

## SECOND ATTACKS OF TYPHOID FEVER

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(With 1 Figure in the Text)

Recurrences of typhoid fever are uncommon, and the recent literature is disappointingly uninformative about them. Despite his vast experience of the disease, Bretonneau (1829) reports that he had never seen a recurrence. Eichhorst (1888) states that of 666 consecutive cases of typhoid fever in Zurich between 1884 and 1886 twenty-eight gave a history of a previous attack; he observes that the severity of the second attack was independent of that of its predecessor, and that the mortality rates of first and second attacks were about equal; the average interval between attacks was about 10 years, and in only one patient was it less than a year. Curschmann (1902) states that the incidence of second attacks in 1888 patients in the Hamburg epidemic of 1887 was 2·4%, and emphasizes that clinical records of the first attacks were often available for verification. He quotes other series with 1·8–2·2% of second attacks. His general observations agree with those of Eichhorst. Sawyer (1914) reports that of 93 victims of an explosive outbreak of typhoid fever in the United States 14 patients had experienced a previous attack. Gay (1918) reviews the literature and quotes numerous estimates of the frequency of recurrences, almost all based on patients' past histories. In general, these estimates vary from 1 to 4%, but are as high as 15% when the character of the outbreak suggests a large infecting dose. He states that second attacks are usually less severe than first attacks, and that recurrences usually occur in epidemics. Many of the estimates quoted by Gay are open to serious question as they were made at a time when the diagnosis of typhoid fever could not have been confirmed bacteriologically or serologically, and typhoid must often have been confused with paratyphoid and even with other continued fevers.

Numerous authors (Dowling, 1948; Kolmer & Tuft, 1941; Rolleston & Ronaldson, 1940; Stuart & Pullen, 1950; Top, 1947; Zinsser & Bayne-Jones, 1939) agree generally with Gay and give no new figures. The general impression conveyed by the literature is that an attack of typhoid fever confers a considerable degree of immunity but that recurrences occasionally take place.

Repeated exposure to infection by *Salmonella typhi* cannot be common in modern civilized communities, and this must greatly restrict the incidence of second attacks irrespective of the degree of immunity conferred by one attack. Two outbreaks of typhoid fever have recently occurred in the same community within a period of 5 months thus exposing a large number of individuals to the risk of infection on two occasions; several contracted typhoid fever twice. This unusual event forms the basis of the present report.

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## THE TWO OUTBREAKS

The outbreaks occurred in a large Royal Air Force unit in the Suez Canal Zone of Egypt. The station received a chlorinated and piped water supply and drew its food from sources common to many other units in the Canal Zone. The kitchen staff was partly British and partly Egyptian. The population exposed in the outbreaks had been protected by T.A.B. vaccine, usually of the alcoholized variety.

*The first outbreak*

This occurred in April and May 1950. Out of 657 men at risk 84 contracted typhoid fever: the diagnosis was confirmed bacteriologically in 69 patients, and 15 were diagnosed on clinical evidence alone. The causative organism was *Salm. typhi* of phage type J. The outbreak was insidious in character, three or four men becoming ill each day. The source of the outbreak was not satisfactorily determined; it was considered likely that a native cook, who was found to be a heavy urinary excretor of *Salm. typhi*, was the cause of the outbreak because it ceased about 10 days after his removal from duty. However, the organism isolated from his urine was rough and could not be phage-typed.

*The second outbreak*

This occurred during July and August 1950. There were 688 men at risk of whom 235 contracted typhoid fever; the diagnosis was confirmed by cultural methods in 221 patients, by a rise in somatic agglutinins in seven, and seven patients were diagnosed on clinical evidence alone. The causative organism was of phage type E1.

This outbreak was explosive in character and showed two waves of incidence, the primary wave during the first week and the secondary wave extending over the next 3 weeks (Fig. 1). Epidemiological evidence indicated that the food eaten at midday on 12 July was the cause of the primary wave of cases, but how the food became contaminated was not discovered. Two food-handlers, who were found to be excreting the organism during the incubation period before they developed the disease, were considered to be the probable source of infection of the secondary wave of cases. The outbreak ceased 10 days after their removal from duty.

The second outbreak was both larger and more severe than the first; compared with the first outbreak, the second outbreak showed not only a higher proportion of seriously ill patients but also showed a lower proportion of patients whose illness ran a mild course.

## THE PATIENTS WHO CONTRACTED TYPHOID FEVER TWICE

Details of diagnostic criteria and phage-typing results are given in Table 1. In the absence of laboratory confirmation, the diagnosis of typhoid fever was made only when the clinical picture was highly characteristic. During both outbreaks several men were admitted to hospital with mild pyrexia and such symptoms as headache, anorexia, lassitude and abdominal pain, but in the absence of laboratory confirmation these patients have not been included in the present series although a number of them may, in fact, have had typhoid fever on both occasions.

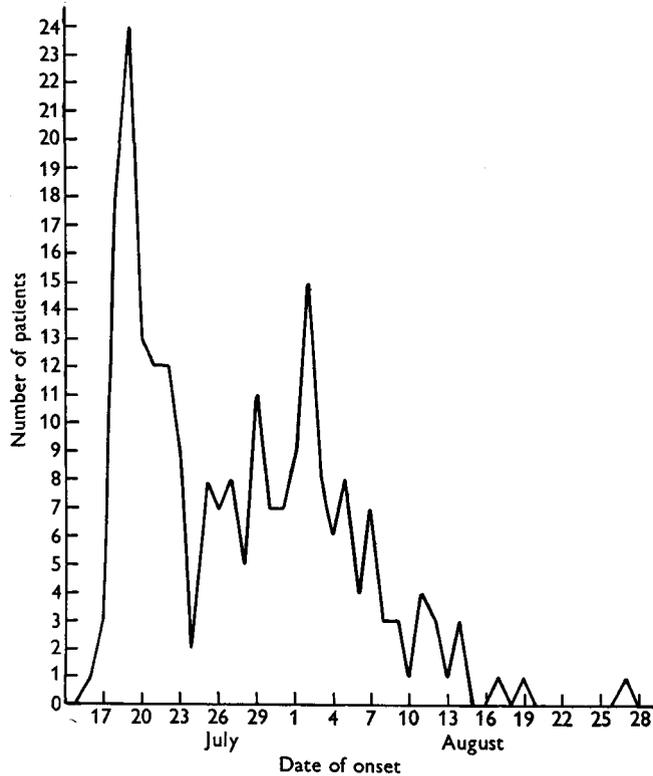


Fig. 1. Number of patients becoming ill during each day of the second outbreak.

Table 1. *Diagnostic criteria*

| Patient no. | April-May outbreak  |            |                           | July-August outbreak |            |
|-------------|---------------------|------------|---------------------------|----------------------|------------|
|             | Basis for diagnosis | Phage type | Chloramphenicol treatment | Basis for diagnosis  | Phage type |
| 1           | FC                  | J          | Yes                       | BC                   | E1         |
| 2           | BC                  | J          | Yes                       | BC                   | E1         |
| 3           | BC                  | J          | Yes                       | BC                   | E1         |
| 4           | BC                  | J          | Yes                       | BC                   | E1         |
| 5           | BC                  | J          | Yes                       | BC                   | E1         |
| 6           | BC                  | J          | Yes                       | FC                   | —*         |
| 7           | BC                  | J          | No                        | A                    | —          |
| 8           | Clin.†              | —          | No                        | BC                   | E1         |
| 9           | Clin.‡              | —          | No                        | FC                   | E1         |
| 10          | Clin.§              | —          | No                        | BC                   | E1         |
| 11          | Clin.               | —          | No                        | BC                   | E1         |

Abbreviations: BC = *Salm. typhi* isolated from blood; FC = *Salm. typhi* isolated from faeces; A = rise in somatic agglutinins to *Salm. typhi*; Clin. = clinical diagnosis.

\* Vi-negative strain.

† Low fever for 2 weeks, rose spots, diarrhoea, vomiting.

‡ Spikes of fever, headache, diarrhoea, abdominal pain, epistaxes.

§ Trivial fever, headache, diarrhoea, anorexia, abdominal pain, neckache, respiratory catarrh.

|| Fever, abdominal pain, bronchitis, bradycardia, pain and tenderness in right iliac fossa.

Six of the patients in the present series received chloramphenicol treatment during their first attack, and five did not.

Patients who had typhoid fever in the first outbreak were not allowed to return to duty until they had completed a long graduated convalescence under medical supervision. All were considered to be (and most considered themselves to be) in a normal state of health by this time; there was no question of their being debilitated or under-weight as a result of their previous illness.

#### *Clinical histories*

Clinical details are given of four patients in whom both attacks were confirmed bacteriologically.

*Patient 1.* Male, aged 18. His first attack was a relatively mild febrile illness with headache, constipation and anorexia, beginning on 5 April. *Salm. typhi* (phage type J) was isolated from his faeces on the 17th day of illness. He was treated with chloramphenicol (25 g. in 8 days), but was almost afebrile at the start of this treatment. His further progress and convalescence were uninterrupted, and he returned to his unit on 10 July. On 18 July he started to feel ill with fever, headache, malaise and anorexia, followed by abdominal pains which were exceedingly severe and colicky in nature. He was admitted to hospital on the 2nd day of his illness, *Salm. typhi* (phage type E1) was isolated from his blood on the 3rd day, and chloramphenicol treatment was commenced on the 7th day. Severe abdominal pain persisted for a further 2 days, but his further progress and convalescence were uneventful.

*Patient 2.* Male, aged 19. His first attack began on 16 April with fever, abdominal discomfort, anorexia and malaise, followed by coryza and backache. He was admitted to hospital on the 3rd day of illness and was found to have rose spots and a palpable spleen. *Salm. typhi* (phage type J) was isolated from his blood, and chloramphenicol treatment (25 g. in 10 days) was commenced on the 9th day of illness. Response to treatment was rapid and he was afebrile on the 13th day. Convalescence was uneventful and he returned to duty on 10 July. On 21 July he experienced abdominal pain, backache, anorexia and nausea, followed by flatulence and abdominal distension. He was admitted to hospital on the 4th day of illness; his spleen was palpable and *Salm. typhi* (phage type E1) was isolated from his blood. Chloramphenicol treatment was started on the 8th day of illness; in the next 2 days he had a profuse crop of rose spots and became very toxæmic with increased abdominal pain and distension, culminating in a moderate-sized bowel haemorrhage, following which he improved rapidly. Further progress was uneventful.

*Patient 3.* Male, aged 21. His first attack began on 30 March with headache and generalized body pains, followed by fever, constipation and abdominal pain. He was admitted to hospital on the 2nd day of illness and *Salm. typhi* (phage type J) was isolated from his blood on the 5th day. He showed signs of moderate toxæmia. Chloramphenicol treatment (25 g. in 9 days) was started on the 9th day, and by the 15th day he was afebrile and fairly well though weak. Further convalescence was uneventful and he returned to duty on 10 July. On 19 July he experienced

severe headache, generalized body and limb pains, followed by severe abdominal pain and great prostration. He was admitted to hospital that day and was found to have a few rose spots. *Salm. typhi* (phage type E1) was isolated from his blood the next day. He was very ill, in constant severe pain, and lay curled up in bed. Chloramphenicol treatment was started on the 6th day of illness, and 48 hr. later there was a dramatic and sudden relief of symptoms. He was afebrile and free from symptoms on the 11th day, and further progress was uneventful, though he remained debilitated for a considerable time. His second illness was much more severe than his first.

*Patient 4.* Male, aged 21. His first attack started on 8 April with rapid development of abdominal pain and distension accompanied by fever. He was admitted to hospital on the 5th day of illness and though he remained ill repeated cultures of blood, faeces and urine remained negative. His spleen became much enlarged, he had profuse rose spots and repeated epistaxes. Chloramphenicol treatment was started on the 15th day (25 g. in 9 days), and *Salm. typhi* (phage type J) was isolated from a sample of blood taken just before the first dose was given; following the start of treatment he became very toxæmic for 36 hr., and then improved rapidly. Further progress and convalescence were uneventful, and he returned to duty on 20 July. On 6 August he felt unwell, with anorexia, vague abdominal discomfort and headache, but no fever. He was admitted to hospital on the 3rd day of symptoms; no physical abnormalities were found and he remained afebrile but *Salm. typhi* (phage type E1) was isolated from his blood. As he continued to have vague symptoms he was treated with chloramphenicol. His further progress was uneventful.

Although a few patients showed similar symptoms in the two attacks (e.g. patient 3, and also patient 11, who had a similar type of pain in the right iliac fossa in both attacks), generally there was no individual pattern of response to typhoid infection. It has been remarked above that the second outbreak was more severe than the first, and in general this is reflected in the patients who had two attacks, the second being more severe than the first.

#### *Bacteriology*

Blood for culture was taken into taurocholate broth and plated after 1, 2, 3, 5, 10 and 15 days' incubation. After removal of the serum from samples of clotted blood the clots were broken up in taurocholate broth by shaking with glass beads and subcultured at similar intervals. Faeces were plated directly on desoxycholate-citrate agar, and also on the same medium after enrichment in selenite F for both 6 and 18 hr. *Salm. typhi* was identified by biochemical reactions and by serological examination of both somatic and flagellar antigens. Cultures were phage-typed by the method described by Craigie & Yen (1938) and Craigie & Felix (1947).

Diagnostic culture results are shown in Table 1.

#### DISCUSSION

The station in which these outbreaks occurred was not a closed community, and there were frequent changes in the population owing to men joining and leaving in the period between the outbreaks.

The attack rate in the first outbreak was 12·8% (84 out of 657 at risk), while that in the second was about three times as great (34·2%, or 235 out of 688 at risk: see footnote (\*) to Table 2). Of 438 men exposed to infection twice, 200 (45·7%) contracted typhoid fever on one or both occasions; this is a somewhat surprisingly high attack rate for a community whose members were nearly all 'protected', according to current practice, by inoculation with T.A.B. vaccine.

Table 2. *Attack rates of various groups in the second outbreak*

| Description of group  | Number in group | Number contracting typhoid | Attack rate (%) |
|---|-----------------|----------------------------|-----------------|
| Men exposed to infection in second outbreak (total)                                 | 688*            | 235                        | 34·2            |
| Men exposed but not infected in first outbreak, re-exposed in second                | 384             | 146                        | 38·0            |
| Men infected in first outbreak, re-exposed in second                                | 54†‡            | 11                         | 20·4            |
| Newcomers to station between the outbreaks, exposed to infection in second outbreak | 250*            | 78                         | 31·2            |

\* Including 57 men who joined the station on 15 July (after the infected meal), only one of whom, a medical orderly employed in the sick quarters, contracted typhoid fever.

† Of these 54 patients, 45 were diagnosed by cultural methods and in nine the diagnosis was on clinical grounds.

‡ Of these, 37 received chloramphenicol therapy in their first attack, six (16·2%) being re-infected in the second outbreak; of the 17 who did not receive chloramphenicol five (29·4%) were re-infected.

The attack rates of various groups of men in the second outbreak are shown in Table 2. There is no significant difference between the attack rates of those who were exposed to infection during the first outbreak but did not contract typhoid (38·0%), and those who joined the station between the outbreaks and had not therefore been recently exposed to the risk of infection (31·2%).

The attack rate in the second outbreak among those who had recovered from typhoid fever contracted in the first was 20·4%, which is significantly lower than the crude attack rate for the outbreak. Taken at its face value, this supports the classical contention that an attack of typhoid fever confers a considerable though incomplete immunity: before drawing any conclusions, however, certain attack rates within this group should be considered further. Many of the 54 men concerned returned to the station after 12 July (the day of the infected meal) and a number left early in the outbreak, so that only a proportion were present on the station throughout the time of the outbreak. Of the 12 who returned to the station before 12 July, seven contracted typhoid fever again (58·3%): these few were, of course, exposed to the presumably large initial infecting dose, which was probably sufficient to break down all but the most solid immunity. None of those who returned after 26 July contracted typhoid fever. These variations in attack rate show how difficult and dangerous it is to draw firm conclusions from the figures quoted.

The influence of chloramphenicol therapy upon immunity is doubtful. There is much clinical evidence that chloramphenicol interferes with the development of immunity (Marmion, 1952), supported by the experimental work of Reber & Bernstein (1950). Most of the patients in the first outbreak had been treated with chloramphenicol. The attack rates in the second outbreak of those who had and had not received chloramphenicol in their first attack were respectively 16.2 and 29.4% (see footnote † to Table 2): these proportions do not differ significantly, but the numbers are too small to be statistically reliable.

The attacks occurred about 3 months apart, so that patients recovered from their first attack would have their immunity at or near its maximum at the time of the second.

Finally, the outbreaks were caused by organisms of different phage type. Lack of cross-immunization between different phage types may account for the occurrence of second attacks, but there is at present no experimental evidence to indicate that immunological specificity extends to phage types of *Salm. typhi*.

#### CONCLUSIONS

The impression conveyed by the literature is that an attack of typhoid fever confers a high degree of immunity, although recurrences may sometimes occur. Repeated exposure to infection cannot be common in modern civilized communities, and this may partly explain the low incidence of second attacks on which this impression is based. The circumstances reported here furnish an example of such repeated exposure to infection, and the incidence of second attacks is seen to be by no means negligible. We must conclude, that, although the numbers are small and the variables many and difficult to evaluate, the evidence drawn from these outbreaks indicates that the specific immunity conferred by an attack of typhoid fever is of no more than moderate degree and, in the event of re-exposure to infection, recurrences are not very unusual.

#### SUMMARY

1. Second attacks of typhoid fever are uncommon. In the literature this has been taken to imply that an attack of typhoid fever confers a high degree of immunity which, nevertheless, may be overcome by such factors as re-infection by a large dose, an organism of a different strain, or one of high virulence.

2. Two large outbreaks of typhoid fever in the same community within 5 months produced eleven examples of second attacks. Clinical descriptions of four of these are given.

3. Details are given of the population at risk and the attack rates in various groups.

4. The evidence of these facts and figures, though inconclusive, suggests that an attack of typhoid fever does not confer more than a moderate degree of specific immunity. The influence of chloramphenicol upon immunity remains *sub judice*.

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