A STUDY OF CERTAIN FEATURES IN CONNECTION WITH ENTERIC GROUP INFECTIONS IN THE ARMY IN INDIA.

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(Continued from p. 421.)

RESULTS OF WIDAL TESTS ON TWENTY-FOUR BACTERIOLOGICALLY PROVEN PARATYPHOID B CASES.

Twenty-four series of tests only are available in which sufficient examinations were carried out. The series is too small to be of any great value, but the results are interesting and raise certain questions which require elucidation. The average number of tests per case is also less than in the other groups examined, viz., 3.83 per case.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Cases</th>
<th>Duration of Pyrexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>British troops</td>
<td>11 cases</td>
<td>23.1 days</td>
</tr>
<tr>
<td>Indian troops</td>
<td>13 cases</td>
<td></td>
</tr>
</tbody>
</table>

Severe cases: 10 (duration of pyrexia 23.1 days)
Mild cases: 14 (duration of pyrexia 11.7 days)

CLASSIFIABLE BY AGGLUTINATION AS PARATYPHOID B, 11, OR 45.8 PER CENT.

Six of the 11 classifiable cases were severe. Of the 11 British cases only 4 are classifiable, and 3 of these are severe in nature. The initial rise in "B" agglutinins was apparent as early as 10th to 11th day in the few tests which covered this period. "T" agglutinins were affected in a higher percentage than those for "A." The peak of the curve of agglutination may be found at a late period after onset, as in the case of "T" and "A" infections.
Enteric Group Infections in the Army in India

Case I, V.

<table>
<thead>
<tr>
<th></th>
<th>12th</th>
<th>19th</th>
<th>25th</th>
<th>27th</th>
<th>35th</th>
<th>43rd</th>
<th>49th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>11</td>
<td>11</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>71</td>
<td>63</td>
<td>37</td>
<td>33</td>
<td>54</td>
<td>37</td>
<td>27</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>8</td>
<td>21</td>
<td>281</td>
<td>117</td>
<td>2,354</td>
<td>370</td>
<td>477</td>
</tr>
</tbody>
</table>

Severe case, pyrexia 27 days. Inoculated with 1 c.c. T.A.B. 42 days before onset.

**Unclassifiable by Agglutination as Paratyphoid B, 13, or 54.1 per cent.**

Nine cases are classed as mild and 4 as severe.

A general rise in T.A.B. is present in 7.

The fluctuation in “B” agglutinations is slight in the majority. In 9 it is under 300 per cent, and in 6 of these it is under 100 per cent. In 2 cases, or 8.2 per cent of the 24 cases, there is no increase in “B” agglutinins.

**Illustrative cases are:**

**Case B, 9.**

<table>
<thead>
<tr>
<th></th>
<th>7th</th>
<th>14th</th>
<th>22nd</th>
<th>32nd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>76.9</td>
<td>48</td>
<td>12.5</td>
<td>5</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>105.2</td>
<td>158.1</td>
<td>114.3</td>
<td>342.8</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>103.6</td>
<td>89</td>
<td>166.6</td>
<td>250</td>
</tr>
</tbody>
</table>

Positive blood-culture 7th day. Mild case, 15 days pyrexia. Inoculated with 1 c.c. T.A.B. 142 days before onset.

Although the “B” agglutinins show a higher percentage rise than “A” on 22nd day, the irregular nature of the rise, and the rise in “A” on 15th and 32nd day, would leave to doubt as to the diagnosis, had not B. paratyphosus B been isolated and confirmed as such.

**Case B, 7.**

<table>
<thead>
<tr>
<th></th>
<th>7th</th>
<th>9th</th>
<th>17th</th>
<th>32nd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>19.2</td>
<td>19.2</td>
<td>19.2</td>
<td>19.2</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>119</td>
<td>297.6</td>
<td>119</td>
<td>39.5</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>15.6</td>
<td>15.6</td>
<td>15.6</td>
<td>15.6</td>
</tr>
</tbody>
</table>

S.A. units

Although the cases under examination are few and the Widal tests not as complete in many cases as they should be, there seems little doubt that satisfactory results would not be obtained with the test as employed at present in more than 50 per cent of cases.

Again, the general rise in agglutinins or the mildness of the majority of the cases leading to small rises only is responsible for the difficulty in diagnosis.

There are, however, other factors involved. The writer noted the unsatisfactory results in paratyphoid B infections when going through the Widal results at the end of 1927, and raised the question with Major R. F. Bridges, R.A.M.C., the officer in charge of the Enteric Laboratory at Kasauli, as to whether many of the bacilli confirmed as B. paratyphosus B on biochemical reactions and agglutination tests were not in reality other organisms of the Salmonella group, which could only be properly classified by absorption tests, etc. If this were so, the irregular rise in the “B” agglutinins in the so-called paratyphoid B cases could be explained as being...
due to a sympathetic rise of group agglutinins. A further point was noted
on scrutinizing the Widal results of "enteric group" cases at the end of
1927, which seemed difficult to explain in view of the irregular results of
the tests on bacteriologically proven paratyphoid "B" cases, namely, that
a considerable proportion on their Widal tests alone would actually be
classified as due to paratyphoid B infection. Similar results were found
at the end of 1928. Of the 295 enteric group cases selected at random for
examination, 14.7 per cent are classifiable as paratyphoid B, and 13.27
per cent as paratyphoid A. *B. paratyphosus* B has always been considered
a rare infection in India, and *B. paratyphosus* A as comparatively
common. (See Table I.)

From the Widal tests it seems as if infection with Salmonella group
organisms, including *B. paratyphosus* B, is much commoner than has been
suspected, and possibly a considerable proportion of our "short fevers"
may be due to infection with this group of bacilli.

It is probable that Salmonella group bacilli are present in the blood-
stream in small numbers and for short periods, and are therefore difficult
to isolate by blood-culture methods. Owing to the difficulties of climate,
and in the collection and despatch of specimens of faeces from hospitals to
laboratories, by far the larger percentage of positive results in enteric fevers
in the Army in India is obtained by blood-culture. It is easy, therefore, to
understand how positive bacteriological results have been few in such cases
in past years. It is only since Dreyer's method of agglutination has been
universally employed in military laboratories that any indication of the
extent of such infections is becoming apparent.

Rosher and Wilson, in 1921 [22], reported a case of enteric-like fever
which gave a typical agglutination curve to *B. enteritidis* (Gaertner). These
authors quote Bainbridge as stating, in his Milroy lectures 1912, that the
consumption of meat infected with Gaertner's bacillus, or *B. suipestifer*,
may cause a pyrexia lasting two or three weeks. They also quote Savage's
"Food Poisoning and Food Infections, 1920" and Buchanan's report to the
Local Government Board in 1896, in which certain cases among those
involved in a food-poisoning epidemic were stated to have suffered from a
continued pyrexia only.

The writer, in 1928 [23], put forward the view that infection with
aertrycke bacilli is probably common among the pariah dogs which infest
India, and suggested that some of the short fevers among the troops might
be due to aertrycke infections carried by those dogs.

Major R. F. Bridges has been carefully investigating all organisms
referred to him during 1928 for confirmation as *B. paratyphosus* B. It is
hoped that in due course he will report his results, but, with his permission,
it may be mentioned that a small number have been proved to be *B. para-
typhosus* C and *B. aertrycke* Newport, and a few others appear to be of a
distinct serological type not previously reported.

In his annual report for 1928, Major Bridges writes: "As the result of
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a single year's working it may be surmised that many organisms have been classified at the E.F.C. Depot as paratyphoid B, when in reality a number of them were undifferentiated Salmonella types, definitely not para B. In his own experience the writer can recall several strains which presented unusual features, and yet were returned by him as paratyphoid B, since it was impossible at Naini Tal in the press of hospital and other work, to carry out prolonged study of these organisms."

Roshier and Fielden, 1922 [24], put forward evidence to show that in normal triply-inoculated individuals agglutination of *B. aertrycke*, and *B. paratyphosus C* may follow as the result of the "B" element of the vaccine, whereas *B. enteritidis* (Gaertner) seems to be co-agglutinated both by the typhoid and paratyphoid B elements. They point out that repeated tests by Dreyer's method would be necessary before a definite diagnosis could be arrived at. In this connection it may be mentioned that a large number of the routine Widal tests are carried out against T, A, B and C emulsions, and that the number showing any agglutinin units to "C" is very small. This is probably due to the fact that the emulsions at present in use are prepared only from the specific phase of diphasic Salmonella group bacilli.

A further element vitiating the results of Widal tests on the enteric group cases which are classified as paratyphoid B, may be the high percentage of cases in which the "B" elements are involved in typhoid infections. It has already been shown that 3.2 per cent of 152 bacteriologically proven typhoid infections would have been classified on their Widal tests alone as paratyphoid "B." In addition, it is shown later that the "B" element of the T.A.B. vaccine appears to give rise to a greater production of agglutinins than either the "T" or "A" elements.

Another element of doubt, according to Major Bridges, is the standardization of the emulsions of paratyphoid B; a procedure which is possibly not as simple as usually considered. This need not be discussed further here, and is only mentioned to show that there are many factors which may lead to error in the readings of Widal tests, as at present carried out, with regard to the paratyphoid B element. It seems certain that the range of organisms used in the test will have to be increased by at least *B. enteritidis* (Gaertner) and *B. aertrycke* (Mutton and Newport), and possibly by others. By the employment of the specific strains of these organisms for the formalized emulsions, it is probable that interesting results would be obtained.

**Enteric Group, 295 Cases.**

Classifiable by agglutination, 56.9 per cent; unclassifiable, 43.05 per cent; average tests per case, 4.63; initial tests on or before 8th day in 80 per cent.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Classifiable as typhoid</th>
<th>Classifiable as paratyphoid A</th>
<th>Classifiable as paratyphoid B</th>
<th>Unclassifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Troops (131)</td>
<td>29 or 22.1 per cent</td>
<td>20, 15.2</td>
<td>24, 18.3</td>
<td>58, 44.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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The severity of the attack again appears to have an important bearing on whether the cases are classifiable on their Widal tests or not.

With the exception of the higher percentage of cases classifiable as paratyphoid B among British troops, and of typhoid among Indian troops, there is little difference in the results. The tests on both British and Indian cases are therefore considered as a whole.
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These cases require little comment, as in all respects the reading of the results has been on the same lines as for the bacteriologically proved cases, and the nature of the agglutination response to infection in these "group" cases has followed in all respects the sequence of events in the proved infections, both as regards the regularity of the rise in the majority, and the various irregularities in the minority. Details are given in Appendix IV.

The general rise in specific, and in one or both elements of the inoculation agglutinins, is again apparent, 62 per cent in the cases classified as typhoid, 63·9 per cent in cases classified as paratyphoid A, and 85 per cent cases classified as paratyphoid B. In "T" and "A" the percentages are practically the same as in the bacteriologically proved cases. The higher percentages in which general rise to all these elements occurs, in the cases classified as paratyphoid B, seem to lend support to the theory that many of these cases are in reality Salmonella group infections, and the general reaction one of group agglutinins only, naturally highest in the "B" element.

The following case suggests the possibility of *B. faecalis* alkaligenes being also a cause of a general rise in T.A.B. agglutinins, greatest in B:—

Case B, 11.

<table>
<thead>
<tr>
<th></th>
<th>9th</th>
<th>13th</th>
<th>17th</th>
<th>21st day</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. typhosus</em></td>
<td>76·9</td>
<td>86·9</td>
<td>155·8</td>
<td>153·4</td>
</tr>
<tr>
<td><em>B. paratyphosus A</em></td>
<td>32·1</td>
<td>64·1</td>
<td>67·2</td>
<td>67·3</td>
</tr>
<tr>
<td><em>B. paratyphosus B</em></td>
<td>297·4</td>
<td>1,113·2</td>
<td>1,113·2</td>
<td>804·1</td>
</tr>
</tbody>
</table>

Mild case, 22 days pyrexia. *B. faecalis* alkaligenes isolated from urine on two occasions.

The Widal tests on another case classified in this series as paratyphoid B are worth recording.

Case B, 21.

<table>
<thead>
<tr>
<th></th>
<th>2nd</th>
<th>7th</th>
<th>12th</th>
<th>15th day</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. typhosus</em></td>
<td>448</td>
<td>234</td>
<td>74</td>
<td>258</td>
</tr>
<tr>
<td><em>B. paratyphosus A</em></td>
<td>143</td>
<td>143</td>
<td>167</td>
<td>75 S.A. units</td>
</tr>
<tr>
<td><em>B. paratyphosus B</em></td>
<td>21</td>
<td>44</td>
<td>446</td>
<td>893</td>
</tr>
</tbody>
</table>

This case was one of very mild catarrhal jaundice, and "definitely apyrexial." A mild form of jaundice with trifling symptoms is of fairly common occurrence in most stations in India, sometimes in mild epidemic form. The necessity for blood-culture and bacteriological examinations of the stools and urine in all such cases is clearly indicated by the tests given above.

The relation between the severity of the illness and the extent of the agglutinin response is well illustrated among the classifiable cases.

**Percentage of Cases Demonstrating over 100 Per Cent Rise in S.A. Units.**

<table>
<thead>
<tr>
<th></th>
<th>Typhoid</th>
<th>Paratyphoid A</th>
<th>Paratyphoid B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe cases</td>
<td>54·3 per cent</td>
<td>Severe cases 66·8 per cent</td>
<td>Severe cases 33·3 per cent</td>
</tr>
<tr>
<td>Mild cases</td>
<td>41·8</td>
<td>Mild cases 52·9</td>
<td>Mild cases 27·0</td>
</tr>
</tbody>
</table>

The classification of cases as severe or mild by medical officers must be very uniform, as can be seen from the closely parallel results of the Widal tests on British and Indian cases, both in the "group" infections and those
bacteriologically proved, e.g., positive Widal results were obtained in 53·8 per cent of mild enteric group infections in both British and Indian troops, and of the mild typhoid (proved) cases, 36·5 per cent among British troops, and 36 per cent among Indian troops are unclassifiable on the results of their Widal tests alone. By a reference to the Appendices it will be seen how uniform the results are in almost all the various groups of tests.

**Unclassifiable Cases, 127, or 43 per cent.**

<table>
<thead>
<tr>
<th></th>
<th>British troops</th>
<th>131 or 45 per cent.</th>
<th>Indian troops</th>
<th>164 or 42 per cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe cases</td>
<td>58</td>
<td>43 per cent.</td>
<td>69</td>
<td>42 per cent.</td>
</tr>
<tr>
<td>Mild cases</td>
<td>69</td>
<td>43 per cent.</td>
<td>69</td>
<td>42 per cent.</td>
</tr>
</tbody>
</table>

The difficulties in the readings of tests of this group are the same in all respects as those recorded before when discussing the unclassifiable cases of typhoid, paratyphoid A and B. Only brief comment is therefore necessary.

A rise in group agglutinins is found in 62·3 per cent of cases, British and Indian, but in only a small percentage in this rise really high. Only 10·2 per cent of the tests show a fluctuation of over 1,000 per cent, and many of these are very irregular in nature. The agglutination indices are unchanged; they definitely drop from the initial test, or show no fluctuation above 100 per cent in 47·8 per cent of the Indian cases, and 58·6 per cent of the British cases. This is a higher percentage than was found by Sir William Leishman in his examination of the results of tests on 223 enteric group cases in France [15], the percentage in these cases showing no change, etc., being 35·4 per cent.

In the British group of cases under review no trace of a rise can be found in 17 cases, or 29·3 per cent. It might be considered that many of these cases were not true enteric group infections, but it has been shown already that no rise in titre to the infecting bacillus may occur in an even larger percentage, e.g., 32·4 per cent of 55 unclassifiable typhoid cases, and 47·3 per cent of 19 unclassifiable paratyphoid A cases.

The small extent of the rise is as important a cause of failure as the rise in group agglutinins. Deducting the cases in which no rise throughout is present, in 46 of 65 Indian cases and in 28 of 41 British cases, the rise is under 300 per cent.

The fact that a definite drop from the initial test in the agglutinin content of the serum may result from an enteric group infection in lieu of a rise does not appear to have been stressed. Some such cases can no doubt be explained on the ground that the medical officer had under-estimated the period of illness prior to the patient coming under observation. But the cases are too many for this to be the explanation in all. This result of infection may be found in both severe and mild cases.
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Tests given below illustrate some of the main difficulties in the readings in this series of cases.

(1) General Rise

Case B, 37.

<table>
<thead>
<tr>
<th></th>
<th>6th</th>
<th>12th</th>
<th>19th</th>
<th>26th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>46</td>
<td>242</td>
<td>184</td>
<td>48</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>55</td>
<td>153</td>
<td>153</td>
<td>75</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>50</td>
<td>266</td>
<td>222</td>
<td>129</td>
</tr>
</tbody>
</table>

Severe case, 21 days pyrexia. Inoculated with 1 c.c. T.A.B. 202 days before onset.

(2) Early Rise followed by Drop.

Case I, 44.

<table>
<thead>
<tr>
<th></th>
<th>4th</th>
<th>9th</th>
<th>13th</th>
<th>17th</th>
<th>24th</th>
<th>31st</th>
<th>38th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>305</td>
<td>985</td>
<td>39</td>
<td>157</td>
<td>157</td>
<td>161</td>
<td>243</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>46</td>
<td>40</td>
<td>16</td>
<td>40</td>
<td>35</td>
<td>49</td>
<td>28</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>47</td>
<td>32</td>
<td>28</td>
<td>32</td>
<td>32</td>
<td>44</td>
<td>22</td>
</tr>
</tbody>
</table>

Mild case, 21 days pyrexia. Inoculated with 1 c.c. T.A.B. 393 days before onset.

(3) Drop from Initial Test followed by Late Rise to one Element, Rise not Persisting.

Case I, 25.

<table>
<thead>
<tr>
<th></th>
<th>8th</th>
<th>13th</th>
<th>21st</th>
<th>26th</th>
<th>37th</th>
<th>43rd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>87</td>
<td>55</td>
<td>23</td>
<td>19</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>14</td>
<td>14</td>
<td>8</td>
<td>8</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>39</td>
<td>20</td>
<td>17</td>
<td>34</td>
<td>7</td>
<td>28</td>
</tr>
</tbody>
</table>

Severe case, 22 days pyrexia. Inoculated 68 days before onset with 1 c.c. T.A.B.

(4) Trace Rise only.

Case I, 22.

<table>
<thead>
<tr>
<th></th>
<th>9th</th>
<th>13th</th>
<th>17th</th>
<th>22nd</th>
<th>27th</th>
<th>34th</th>
<th>42nd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. typhosus</td>
<td>43</td>
<td>38</td>
<td>52</td>
<td>43</td>
<td>43</td>
<td>29</td>
<td>38</td>
</tr>
<tr>
<td>B. paratyphosus A</td>
<td>60</td>
<td>52</td>
<td>77</td>
<td>60</td>
<td>39</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>43</td>
<td>21</td>
<td>56</td>
<td>43</td>
<td>56</td>
<td>22</td>
<td>38</td>
</tr>
</tbody>
</table>

Mild case, 14 days pyrexia. Inoculated 53 days before onset.

The unsatisfactory results obtained, both in the above group and with the unclassifiable cases in the bacteriologically proved group, are in no way connected with the effects of "recent inoculation." For example, among the 69 Indian unclassifiable enteric group cases, the average period which has elapsed since inoculation and prior to the onset of the disease works out at 196.4 days. The infection occurred in 5 cases within one month of inoculation, in 8 cases between thirty and sixty days after inoculation, and in 7 cases between sixty and ninety days after inoculation; a total of only 28.9 per cent within three months of inoculation.

B, 37, I, 22 and I, 25 illustrate cases in which the infection occurred under one month, between one and two months, and between two and three months after inoculation. Exactly similar results are found in those cases in which many months have elapsed since inoculation.

The following two cases are interesting in that the patients were inoculated with 1 c.c. T.A.B. on the 2nd and 5th day after the onset of the disease and that in both the development of agglutinins is high. In a later section evidence is brought forward that the 1 c.c. dose of T.A.B. appears to cause a lowering of resistance to infection for a certain time, and that in a certain percentage of cases there may result a reduction in agglutinin content at first rather than an increase. In these two cases, inoculated after infection, the production of agglutinins does not appear to have been hindered in any way.
The results of the Widal tests on these 522 enteric cases may be summarized as follows:

I. ONE HUNDRED AND FIFTY-TWO TYPHOID INFECTIONS.

(1) Of the 152 cases 64 per cent are classifiable.
(2) Of the severe cases 75 per cent are classifiable.
(3) Of the mild cases 50 per cent are classifiable.
(4) Of the very mild cases (eight to eleven days pyrexia) 37·5 per cent are classifiable.
(5) The severity of the attack has, in the majority of cases, a marked effect on the development of specific agglutinins, so that a distinctive rise is found as compared with the rise in the inoculation agglutinins. "A" inoculation agglutinins are increased in severe typhoid infections to a greater extent than in the milder cases, whereas "B" inoculation agglutinins are affected in higher percentage of mild cases. In both severe and mild the "B" element is affected in a larger number of cases than "A."
(6) Although the above statement applies to the majority, a considerable number of cases occur in which the effects on the development of agglutinins is quite the reverse, i.e., a severe case may show no rise, and a very mild case a high rise, in specific agglutinin content during the period of the tests.
(7) The difficulty, and in 37 per cent the impossibility, of classifying the cases is due to the synchronous rise in inoculation agglutinins, mainly the "B" element, and also to the small rise in agglutinin content of the infection agglutinins which occurs in many cases, particularly when very mild. In 11·1 per cent (16 to 18 very mild or abortive) of the group under discussion no rise in specific agglutinins is evident throughout the series of tests for each case.
(8) A small percentage of cases (4·4 per cent) would have been incorrectly classified on Widal tests alone, viz., 1·2 per cent as paratyphoid A and 3·2 per cent as paratyphoid B.
(9) Although the majority of the classifiable cases show a rise and fall in agglutinin content which agree with the classical teaching, a large minority differ markedly in many respects. It is therefore necessary to commence the tests early in the illness and continue them to about the
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30th day, if as many cases as possible are to be correctly diagnosed. Five tests will be required in many cases to establish a correct diagnosis.

(10) The large majority of severe toxic cases which resulted in death have shown a high development of infection agglutinins during the illness, and up to the period at which death occurred.

(11) The effect of a relapse is almost invariably to cause an increased development in the agglutinin content of the patient's serum in the infection agglutinins and in some cases of the inoculation agglutinins.

II. Fifty-one Paratyphoid A Infections.

(1) 62·7 per cent are classifiable.
(2) 37·2 per cent are unclassifiable.
(3) Among the classifiable cases the relative rise of the infection agglutinins is higher than is found in the milder typhoid cases, but not quite as high as in the severe.
(4) In the unclassifiable cases the failure in the development of infection agglutinins is the main difficulty in the reading of the tests rather than the general rise in the inoculation agglutinins. In 17·6 per cent no rise is found.
(5) In general the curve of agglutination to the "A" element in the classifiable cases was precisely similar to that seen for "T" in typhoid infections, both as regards regularity and irregularity of the curves. Late rises of the infection agglutinins were not more frequent in the case of paratyphoid A infection than in typhoid infections.
(6) The effect of "A" infection on "T" inoculation agglutinins was rather less than on "B" inoculation agglutinins, 41·1 per cent being raised in the former, and 47·8 per cent in the latter.
(7) Although a greater relative rise may occur in both "T" and "B" agglutinins than in "A" as the result of "A" infection, in this series of cases the rise was either so irregular, or so closely followed by that of the "A" element, that no diagnosis other than enteric group is possible.

III. Twenty-Four Paratyphoid B Infections.

(1) Classifiable, 45·8 per cent.
(2) The severity of the illness appears an important factor in the development of specific agglutinins. In the milder cases the slight extent of the rise in specific agglutinin content is as important a source of difficulty as the rise in inoculation agglutinins.
(3) It is probable that this group includes a certain number of cases of Salmonellas group infections as distinct from paratyphoid B.
(4) In 8·2 per cent of cases there is no increase in the "B" agglutinins.
(5) The number of cases under review is too small to give information of any real value.
IV. Two Hundred and Ninety-five "Enteric Group" Infections.

1. Classifiable, 56.9 per cent
   - 29.1 per cent typhoid infections.
   - 13.2 per cent paratyphoid A infections.
   - 14.5 per cent paratyphoid B infections.

2. Unclassifiable, 43 per cent.

3. The severity of the illness is an important factor as regards whether the case is ultimately classifiable by Widal tests.

4. The high percentage of cases classified as paratyphoid B, particularly among British troops, is probably due to Salmonella group infections other than B. paratyphosus B causing a rise in group agglutinins, and possibly also to a small percentage of typhoid infections which have given rise to a greater response in the "B" element than in "T."

5. In all other respects the tests on both classifiable and unclassifiable cases correspond with those on the bacteriologically proved infections, and results are very similar, the synchronous rise in inoculation agglutinins and also the small extent of the rise being the cause of the negative results.

6. The number of cases in which no rise is found to "T," "A" and "B" corresponds very closely with the bacteriologically proved cases, i.e., 7.1 per cent of 295 "enteric group" cases, of which 5.7 per cent is among the British group, as compared with 11.1 per cent of proved typhoid infections and 17.6 per cent of proved paratyphoid A infections.

DISCUSSION.

Since the above was written, an important paper concerning the value of the Widal test has been published by A. Felix [25]. The author summarizes the literature both from British and German sources, and points out the paucity of published information containing accurate figures of the results of tests on bacteriologically-proven enteric fever infections, and the wide claims which have been made in the absence of such published figures. The necessity of obtaining some exact figures in lieu of accepted generalizations was the cause of the present inquiry.

The assumption of Dreyer that there exists in enteric infections one type only of the curve of agglutinin production is queried, and attention is directed to the work of various investigators indicating that a variety of forms of agglutination curves may occur in typhoid fever, and that the maximum peak of the curve occurs just before defervescence, irrespective of any particular day after onset of the disease. The present series of tests also indicate that irregular curves occur in a large minority of cases, but the peak of the curve of agglutination may be met with either early or late in the course of the disease, and is not particularly related to the period just before defervescence.

The absence of definite figures as to the incidence of the synchronous fluctuation of the inoculation agglutinin is also commented upon. Such figures are given in the present paper for typhoid, paratyphoid A, and enteric group cases, and may be of some value.
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Felix concludes, however, that no technique based on the quantitative method of the agglutination reaction hitherto used is capable of differentiating between inoculation and infection agglutinins. This seems a very extreme statement, as extreme indeed as the claims of those who considered that positive results could be obtained in almost all cases. This is not the experience of workers in the military laboratories in India, by whom probably more Widal tests are carried out on inoculated individuals than by any other body of laboratory workers. It is agreed that in a fair percentage of cases the method does fail to enable a "definite classification" to be carried out, but the percentage in which it fails to enable an enteric group diagnosis to be made, if Dreyer's technique is followed, is small when applied to a large group of cases of moderate or high severity. In the very mild or abortive cases the percentage of failures is certainly high.

It has been shown conclusively in the present series that the severity of the attack, as judged by duration of pyrexia, toxæmia, etc., is an important feature as regards whether a distinctive rise in infection units as contrasted with inoculation units will result.

In severe typhoid cases such a distinctive rise occurred in 75 per cent of cases, a result practically as good as that found by Pijper (1923) in cases apparently uninoculated. In a mixed group of typhoid cases, of which 44 per cent were clinically mild (pyrexia 14-9 days only on the average), a distinctive rise was present in 64 per cent of cases.

In the very mild or abortive cases, however, the stimulus due to the infection is apparently too weak to enable a high percentage of cases to produce H agglutinins in sufficient amount to be distinctive, and in some cases there appears to be no response at all. If by the use of alcoholized O emulsions it will be possible to distinguish all such cases as "enteric group," a great advance will be made in the sorting out of the short pyrexias of doubtful origin so common in India. In such literature as the writer has seen on the subject no distinction, however, is drawn between the mild cases and the ordinary case of average severity, and it seems yet to be proved that an abortive or mild typhoid case with a pyrexia of five to eight days' duration will invariably show a titre for O agglutination above the limit of normal or inoculation O agglutinins. In cases with pyrexia of over fourteen days' duration, the usual clinical signs plus the ordinary Widal tests, using H emulsions and Dreyer's technique, enable a diagnosis of "enteric group" to be made at least in the very great majority of cases. It is in the cases doubtful both on clinical grounds and by Widal tests that some reliable test is required. If the use of O emulsions will help in this respect, a great advance on our present methods will have been made.

Felix also in the same paper emphasizes the fact that curves of agglutination diagnostic for enteric group infection occur in large numbers in non-enteric pyrexias among T.A.B. inoculated cases, and that the re-stimulation of the heterologous H agglutinins in the course of an enteric
infection is of the same non-specific character as in the case of any other febrile condition.

Fluctuation was observed by Weil and Felix in “T” agglutinins in 40 per cent of typhus cases [26], but the percentage which would have been diagnostic of enteric group infection, using Dreyer’s method, is not stated. Diagnostic curves were obtained in such diseases as pneumonia and influenza, etc. A. D. Gardner [27], in the same number of the Journal of Hygiene, states:—

“The view that non-specific T curves of diagnostic magnitude occur as the result of non-enteric infections (Anamnestic reaction) does not seem convincingly proved. Evidence against it is strong.”

At the end of 1928 the writer asked eight of the officers in charge of district laboratories to send him details of Widal tests from cases of non-enteric pyrexias in which fluctuation of inoculation agglutinins had been observed. Widal tests on 1,129 cases were carried out during the year by these laboratories, the number of actual tests being probably in the neighbourhood of 5,000. 792 cases were diagnosed as non-enteric in origin. A rise or fall of the inoculation units as the result of infection was observed in 50 cases. The diagnoses included such diseases as malaria, hepatitis, bronchitis, influenza, rheumatic fever, tubercle of lung, tick fever, pleurisy, jaundice. The temperature charts of several cases were distinctly suspicious of enteric fever infection. In many cases the date of inoculation was not given, but in at least 20 the period between the illness and date of inoculation varied from five to twelve months. Fourteen cases might have been considered as belonging to the enteric group on Widal results, i.e., 5 malaria, 2 tubercle lung, 1 broncho-pneumonia, 2 bronchitis, 1 rheumatic fever, 1 pleurisy, 1 amœbic hepatitis, 1 inflammation areolar tissue groin. Bronchitis is a common symptom of typhoid infection among Indian troops. Malaria and enteric fever, as is well known, commonly occur in the same patient. The temperature chart of the amœbic hepatitis case referred to was distinctly suspicious of a paratyphoid infection. The pyrexia in this case lasted thirteen days. Emetine was administered for the first time on the twelfth day of pyrexia, and the temperature dropped to normal on the fourteenth day of illness, which would have been quite consistent with the diagnosis of paratyphoid B which was indicated by the Widal tests. Regarding one case of tubercle of lung, Major Smith, who forwarded details of the case, writes, “The case resembled one of typho-pneumonia, and it is questionable whether an enteric infection has not lit up an old T.B. focus.”

In a few cases the fluctuation of inoculation agglutination was in the nature of a fall in lieu of a rise.

Experience in India therefore indicates that if Dreyer’s method of agglutination, using formolized H emulsions, is employed, pyrexias of non-enteric origin give rise to a fluctuation of inoculation of agglutinins in a certain percentage of cases, but the number of curves of agglutination which would lead to a diagnosis of enteric group infection in cases of
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definitely non-enteric origin must be extremely few, although it is probable that such cases occasionally occur.

That the rise in inoculation units in enteric group infections is of the same non-specific nature as in non-enteric pyrexias seems difficult to credit. In the series of cases of bacteriologically proven typhoid cases, etc., synchronous rises in inoculation agglutinins are found in from 50 to 70 per cent. In non-enteric infections the inoculation agglutinins are not raised so frequently nor in the same degree. Rosher and Fielden [24] found that in normal inoculated individuals agglutination of B. aertrycke and B. paratyphosus C followed as the result of the "B" element of the vaccine, and that B. enteritidis (Gaertner) was co-agglutinated by the typhoid and paratyphoid B elements. Rosher also [28] showed that in a rabbit inoculated with B. paratyphosus B the titre of the serum to B. paratyphosus C was raised from 1 in 320 to 1 in 5,120 in seven days.

In typhoid infections the "B" agglutinins are definitely affected in a higher percentage than "A" agglutinins.

Hood [29] quotes two uninoculated cases of paratyphoid B infection in which co-agglutinins to B. typhosus appeared in the serum during the third week of infection.

Such cases are admittedly rare, but the following tests on an uninoculated infant (eighteen months old) suffering from an enteric group infection, both clinically and on the results of the Widal test a typhoid infection, appear to indicate that the production of co-agglutinins can occasionally occur in uninoculated cases.

<table>
<thead>
<tr>
<th>B. typhosus</th>
<th>10th</th>
<th>15th</th>
<th>21st day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. paratyphosus A</td>
<td>0</td>
<td>0</td>
<td>0 S.A. units</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
</tbody>
</table>

Another case suggesting a paratyphoid B infection is illustrated, although in this case no organism was recovered.

<table>
<thead>
<tr>
<th>B. typhosus</th>
<th>7th</th>
<th>14th</th>
<th>23rd</th>
<th>32nd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. paratyphosus A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>288 S.A. units</td>
</tr>
<tr>
<td>B. paratyphosus B</td>
<td>19</td>
<td>46</td>
<td>99.5</td>
<td>325</td>
</tr>
</tbody>
</table>

Leishman, when summing up the results of inoculation at the end of the Great War, was definitely of the opinion that the steady fall in the incidence of paratyphoid fevers which commenced in the middle of 1915 was connected with the steady rise in the percentage of T.V. inoculation in the British Armies in France, and that an appreciable degree of protection against paratyphoid fevers was given by the typhoid vaccine used.

He states, however, that "no trace of agglutinins or other antibodies to paratyphoid bacteria was ever found to develop in the blood of men or animals inoculated with typhoid vaccine, although this was carefully looked for, since in view of their belonging to the same bacterial group, such a development of co-agglutinins or other substances might not unreasonably have been expected."
Practical experience with typhoid inoculation appears to have differed from the laboratory results, and also shows that co-agglutinins may occasionally be found as the result of infection with living bacilli.

One point which has forcibly impressed itself on the mind of the writer from the study of these Widal results is that the average inoculated individual cannot be looked upon as a machine to produce agglutinins by rule of thumb, as the result of a naturally acquired infection. Although in men or animals inoculated subcutaneously with graduated doses of T.A.B. an agglutinin curve exhibiting certain definite features may result, in a very large number of individuals who acquire infection naturally by the mouth such regular curves are not met with. The reasons appear numerous and obvious, and would include such matters as dosage, virulence of the infecting organism, extent and nature of previous immunity, natural or acquired, on the part of the patient, and many other imperfectly understood factors.

Finally, we may ask whether the results as ascertained by the examination of these 500-odd cases merit the routine employment of the Widal test in undiagnosed cases of pyrexia in the Army in India. If diagnostic results can be obtained in 60 per cent of a mixed group of cases, and a diagnosis of enteric group infection in 80 per cent of cases of average severity, the tests appear to remain a valuable aid in diagnosis, provided the limitations are realized and Dreyer’s technique is employed in all details.

The test is, however, no substitute for careful bacteriological investigation or clinical observation and, if only two or three blood-cultures with aseptic precautions were taken during the first week of all pyrexias, would seldom be required. The taking of repeated blood-cultures in the early stages of the disease would be no more irksome either to the patient or the physician than the present system of vein puncture at weekly intervals to enable the necessary number of Widal tests to be carried out in accordance with the regulations in force. That a high percentage of positive results can be obtained by blood-culture methods in inoculated cases is shown in a further section. The test as employed at present distinctly fails in a high percentage of very mild and abortive cases. Atypical typhoid in India is no myth, and cases have recently occurred in which B. typhosus has been isolated by blood-culture from patients with a pyrexia of only two to three days’ duration, who have actually been discharged to duty apparently fit, and brought back to hospital on receipt of a laboratory report stating that B. typhosus had been grown from the blood-culture. It is in these cases that the employment of O emulsions may be of the greatest assistance. If all claims are justified by further experience by using a combination of O and H emulsions, it may be possible to obtain a true diagnosis of enteric group in all cases, and a definite classification in 60 per cent of cases in which bacteriological investigations have failed.

Certain other details regarding enteric group infections are available from a study of A. Form I 3056, and may be of general interest.

(To be continued.)