

COMBINED ENTERIC INFECTION

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Enteric fever is a systemic clinical syndrome which may result from infection with a variety of distinct but related organisms of the salmonella group. In addition to classical typhoid fever, due to *Salmonella typhi*, and paratyphoid fever due to any of the three *S. paratyphi* strains, certain other salmonella strains may produce the picture of enteric infection though the more usual result is an acute gastroenteritis. Chief amongst these according to Topley and Wilson¹ are *S. cholera-suis*, *S. blegdam*, *S. dublin*, *S. enteritidis* var. *chaco* and *S. sendai*.

Enteric infection associated with systemic invasion by more than one organism of the salmonella group is by no means common but occurs with sufficient frequency to make the association a recognized entity. It was originally described under the term *fièvre typhoïde intriquée*, by Chantemesse and Grimberg,² and the term 'double enteric infection' was introduced by Shaw and MacKay.³ Several examples of triple infection have however been recorded, and for this reason we have preferred to use the term 'combined enteric

infection'. Shaw and MacKay's paper contains an extensive review of the literature and they quote a series of 28 cases of their own occurring in an epidemic outbreak in the Middle East. These infections were due to *S. typhi* (Vi phage type T) and *S. paratyphi B* (Vi phage type 'Dundee').

This brief report concerns a series of 4 cases of combined infection due to *S. typhi* and *S. dublin*. In each case the organisms were isolated from the blood stream. A 5th patient is included where one of the organisms was isolated from the blood and the other from the faeces. However, it is uncertain whether this is a true example of combined infection or whether the patient was a faecal carrier of one type and merely had a superadded single infection with the other organism.

PRESENT SERIES AND BACTERIOLOGICAL METHODS

Whole-blood cultures were performed by the addition of approximately 8.0 ml. of blood to 50 ml. of bile-salt broth. Clot cultures were made by the addition of the residual clot

from 5.0 ml. of blood to 15 ml. of bile-salt broth containing 100 units/ml. of streptokinase, as we have previously described.⁴ In both cases subcultures were plated, after incubation at 37.0°C, onto Wilson and Blair's medium. Agglutination reactions were tested by the usual standard methods.

The clinical features of enteric infection are well known and it is not proposed to describe the case histories in any detail. It has previously been suggested that the clinical picture of a combined infection is usually severer than that of a single infection. Shaw and MacKay,³ however, were unable to observe any specific features in their 28 double-infection patients, as compared with 43 patients suffering from *S. typhi* infection alone.

Of the 4 patients in this series 2 were classified as moderately severe on admission. The 3rd patient had apparently only a mild infection but in spite of this developed a perforation of the gut during the fourth week of illness and died. The 4th patient was admitted with a history suggestive of incomplete abortion and only developed the clinical features of enteric infection after 3 days in hospital. This patient was classified as severe. She also had radiological evidence of tuberculosis of the right upper lobe with cavitation, and died 7 days after admission in spite of chloramphenicol and cortisone therapy.

In cases 1, 2 and 3 both *S. typhi* and *S. dublin* were isolated from the same blood-clot specimens. In case 3 *S. dublin* was also isolated from the urine. In case 4 *S. dublin* was isolated from the blood clot and *S. typhi* from whole blood culture taken at the same time. In the 5th patient referred to, *S. dublin* was present in a blood-clot specimen and *S. typhi* was found in the faeces. In none of the cases was the agglutination reaction of much significance. Patients 1 and 2 responded well to antibiotic therapy.

DISCUSSION

The review of the literature by Shaw and MacKay³ includes records of 39 isolated cases of double infection and 1 of triple infection as well as 10 epidemic outbreaks of double infection and 4 of triple infection, occurring between the years 1904 and 1951. In all of these the organisms incriminated were *S. typhi* and *S. paratyphi A* and/or *B*. We have been unable to find any previous account of the association of *S. typhi* with a salmonella other than *S. paratyphi*. However, since it is only within recent years that elucidation of the antigenic structure of the salmonella group has been achieved it may be that some of the earlier reports refer in actual fact to salmonellas other than *S. paratyphi*, but which have been designated as such because of lack of the necessary antisera for proper identification.

The mode of infection in the present series of cases was not established. All were admitted to hospital within a matter of 10 days of each other. In addition, 2 further patients were admitted at the same time from whom *S. dublin* alone was isolated from blood-clot specimens. There was no evidence of a possible common source of infection outside the hospital, the patients coming, in fact, from widely scattered areas.

The origin of mixed infections is not definite and it may be that the same mechanism is not involved in each case. The most obvious possibility is that both organisms are ingested at the same time. This is particularly likely to be

the case in waterborne epidemics of combined infection. The second possibility is that a carrier of one type of salmonella may acquire an infection with a second salmonella. The resulting infection from the second organism may then in some way allow of re-invasion of the blood stream by the 'carrier' organism. It has previously been shown that *S. typhi* may remain viable within plasma cells in the intestinal lesions and it seems highly probable that similar viable organisms occur in other sites, especially in the spleen and liver. These intracellular organisms appear to acquire a balanced existence with the symptomless carrier host, but it may be that a second infection with another salmonella type precipitates the balance in favour of the parasite with consequent multiplication and re-invasion of the blood stream in sufficient numbers to be detectable by the usual bacteriological procedures.

A third possibility has been put forward in the past, namely that an infecting salmonella strain may undergo mutation to a second salmonella type. The evidence in favour of such spontaneous mutation is not convincing. Recent work on bacterial genetics, particularly with regard to the phenomena of transduction and lysogenic conversion, has shown that bacteriophage isolated from one salmonella strain may produce lysogenization of certain other salmonella strains with the resulting production of a new antigenic component. In the same way it is possible to show experimentally the acquisition of flagellar antigens of *S. typhi-murium* by strains of *S. typhi* so that the resultant cells have the somatic 'O' antigens of *S. typhi* and the flagellar 'H' antigens of *S. typhi-murium*. It is uncertain, however, to what extent transduction phenomena occur in nature. The production of a different salmonella strain in this way (for example, conversion of *S. typhi* to *S. paratyphi A*) is highly unlikely since this would involve the genetic exchange of more than one antigenic factor in addition to alterations of metabolic properties. Normally in the phenomenon of bacterial transduction only one genetic characteristic is transmitted to any one receptor cell.

Several of the earlier reports on combined enteric infections must be treated with reserve since the diagnosis has been made as the result of agglutination tests or else by the demonstration of the organisms in the faeces. There is no doubt that quite unwarranted assumptions are often made from the results of the former test and the demonstration of the organisms in the faeces may merely reflect the carrier state resulting from a past infection.

SUMMARY

Combined enteric infection with two or more salmonella strains is a recognized entity. Four patients, and a possible fifth, with infection due to both *S. typhi* and *S. dublin* are described. Mechanisms for the possible occurrence of such infections are mentioned.

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