutaneous inoculation of ordinary doses does not cause any symptoms in rabbits and guinea-pigs.

<sup>1</sup> Lemco 5 gr., Witte's Peptone 10 gr., Salt 5 gr., Water 1000 c.c.



*Description of "Bacillus ceylanensis B" found in case 4.*

A short non-motile bacillus 2 to 4 $\mu$  in length, easily stained by the usual aniline dyes, not stained by Gram.

*Cultural Characters. Broth*:—Abundant growth; diffuse turbidity; after 4 to 6 days a pellicle is present in the Colombo Laboratory broth. Very little sediment. No gas bubbles.

*Peptone Water*:—Diffuse turbidity, no pellicle, no gas bubbles, very slight amount of sediment after some days.

*Gelatin*:—No liquefaction. Colonies not so delicate as those of the germ found in cases 1, 2, and 3.

*Agar*:—Rounded whitish colonies. Growth very abundant.

*Action on the various sugars*:—

*Saccharose*:—Acid formed, but no gas.

*Glucose*:—Acid, no gas.

*Mannite, Dulcitol, Maltose, Lactose*:—Acid formed, but no gas.

*Milk*:—The medium is quickly acidified and clotted.

*MacConkey's neutral-red agar*:—The germ grows abundantly, the colonies taking up a deep red colour.

*Serum, Serum-agar, Blood-agar*:—Growth not characteristic.

*Pathogenicity*:—Intra-peritoneal injection of 1 c.c. of broth culture kills guinea-pigs and rabbits in 20 to 36 hours. Subcutaneous inoculations of 2 to 5 c.c. does not kill guinea-pigs or rabbits.

*Agglutination Reactions of the Strains isolated in cases 1, 2, and 3, and of the Strain isolated in case 4.*

The strain isolated in case 1 was not agglutinated at first (7th day of the disease) by the blood of the patient. Agglutinins however appeared on the 10th day and gradually increased in amount during convalescence, the agglutination limit being dilution 1 in 500.

This germ was tested later on with the blood of cases 2 and 4. It was easily agglutinated by the blood of case 2, using a dilution of 1 in 400, but was not influenced in the least by the blood of case 4.

The strain isolated from case 2 was agglutinated by the blood of the patient, from whom it was grown, using a dilution of 1 in 500. It was not tested with the blood of the other patients.

The strain isolated from case 3 was agglutinated by the blood of this patient (dilution 4 in 300) and also by the blood of cases 1 and 2, (dilution 1 in 400), but not by the blood of case 4.

The strain grown from case 4 was agglutinated by the blood of case 4 (dilution 1 in 300). It was also tested with the blood of case 2 but with negative results.

In the following table are collected the agglutination reactions of the organisms isolated from the four cases, with sera derived from rabbits inoculated with them.

Serum	Agglutination limits with			
	Strain 1	Strain 2	Strain 3	Strain 4
Strain 1	2000	1500	2000	0
Strain 2	4000	4000	3500	50
Strain 3	5000	4000	5000	50
Strain 4	0	0	0	2500

These agglutination reactions, and the cultural characters already described, show that the four strains may be divided into two groups: the strains isolated from cases 1, 2, and 3, on the one hand and the strain isolated from case 4 on the other. The strains grown from the first three cases represent one and the same organism; not so the strain obtained from case 4. For convenience I shall indicate the germ found in cases 1, 2, and 3 by the name of *B. ceylanensis* A and the germ grown from case 4 with the name *B. ceylanensis* B.

#### *Relation of the Organisms Described to other Bacteria.*

The following table, largely based on data regarding paratyphoid and allied organisms given by Morgan<sup>1</sup> and Boycott<sup>2</sup>, will show the principal differential characters of various intestinal bacteria and of the organisms observed by me.

From this table it is seen that the two strains differ from the other intestinal bacteria. They differ also from one another in several important respects, *B. ceylanensis* A producing acid only in glucose, while *B. ceylanensis* B produces acid in all sugars tried; besides *B. ceylanensis* A, does not form indol while *B. ceylanensis* B does. In fact, *B. ceylanensis* B is much more closely related to other intestinal bacteria (*B. pyogenes foetidus*) than to *B. ceylanensis* A.

<sup>1</sup> Morgan (1905). *Brit. Med. Journ.* vol. i. p. 1257.

<sup>2</sup> Boycott (1906). *Journ. of Hygiene*, vol. vi. p. 33.

Bacillus	Motility	Broth	Glucose	Mannite	Lactose	Saccha-rose	Dulcette	Litmus milk	Indol
<i>Typhosus</i>	+	G.T.	Ac.	Ac.	Nil	Nil	Nil	Ac.	-
<i>Dysentery</i> (Kruse-Shiga)	-	G.T.	Ac.	Nil	Nil	Nil	Nil	Ac. then slightly alkaline	-
<i>Dysentery</i> (Flexner)	-	G.T.	Ac.	Ac.	Nil	Nil	Nil	Ac. then alkaline	+
<i>Enteritidis</i> (Gaertner) Strain I	+	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac. then alkaline	-
<i>Enteritidis</i> (Gaertner) Strain II	-	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac. then alkaline	-
<i>Hog cholera</i> (Evans)	+	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac. then alkaline	- or trace
<i>Coli</i>	+	G.T.	Ac.G.	Ac.G.	Ac.G.	Nil	Ac.G.	Ac. C.	+
<i>Acidi lactici</i> (Hüppe)	-	G.T.	Ac.G.	Ac.G.	Ac.G.	Nil	Nil	Ac. C.	+
<i>Lact. aërogenes</i>	-	G.T.P.	Ac.G.	Ac.G.	Ac.G.	Ac.G.	Nil	Ac. C.	-
<i>Pyogenes foetidus</i>	-	G.T.	Ac.	Ac.	Ac.	Ac.	Ac.	Ac. C.	+
<i>Paracolon</i> "Mair"	+	G.T.	Ac.	Ac.G.	Ac.	Nil	Nil	Ac. C.	+
<i>Paracolon</i> "Day"	+	G.T.P.	Ac.G.	Ac.G.	Nil	Nil	Nil	Ac. then alkaline	-
<i>Valérie 25</i> (Boycott)	+	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac.	+
<i>Valérie 21</i> (Boycott)	+	G.T.	Ac.G.	Ac.G.	Nil	Ac.G.	Ac.G.	Ac. C.	+
<i>Paratyphoid A</i>	+	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac.	+
<i>Paratyphoid B</i>	+	G.T.	Ac.G.	Ac.G.	Nil	Nil	Ac.G.	Ac. then alkaline	- slight
<i>Ceylanensis A</i>	-	G.T.P.	Ac.	Nil	Nil	Nil	Nil	Ac. C.	-
<i>Ceylanensis B</i>	-	G.T.P.	Ac.	Ac.	Ac.	Ac.	Ac.	Ac. C.	+

Ac. = acid.

Ac. C. = acid and clot.

Ac. G. = acid and gas.

G. T. = general turbidity.

G. T. P. = general turbidity and presence of pellicle.

The sign + in the motility column indicates that the bacillus is motile; the sign - that it is not motile.

The sign + in the indol column means that there is formation of indol; the sign - that there is not formation of indol.

### Conclusions.

1. There are cases of unclassified fever occurring in Ceylon which on superficial examination may be taken for atypical forms of typhoid, paratyphoid, or malaria.

2. Four such cases have been examined by me bacteriologically. Of these the fourth case showed clinical symptoms somewhat different from the first three cases and the disease lasted longer.

3. From the first three cases a bacillus was grown (in two cases from the blood). The bacillus was non-motile, it produced a pellicle in

broth, acidified and coagulated milk slowly, produced acid but no gas in glucose, and produced neither gas nor acid in saccharose, mannite, dulcitate, lactose; no indol formation. The germ was agglutinated by the blood of the patients.

4. From the fourth case a bacillus was isolated which was non-motile. The bacillus produced a pellicle in broth, acidified and clotted milk quickly, produced acid but no gas in saccharose, glucose, mannite, dulcitate, lactose; it formed indol. The germ was agglutinated by the blood of the patient from whom it was recovered.

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