DOUBLE ENTERIC INFECTION ('LA FIÈVRE TYPHOÏDE INTRIQUÉE'). AN ACCOUNT OF AN EPIDEMIC

By A. BATTY SHAW* and H. A. F. MACKAY

(With Plate 14 and 2 Figures in the Text)

DOUBLE ENTERIC INFECTION

Kayser (1904) was among the first to describe a case of enteric fever in which two organisms of the enteric group (*Salmonella typhi* and *Salm. paratyphi A*) were isolated during the course of the disease. Further cases were described independently by Conradi (1904) and Gaehtgens (1906). In 1916, Chantemesse & Grimberg introduced the term 'fièvre typhoïde intriquée' to describe this association, which has also been termed 'une infection mixte' (Achard, 1916). In the literature of enteric fever 'mixed infection' is usually applied to those cases in which secondary infection has taken place with an organism other than of the enteric group, e.g. the streptococcus or staphylococcus (Osler & McCrae, 1935). 'Double enteric infection' is considered a preferable term to 'intricate infection' for a description of those cases, or epidemics, of enteric fever in which infection with two organisms of the enteric group has taken place. Cases of triple enteric infection have been described (Castellani, 1915), and with the identification of enteric organisms by phage typing, several enteric organisms of different phage type may be found responsible for an epidemic, 'multiple enteric infection' (e.g. Boyd, 1943).

An account will be given of an epidemic of seventy-six cases of enteric fever, in which *Salm. typhi* (Vi-phage type T) and *Salm. paratyphi B* (Vi-phage type 'Dundee') were the causal organisms. The literature of double enteric infection, which has been published principally in Germany (see Nerlich, 1934) and France (see Levy, 1936), will be reviewed, and the significance of such infections will be discussed.

Previously reported cases

A double enteric infection may be defined as the simultaneous infection of an individual, or a group of individuals, with two organisms of the enteric group. Such infection is unusual, and Leboeuf & Braun (1917) found only one case in a series of 12,028 blood cultures. The records of thirty-nine isolated cases, in which the diagnosis can be accepted, have been traced and are shown in Table 1. One reported case of triple infection is also shown in this table (Castellani, 1915). In Table 2 are shown the main features of nine recorded epidemics of double enteric infection and the epidemic described in this article. In addition, four outbreaks of triple enteric infection are included (Bernard & Paraf, 1915; Wagner, 1915 (quoted by Nerlich, 1934); Neuhaus, 1926; Dubrowinski, 1929) and those epidemics

* Guy's Hospital, London.

https://doi.org/10.1017/S002217240004417X Published online by Cambridge University Press

of multiple enteric infection, which occurred among Italian prisoners-of-war, in Egypt, between 1941 and 1942 (Boyd, 1943).

The diagnosis of a double enteric infection may be proved by the isolation of two organisms from blood culture taken early in the disease. When one organism has been isolated from the blood and the second from the excreta, the possibility arises that such cases may have been carriers of enteric infection prior to their attack of fever. This is considered unlikely in the fourteen cases so diagnosed, and it is more probable that they represent a simultaneous systemic infection with two organisms. If a known carrier of one enteric group organism should, however, contract infection with a second organism, he could still represent an example of double enteric infection, though no such case has been described. When one enteric group organism has been isolated early in the disease, and a second organism later in the disease, or during a relapse, the alternatives are either that the second organism was missed by the earlier culture, or that separate infection has been contracted. Cases of 'mixed infection' have been recorded, in which there has been an afebrile period of several months to 3 years between the first attack and the 'relapse' (Chevrel, 1913; Courmont & Chattot, 1916), and which clearly represent two dissociated infections. In the majority of cases the second organism has been isolated later in the first attack of fever, or in a relapse following a period when the temperature has not settled to normal (intercurrent relapse). It is considered justifiable to regard such cases as examples of a simultaneous infection with two organisms (Kayser, 1904; Hébert & Bloch, 1917; Heymer & Wohlfeil, 1933). Two interesting cases have been described in which one organism has been isolated from the blood and the second from the sputum (Minet, 1917), and Dawson & Whittington (1915–16) and Leboeuf & Braun (1917) have described the isolation of an organism at post-mortem, which has differed from that cultured during life. A number of cases have been reported in which the diagnosis of a double infection has been made upon the results of the Widal agglutination test. In three reports there has been no history of previous anti-typhoid inoculation (Savage, 1905; Achard, 1929, cases 2 and 3; Dubrowinski, 1929). But the majority of the cases so diagnosed have been previously inoculated, and either one organism has been isolated by cultural methods and the Widal has given a positive agglutination with a different enteric group organism (Gerard & Fenestre, 1917; Germani, 1927; Montel, 1939), or the Widal has shown a raised titre to two organisms of the enteric group (Fornet, 1907; Étienne, 1915; Jeanselme & Agasse-Laffond, 1915; Siredey, 1915; Sacquépée, 1916; Pirera, 1919; Germani, 1927; Achard, 1929).

Grattan & Harvey (1911) were the first to appreciate that a rise in the agglutinins against a heterologous organism in inoculated persons did not necessarily indicate a double enteric infection. In bacteriologically proven paratyphoid fever, occurring in soldiers previously inoculated with 'T' vaccine, they demonstrated a rise in both the paratyphoid and typhoid agglutinins. Their findings were confirmed by Firth (1912), Safford (1913) and Martin & Upjohn (1916). However, no less an authority than Perry (1918) wrote of Martin & Upjohn's findings at Gallipoli that 'the only justifiable conclusion was that such patients were suffering from a dual infection'. These observations were made before the existence of both

Table 1. *Previously reported cases of double enteric infection*

Author	Year	No. of cases	Isolation of organism from: Blood	Stools	Urine	Sputum	Post-mortem	Comment
Conradi	1904	1	—	T, B	—	—	—	—
Kayser	1904	1	—	T, A	—	—	—	*Salm. typhi* was isolated from the blood and the stools at the start of the fever. *Salm. paratyphi A* was recovered from the stools when the temperature was settling
Gaehtgens	1906	1	T	T, B	—	—	—	—
Castellani	1907	1	—	T, B	T, B	—	—	—
Nieter	1907	1	—	T, P	—	—	—	—
Rimpau	1914	1	—	T, B	—	—	—	—
Castellani	1915	1	—	T, A, B	—	—	—	The patient's relatives refused to allow blood culture to be performed
Bernard & Paraf	1915	1	A, B	—	—	—	—	—
		1	B	A	—	—	—	—
Dawson & Whittington	1915–16	1	A	—	—	—	T	*Salm. paratyphi A* isolated in life. Patient died from a femoral thrombosis and pulmonary infarction. *Salm. typhi* recovered from the gall-bladder and spleen at post-mortem
Fortescue-Brickdale	1915	?	E	E	E	—	—	Reported a few cases of double enteric infection among British troops in France, in which one organism had been isolated from the blood and another from the stools or urine
Rist	1916	1	T, B	—	—	—	—	—
		1	T	A	—	—	—	—
Gautier & Weissenbach	1916	1	B	T, B	—	—	—	—
Labbé	1916	1	T	—	B	—	—	—
Sacquépée	1916	1	T, A	—	—	—	—	—
Chantemesse & Grimberg	1916	7	T, A	—	—	—	—	Isolated cases diagnosed by blood culture
		4	T, B	—	—	—	—	
Leboeuf & Braun	1917	5	E?	—	—	—	E	Cultured the bile in five fatal cases and isolated an organism different from that recovered in life
		1	T, B	T, B	—	—	—	
Hébert & Bloch	1917	1	T, B	—	—	—	—	*Salm. paratyphi B* isolated in first week and *Salm. typhi* during an intercurrent relapse
Minet	1917	1	T	—	—	B	—	—
		1	T	—	—	A	—	—
Étienne & Voirin	1917	1	T, A	—	—	—	—	—
Bourges	1919	1	T, A	T, A	—	—	—	—
		1	T, B	—	—	—	—	—
Heymer & Wohlfeil	1933	1	T, B	—	—	—	—	*Salm. paratyphi B* isolated from the stools during an intercurrent relapse
Elkeles*	1934	1	T	B	—	—	—	From drinking well-water

* Quoted by Nerlich (1934).

E = enteric group bacillus; T = *Salm. typhi*; A = *Salm. paratyphi A*; B = *Salm. paratyphi B*; P = paratyphoid bacillus.

https://doi.org/10.1017/S002217240004417X Published online by Cambridge University Press

Table 2. *Previously reported outbreaks of double enteric infection*

Author	Year	Place	Total no. of cases	Division of cases	Method of diagnosis	Comment
Thomas	1907	Posen	?	10, T and P	Stool culture	Occurred in one epidemic. Included among 1804 cases of enteric fever observed at Posen between 1904 and 1906
Wagner*	1913	Kiel	20	19, T 1, T and B	Organisms isolated by culture, ? method	A milk-borne epidemic. The diagnosis in the twenty cases was proved bacteriologically, but whether by blood, stool or urine culture is not stated
Wagner*	1915	Schleswig-Holstein	8	6, T 1, B 1, A	All cases were proved by blood culture	A milk-borne epidemic. All the cases appeared to form part of an epidemic. No organisms were isolated from the milk, therefore these cases were not proved to arise from a common source
Grisar*	1914	Waldbreitbach	72	50, T 12, P	?	Caused by contamination of the drinking water with sewage
Rimpau	1914	Munich	—	1, T 2, T and B 1, B	Blood culture Stool culture Stool culture	A small epidemic caused by *Salm. typhi* and *Salm. paratyphi B* in which both organisms were isolated in two cases
Bernard & Paraf	1915	France	64	6, T 11, A 47, B	All cases were proved by blood culture	The outbreak occurred in an isolated military unit. All the patients fell ill concurrently and appeared to form one epidemic
Sacquépée	1916	France	30	26, T 4, T and B	Proved bacteriologically	*Salm. typhi* was present in the blood, and *Salm. paratyphi B* in the stools in four cases
Étienne	1918	France	2	2, T and A	Both proved by blood culture	Occurred in a woman and boy at the same factory. Complete absence of T and A agglutinins in both cases
Neuhaus	1926	Anklam	275	3, T and P 5, P 267, T	Bacteriologically proven in all cases (? blood, stools or urine)	Three cases were shown to be a double infection with *Salm. typhi* and *Salm. paratyphi*. The outbreak was caused by contamination of milk with infected water
Hahn & Reichenbach	1928	Hanover	2423	2220, T 154, P (36, T and P) 13, T and P	By Widal or bacteriological culture Proved bacteriologically By Widal only Proved by isolation of both organisms	A large epidemic caused by contamination of the water supply. The diagnosis of a double enteric infection is probable, but not certain in those thirty-six cases diagnosed by the Widal reaction
Dubrowinski	1929	Rostov-on-Don	1270	1060, T, or T and P 210, A or B	'Most of the cases' were diagnosed by the Widal test	The epidemic was caused by infection of a stream with sewage. The diagnosis of typhoid and paratyphoid must be doubted in those cases, in which it was made by the Widal test. There remain those cases of single infection with T, A or B, which justify the inclusion of this epidemic (triple infection)
Seiderer	1929	Munich	(*a*) 500	25, T and B	Both organisms isolated by blood culture	An outbreak of 'food poisoning' occurred on a Rhine steamer. From a total of 500 cases of 'diarrhoea and vomiting', twenty-five were admitted to hospitals in Munich and shown to be double enteric infections
Seiderer	1929	Munich	(*b*) 97	25, see (*a*) above 5, T and B	Both organisms isolated by blood culture	Of the total of ninety-seven cases of enteric fever admitted to the Munich hospitals during 1928, there were thirty of double enteric infection. Twenty-five of these thirty cases are included in (*a*) above. It is not stated whether the remaining five were isolated cases, or occurred in an epidemic
Leuchs*	1932	Schweinfurst	66	50, T 16, B	? Bacteriologically proven	A water-borne epidemic
Batty Shaw & Mackay	1951	Acre	76	43, T 28, T and B 3, B (2, 'clinical enteric')	Confirmed bacteriologically in 74 cases	Probably a water-borne epidemic. For further details see text
Boyd	1943	Egypt	—	Recorded several outbreaks of enteric fever among Italian prisoners-of-war. Two epidemics were caused by 'multiple enteric infection'. Summer 1941: paratyphoid A, and *Salm. typhi* (Vi-phage Types A, B4, C, G, Imperfect Vi, and no Vi antigen); winter 1942: paratyphoid B, and *Salm. typhi* (Vi-phage Types A, B4, C, D2, G, Imperfect Vi, and no Vi antigen)		

* Quoted by Nerlich (1934).
T = *Salm. typhi*; A = *Salm. paratyphi A*; B = *Salm. paratyphi B*; P = Paratyphoid bacillus.

https://doi.org/10.1017/S002217240004417X Published online by Cambridge University Press

O and H agglutinins had been described, and it is presumed therefore that they refer only to the H agglutinins.

Recent work has emphasized the complexities of the Widal test, and the precautions for time, temperature, etc., that have to be taken, in order to ensure its correct interpretation (Felix, 1924, 1929; Gardner, 1937; Wilson & Miles, 1946). These advances cast doubt upon a number of the diagnoses made by this method in the past. It is now generally appreciated that estimation of the H agglutinins is of little diagnostic value in the previously inoculated, and would certainly be unreliable in the diagnosis of double enteric infections in such persons. No O agglutinins have been estimated in any of the previously reported cases, though even these may sometimes be affected by previous inoculation (Gardner, 1929; Horgan, 1932), and in a number of cases the diagnosis has rested upon the result of one Widal reading (e.g. Pirera, 1919; Germani, 1927; Achard, 1929, cases 1 and 4). It has therefore been decided to exclude from Tables 1 and 2 all those cases of double enteric infection in which this diagnosis has been based upon the results of agglutination tests. An exception has been made for the epidemic of 1270 cases of enteric fever described by Dubrowinski (1929) at Rostov-on-Don. The majority of these cases were diagnosed by the Widal test, and a claim was made for the diagnosis of individual cases of double enteric infection. However, the epidemic also included examples of single infection with one of three different enteric organisms, and thereby justifies its inclusion in this series.

THE ACRE ENTERIC OUTBREAK

Epidemiology

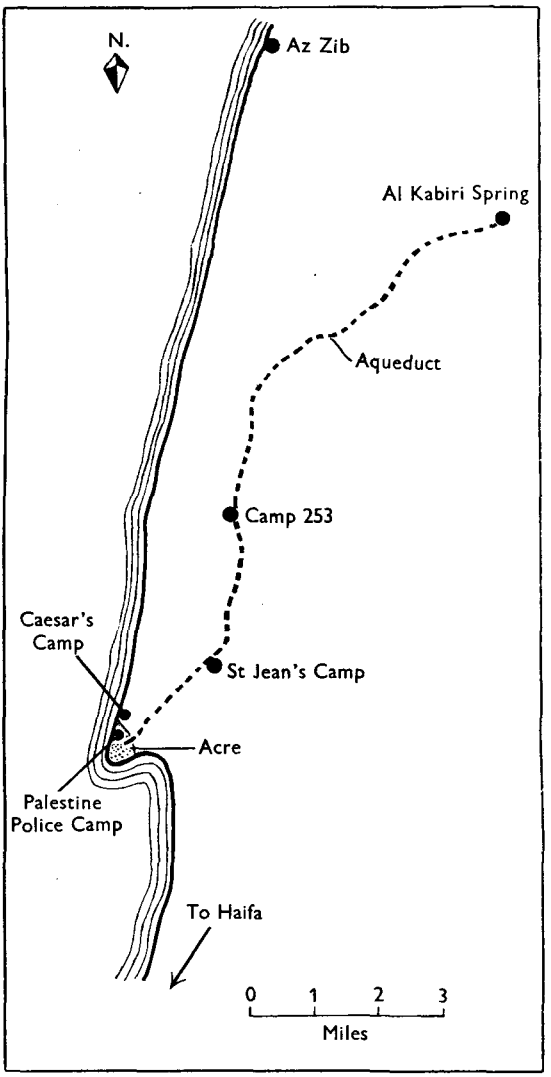
In April 1948, 2 months before the final evacuation of British troops from Palestine, an outbreak of enteric fever occurred at Acre. At this time the British forces had withdrawn to an enclave around Haifa, whence they finally departed on 22 June 1948. In the predominantly Arab town of Acre, a company of British infantry and a British detachment of the Palestine police were stationed in two separate camps. The incidence of enteric fever in these two groups is shown in Table 3.

Table 3

	Total strength	No. of cases of enteric	Percentage
Infantry company	107	65	60
Palestine police	64	11	17

It was also known that a number of cases of enteric fever occurred among the Arab civilians. On 21 April 1948, the Jews attacked and routed the Arab population in Haifa (Wilson, 1949); deserted by their effendi and depleted of ammunition, the Arabs fled to the outlying villages, and especially to Acre, where the population was increased from 25,000 on 21 April to 40,000 three days later. But with the further dispersal of Arabs to Syria and the north, this figure had fallen to 8000 on 7 May. Owing to this scattering of the population, and the concomitant breakdown in the civilian medical services, it was not possible to obtain an accurate figure of the incidence of enteric fever amongst the Arabs, though it was estimated at 70, on 6 May, by a representative of the International Red Cross.

As a result of detailed inquiries and investigation, it was considered that the epidemic was due to a water-borne infection. The water supply for Acre came from springs at Al Kabiri 10 miles to the north-east of the town (Text-fig. 1). It was conveyed by a stone aqueduct, originally of Roman construction (Pl. 14), which was carried on arches until it reached ground level in the later part of its course. The



Text-fig. 1. Map of the enteric outbreak at Acre, Palestine, in April–May 1948.

channel was approximately 18 in. wide and 2 ft. deep, and for three-quarters of its length was open; it was closed by stone-work in its later course and passed through both Jewish and Arab land. During the civil disturbances it had been the object of attack on several occasions when damage to the stone-work had taken place. Although certain repairs had been carried out by the British and Arab authorities, it had not been possible to service and maintain the aqueduct satisfactorily, owing

to these inter-racial differences. The water was conveyed to storage tanks in Acre, where it was sterilized by an automatic chlorinator. It was subsequently discovered that the Arab municipal engineer in charge of the chlorinator had exhausted his supplies of chlorine on 17 March 1948, but did not inform his consumers of the fact, and left for the Lebanon on 18 March.

The water supply to Acre was satisfactory when the aqueduct and the chlorinator were adequately maintenanced, and this had been confirmed by repeated bacteriological examination of the water in the British camp. But in the early half of April 1948, a number of cases of diarrhoea occurred amongst the British troops stationed in the town and complaints were made that the water had become of unpleasant taste. In addition, the flow of water from the Acre main became intermittent. On 13 April a sample of the drinking water was examined by routine methods and this revealed a *Bacterium coli* count of 180 per ml. On 17 April instructions were issued for all drinking water to be boiled and, both because of its contamination and the intermittency of flow, arrangements were made for water to be obtained from deep wells at St Jeans (Text-fig. 1). The first British cases of enteric fever to be admitted to hospital became ill on 23 April. Accepting 10–14 days as the usual incubation period for enteric fever, the dates of infection lie between 9 and 13 April. The outside limits for the incubation period are 3–40 days (Miner, 1922), and it is therefore possible that the infection may have been contracted between 18 March and 19 April. An examination for salmonella group organisms was not made on 13 April when the *Bact. coli* count was performed, but it is possible that they may have been present at this time. In the first week of the epidemic specimens of water were examined both from the Kabiri aqueduct and from Acre, but although they revealed gross contamination with *Bact. coli*, which became greatest in Acre town, no salmonella organisms were isolated. It is unusual to find an epidemic of paratyphoid fever, caused by a water-borne infection, but in the investigation of a number of paratyphoid B epidemics, this organism has been isolated from sewage or sewage effluents (Savage, 1942).

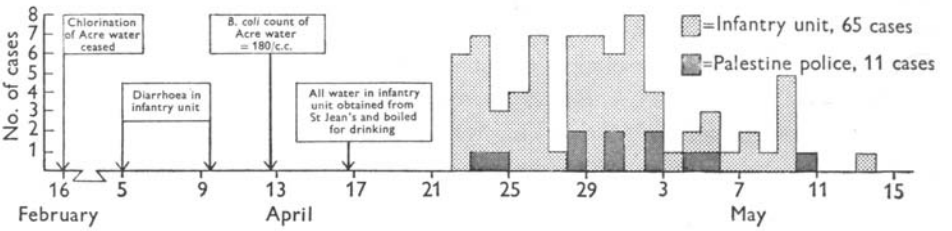
Morbidity

An interesting feature of this epidemic was the difference in morbidity between the infantry unit (60 %), the Palestine police (17 %), and the 25,000 Arab civilians, among whom only seventy cases were known to have occurred. Enteric bacilli were never isolated from the water supply, but, when this was examined at the end of April, gross faecal contamination in all parts of Acre was demonstrated. It cannot be shown that enteric bacilli were present in equal numbers in the water supply to the three communities, and it is likely that the consumption of water varied between them, viz. less among the Arabs than the Europeans. No further information concerning the enteric fever amongst the Arabs is available, but a study was made of the factors which might have influenced the differing rate of morbidity between the infantry unit and the police. It is appreciated that a similar exposure to infection cannot be proven, but that the degree of infection was similar is suggested by the proximity of the two units, that their cases of enteric occurred simultaneously (Text-fig. 2), and that their water supply showed a comparable

degree of faecal contamination when examined. The hygiene in both camps was satisfactory, being of a slightly higher standard in the infantry unit.

In Tables 4*a* and 4*b* are shown the difference in age and length of overseas service between the two units, and their relationship to the incidence of enteric fever.

Both units had been inoculated with T.A.B. vaccine. All men in the infantry unit had received an inoculation with alcoholized T.A.B. vaccine, prepared in the United Kingdom, within the previous year. Two of the Palestine policemen had received no inoculation with T.A.B. vaccine and neither of them contracted enteric



Text-fig. 2. Chart of date of onset of seventy-six cases of enteric fever at Acre, Palestine, April–May 1948.

Table 4

(*a*) *Relation of age to incidence of enteric fever*

	Average age (years)		
	Of whole unit	Of those who contracted enteric fever	Of those not affected
Infantry company	20·5	20	21
Palestine police	26	24·5	27

(*b*) *Relation of length of overseas service to incidence of enteric fever*

	Average length of overseas service (years)		
	Of whole unit	Of those who contracted enteric fever	Of those not affected
Infantry company	0·9	0·6	1·4
Palestine police	5·5	3	6

fever; of the remaining sixty-two all had been inoculated within the previous 2 years with alcoholized T.A.B. vaccine, which Dr A. Felix informs us was prepared at the Government Laboratories, Jerusalem.

Boyd (1943) has shown that the protection conferred by Italian vaccine was inferior to that following inoculation with the British phenolized vaccine. Jordan & Everley Jones (1945) recorded a morbidity rate of 30% in an outbreak of eighty cases of typhoid fever among inoculated troops in France in September 1944; of the forty-four cases treated by Jordan & Everley Jones, all were up to date with their yearly T.A.B. inoculations, and from only two was definite evidence obtained that the alcoholized preparation of T.A.B. had been given in their last dose.

Anderson & Richards (1948) observed an incidence of 14·7 % in an outbreak of 110 cases in Egypt in the summer of 1945; 91 % of the patients had been inoculated with T.A.B. vaccine during the previous 12 months, and in about 75 % of cases the most recent inoculation had been with the alcoholized vaccine.

The epidemic at Acre is considered to have been due to an overwhelming infection with enteric organisms, in association with gross faecal contamination of the water supply. It is felt that, if the Palestine police and the infantry unit were exposed to the same risk of enteric infection, the difference in morbidity between 60 and 17 % can probably be explained by the policemen being older men than those of the infantry unit, and with greater 'seasoning' in the life of a subtropical climate.

Clinical features

The course of the disease in the seventy-six cases was variable and has been classified as mild, moderate or severe.

The mild cases, of which there were thirty-two, have been defined as those who were pyrexial for a period of up to 3 weeks. The majority were febrile for a period of 10–14 days and they presented the characteristic features of mild enteric fever. Eighteen of the cases were proved bacteriologically and in two cases no organism was isolated, and the diagnosis was made on clinical grounds.

The moderately severe cases, seventeen in number, were those who ran a fever for 3–4 weeks, but in whom this did not rise above 103° F. Their clinical condition never gave rise to anxiety.

The remaining twenty-seven cases were classified as severe. These cases all showed the features of fully developed typhoid fever with toxaemia, delirium, incontinence, etc. Intestinal haemorrhage occurred in three cases, in one of which it was fatal. Two cases in this group died from toxaemia and two cases presented with haemoglobinuria (Batty Shaw, 1951).

Table 5. *The relation of the severity of disease to the type of infection*

Organism	No. of cases		
	Severe	Moderate	Mild
Salm. typhi	12 (3 deaths)	13	18
Salm. paratyphi B	0	1	2
Salm. typhi and *Salm. paratyphi B*	15	3	10
Clinical enteric	0	0	2

The mortality in the epidemic was low (3·94 %). There were more severe cases among the proved cases of double enteric infection than in those from whom *Salm. typhi* alone was isolated, but the three fatal cases all occurred in the latter group (Table 5). The fatal cases all occurred in fully inoculated men from the infantry unit; one of these was the man with the longest period of military service in the infantry unit; he had received his initial T.A.B. inoculations in England in 1944, when it is probable that the alcoholized preparation of the vaccine was employed.

Treatment

The cases were treated on routine lines with rest in bed, nursing and an adequate intake of fluids, as the mainstays of treatment. Tepid sponging was administered three times a day, and more frequently to those who were severely ill. A minimum of 15 g. of salt were given daily in addition to supplements of vitamins. All patients were given a high calorie, roughage-free diet, except when they were so ill that they could only take fluids.

During the third week of the epidemic a supply of polymyxin B was made available for its first therapeutic trial, in the treatment of enteric fever, through the kindness of the Wellcome Physiological Research Laboratories. Polymyxin A ('aerosporin') was identified by Ainsworth, Brown & Brownlee (1947), and shown (Brownlee & Bushby, 1948) to have a selective action against Gram-negative organisms (including *Salm. typhi*) in experimental infections. Swift (1948) reported promising results with polymyxin A in ten cases of pertussis. Nine of Swift's cases developed a transient albuminuria, and experimental work at the Wellcome Laboratories suggested that a related antibiotic, polymyxin B, was free from this nephrotoxic action when administered to the rat and dog. Polymyxin D was isolated independently in America (Benedict & Langlykke, 1947; Stansly, Shepherd & White, 1947), and was demonstrated to exert a similar range of anti-bacterial activity against Gram-negative organisms as polymyxin A, and in the presence of serum (Schoenbach, Bryer & Long, 1948).

Thirteen of the severe cases at Acre were treated with 0·2 mg. of polymyxin B (batch no. 135P) per kg. of body weight, by 4-hourly intramuscular injection, for a period of 5 days. It was not possible to treat the cases early in the course of the disease, and in the small dosage employed, approximately 15 mg. 4-hourly, little beneficial effect was observed when the treated cases were compared with a series of untreated controls. It was not possible to estimate the blood concentration of polymyxin achieved, but that it was not at a chemotherapeutic level was shown by the fact that the blood was not sterilized in any one case. Ten out of the thirteen cases showed renal damage of varying degrees while under treatment; vomiting, pallor, a fall in blood pressure and diarrhoea also occurred in six cases. It was later estimated that there were 15 μg. of a histamine-like substance in each 15 mg. dose of polymyxin B that was used, and these latter toxic effects could all be attributed to a histamine-like impurity.

Ross (quoted by Stansly, 1949) reported no striking clinical improvement in two cases of typhoid fever treated with polymyxin B, although the organism was sensitive *in vitro*. Schoenbach (quoted by Stansly, 1949) treated three cases of typhoid fever with polymyxin D in doses of 4 mg./kg. of body weight daily, intramuscularly, for a period of 2–5 days. One patient was treated in the fourth week of disease, when he was already delirious, and died 60 hr. after treatment was instituted. A second case responded well to minimal doses of polymyxin, which was scarce at the time, but relapsed 3 weeks after the course was discontinued. A third case, in an elderly man, appeared to show a dramatic response to the treatment, and blood and stool cultures, positive prior to treatment, became negative.

Stansly (1949) confirmed that polymyxin B, in addition to polymyxin A and D, may have a nephrotoxic action, in addition to producing subjective nervous effects of paraesthesiae, dizziness, etc.

In a recent review of the modern anti-biotics, Cruickshank (1950) has cited the action of polymyxin on the typhoid bacillus as an example of the way in which an antibiotic may be very active against an organism *in vitro*, but have no therapeutic effect in the treatment of infection with that organism. In addition, the toxic effects of the polymyxins upon the kidney, which we encountered in the cases from the Acre outbreak, have influenced the majority of physicians and pathologists against their parenteral use (Garrod, 1950). Chloramphenicol has now become the antibiotic of election in the treatment of enteric fever.

Diagnosis

The diagnosis in seventy-four of the seventy-six cases (97·3 %) was confirmed bacteriologically, and in the remaining two cases the diagnosis was made on clinical grounds. Blood culture was the main method of diagnosis, and a discussion of the factors which influenced these results is given elsewhere (Batty Shaw & Mackay, 1951). Enteric organisms were isolated by blood culture in seventy-one of the seventy-six cases (93·4 %); stool and urine culture were performed in those cases in which repeated blood culture had been negative. The results of the bacteriological investigations were as follows: *Salm. typhi* alone, 43 cases; *Salm. paratyphi B* alone, 3 cases; *Salm. typhi* and *Salm. paratyphi B*, 28 cases.

The distribution of these cases between the infantry company and the Palestine police is shown in Table 6.

Table 6

	Infantry company	Palestine police	Total
Number of cases of typhoid fever	35	8	43
Number of cases of paratyphoid fever	3	0	3
Number of cases of typhoid and paratyphoid fever	26	2	28
Number of cases of clinical enteric fever	1	1	2
Total	65	11	76

The twenty-eight cases of double enteric infection were diagnosed by one of four methods. In fifteen, both organisms were isolated from the same blood culture, and in two from the same specimen of stools or urine. Ten cases were diagnosed by the isolation of one organism from blood culture and the second from the stools or urine later in the disease (in one instance (Batty Shaw, 1951, case B), the stool isolation was made on the patient's return to England). On one occasion the first organism was isolated by a blood culture taken early in the disease and the second organism from a later culture. At the Central Pathology Laboratory, Fayid, Egypt, all the specimens of *Salm. typhi* were shown to be of Vi-phage type T. The specimens of *Salm. paratyphi B* were identified at the Central Enteric Reference Laboratory, London, as belonging to Vi-phage type 'Dundee' (Dr A. Felix, personal communication).

DISCUSSION

Double enteric infections introduce several problems of bacteriological, epidemiological and clinical interest.

In their paper on 'les fièvres typhoïdes intriquées', Chantemesse & Grimberg (1916) showed that, in glucose broth, a culture of *Salm. typhi* completely inhibited growth of paratyphoid organisms, as judged by sugar fermentations. However, Hébert & Bloch (1917), in the following year, demonstrated that if one mixed *Salm. typhi* and *Salm. paratyphi A* organisms in the proportion of 9:1, then the resulting culture had all the characteristics of *Salm paratyphi A*. This antagonistic action of paratyphoid bacilli against typhoid bacilli was confirmed by the experimental work of Achard (1916) on rabbits and guinea-pigs. He inoculated these animals with a mixture of 'one-quarter' of *Salm. paratyphi B* and 'three-quarters' of *Salm. typhi*. He cultured the bacilli from all the organs of those animals which died, or were killed, and only grew *Salm. paratyphi B*. However, Achard concluded that these animal experiments could not be applied to man, who, he stated, was more sensitive to typhoid bacilli, and in whom a typhoid infection might obscure an underlying concurrent infection with paratyphoid organisms. Rist (1916) considered that the experimental demonstration of an antagonism between typhoid and paratyphoid organisms explained the infrequency with which cases of double infection were diagnosed. For this reason he suggested the importance of prolonged incubation of a diagnostic blood culture (Batty Shaw & Mackay, 1951). In spite of their experimental demonstration of an antagonism between paratyphoid and typhoid bacilli, Chantemesse & Grimberg (1916) considered that human invasion by one organism, especially typhoid, favoured invasion by other enteric group organisms, e.g. *Salm. paratyphi A* or *B*. Levy (1936) concluded that, in view of the clinical experience that mixed typhoid and paratyphoid infections are not infrequent, a synergism between the two organisms was more probable than an antagonism.

Many of the earlier papers on double enteric infections include a discussion of the possibility of a mutation between two organisms of the enteric group. Siredey (1915) described six cases of paratyphoid B fever, diagnosed by agglutinations, which, after 15–20 days of apyrexia, were followed by a recrudescence of fever with a raised agglutination against *Salm. typhi*. He suggested that such cases might be due to a transformation from one bacillus to another. Achard (1929) considered that there was reliable evidence to show that there exist various types of organisms between the four classical groups of enteric organisms, and Borcinelli (1930, quoted by Levy, 1936) claimed to show that *Salm. paratyphi B* might acquire all the cultural characteristics of *Salm. typhi*. The evidence for such a mutation is, however, slender, and such observations may have been due to contamination or faulty agglutination technique. Geiger, quoted by Nerlich (1934), based his claim for mutation on the fact that he was unable to isolate *Salm. typhi* from the water or from carriers in an outbreak of 4058 cases of typhoid fever at Dresden, due to a probably water-borne infection. Earlier in the same year there had been a small outbreak of paratyphoid A fever in the neighbouring countryside, and he postulated that he was dealing with a mutation from *Salm. paratyphi A* to *Salm. typhi*. It

is a common experience to be unable to isolate the causal organism from a suspected source of enteric infection, and Geiger's claim is based on slender and circumstantial evidence. Rimpau (1932) considered that it was not necessary to invoke a bacterial mutation to explain those cases of enteric fever in which two enteric group organisms had been isolated. He considered that such cases were either examples of a mixed ('double') infection, or that such persons had been symptomless carriers prior to contracting their second infection. There has been no later work to suggest that typhoid bacilli may acquire the characteristics of paratyphoid bacilli, though recently the occurrence of a mutation between different phage types has been suggested.

Nerlich (1934), who investigated the records of many German institutions for double enteric infections, considered that such infections were of considerable epidemiological importance, and usually suggested a water or food-borne infection. It will be seen from Table 2 that the majority of recorded epidemics have been spread by water or milk which, in a number of instances, has been contaminated with sewage. The epidemic of five hundred cases on a Rhine steamer (Seiderer, 1929) was attributed to potato-salad, but no further information is available as to whether this was itself infected from the water in which it was prepared. The evidence at Acre suggested that this epidemic was caused by gross contamination of the water supply with sewage. The 'multiple enteric' outbreaks described by Boyd (1943) occurred amongst Italian prisoners who had been captured in unexpectedly large numbers in the North African battles, and had, perforce, to live under bad conditions of hygiene for a considerable period. By the isolation of two enteric organisms from one individual, it may be possible to relate other cases of a single infection to the same source of infection. Analogous studies may be of great value in the investigation of an enteric epidemic, and more recently the introduction of phage typing has extended the scope of this line of investigation (Craigie & Yen, 1938; Felix & Callow, 1943; Craigie & Felix, 1947).

It has been claimed by Vincent & Muratet (1916), and others, that a double enteric infection has a definite clinical picture, and that the prognosis of such cases is worse than for a single infection. Étienne (1918*a*, *b*) observed that although the onset of such infections is more sudden than with double infections, and the fever is more irregular, the fundamental symptomatology and signs differ little in the two types. Our observations at Acre confirmed the conclusions of Levy (1936), that there are no specific features of a double enteric infection. There was no distinguishable difference between the different groups in our cases, and, indeed, the manifestations of enteric fever are so variable that it is felt that this will explain the observations of Vincent & Muratet. With regard to the bad prognosis of double enteric infections, it is noteworthy that the three deaths in the Acre outbreak all occurred in those patients from whom *Salm. typhi* alone had been isolated, and that in the twenty-eight cases of double infection there were no deaths.

The diagnosis of double enteric infection may be established by any of the standard cultural methods. Isolation of both organisms by blood culture is the most certain, for, as has been discussed, the presence of one organism in the excreta does not exclude the possibility that the patient was previously an enteric carrier.

However, unless a double infection is suspected, or a careful bacteriological examination made, such cases may readily be overlooked. Torrens (1922) stated that although there were a number of double infections in the British Army in France during the 1914–18 war, probably many more went undiagnosed, since further investigations would not be undertaken as a routine in those cases where the presence of one enteric infection had been established. In his work on blood cultures, Rist (1916) observed on several occasions that he was able to isolate *Salm. typhi* after 2 or 3 days' incubation, but after a further 8–15 days' incubation, the organism produced gas and gave the agglutination reactions of paratyphoid organism. Rist explained this phenomenon by postulating the presence of a small number of paratyphoid organisms in the original culture and that these, being initially overgrown by the typhoid organisms, required a longer period of incubation for their growth and subsequent detection. The diagnosis of a double enteric was established by this method in ten cases. We have discussed elsewhere (Batty Shaw & Mackay, 1951) the factors affecting the results of blood culture in the Acre outbreak; other possible reasons for the unusual length of incubation required may have been previous inoculation or that only 5 ml. of blood were withdrawn for each culture.

Although the diagnosis of double enteric infection has been disputed in those cases in which it has been established by the Widal reaction, it is not intended to cast doubt upon the value of this test in certain instances. It is probable that some cases of true double infection have been excluded, especially in those reported cases who were previously un-inoculated (Savage, 1905; Achard, 1929, cases 2 and 3), but it was decided not to include in this series those cases in which the diagnosis was in doubt. The role which the Widal test can play in the diagnosis of double infection is demonstrated by the cases reported by Castellani (1907), Gautier & Weissenbach (1916) and Étienne (1918*b*). These authors, as a result of finding raised agglutinins against two enteric organisms, intensified the search for two organisms and demonstrated their presence by cultural methods, thus firmly establishing the diagnosis of a double infection.

SUMMARY

1. A double enteric infection is defined as the simultaneous infection of an individual or group of individuals with two organisms of the enteric group. The literature of the previously recorded cases and epidemics, in which the diagnosis of double enteric infection has been established by cultural methods, is reviewed.

2. An account is given of a double enteric outbreak of seventy-six cases which occurred amongst British troops and police at Acre, Palestine, in 1948. The infection is thought to have been due to contamination of the water supply with sewage during the civil disturbances. The diagnosis was established bacteriologically in seventy-four cases (97·3%); *Salm. typhi* was isolated in forty-three cases, *Salm. paratyphi B* in three, and both *Salm. typhi* and *Salm. paratyphi B* from twenty-eight cases. There were three fatal cases in the epidemic (mortality rate = 3·94%).

3. The morbidity rate from enteric fever among the infantry unit was 60%,

and among the Palestine police, 17%. The possible reasons for this difference is discussed, and the conclusion drawn that it was probably due to the Palestine policemen being older men, with longer overseas service and more 'seasoned' to life in subtropical conditions.

4. Thirteen cases were treated with polymyxin B (15 mg. 4-hourly for 4-day periods); with this small dose no beneficial therapeutic effects were observed, and ten cases showed evidence of renal damage while under treatment.

5. The bacteriology, epidemiology and clinical aspects of double enteric infections are discussed. The diagnosis of a double enteric infection may be established with the greatest certainty by blood culture. Such infections are usually water-borne or milk-borne, and tend to occur when there has been a severe breach of hygiene, e.g. in the contamination of a water supply by sewage. The claim that the prognosis in instances of double enteric infection is worse than with single infections is not supported by the experiences at Acre where the three fatal cases occurred in cases infected with *Salm. typhi* alone.

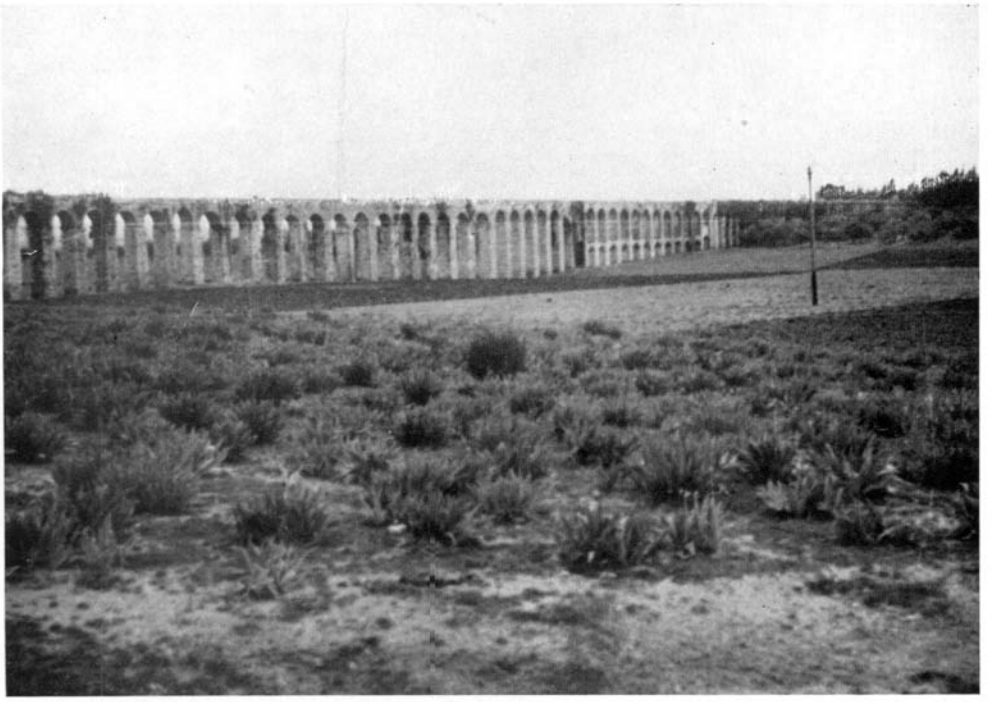
We would like to thank our various colleagues for their assistance in the management of this epidemic, and the Wellcome Physiological Research Laboratories for the supply of polymyxin B. For advice in the preparation of this manuscript we are indebted to Dr E. R. Boland, Prof. R. Knox and Prof. G. Payling Wright. Acknowledgements are due to the Director-General of Medical Services for permission to publish.

REFERENCES

ACHARD, C. (1916). *C.R. Soc. Biol., Paris*, **79**, 751.
ACHARD, C. (1929). *Les Maladies Typhoïdes*, p. 34. Paris.
AINSWORTH, G. C., BROWN, A. M. & BROWNLEE, G. (1947). *Nature, Lond.*, **160**, 263.
ANDERSON, E. S. & RICHARDS, H. G. H. (1948). *J. Hyg., Camb.*, **46**, 164.
BATTY SHAW, A. (1951) (in the Press).
BATTY SHAW, A. & MACKAY, H. A. F. (1951). *J. Hyg., Camb.*, **49**, 315.
BENEDICT, R. G. & LANGLYKKE, A. F. (1947). *J. Bact.* **54**, 24.
BERNARD, L. & PARAF, J. (1915). *Ann. Méd.* **2**, 443, 469.
BOURGES, H. (1919). *Arch. Méd. Pharm. nav.* **118**, 222.
BOYD, J. S. K. (1943). *Brit. med. J.* **1**, 719.
BROWNLEE, G. & BUSHBY, S. R. M. (1948). *Lancet*, **1**, 127.
CASTELLANI, A. (1907). *Lancet*, **1**, 284.
CASTELLANI, A. (1915). *J. trop. Med.* (Hyg.), **18**, 37.
CHANTEMESSE, A. & GRIMBERG, A. (1916). *Pr. méd.* **24**, 265, 273.
CHEVREL, F. (1913). *Progr. méd., Paris*, **41**, S 3, 439.
CONRADI, H. (1904). *Dtsch. med. Wschr.* **30**, 1165.
COURMONT, P. & CHATTOT (1916). *C.R. Soc. Biol., Paris*, **79**, 567.
CRAIGIE, J. & FELIX, A. (1947). *Lancet*, **1**, 823.
CRAIGIE, J. & YEN, C. H. (1938). *Canad. publ. Hlth J.* **29**, 448, 484.
CRUICKSHANK, R. (1950). *Proc. R. Soc. Med.* **43**, 760.
DAWSON, B. & WHITTINGTON, T. H. (1915–16). *Quart. J. Med.* **9**, 98.
DUBROWINSKI, S. B. (1929). *Zbl. Bakt.* **113**, 225.
ÉTIENNE, G. (1915). *Bull. Soc. méd. Hôp. Paris*, **39**, S 3, 456.
ÉTIENNE, G. (1918*a*). *Ann. Méd.* **5**, 63.
ÉTIENNE, G. (1918*b*). *Bull. Acad. Méd. Paris*, **79**, S 3, 86.
ÉTIENNE, G. & VOIRIN (1917). *Bull. Soc. méd. Hôp. Paris*, **41**, S 3, 973.
FELIX, A. (1924). *J. Immunol.* **9**, 115.
FELIX, A. (1929). *J. Hyg., Camb.*, **28**, 418.

FELIX, A. & CALLOW, B. R. (1943). *Brit. med. J.* **2**, 127.
FIRTH, R. H. (1912). *J. R. Army Med. Cps*, **19**, 157.
FORNET (1907). *Arb. GesundhAmt., Berl.*, **25**, 247.
FORTESCUE-BRICKDALE, J. M. (1915). *Brit. med. J.* **2**, 938.
GAEHTGENS, W. (1906). *Zbl. Bakt.* **40**, 621.
GARDNER, A. D. (1929). *J. Hyg., Camb.*, **28**, 376.
GARDNER, A. D. (1937). *J. Hyg., Camb.*, **37**, 124.
GARROD, L. P. (1950). *Proc. R. Soc. Med.* **43**, 689.
GAUTIER, C. & WEISSENBACH, R. J. (1916). *Bull. Soc. méd. Hôp. Paris*, **40**, S 3, 450.
GÉRARD, P. & FENESTRE (1917). *Progr. méd., Paris*, **44**, S 3, 65.
GERMANI, A. (1927). *Studium*, **17**, 104.
GRATTAN, H. W. & HARVEY, D. (1911). *J. R. Army Med. Cps*, **16**, 9.
HAHN, M. & REICHENBACH, H. (1928). *Veröff. MedVerw.* **27**, 361.
HÉBERT, P. & BLOCH, M. (1917). *Bull. Soc. méd. Hôp. Paris*, **41** (S 3), 937.
HEYMER, A. & WOHLFEIL, T. (1933). *Klin. Wschr.* **12** i, 277.
HORGAN, E. S. (1932). *J. Hyg., Camb.*, **32**, 523.
JEANSELME, B. & AGASSE-LAFFOND, E. (1915). *Bull. Soc. méd. Hôp. Paris*, **39**, S 3, 371.
JORDAN, J. & EVERLEY JONES, H. (1945). *Lancet*, **2**, 333.
KAYSER, H. (1904). *Dtsch. med. Wschr.* **30**, 1803.
LABBÉ, M. (1916). *Ann. Méd.* **3**, 13.
LEBOEUF, A. & BRAUN, P. (1917). *Ann. Inst. Pasteur*, **31**, 138.
LEVY, J. (1936). *Gaz. hebd. Sci. méd.* **57**, 470, 484, 504, 522, 534, 552, 562, 584.
MARTIN, C. J. & UPJOHN, W. G. D. (1916). *Brit. med. J.* **2**, 313.
MINER, J. T. (1922). *J. infect. Dis.* **31**, 296.
MINET, J. (1917). *Bull. Soc. méd. Hôp. Paris*, **41**, S 3, 861.
MONTEL, F. L. (1939). *Marseille méd.* **76** i, 678.
NERLICH, G. (1934). *Arch. Hyg., Berl.*, **112**, 1.
NEUHAUS (1926). *Veröff. MedVerw.* **23**, 153.
NIETER, A. (1907). *Münch. med. Wschr.* **54**, 1622.
OSLER, SIR W. & MCCRAE, T. (1935). *The Principles and Practice of Medicine*, pp. 5, 25, 12th ed. New York: D. Appleton.
PERRY, H. M. (1918). *Lancet*, **1**, 593.
PIRERA, A. (1919). *Gazz. med. napolet.* **2**, 372.
RIMPAU, W. (1914). *Münch. med. Wschr.* **61**, 354.
RIMPAU, W. (1932). *Münch. med. Wschr.* **79**, 2067.
RIST, E. (1916). *Ann. Méd.* **3**, 88.
SACQUÉPÉE, E. (1916). *Bull. Soc. méd. Hôp. Paris*, **40**, S 3, 443.
SAFFORD, A. H. (1913). *J. R. Army Med. Cps*, **20**, 567.
SAVAGE, W. G. (1905). *J. Path. Bact.* **10**, 341.
SAVAGE, W. G. (1942). *J. Hyg., Camb.*, **42**, 393.
SCHOENBACH, E. B., BRYER, M. S. & LONG, P. H. (1948). *Ann. N.Y. Acad. Sci.* **51**, 267.
SEIDERER, F. (1929). *Z. MedBeamt.* **42/51**, 439.
SIREDEY, A. (1915). *Bull. Soc. méd. Hôp. Paris*, **39**, S 3, 371.
STANSLY, P. G. (1949). *Amer. J. Med.* **7**, 807.
STANSLY, P. G., SHEPHERD, R. G. & WHITE, H. J. (1947). *Johns Hopk. Hosp. Bull.* **81**, 43.
SWIFT, P. N. (1948). *Lancet*, **1**, 133.
THOMAS (1907). *Klin. Jb.* **17**, 207.
TORRENS, J. A. (1922). *Official History of the War. Medical Services*, **1**, p. 45. London: H.M.S.O.
VINCENT, H. & MURATET, L. (1916). *Fièvres typhoïdes et paratyphoïdes*. Paris. Translated into English by J. D. Rolleston, University of London Press (1917), pp. 133, 142.
WILSON, G. S. & MILES, A. A. (1946). Topley and Wilson's *Principles of Bacteriology and Immunity*, **2**, p. 1529, 3rd ed. London: Arnold.
WILSON, R. D. (1949). *Cordon and Search*, p. 190. Aldershot: Gale and Polden.

(*MS. received for publication* 26. IV. 51.)



The Al Kabiri aqueduct.

https://doi.org/10.1017/S002217240004417X Published online by Cambridge University Press