AN OUTBREAK OF TYPHOID FEVER IN THE MIDDLE EAST

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INTRODUCTION

During the period 1939–46, a large number of British personnel were stationed for considerable periods abroad. This new population, unprotected by any natural immunity, and coming from countries in which the incidence of the enteric fevers is very low, moved into regions in Mediterranean countries and the Middle and Far East in which these diseases are endemic. The standards of hygiene in these areas are lax, the native community often uneducated, and the enteric-carrier rate undetermined but undoubtedly significant. In the absence of prophylactic measures, therefore, it would not have been surprising to encounter a high incidence of enteric infections among British personnel. The final figures are not yet available, but it is known that they were quite low. Sporadic cases were relatively infrequent and the greatest incidence occurred in epidemics in camps. Such outbreaks could usually be traced to native carriers working as cooks, food handlers or waiters. Some of the outbreaks have been reported in the literature, but a strong clinical bias has been apparent in most of these accounts, and the epidemiological investigations have often been awarded a position of minor importance.

REVIEW OF RECENT LITERATURE

Typhoid outbreaks in British Service personnel were reported by Scott (1943) in England, Bookless & Naftalin (1945) in Egypt, St John-Brooks (1945) in India, Jordan & Everley Jones (1945) in France, and Downie & Phillips (1945) in England. The outbreak described by Scott (1943) showed an attack rate of 26 % (13 cases, 50 persons at risk) with no deaths. That reported by Jordan & Everley Jones (1945) had also a high attack rate—30 % of 230 at risk—and in this instance the case-fatality rate was 11 %. Bookless & Naftalin (1945) emphasized the difficulties of diagnosing typhoid in the presence of a coincident malarial infection. Downie & Phillips (1945) gave an account of a small outbreak in a Royal Air Force camp in Bedfordshire. Epidemiological study revealed sewage contamination of the water supply, but no carrier was found, although it was evident that the water pollution had occurred in the camp.

Domrachev (1944) reported an outbreak in the Russian Army, and pointed out that the clinical and serological features in inoculated patients frequently departed from the classical picture. In his series a normal leucocyte count was present in 32 % of cases, and 10 % showed leucopenia with a relative increase in polymorphs.

Raettig (1944), describing an outbreak of 32 cases of typhoid in inoculated soldiers in the German Army on the Eastern Front, stated that the course was severe, complications frequent, and the case mortality 25 %.

Tullis (1945), in an account of one Italian and six American cases in Italy, emphasized (in spite of the small number) that the classical picture of typhoid fever was not presented by inoculated patients suffering from the disease. Syverton, Ching, Cheevor & Smith (1946), however, describing 21 cases of paratyphoid A and three of typhoid in American soldiers in Guam, stated that previous immunization did not appear to alter the clinical picture of the disease.

Other aspects of typhoid fever were discussed by Boyd (1943) and Bhatnagar (1944). Boyd showed that the protection conferred by Italian T.A.B. vaccine was inferior to that following inoculation with the British vaccine. Bhatnagar (1944) combined the information provided by a large number of cases in India, and attempted to correlate the clinical and serological features from a prognostic point of view. He claimed that very high O titres, with an absence of Vi agglutinin, were associated with the 'toxic' type of case, frequently terminating fatally, and that a fall in the O titre with a concomitant rise in the Vi titre was of good prognostic significance.

The epidemic in the civil population in Malta during 1943, of which a description was given by Galea (1944), showed a case-fatality rate of 6·2 % in 159 inoculated patients, and 13·3 % in 937 uninoculated patients—a significant difference. The overall case-fatality rate was 12·2 %. This was a water-borne outbreak. Although the exposure rate must have been high, the attack rate was only 9·9 per 1000 in the districts involved. Unfortunately, it was not possible to determine the precise proportion of inoculated to uninoculated persons in these areas.

Reitler & Marburg (1944), in Palestine, had the opportunity of comparing attack rates in inoculated and uninoculated groups. Their figures were 9·7 and 4·0 % respectively, but they pointed out that this apparent paradox was caused by the closer contact of the inoculated group with the sources of infection. They concluded also that, judging from their series, there was no evidence that inoculation of persons at risk created the danger of 'provocation' typhoid.

Murphy, Petrie & Morris (1944), in the United States, were able to trace 701 persons known to have drunk sewage-contaminated water. *Salmonella typhi* was isolated from 80 persons, of whom 11 were completely asymptomatic and a further 11 not sufficiently ill to be confined to bed. In many instances the investigation of asymptomatic persons was limited to the cultivation of one stool, which suggests that a more thorough search would have resulted in the discovery of more infected individuals. Of 531 uninoculated persons, 61 became clinically ill (11·5 %), while the corresponding figure for 170 inoculated people was 8 (4·7 %), a statistically significant difference. The overall case-fatality rate was 2·9 %. Uniform exposure to infection was indicated by the fact that of 400 persons interrogated, 74 % gave a history of gastro-enteritis. It is evident that in spite of the high numbers exposed to infection, the attack rate was relatively low. These findings also indicate that, in any typhoid epidemic, a considerable proportion of infections are sufficiently mild to escape detection, and that symptomless transient carriers of *Salm. typhi* may be numerous.

Archila (1945) reviewed a protracted epidemic in Venezuela. 243 cases occurred during a period of more than 2 months. The infection was traced to an intermittent excretor of *Salm. typhi*, living near an aqueduct carrying water to the town, and was probably precipitated by the interruption of water chlorination for about 3 weeks before the commencement of the epidemic. The case-fatality rate was 6·9%.

Lacambre-Dudevant (1945), in France, discussed the incidence of enteric fevers in the civilian population in Nantes under hazardous battle conditions, and stated that, in spite of periodic complete absence of hygienic control of the water supply, the enteric fever morbidity rate during 1944 was no higher than that of the preceding 4 years. She attributed this limitation to the institution of compulsory T.A.B. vaccination in the 10–30 years age groups in June 1944.

A report by Grasset (1945), in South Africa, gave a statistical survey of the results of 10 years of typhoid endotoxoid inoculation in the Witwatersrand Gold mines. He claimed, rather surprisingly, that until the adoption of his method, the endemicity of typhoid fever was unaffected either by rigid supervision of hygiene, or by the administration of a bile vaccine given orally or of a heat-killed phenolized

vaccine given parenterally. The incidence fell from 5·26 to 0·25 per 1000 and the mortality rate from 1·18 to 0·05 per 1000 when endotoxoid immunization was generally adopted. It will be seen, however, that on this basis the case-fatality rate was not appreciably altered.

THE SHALLUFA OUTBREAK

The outbreak outlined below is of considerable interest because it occurred in a closed community of inoculated persons. It presented, therefore, an opportunity to examine the degree to which prophylactic immunization against typhoid fever affected the incidence of clinical typhoid and the severity of the developed disease. The epidemiological investigations resulted in the discovery of the carrier responsible for the outbreak, and in establishing the identity of the organism he was excreting with that infecting the patients. With the exception of a classification on the basis of clinical severity, the clinical findings have been omitted and other aspects amplified.

Development of the outbreak

The outbreak occurred in June and July 1945, in the airmen's mess of a large Royal Air Force camp situated at Shallufa near Suez. The commencement of the series was marked by four men reporting sick on 12 June. The first patient dated his symptoms from 9 June and the last from 24 July 1945.

The 13th General Hospital (Hospital A) dealt mostly with the first half of the epidemic and the 19th General Hospital (Hospital B) with the second half. The distribution of patients was as follows:

Hospital A	56 cases
Hospital B	49 cases
Other hospitals	5 cases
Total	110 cases

Attack rate

The total number at risk was 747. As these men fed under uniform conditions in the same mess, it can be assumed that they were practically all exposed to infection. 110 cases occurred, an attack rate of 14·7 %.

Mortality and severity

Table 1 summarizes the types of cases in the two hospitals under review. It should be noted that the clinical classification on the basis of severity was carried out by different physicians in the two hospitals, and must be regarded as arbitrary. However, as will be seen from Table 2, this classification accords well with the frequency distribution of positive blood cultures, indicating that it is not grossly inaccurate. The six patients with perforation or haemorrhage died. Statistical analysis does not

reveal a significant difference between the mortality figures in the two hospitals. The overall case-fatality rate, including patients treated in other hospitals, was 10 %.

Bacteriological and pathological aspects of the outbreak

(a) Diagnostic isolation of organisms

Blood culture. This was instituted as a routine as soon as an enteric fever outbreak was suspected. During the initial phase a certain amount of delay occurred between the onset of illness and admission to hospital, because of the obscurity of the symptoms. Blood culture was therefore carried out rather later in the early cases than in the remainder. When a negative result was obtained the test was repeated, usually more than once, at about 3-day intervals.

Urine. This was investigated concurrently with stools in Hospital B only. Mid-stream specimens were incubated overnight, and plated on MacConkey's agar the following morning. One urine out of eighteen so examined yielded *Salm. typhi*. The blood and faeces of this patient gave consistently negative results.

(b) Clearance tests

At least six stools and six specimens of urine per patient were examined during the convalescent period. Intervals of 3 or 4 days were allowed to elapse between successive specimens. Selenite F enrichment medium was used throughout. It was found by experiment in Hospital B that the optimum enrichment period for the batch of Selenite F in use was not longer than 18 hr. When this was exceeded, a sharp drop occurred in the number of colonies of

Table 1. *Clinical types of cases in Hospitals A and B*

Hospital	No.	Severe	Moderate	Mild	Deaths	Intestinal perforations	Intestinal haemorrhage
A	56	26	14	16	7	3	2
B	49	14	27	8	3	Nil	1
Totals	105	40	41	24	10	3	3

Table 2. *Clinical classification related to the isolation of* Salmonella typhi

Clinical type	Positive blood culture	Negative blood culture	Totals
Severe	31 (78 %)	9	40
Moderate	25 (61 %)	16	41
Mild	6 (25 %)	18	24
Totals	62 (59 %)	43	105

In Hospital A, glucose broth and bile-salt broth were used separately; in Hospital B, glucose broth only was employed. The results indicated no difference in efficiency between the two media. Total isolations of *Salm. typhi*: 62 out of 105 cases (59 %). The majority of isolations yielded *Salm. typhi* in the Vi phase, and O agglutination could only be demonstrated by using boiled suspensions. The organisms were Vi phage type D 1.

Faeces. Owing to the pressure of work, diagnostic investigation of stools was largely restricted to those cases in which blood culture was negative, and therefore the number tested was relatively small. Specimens were examined during the second and third weeks at intervals of 4–7 days. The stools were plated out on MacConkey's agar after preliminary growth in fluid enrichment medium. For the latter purpose, Selenite F was used in Hospital A, and 1/200,000 brilliant green in Hospital B. *Salm. typhi* was isolated from four patients, including one in whom the organism was first isolated from a 'clearance' stool.

Salm. typhi appearing after plating out on MacConkey.

Typhoid bacilli were found in the stools of five out of 95 convalescent cases (5·3 %). In one instance, one stool only yielded the organism, although many further examinations were carried out on this case. In another, a carrier state persisted for some weeks.

Mid-stream specimens of urine were incubated overnight and then plated on MacConkey's agar. The organism was isolated from the urine of three patients (3·1 %). In one of the patients, whose urine contained typhoid bacilli at this stage, the original diagnosis had been made by urine culture, 16 days after the onset of symptoms (see above). He ceased to excrete the organism 84 days after the commencement of his illness.

The total percentage of convalescent excretors of *Salm. typhi* was thus 8·4. None of these became a persistent carrier, although excretion lasted for weeks in some instances.

(c) Leucocyte counts

These examinations were performed during the first 2 weeks in 71 cases.

The following points emerged:

(1) Leucopenia: counts of less than 5000 were encountered in 21 out of 71 cases (30 %).

(2) 62 % of these low counts occurred in severe infections.

(3) Extremes: Lowest count 2000 per cu.mm.; highest count 15,000 per cu.mm. (typhoid proved bacteriologically).

(4) 62 % had total leucocyte counts lying between 5000 and 10,000 per cu.mm., i.e. within normal limits.

(5) Differential counts (as percentages) were normal in most cases, even when the total count was low.

These findings indicate that the leucopenia classically described in typhoid fever is not invariably present.

(d) Post-mortem findings

Autopsies were performed on seven patients. Features of interest were:

(1) Variability of the intestinal lesions. In six cases a severe enteritis was the most striking feature, and was associated with marked thinning of the bowel wall. In one instance it was very pronounced and was accompanied by general weeping of blood into the lumen.

(5) In no instance was a true pneumonia with consolidation found, but pronounced vascular engorgement of the lungs was always evident.

(e) Serology

Two aspects of the serology were investigated—typhoid O and typhoid Vi agglutination. In Hospital A, O agglutination was carried out at least once in all cases, and repeated in many. Vi titration was performed once in each of 44 cases during convalescence.

In Hospital B, O agglutinations were rarely performed. Vi agglutination was investigated in all convalescent excretors of *Salm. typhi* and in 39 cases on discharge. It was repeated after a further 6 weeks on 22 patients, in order to assess falling or static titres, and to correlate them with the bacteriological findings.

Table 3. *O titres during the third week of the disease*

	Less than 1/100	1/100	1/200	1/400	1/800	1/1600	1/3200	Totals
Severe	3	6	4	7	4	1	1	26
Moderate	3	1	2	2	2	1	1	12
Mild	1	7	2	3	2	1	0	16
Totals	7	14	8	12	8	3	2	54

Table 4. *O titres during the fourth, fifth and sixth weeks of the disease*

	Less than 1/100	1/100	1/200	1/400	1/800	1/1600	1/3200	Totals
Severe	0	4	5	7	4	1	3	24
Moderate	1	0	3	1	5	4	0	14
Mild	1	3	2	5	5	0	0	16
Totals	2	7	10	13	14	5	3	54

(2) The appearance of the ulcers varied considerably from case to case. In one instance, where enteritis was not a salient feature, the ulcers were large and their sloughs projected into the lumen, although the intervening mucosa was relatively normal. In another, the ulcers were large but extremely shallow and seemed part of a general shedding of the mucosa. In yet a third, they were small and insignificant, although the general enteritis was severe.

(3) The state of the peritoneum was noteworthy in all cases. If frank peritonitis with fibrin flakes and soft adhesions was not present, general hyperaemia was invariably noted on the surface of the bowel, the omentum and the mesentery. The mesenteric lymph nodes were enlarged, but the degree of enlargement was sometimes slight, even when ulceration was present in the ileocaecal area.

(4) An obvious toxic and flabby condition of the myocardium was apparent in only two out of seven cases. In the remainder the heart was macroscopically normal.

(1) *O titres*. The sera were titrated in doubling dilutions from 1 : 100 to 1 : 3200, using Dreyer's tubes. The results are shown in Tables 3 and 4. Seventeen of 26 severe cases (65 %), 8 of 12 moderately severe cases (67 %) and 8 of 16 mild cases (50 %) had O titres of 1 : 200 or higher during the third week of the disease. A total of 33 out of 54 patients (61 %) had O titres of this magnitude during this period. Of the severe cases, one with an O titre of 1 : 400 and another with a titre of 1 : 1600 died.

Twenty of 24 severe cases (83 %), 13 of 14 moderate cases (93 %) and 12 out of 16 mild cases (75 %) had O titres of 1 : 200 or higher during the fourth, fifth and sixth weeks of the disease. Forty-five out of 54 patients (83 %) showed these O titres at this time. Deaths occurred in the severe case groups in two patients with O titres of less than 1 : 100, and in three patients with O titres of 1 : 200, 1 : 400, and 1 : 800 respectively. Two moderately severe cases had their first O titrations performed in the fourth week of their illness.

(2) *Vi titres*. Serial dilutions of serum, 1 : 5 to

11-2 .

1:320 (or higher if necessary), were made in 3 in. by $\frac{3}{8}$ in. test-tubes. 0·05 ml. of freshly prepared live Vi I suspension (Bhatnagar, Speechly & Singh 1938) was added to each tube (total volume 1·05 ml.). The racks were incubated at 37° C. for 3 hr., and then transferred to the refrigerator overnight. This technique was followed in both hospitals.

Vi agglutinin titration of most patients was performed immediately prior to discharge. The titrations were usually carried out between 70 and 95 days following the onset of symptoms. Extremes of this interval were 52 and 111 days. The number was reduced by deaths and early discharge of mild cases, but a total of 81 primary Vi titrations were performed. In Hospital B where 39 cases were so investigated, a further titration was carried out in twenty-two instances after a 6-week interval. It was unfortunately impossible to institute this investigation earlier in the disease.

Table 5. *Vi agglutinin titres during convalescence*

	1/10 or less	1/20	1/40	1/80	1/160 or over	Totals
Severe	13	6	4	5	1	29
Moderate	21	8	3	2	3	37
Mild	5	4	5	1	0	15
Totals	39	18	12	8	4	81

(a) The primary titres are set out in Table 5. Sixteen of 29 severe cases (55·2 %), 16 of 37 moderate cases (43·3 %) and 10 of 15 mild cases (66·7 %) showed Vi titres of 1:20 or higher during convalescence.

(b) Patients with an initially high titre of Vi agglutinin tended to lose this slowly, and generally presented a titre above 1:20 after a 6-week interval. Those with low primary titres—1:20 or less—exhibited a diminution, falling as a rule to 1:5 or less after 6 weeks.

(c) The highest titres encountered, with one exception (see below), were associated with persistence of the organism in the body. This obtained in both hospitals. The disappearance of typhoid bacilli from the stools or urine was accompanied by a falling Vi agglutinin titre, but there was usually a considerable delay before this dropped to normal limits. The temporary urinary carrier mentioned earlier had a Vi titre of 1:480, 64 days after the onset of symptoms, at which time his urine was bacteriologically positive. Excretion of the organisms ceased at the 84th day when his Vi titre was 1:160, and it was still 1:120 after a further 23 days.

Typhoid bacilli were isolated from the faeces of another convalescent patient 63 days after the onset of symptoms, when his serum Vi titre was 1:160. He was still excreting *Salm. typhi* 9 days later when the titre had dropped to 1:40, but was finally discharged after a full set of negative clearance tests

with a Vi titre of 1:30, 106 days after the commencement of his illness. The presence of typhoid bacilli in the stools of convalescents was not invariably associated with a high Vi titre in the serum. One patient, for example, showed a Vi titre of 1:5 with positive stools.

(d) In one case, clinically mild and never bacteriologically confirmed, the Vi titre was 1:40 on discharge, rising to 1:240 after 6 weeks, and to 1:320 after a further 21 days. Repeated investigations of stools and urine, and duodenal intubation, failed to isolate *Salm. typhi* from this patient.

Inoculation state

This was very satisfactory. 100 patients had been inoculated with T.A.B. vaccine during the preceding 12 months. In about 75 % of cases the most recent inoculation had been carried out with alcoholized T.A.B. vaccine. Table 6 summarizes the situation in 105 patients treated in Hospitals A and B.

Table 6. *Frequency distribution of number of inoculations*

No. of inoculations	No. of patients
1	8
2	4
3	17
4	42
5	18
6	3
7	5
8	2
Not stated	6
Total	105

The mean number of inoculations per man was 3·98 and the standard deviation was 1·47. The cases were divided into three groups according to clinical severity—severe, moderately severe and mild, and the mean number of T.A.B. inoculations per man was estimated in each group. This mean was slightly but not significantly *higher* in the severe case group than the other two groups. There was thus no evidence that the severity of the typhoid fever was inversely proportional to the number of T.A.B. inoculations a patient had received.

Epidemiology

All but two of the patients belonged to the airmen's mess. The two exceptions—an officer and a Police N.C.O.—had eaten in the affected mess during the epidemic period, and were shown to be infected with *Salm. typhi*, phage type D 1. They thus constituted part of the epidemic.

The strict localization of the outbreak facilitated the search for its origin. Water source and sewage disposal were satisfactory. As soon as it was suspected that an outbreak was in progress all cookhouse employees, locally employed and British, were changed, and a carrier investigation was carried out

on the suspended workers. The men were purged with magnesium sulphate and the second and third stools following this were seeded immediately into Selenite F enrichment medium. Specimens were received in the laboratory within an hour or two of being passed. Mid-stream specimens of urine were collected in sterile containers and forwarded with stools. Six stools and six specimens of urine were examined in each case, with a minimum interval of 3 days between stools. The bacteriological methods employed were identical with those used in clearance tests of patients.

A British cook yielded *Salm. typhi* Vi phage type D 1 in his first stool, 5 days after the commencement of the investigation. Two days later an Egyptian plate-washer gave a positive urine culture of the same phage type. After a further 3 weeks a second Egyptian carrier was found—a N.A.A.F.I. employee—with *Salm. typhi* in his stools. This organism could not be typed with any of the available phages.

The total number of native cookhouse employees examined was 68. Two carriers of *Salm. typhi* were found (3 %).

The British cook failed to produce the organism again, although exhaustive examination of his stools was carried out. It was therefore decided that he was a transient carrier, and was not the main cause of the epidemic. The native urinary carrier, however, gave a profuse growth of *Salm. typhi* from his urine without either concentration or preliminary enrichment, and was incriminated as the source of the infection. He gave a history of mild febrile illness 2 months earlier; this had not been sufficiently severe to incapacitate him. Treatment with sulphadiazine freed his urine of infection temporarily, but the organism returned within 24 hr. of withholding the drug.

The locally employed faecal carrier must be regarded as a fortuitous discovery, since phage typing of his organism showed that it was not associated with the outbreak. He had been employed for only 4 days before the institution of the carrier investigation and his exposure possibly forestalled another epidemic.

Vi agglutination tests were performed on the sera of all three carriers. The serum of the British transient carrier was negative at 1:5. That of the native urinary carrier showed an initial Vi titre of 1:30, rising to 1:40 a month later. The native faecal carrier gave a Vi titre of 1:5, increasing to 1:30 after a month. It is of interest to note that this man provided three negative stools during the first half of the investigation. His fourth stool, taken after an interval of 14 days, was positive, as were many subsequent specimens.

The case incidence showed a rapid decline commencing about 10 days after the change of cookhouse staff.

DISCUSSION

The percentage of bacteriologically confirmed cases in this epidemic was relatively low by modern standards, and criticism might be offered concerning the wisdom of accepting a purely clinical diagnosis as proof of typhoid infection. Most of the bacteriologically negative patients gave serological evidence of typhoid; three of them died, and were demonstrated to have characteristic typhoid lesions at post-mortem. In addition, since all investigations for other causes of prolonged pyrexia proved fruitless, it was felt justifiable to accept the diagnosis of typhoid as accurate, although the organism could not be isolated. A statistical comparison of bacteriologically proved and unproved cases on the basis of case mortality showed that the difference in mortality between the two groups was not significant, and that they could be random samples from the same series. It seems therefore reasonable to conclude that, with the other evidence available (history, symptomatology, serology and morbid anatomy), the bacteriologically negative cases were in fact cases of typhoid.

The serological investigations were not entirely diagnostic in their object. It was hoped to gain some information concerning the serological reaction to typhoid infection, of patients who had been regularly inoculated with T.A.B. vaccine over a period of years. In such subjects it might reasonably be expected that the antibody-forming mechanism, previously sensitized by inoculation, would react more energetically to the infection than that of uninoculated patients. Higher O titres were therefore expected on the average in this outbreak than would be encountered in outbreaks in uninoculated communities. An examination of Tables 3 and 4 will show that this expectation was not realized; the titres found did not differ in average height or frequency distribution from those usually encountered in civilian epidemics.

We hoped also to learn more about the formation of Vi agglutinins in patients inoculated with the recently introduced alcoholized vaccine.

H agglutinin titration was not undertaken because it has been shown to be of little value in inoculated patients, either from the point of view of diagnosis or as an indication of the protective response. O agglutination is of considerable diagnostic value, however, since healthy inoculated persons rarely show appreciable O titres (see Downie, 1942), and anamnestic reactions are uncommon. Titres of 1:100 are accepted as suspicious, and rising titres and those above 1:200 as strongly suggestive, of enteric fever.

Felix (1924) pointed out that low O agglutinin titres were indicative of poor resistance to the infection. He showed, also, that mild cases could present low O titres because of scanty bacterial

invasion of the blood or the low virulence of the infecting strain. It will be seen from Table 3 that the percentage of cases with O titres lower than 1:100 was highest in the mild group (50%), and somewhat lower but approximately equal in the severe and moderately severe groups (35 and 33% respectively). Differences were more distinct during the fourth, fifth and sixth weeks of illness, when 25% of mild cases, 17% of severe cases and only 7% of moderately severe cases showed titres of 1:100 or lower (Table 4). The total numbers are small, however, and it is not claimed that they present conclusive evidence on these points. Of the fatal cases, two dying in the third week had titres of 1:400 and 1:1600. The five patients dying in subsequent weeks showed O titres ranging from less than 1:100 (two cases) to 1:800. In only one case, therefore, was a high O titre associated with fatality. These findings differ from those of Bhatnagar (1944) who claims that very toxic cases may show O titres as high as 1:20,000, and that this feature is associated with a high case-fatality rate. Assuming that the toxaemia of typhoid fever is largely caused by the somatic antigen, which is the generally accepted view, and that the O titre is indicative of the magnitude of the protective response to this toxin, it is difficult to interpret Bhatnagar's findings, unless the antibody concerned is deficient in protective power. The serological picture from the point of view of O agglutination in the epidemic described conforms more closely to that reported by Felix (1924).

The Vi agglutinin titrations show a higher proportion of significant titres than the series described by Felix, Krikorian & Reitler (1935), but Bhatnagar (1938) found Vi antibody in all cases of typhoid investigated by him. Our initial Vi titrations were all carried out during the convalescent stage of the disease, which possibly accounts for the large number of positive results. The frequency distribution of Vi titres in severe cases did not appear to be markedly different from that in moderate and mild cases.

The second Vi titrations were undertaken with the object of determining whether the persistence of significant titres was always associated with the carrier state. The results indicated a relation between a falling titre and the cessation of excretion of typhoid bacilli, although titres above normal persisted for at least 6 weeks after the excretion had ceased. The absence of a carrier state was not proved in the cases concerned, since investigations could only be directed to the detection of excretion of organisms. Some patients, who did not excrete typhoid bacilli during convalescence, still presented significant Vi titres at the second titration, 6 weeks after discharge from hospital. It was concluded, therefore, that an interval of 6 weeks following discharge of the average case was not always sufficiently

long to permit the reactive Vi titres of the disease to fall to zero. It was also shown that a temporary carrier state was not invariably associated with a high Vi titre, and, conversely, that high titres were occasionally found late in convalescence in the absence of a demonstrable carrier state. These points are at variance with the statement by Bhatnagar (1944) that the presence of Vi agglutinin in the blood is invariably associated with the presence of the typhoid bacillus in the body. It seems unwise to lay down such a hard and fast rule, as it has been established that a small percentage of persons in whom there is no reason to suspect exposure to typhoid infection may have low titres of Vi agglutinin in their serum, possibly because of the presence of Vi-containing strains of *Bact. coli* in their intestine.

As far as the native carriers are concerned, the second Vi titration revealed significant titres in both men, but the Vi titre of the faecal carrier rose from 1:5 in the first titration to 1:30 in the second. It is possible that this man contracted his infection immediately before, or shortly after, the commencement of the carrier investigation, and that the sixfold rise in titre was related to the establishment of the chronicity of his condition. This argument is supported by the fact that typhoid bacilli were not present in his first three stools.

In spite of the fact that most enteric epidemics in the Services in the Middle East were caused by locally employed cookhouse workers, a comprehensive survey of the carrier rate among such employees has not yet been performed. This is due to the large number of persons involved, the constant changing of cookhouse staff, the unco-operative mentality of the Egyptian peasant and the shortage of laboratory personnel. It should be noted that in carrying out a systematic carrier investigation of local employees in the Middle East, it is important that the passage and collection of faeces for dispatch to the laboratory should be strictly supervised by British overseers, otherwise a large number of substituted and sterilized specimens will be encountered, since a 'fellah' will often resort to tricks to avoid losing his employment.

Vi agglutinin titration was attempted as a screen test of prospective cookhouse employees in the area in which the epidemic occurred, but the series was too small and the results were too equivocal to permit useful conclusions to be drawn. However, the major weight of evidence presented by other workers is in favour of the reliability of such tests in the exclusion of non-carriers. This was first suggested by Felix *et al.* (1935), and supported later by Pijper & Crocker (1937, 1938), Felix (1938), Bhatnagar (1938), Bensted (1940), Almon & Stovall (1940), Almon (1943), and others; although Horgan & Drysdale (1940), and Davis (1940), were less favourably disposed to the test because they found occasional

Vi negative carriers, and were able to demonstrate raised Vi titres in subjects from whom the typhoid bacillus could not be isolated. A large-scale survey of this type in Egypt would certainly be of great value, for there is little doubt that the number of typhoid carriers among the 'fellahin' must be high.

The identification of strains of typhoid bacilli by means of anti-Vi bacteriophages has assumed a position of major importance in the epidemiological study of typhoid fever. Its value was again demonstrated in the outbreak reported above, in which it showed that only one of the two native carriers discovered was responsible for the epidemic.

The belief that inoculation with T.A.B. vaccine confers a high degree of immunity against the enteric fevers was responsible for the false sense of security from these diseases which prevailed during the recent war in units which could show a good inoculation state. The factors influencing the incidence of enteric fever are hygiene on the one hand, and protective inoculation on the other. When a breakdown in hygiene occurs, and the typhoid bacillus is able to gain access to the body, the resistance of the individual is not the only factor to be considered, since the magnitude of the infecting dose varies greatly, and there may also be variation in the virulence of different strains of the organism. The enteric fever epidemics in the Services presented an opportunity to examine the result of mass assaults in closed communities on the immunity resulting from T.A.B. vaccination, and it cannot be disputed that under such conditions a high attack rate resulted. Thus the typhoid epidemic in France, reported by Jordan & Everley Jones (1945), showed an attack rate of 30%, and in the outbreak described in this paper this rate was 14.7%. The immunity following T.A.B. inoculation cannot therefore be of a high order. The prevention of the contamination of foodstuffs by organisms of the enteric group is probably the most important single factor in restricting the incidence of the enteric fevers in Service personnel stationed in tropical and sub-tropical countries, and in this respect good hygiene in cookhouses and messes generally is the only real safeguard. But to maintain a high standard of hygiene it is also important to screen-test all native workers who handle food, in order to avoid the employment of carriers. Although this is recommended it is seldom enforced, and a few disastrous epidemics in the Services testify to the need for its compulsory institution.

An assessment of the influence of protective inoculation on the clinical course of typhoid is also difficult. Most workers maintain that the course of the disease is mild and the mortality significantly less in previously inoculated patients. Topley & Wilson (1946) state that during the War of 1914–18, the case-mortality rate among 1728 inoculated British patients was 4.57%, whereas among 703 uninoculated men it was 18.35%. This difference is highly significant. Without uniform conditions of infection, however, in order to arrive at as accurate a test of immunity as possible, comparison of mortality figures could be misleading.

Our own impression has been that, once the disease is established, the clinical course is not materially influenced by previous immunization, and this is supported by a survey of the severity of cases in this and other epidemics, and by the statistical analysis of inoculation states in the three clinical groups quoted earlier in the paper. That different T.A.B. vaccines may vary in potency was shown by Boyd (1943), and the case-mortality rate of 25% reported by Raettig (1944) in inoculated German troops does not suggest that the vaccine employed in immunizing these men had effectively reduced the mortality. The work of Felix & Pitt (1934, 1936), Bhatnagar (1935), Felix & Petrie (1938), Felix (1941), Felix, Rainsford & Stokes (1941), and others, indicates that greater protection may be afforded by the use of alcoholized vaccines containing Vi antigen. Such a vaccine has been introduced into general use in the Services, but it is too early as yet to assess its efficacy. In the outbreak described in this paper 75% of the cases had been immunized with the new alcohol-preserved vaccine within the 12 months preceding the outbreak, yet the figures of morbidity rate and severity show no significant divergence from those of earlier Service epidemics. When a full statistical survey of typhoid fever in the Services during the recent war is published, some of these points may be clarified.

SUMMARY

1. An outbreak of typhoid fever in a Royal Air Force camp in the Middle East is discussed.

2. A total of 110 cases occurred of which 105 are analysed. The case-fatality rate was 10%.

3. Of the 105 cases 59% gave a positive blood culture. The percentages of diagnostic isolations from stools and urine were small.

4. Clearance tests of stools and urine showed that 8.4% of patients excreted *Salm. typhi* during convalescence.

5. Leucocyte counts during the first 2 weeks of the illness showed that only 30% of the patients had a count below 5000 per cu.mm.; 62% of these low figures were encountered in severe cases.

6. Autopsies on seven fatal cases showed considerable variability in the macroscopic appearance of the intestinal lesions.

7. Serological investigation confirmed that higher percentages of cases with low titres of O agglutinin were found in the severe and mild clinical groups, and that most O titres in the moderately severe cases exceeded 1:200.

8. Of the patients 52 % showed Vi titres exceeding 1 : 20 during convalescence.

9. The significance of various findings is discussed.

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