

## THE ERYTHROCYTE SEDIMENTATION RATE IN TYPHOID

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Although the erythrocyte sedimentation rate (ESR) is measured as a routine in medical wards, I cannot find any description of its behaviour in typhoid fever written in English. Even text-books devoted to infectious fevers<sup>1, 2</sup> do not mention it.

The records of all cases of typhoid admitted to Groote Schuur Hospital from 1950 to early 1957 were examined. In 64 the clinical picture was typical, diagnosis was proven by culture of *Salmonella typhi*, the ESR had been recorded (Table I) and there was no background illness likely to have

TABLE I. ESR IN 64 TYPHOID CASES VERIFIED BY CULTURE OF *S. typhi*

Technique	No. of Cases
Westergren .. .. .	39
Wintrobe .. .. .	8
Not specified, but either Westergren or Wintrobe ..	17
Total Westergren and Wintrobe .. .. .	64

affected it. The sedimentation rate is always read at 1 hour in this hospital. It is not usually measured in the surgical wards, so that cases presenting with perforation are likely to have been inadequately represented in the sample.

As Groote Schuur is a general hospital, typhoid mostly presents as a problem in early diagnosis. When the diagnosis of typhoid is established patients are transferred to an infectious diseases hospital.

The arithmetic mean ESR was 26 mm. Fig. 1 shows the frequency distribution. Taking 10 mm. in males and 20 mm. in females as the upper limits of normal,\* the ESR was normal in 22 cases (34%). It was below 25 mm. in both sexes in a further 20 (31%). In the remaining 22 cases (34%) it was distinctly elevated.

The records were analysed further to try and find why the ESR was low in some cases of typhoid but high in others. There was no correlation between sedimentation rate and the method used, the age, sex, race, haemoglobin, white cell count, height of pyrexia, severity of illness or mortality.

TABLE II. ESR IN 64 TYPHOID CASES VERIFIED BY CULTURE OF *S. typhi*

No. of days from onset of first definite symptoms	Mean ESR	S.D.
Up to 10 .. .. .	19.8	14.5
11 to 35 .. .. .	38.6	26.1

S.E. of difference—6.2.

Difference of means—18.8, which is 3 times the S.E. of difference. ∴  $p=0.003$ .

\* From the data of Karvonen *et al.*<sup>3</sup> on 134 young, healthy subjects the 95% confidence upper normal limit of 1 hour Westergren calculated from mean plus 2 S.D. should be 10 mm. for males and 17 mm. for females. Westergren<sup>4, 5</sup> has likewise suggested that normal-confidence limits up to 10 mm. for males and 15-20 mm. for females be used when considering a group of cases. These limits for the Westergren correspond well with those defined for the Wintrobe method, viz. up to 9 mm. in males and 20 mm. in females (Wintrobe<sup>6</sup>).

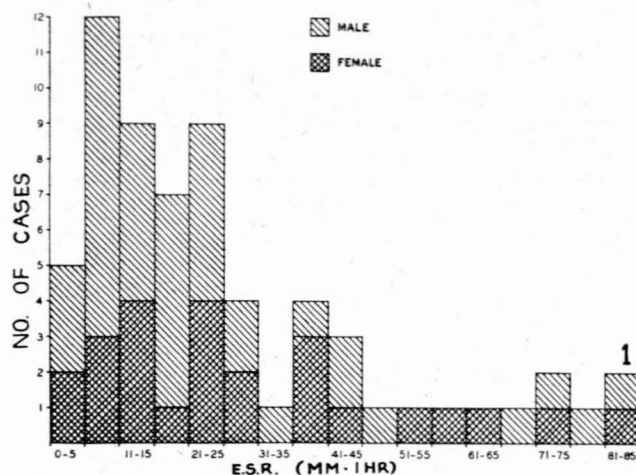


Fig. 1. Frequency distribution of the sedimentation rate in 64 cases of typhoid. (The ESRs of 55 of these are plotted against duration of illness in Fig. 2.)

However, a positive correlation was found with duration of illness. In 55 cases the duration of illness given in the history appeared to be reliable—either the patient was not mentally confused or, if he was, the history had been obtained from a close and observant relative. In this group (Fig. 2) the correlation coefficient between ESR and the duration was plus 0.48. With a standard error of 0.136 this is statistically significant ( $p < 0.003$ ). An alternative way of expressing the relationship is presented in Table II.

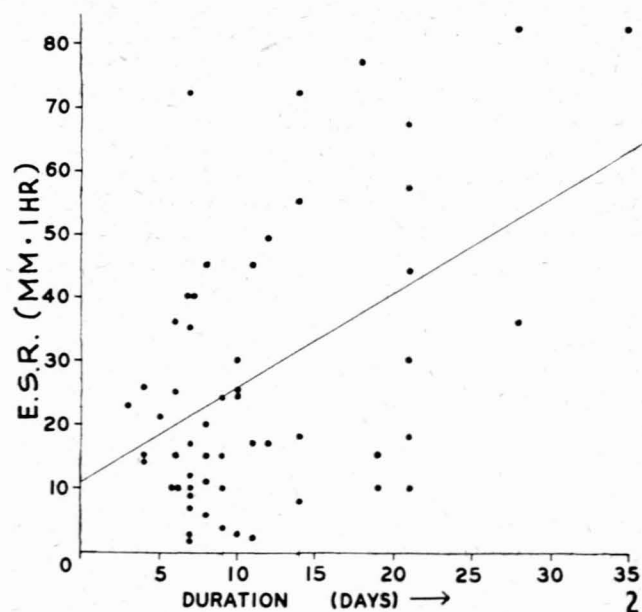


Fig. 2. Partial correlation between ESR and duration of typhoid in 55 cases: scatter diagram and regression line.

## DISCUSSION

It has been found that the ESR is usually normal or only slightly increased during the first 10 days of typhoid but thereafter shows a more definite increase. The finding that 1/3rd of cases of typhoid have a normal ESR is surprising, because 'in general the sedimentation rate is increased in all acute general infections' (Wintrobe<sup>6</sup>). Seven types of exceptions to this statement are known:

1. The sedimentation rate may be retarded if measured several hours after withdrawal of blood<sup>7, 8</sup> or at a temperature below 15 C.<sup>9</sup>
2. Methods using undiluted blood, such as Wintrobe's, are more likely to give false negatives.<sup>10, 11</sup>
3. Often the ESR is not accelerated if an acute infection is localized, mild or incipient. Thus it is minimally affected by a cold.<sup>12</sup> It is normal in acute appendicitis, but elevated if an appendix abscess forms.<sup>13</sup>
4. Where there is associated cardiac failure,<sup>14</sup> cyanosis or polycythaemia, retardation of the ESR by these conditions may mask the accelerating influence of infections.
5. In some diseases such as tuberculosis where an increased sedimentation is the rule, exceptions have been documented.<sup>15</sup> These illustrate the limited reliability of the test.
6. There are 2 infections which are not mild, brief or localized but are usually associated with a normal ESR: in pertussis<sup>16</sup> the normal sedimentation rate is restricted to the paroxysmal stage, and in infectious hepatitis<sup>17</sup> to the icteric stage.
7. Patients with agammaglobulinaemia have low ESR readings when they develop infections.<sup>18</sup>

My present findings in typhoid do not fit well into any of these categories. One way of classifying typhoid might be in group 3 with the qualification that the early delay before the ESR rises is peculiarly prolonged. In pneumonia, for instance, Lesser and Goldberger<sup>13</sup> found the ESR was over 15 mm./1st hour (Westergren) in all of 60 cases. Some of these are likely to have presented within a day of the onset of symptoms.

The literature was searched and two articles in German found which the present results seem to confirm. Gerecke,<sup>19</sup> in 1926, reported that in 17 cases of typhoid the Westergren ESR was 4-8 mm. in the 1st week. It rose to 14 mm. in the 2nd week and the high value of 30 mm. or more first appeared in the 3rd week.

The delayed rise of the ESR in typhoid ('typhus abdominalis') was analysed in detail by Tamura<sup>20</sup> in 1940. He measured the sedimentation rate serially in 41 cases and found that it correlated better with the *stage* of the disease than the number of days the patient had been ill. Throughout the stages of rising temperature and continuous pyrexia the ESR was normal or only slightly elevated (7-27 mm. Westergren). During the stage of remittent fever a gradual acceleration began in all cases and the maximum ESR (usually 51-85 mm.) was reached on the day when the defervescence was complete. Thereafter it slowly returned to normal over 1-6 or more weeks. The ESR tended to rise earlier in the disease when secondary infections like pneumonia and stomatitis were present but was smaller than usual with the dangerous complications—perforation, bowel haemorrhage or violent brain symptoms.

The importance of Tamura's careful study is that it was made before the introduction of chloramphenicol and therefore on untreated patients going through the natural course of typhoid. This work can no longer be repeated but it appears to have passed unnoticed in the English-speaking medical world. In addition to these two articles,<sup>19, 20</sup> several others<sup>21-24</sup> are indexed as dealing with the ESR in typhoid; none of them is accessible to me.

The mechanism of the behaviour of the sedimentation rate in typhoid has not been studied with modern serum-protein techniques. Gerecke<sup>19</sup> ascribed it to the fibrinogen falling at first and rising later than in any other infection.

A practical application of the present finding may be that it provides an additional diagnostic feature for typhoid. In several of the case reports used in my analysis differential diagnoses like miliary tuberculosis and collagen disease had been entertained. A low or moderately raised ESR would argue against either of these and in favour of typhoid. On the other hand a distinctly elevated sedimentation rate has less weight than a leucocytosis in excluding typhoid. Of the 64 patients represented in Fig. 1, only 33 (51.5%) had an ESR of 20 mm. or less, compared with 53 (83%) who had a white-cell count of 10,000 or less. The maximum ESR seen in Tamura's cases was 154 mm. and in my series 82 mm.

However, a higher ESR—141—was seen in one of the *probable* cases amongst the records I examined; it was not analysed. This patient had had symptoms suggesting typhoid for over a month. The physical findings, rising titre of Widal, and response to chloramphenicol, supported the diagnosis. Failure to confirm it by culture may have been because he was first seen at a late stage of the disease. It is noteworthy that this patient had both the highest ESR and the longest duration of illness of all the case records examined.

## SUMMARY

The erythrocyte sedimentation rate is often not elevated in the first 1-2 weeks of typhoid but rises later in the disease. Because of this the ESR may assist in diagnosis.

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