

TYPHOID FEVER COMPLICATED BY BENIGN TERTIAN MALARIA

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The difficulties in making an early diagnosis of enteric fever are considerably increased if the patient is already suffering from other febrile diseases. We are here describing our observations on 34 patients with typhoid fever, because 10 of them also had benign tertian malaria. In two others the onset of malaria preceded that of typhoid fever by 17 days. Other conditions, such as sinusitis, recent T.A.B. vaccination, and suspected hepatic amoebiasis, caused confusion; while in two cases the question of kala-azar was raised.

The majority of our patients admitted to a Middle East hospital during the autumn of 1944 were involved in two small epidemics (see Table I). The first eight to arrive, all of whom suffered from a similar febrile illness, came from an Italian prisoner-of-war camp hospital. Benign tertian parasites had been found in the blood of two of them. All had received antimalaria treatment, but none had responded. The death of one of them from perforation of the small bowel finally revealed the true state of affairs. Investigations failed to show the source of this epidemic. Sixteen British patients from one mess in a malarious site were infected by a typhoid carrier—a native employed in the mess kitchen.

TABLE I.—Distribution of Cases before Admission

An Italian P.O.W. camp ..	14 (2 with concurrent B.T. malaria)
A static British unit ..	16 (8 " " " " " ")
A British unit in transit ..	3 (No malaria) " " ")
Sudanese ghaffir ..	1 (" " ")

Most of the recognized clinical manifestations of an enteric fever were present at some time, and they are classified in Table II. We propose to discuss only a few of them.

TABLE II.—Chief Clinical Manifestations

	Typhoid Fever (24 patients)	Typhoid with Concurrent B.T. Malaria	Total
Infections:			
Benign tertian malaria (concurrent only)	—	10	10
Miscellaneous:			
Typhoid stupor, severe ..	5	1	6 } 12
" " mild ..	4	2	
" " exanthem ..	3	1	
Circulatory:			
Bradycardia ..	14	3	17
Dicrotic pulse ..	6	6	12
Alimentary:			
Intestinal haemorrhage ..	3	0	3 (all died)
Perforation of typhoid ulcer ..	1	0	
Meteorism, severe ..	2	1	
" " moderate ..	8	2	10 } 13
Enlarged liver ..	8	1	
" " spleen ..	10	5	15
Respiratory:			
Tonsillitis ..	5	0	5
Sinusitis and pharyngitis ..	2	3	5
Bronchitis ..	4	3	7
Bronchopneumonia ..	2	0	2 (terminal)
Pleural effusion ..	1	0	
Urinary:			
Albuminuria (temporary) ..	4	2	6
Typhoid pyelonephritis ..	1	0	1

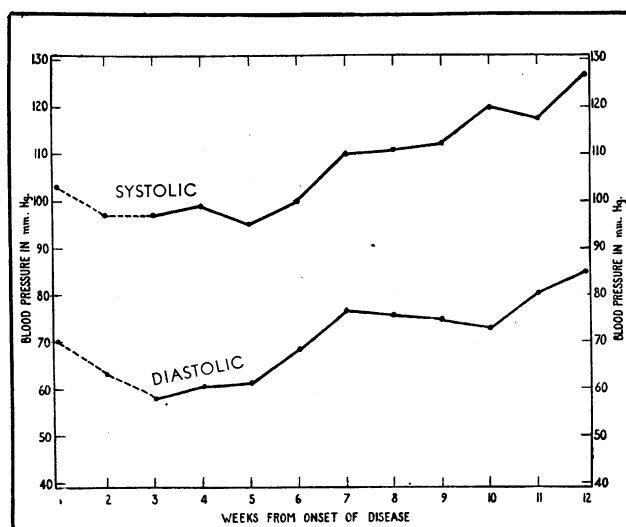
Clinical Manifestations

Fever.—Only on two occasions did the temperature charts suggest double infection—showing alternating hectic and remittent fever for the first four days. The other eight patients with both infections had an irregular remittent fever at the onset which became intermittent during a prolonged lysis (see Table III). Only one had a relapse (not malaria), whereas eight patients suffering from typhoid fever alone had relapses—which on three occasions exceeded the initial attack in length and severity.

TABLE III.—Severity of Typhoid Fever in Relation to Concurrent B.T. Malaria

	Severity					Fever	
	Mild	Moderate	Severe	Deaths	Total	Relapses of Fever	Average Duration Initial Fever (Days)
Typhoid fever only	12	6	3	3	24	8	22
Typhoid, with B.T. malaria concurrent	4	3	3	—	10	1 (Not malaria)	29
Total ..	16	9	6	3	34	9	24
No T.A.B. T.A.B. vaccination incomplete	3	2	—	1	6	1	27

Circulatory System.—Relative bradycardia was present in 17 cases, only three of which had malaria. The pulse rates increased towards the end of prolonged fever and during relapses, and were unstable during convalescence. Twelve patients had a dicrotic radial pulse during the first weeks of illness. Blood pressures were always low during the first five weeks, returning to normal about the tenth week. The weekly average blood pressures of seven severe cases observed over a long period are shown in the accompanying Graph.



The weekly average blood pressure in 7 severe typhoid cases. There was no significant difference between the B.P. in typhoid alone (3 cases) and concurrent typhoid and B.T. malaria (4 cases). The averages were compiled from readings taken every third day.

Although apparently unrelated to fever, relapses, pulse rate, dicrotic pulsation, or concurrent B.T. malaria, blood-pressure readings proved useful as indices of the general condition and as guides during convalescence.

Respiratory System.—Nasopharyngitis and tonsillitis were common during the first three weeks. Two malarial patients were found to have frontal and maxillary sinusitis respectively. Typhoid fever—the third concurrent febrile disease—was recognized only when they failed to respond to treatment for the other two diseases. Subacute bronchitis occurred after the fourth week—sometimes as an exacerbation of chronic bronchitis. One patient developed a small pleural effusion associated with a relapse of fever.

Exanthem.—Only four patients had a recognizable enteric rash, but one or two doubtful maculae were seen on seven others.

Spleen.—Enlargement of the spleen was noticed on 15 occasions (44%). The incidence in doubly infected patients was 50%, and in patients with typhoid fever alone 42%. The sera of two non-malarial patients whose spleens were considerably enlarged reacted positively to Chopra's antimony test and to Napier's aldehyde test. No leishmania were found in smears from sternal bone-marrow (both cases) or the spleen (one case post mortem).

Liver.—The livers of nine patients were found to be slightly or moderately enlarged during the first five weeks of illness. Only one of these patients had both infections.

Fatal Cases.—Essential facts about the three patients who died are shown in Table IV. None of them were British. Not one of the doubly infected patients died, although they were febrile for a longer period than the average (see Table III). The warnings of Bhatnagar (1944) concerning the dangers of delayed diagnosis, lack of rest, and the administration of anti-pyretic drugs in typhoid fever are exemplified in the deaths of two Italian patients.

T.A.B. Vaccination.—One patient who died (Table III; Table IV, Case 3) received a full quota of T.A.B. vaccinations.

TABLE IV.—Deaths

Case	Age	T.A.B. Protection	Day of Death After Onset	Outline of Course of Disease	Necropsy
1	34	Incomplete (0.5 c.cm.) 1 month before admission	14	Gradual onset with diarrhoea. Treated for this and for malaria in camp. 11th day: small haemorrhage. 12th day: meteorism, abdominal pain and rigidity	Many typhoid ulcers in ileum. One ulcer had perforated—purulent peritonitis
2	28	No protection	23	Temperature normal by 6th day; relapse fever, 8th day; 2nd blood culture positive 12th day; intestinal haemorrhage 21st day. Napier's and Chopra's tests positive	Spleen showed typical typhoid changes. No Leishman-Donovan bodies seen
3	34	Full quota T.A.B.	45	Persistent high fever. 3rd week: meteorism. 20th day: haemorrhage followed by remission and improvement. Finally died in typhoid stupor	Many typhoid ulcers in ileum. Bronchopneumonia

A second was partially protected; the third had had no T.A.B. vaccine. Table III shows the relation between the severity of the attacks of typhoid and T.A.B. vaccination state. The data do not provide sufficient grounds for any conclusions. Four British patients were admitted within three days of T.A.B. vaccination apparently suffering from severe reactions. *B. typhosus* was cultured from the blood taken on the second, third, and eleventh days respectively after administration of the vaccine. Apparently these were the only four patients who received the new alcoholized vaccine.

Diagnosis

In 28 out of 34 cases *B. typhosus* was cultured from the blood—taken as early as the second or as late as the 24th day of the initial fever. Here we should mention that it is not always possible to decide with accuracy the date of onset of typhoid fever, especially in cases with mixed infection. Apparently, recent or simultaneous administration of quinine, mepacrine, or pamaquin does not reduce the chances of obtaining a positive culture. The first blood culture was positive in 26 out of 28 cases. In the remaining two *B. typhosus* was cultured from the blood at the second and the third attempt respectively. Positive cultures of urine (1) and faeces (1) established the diagnosis in two other cases, whereas another was diagnosed post mortem the day after admission.

A diagnosis of typhoid fever was eventually made on three occasions in spite of repeatedly negative cultures of blood, urine, and faeces. These three patients, of whom two also had malaria, were the first arrivals from a British unit.

We attached little importance to the leucocyte counts, as the results were usually compatible with the diagnosis of either of the two prevalent diseases. "O" and "Vi" agglutination tests were not carried out systematically. No conclusions can be drawn from our incomplete results, which are therefore omitted.

Discussion

Medical officers still too often fail to consider the possibility of a double infection during the first week of illness. We have found that patients with uncomplicated B.T. malaria always improved on quinine. Tests of the urine of some of our

patients with Tanret's reagent showed that quinine was being absorbed.

Our initial examination seldom revealed any signs suggestive of an enteric infection. Temperature charts gave us little help. The pulse rates of doubly infected patients were as a rule proportionally accelerated.

A typhoid rash was observed on only four occasions during the second week of disease. The finding of splenic enlargement was no help to diagnosis. So far we have not observed the blood-pressure changes during the last two weeks often enough to enable us to judge whether they are constant or specific.

Evidently the only two early distinctive signs of an enteric fever—progressive stadium incrementi and relative bradycardia—may both be absent, especially in patients simultaneously afflicted by some other febrile disease, such as B.T. malaria.

The value of taking blood for culture is diminished if it is postponed until the full enteric syndrome has developed.

Summary and Conclusions

We have recorded observations on 34 patients suffering from typhoid fever, three of whom died.

The early clinical diagnosis was hindered on 12 occasions by the simultaneous presence of or immediate recovery from B.T. malaria. None of those suffering from malaria died.

Blood pressures were low during the first five weeks and did not reach normal levels until the tenth week.

B. typhosus was cultured from the blood in 28 out of 34 patients. Blood cultures should be carried out early and repeatedly while the cause of fever remains unknown.

Blood cultures should always be carried out when there is a relapse of fever, whatever the initial condition.

We wish to express our gratitude to Col. A. C. MacDonald, M.C., T.D., our late commanding officer, for permission to publish these cases; and to Lieut.-Col. J. Gibson-Graham, officer in charge of the Medical Division, for his advice and help.

REFERENCE

Bhatnagar, S. S. (1944). *British Medical Journal*, 1, 417.

Medical Memoranda

Neurological Complications in Cerebrospinal Meningitis treated with Penicillin

The following case, in which neurological complications arose after treatment with penicillin, may be thought of interest.

CASE HISTORY

On June 30 the patient, a boy aged 12, was "off colour"; he had no definite complaints and was not confined to bed. Next day he complained of headache and stiffness of the neck; his face was flushed. His parents thought it was a chill or influenza, and, it being Sunday, did not call for medical aid. The family doctor was called early in the morning of July 2 and found the boy unconscious but extremely restless, with flushed face, increased pulse and temperature, and neck rigidity. The patient was removed to hospital in an unconscious state. Lumbar puncture was performed; the fluid was very turbid and under pressure. The laboratory report was as follows: Cells, 45,000 per c.mm.; protein, 350 mg./100 c.cm.; chloride, 630 mg./100 c.cm. Gram film: polymorphs +++; Gram-negative intracellular diplococci. Meningococci were isolated on culture.

The patient was put on sulphapyridine treatment on July 2 and 3 (8 g. in 24 hours), but he continued unconscious and was extremely restless. The temperature remained in the region of 103° F. and the neck rigidity was more pronounced, almost amounting to opisthotonos. Strabismus with unequal pupils and a left facial paresis developed; knee-jerks were exaggerated and the plantar reflexes were flexor. There was incontinence of urine and faeces. Apparently he was not responding to sulphapyridine treatment, so penicillin was substituted on the evening of July 3. The first injection of 18,000 units was given intrathecally; the cerebrospinal fluid had now become very purulent and thick, and was withdrawn with difficulty. Subsequent injections of 18,000 units were given intramuscularly every 3 hours. The patient was still unconscious, and became extremely restless after the intrathecal injections.

July 4.—Lumbar puncture; fluid less purulent but still under pressure. Laboratory report: Cells, 3,000 per c.mm. Gram film: cells, polymorphs; no organisms seen. Culture, sterile. Penicillin 18,000 units was given 3-hourly, once intrathecally. The treatment was continued 3-hourly for 5 days, three injections being given intrathecally, the remainder intramuscularly.