THE CLINICAL SIGNIFICANCE OF THE ERYTHROCYTE SEDIMENTATION RATE WITH SPECIAL REFERENCE TO PULMONARY TUBERCULOSIS

By

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'Whatsoever things are true.... think on these things.'
Philippians 4:8

'Truth is the aim of all research, no matter how sharply this truth may conflict with our social, ethical and political conditions.'
Theodore Billroth.

CHAPTER I - INTRODUCTION.

There are few subjects in medicine about which there is more controversy than the Erythrocyte Sedimentation Rate. Some authorities place great reliance on the test, while others have discarded it as having no practical importance. There is little agreement as regards either the methods of estimation and interpretation or the clinical value of the test. This thesis will deal only with practical considerations. Theories as to the mechanism of sedimentation will not be discussed.

The material to be analysed consists of approximately 6000 sedimentation tests on 1000 patients with active pulmonary tuberculosis. There has been no selection of these cases except in one respect: cases with some concurrent condition which might affect the E.S.R. (such as pregnancy or rheumatic heart disease) have been excluded. Apart from this precaution the number of 1000 is made up of consecutive cases seen either as in-patients or out-patients at King George V Hospital for Tuberculosis. In addition a single sedimentation test was performed on 619 apparently healthy people.

The method for all tests was that described by Cutler, using the 5 cc. Cutler tube with a column of blood 50 mm. high. The anticoagulant was 1 part of 3.8% Sodium Citrate solution to 9 parts of blood. The rate of sedimentation was charted on the Cutler chart every 5 minutes for one hour, and the significant reading was taken as the number of mm. which the red cells had fallen after one hour. This one-hour reading is used throughout this thesis except where otherwise specified.

The object of this study is to determine how reliable the E.S.R. is in Pulmonary Tuberculosis. There are two

- aspects -

aspects of this problem: diagnosis and observation of progress. Diagnosis in this connection means not diagnosis of the etiology of a pulmonary lesion but of its activity. This will form the subject of Chapter II. Observation of progress can for convenience be considered under two headings. Chapter III will deal with the use of the E.S.R. in the control of a case while under treatment, that is, in hospital. The accuracy of the E.S.R. in prognosis will be considered in Chapter IV. In Chapter V the various methods of interpreting the E.S.R. will be compared.

Up to this point the E.S.R. will be discussed only in its relation to Pulmonary Tuberculosis. In Chapter VI the use of the E.S.R. in other diseases will be described. No original work has been done on this part of the subject, and this chapter, therefore, is a summary of existing literature.

CHAPTER II - DIAGNOSIS.

In the absence of a positive sputum it is often very difficult to know whether a pulmonary lesion is an active tuberculous focus or not. The E.S.R. is frequently used as a guide in deciding this point, but there is much dispute as to whether it is a reliable indication. The point at issue is: With what degree of certainty does a normal E.S.R. exclude the presence of active disease?

Perhaps the greatest difficulty in answering this question lies in the lack of agreement as to what is a normal E.S.R., and the various values stated vary within very wide limits as shown by the following figures given for the one-hour reading. Roche (83) says the normal is up to 4 mm. in men and 6 mm. in women. Wingfield (105) gives the same figures. Kayne, Pagel and O'Shaughnessy (52) give 7 mm. in men and 10 mm. in women. McGee (61) gives up to 10 mm. and goes so far as to specify definite ranges corresponding to definite degrees of activity - slight, moderate or severe. Using a micromethod, Landau (56) gives 5 mm. in men and 8 mm. in women. Wintrobe (106) found that 86% of healthy men were below 6.5 mm. and 86% of women were below 15 mm. This marked discrepancy in women is confirmed by Edwards and Penman (29) who state that the normal E.S.R. in women can be "surprisingly rapid". Some authors give much higher normals than these. Vanni (99) quotes up to 16 mm; Agnor (2) up to 20 mm; and Osgood (72) up to 30 mm. for a 45 minute period.

There is a similar disagreement among authors using other methods of reading the E.S.R. Expressing the result as mm. per minute (during the maximum rate of fall), Cutler (19) gives the normal as not more than .2, Muller (66) as not more than .3, and for the Rourke-Ernstene method it is

given as .4.[86] Using Day's Sedimentin Index, Day himself[22] gives the normal as 0.5, whereas Vida[100] says it is from 0.5 to 1.4.

Even more confusing than these variable figures is the fact that many authors, when discussing the significance of a normal E.S.R. in pulmonary tuberculosis, omit to state what they regard as "normal". A study of sixty-two articles dealing with this subject revealed that no less than forty of them failed to mention the normal values on which their findings were based.

Returning to the original question, there are great differences of opinion as to the value of the E.S.R. in excluding active disease. Ringer and Roach[82] state that a normal E.S.R. is found in less than 1% of cases. Cutler[18] found it only five times in 5000 cases of active tuberculosis. Banyai and Caldwell[8] found the E.S.R. normal in 2% of 5274 cases. Hollins[44] places so much reliance on the E.S.R. that he suggests mass surveys for finding tuberculosis cases using the test and only X-raying those with an abnormal reading. Kayne, Pagel and O'Shaughnessy[52] make a similar suggestion, and state that a normal E.S.R. is a "valuable confirmation of the non-progressive character of a tuberculous pulmonary lesion".

Other authors are more critical. Banyai and Cadden[7] report a normal E.S.R. in 8% of 2640 cases of active tuberculosis and consider its value greatly over-estimated. Rest[81] states that nearly one-quarter of cases showed constantly normal rates. Abeles and Pinner[1], using 9 mm. as the upper limit of normal, found that only 63% of 86 "accidentally discovered" cases of tuberculosis had a raised E.S.R. Trenchard[97] found 107 of 287 cases with an E.S.R. of under 8 mm. It should be noted, however, that these were cases discovered by mass radiography, and

the majority would, therefore, have early disease. This is shown by the fact that in 90 of the 107 cases the sputum was negative. Bobrowitz (11) reports 200 cases of minimal tuberculosis in which the E.S.R. was less than 10 mm. in 45%.

The frequency of a raised E.S.R. in primary tuberculosis is also in dispute. Vanni (99) states that it may be normal in the presence of tuberculous glands. Landau (56) has found it normal even when X-ray showed definite enlargement of mediastinal glands. Ustvedt (98) states that in some cases of primary tuberculosis all that can be demonstrated clinically is a raised E.S.R. Edwards and Penman (29) consider that the E.S.R. is of more value in primary infection than at any other stage of tuberculosis. It increases, sometimes considerably, at the time when the tuberculin reaction becomes positive. Hurford (47) reports that in primary tuberculosis in children the sedimentation rate may remain above normal for a long period.

It seems clear from the figures quoted that the E.S.R. is of no value as a test of activity if the upper limit of normal is regarded as being in the region of 8 to 10 mm. The question then arises as to whether it is possible to fix any lesser sedimentation rate which will exclude activity with a reasonable degree of certainty.

In order to ascertain this point, 1000 cases of active tuberculosis are analysed in Table 1. The E.S.R. for each case is the reading obtained when the patient was first diagnosed as having active disease. The sedimentation rates for each mm. up to 10 are recorded separately, and all those over 10 mm. are classed together. The cases are also divided according to the stage of the disease. Group I indicates minimal disease, Group II

moderately advanced disease, and Group III extensive disease.

TABLE 1.

E.S.R.	Group I	Group II	Group III	Total
1 mm.	0	0	0	0
2	2	3	0	5
3	1	1	1	3
4	0	1	0	1
5	0	3	0	3
6	6	7	1	14
7	3	4	1	8
8	7	4	3	14
9	5	11	2	18
10	4	7	4	15
Over 10	38	115	766	919
Total	66	156	778	1000

A study of this table shows that it is rare to find active tuberculosis with an E.S.R. of 5 mm. or less. However, with a crude test such as this it is as well to allow a margin for experimental error. Vanni (99) states that two tests from the same specimen of blood may vary 1 mm., and tests from the same person at different times of day may vary 2 mm. Landau (56) states that it is common to find duplicate tests varying by 3 mm. in an E.S.R. of 25 mm. As a working hypothesis it is suggested that 2 mm. be allowed for experimental error, and therefore 3 mm. is the highest reading that should be regarded as indicating a probable absence of activity. Before this figure can be accepted as having any practical value, it is necessary to determine the probability of error. In other words, in what proportion of active cases will the E.S.R. be 3 mm. or less, thereby giving an erroneous impression?

Taking all the cases together, the proportion is only 8 in 1000 - a degree of error which is almost negligible in a clinical test. However, as the activity

of extensive disease is usually obvious, the usefulness of the test depends on its accuracy in less advanced disease. If Group I and Group II are combined, the probability of error is 7 in 222 or 3.1%. In Group I alone the error occurs 3 times in 66 cases or 4.5%. This error is considerable, but not so great as to make the test useless. A test that is wrong only once in 22 cases is not to be despised when it is remembered how inaccurate are the other diagnostic procedures. For example, a repeatedly negative sputum does not exclude tuberculosis with certainty, and normal radiological findings may occur with active disease and a positive sputum. As a negative diagnostic test the E.S.R. may therefore be useful, but it is certainly not reliable enough for excluding tuberculosis in mass surveys as suggested by the authors already quoted.

The solitary case in Group III with an E.S.R. as low as 3 mm. requires special comment. This patient had miliary tuberculosis, and the E.S.R. was 3 mm. on admission to hospital. It increased with each monthly test, and was 24 mm. shortly before he died four months later. This anomaly of a low E.S.R. associated with miliary tuberculosis has been noted before by Landau. (56)

If 3 mm. is to be the maximum significant reading, it is necessary to consider how frequently the E.S.R. is as low as this in healthy people. There would be no advantage in doing a test if the "normal" value was seldom found in normal subjects. To determine this point, a sedimentation test was performed on 619 apparently healthy people. Of these, 47 were subsequently found to have some disease which would increase the E.S.R. The sedimentation rates of the remaining 572 are analysed in Table 2. The total number with a rate of 3 mm. or less is 298 or 52%. It must be pointed out that the majority

of this series were men. Only 89 were women, and they tend to have a higher rate than men. However, even among the women there were 27 (or 30%) with a reading of 3 mm. or less. It is apparent that the E.S.R. is as low as 3 mm. in normal subjects often enough to make it worth while doing. In a considerable proportion of healthy people the test will be able to provide fairly reliable evidence that active pulmonary tuberculosis is not present.

TABLE 2.

E.S.R.	No. of Cases
1 mm.	87
2	110
3	101
4	75
5	66
6	36
7	30
8	22
9	19
10	10
Over 10	16
Total	572

A point of some practical importance is that with low sedimentation rates the one hour reading is approximately the same whatever the size of the tube used. This fact has been noted by Shackle (92) and by Pessar and Hurst, (77) although the latter authors exaggerate when they say that the rate is the same in all tubes as far as 18 or 20 mm. Experiment shows that there are considerable variations at this level, but the important fact is that the rate is much the same for the first 3 mm. - the level of diagnostic significance. To test this point, four different tubes were used in each of three cases with a low sedimentation rate. Sodium Citrate was the anticoagulant, and blood was used from the same syringe. The sedimentation time in minutes was recorded for the first 4 mm. It is obvious

that minor variations occur, but these affect the one-hour reading by less than 1 mm.

Type of Tube:	Cutler (Large)	Cutler (Small)	Wintrobe	Westergren
Case 1:				
1 mm.	30	30	25	30
2 mm.	40	40	35	40
3 mm.	50	50	45	50
4 mm.	60	60	50	60
Case 2:				
1 mm.	40	60	40	60
2 mm.	70	85	70	80
3 mm.	100	105	85	105
4 mm.	120	120	100	120
Case 3:				
1 mm.	30	30	20	20
2 mm.	50	50	40	40
3 mm.	65	60	50	50
4 mm.	75	75	60	60

The use of different anticoagulants would also cause some variation, but even if this were as much as 33% as has been reported (40), the difference is only 1 mm. in 3. The 3 mm. diagnostic standard can therefore be applied to all methods of determining the E.S.R.

So far the E.S.R. has been considered purely as a negative test. Such wide limits of normal have been given by some authors (already quoted) that it is perhaps impossible to fix a sedimentation rate that indicates definitely the presence of disease. Surveys have been done to estimate the value of the E.S.R. in this respect, Cutler (18) tested 328 people and found 177 with a reading above 10 mm. These were investigated, and 169 were found to have some active disease. Agnor (2) in a study of 2063 cases (using the Westergren method) found that 95% of those with a reading above 20 mm. had organic disease. These surveys are not comparable due to the difference in

methods. In the present series of 619 apparently healthy people, 63 were found to have an E.S.R. above 10 mm. On investigation, 47 of these were found to have some disease.

The most that can be said about the positive significance of the E.S.R. is that there is no definite upper limit of normal, but that any case with a rate above 10 mm. should be further investigated. A corollary to the findings of this chapter is that sedimentation rates from 4 mm. to 10 mm. have neither positive nor negative significance, and are therefore of no value in assessing a case.

CHAPTER III - CONTROL.

While for convenience the question of prognosis will be dealt with separately in the next chapter, the literature to be discussed here will of necessity concern both control and prognosis. There are remarkable extremes of opinion as to the value of the E.S.R. in showing the progress of a patient with tuberculosis. Some of these will be summarised briefly.

Obermer (70): It is not a reliable guide to prognosis and treatment. In another publication (71) the same author states: "The test is of doubtful utility in tuberculosis..... The educated senses of a good clinician provide a better guide to progress than laboratory findings; isolated laboratory findings expressed with the authority of mathematical accuracy may even interfere with clinical judgment". Courmont and Moulinier (16): The prognostic significance is slight because it is limited to the present time. Landau (56): In several cases the E.S.R. came down to normal and yet acute pleurisy followed. Pessar and Hurst (77): Investigation casts serious doubt on the value of the E.S.R. in prognosis. De Cecio and Elwood (24): It is not of sufficient value to be essential in the care of T.B. cases. Hilliard (42): I have abandoned the use of sedimentation tests long ago. McIntosch and Keay (62): In males it is of limited value and a case can generally be assessed more accurately without its use. In females it is valueless. Pinner (79): The E.S.R. is a frequently deceiving indication. A normal rate does not exclude either activity or progression. An elevated rate may be associated with non-pertinent developments.

Equally emphatic are numerous authors who report favourably on the E.S.R. Rest (81): It has considerable

value in prognosis. McGee[61]: If the sedimentation rate does not parallel the clinical course of the disease, it is better to rely on the E.S.R. British Encyclopedia of Medical Practice[13]: It has great value in assessing progress Aranda[5]: The E.S.R. is valuable because the radiological and clinical findings may mask the true state of progression. Penman[74]: It is a reliable prognostic test. The prognosis is bad in cases with fluctuating readings. Ham and Curtis[40]: It is a sensitive index of activity as it may be the last non-specific test to return to normal. Kelley[53]: The E.S.R. may give warning of relapses even before new shadows are found on X-ray. Roche[83]: It may be the first warning of a complication and is of proved value in management of tuberculosis. Wingfield[105]: It is very useful both in prognosis and in managing cases after discharge from hospital.

The use of the E.S.R. in assessing results of collapse therapy has been the subject of special comment. Banyai and Cadden[7] state that the E.S.R. may return to normal without healing of the disease, especially in collapse therapy. Cutler[18] gives a contrary opinion: "It is better than any clinical or laboratory method for estimating progress and is especially important in pneumothorax treatment". Muller[66] states that conversion of sputum and mechanical result are not sufficient evidence of satisfactory pneumothorax. Confirmation by haematological studies is necessary. She goes on to say that the higher the E.S.R. before collapse therapy, the longer is the time necessary to control the disease. Wollaston and Landau[107] are not in agreement with this for they could find no correlation between the initial E.S.R. and the result of the pneumothorax treatment. Muller also made the important observation that the sedimentation rate

is not influenced by the pneumothorax per se.

In order to test the value of the E.S.R. as an indication of progress, it is necessary to compare the information obtained from serial readings with the information given by other methods of observation. In this series tests were done at monthly intervals. A satisfactory idea of the trend of the sedimentation readings cannot be obtained with less than four serial tests. All cases that had less than four tests done (that is, they were under observation less than three months) have been excluded from this part of the study. In addition all cases have been excluded that had an E.S.R. below 6 mm. throughout. Below this level changes in the E.S.R. are so slight as to be of doubtful significance. Of the original 1000 cases the number fulfilling these criteria is 577.

The progress of each of these patients has been followed carefully by X-ray, sputum and clinical examinations. These findings have then been correlated with the serial sedimentation tests to determine whether the E.S.R. parallels the actual progress of the case. On this basis they have been divided into three groups as follows:
I There is close correlation between the E.S.R. and the actual progress. Only rarely does an isolated sedimentation reading fail to follow the correct trend. II There is a useful degree of correlation. Anomalous readings occur not infrequently, but on the whole the correct trend is followed and in any case the information given is not misleading. III The correlation is so inaccurate as to be useless or the general trend is actually misleading.

The result of this analysis is shown in Table 3. A similar study was carried out by De Cecio and Elwood (24) in a series of 338 cases and similar results were reported:

Accurate - 55%; some significance - 34%; no significance - 11%. These authors, however, regard the E.S.R. as being useless in both their second and third groups and conclude that the test is too frequently inaccurate to be of value.

TABLE 3.

Group	No. of Cases.	Percentage
I Close correlation	357	62
II Useful correlation	162	28
III Useless or misleading	58	10
Total	577	100

This conclusion hardly seems justifiable, for from their description the E.S.R. in their second group was probably useful and certainly not misleading. If it is useless only in the third group, the position is entirely different from what they suggest.

The 58 cases falling into Group III in Table 3 must be studied further. The E.S.R. in these cases was classed as useless because it gave information different from that obtained by other methods of observation. For example, in some cases the E.S.R. increased or remained elevated even though there was considerable clinical and radiological improvement. However, these methods are not necessarily infallible. To find out which tests had provided the more accurate information, those of the 58 patients who did not die in hospital were followed up after their discharge. In 10 of the patients in whom the E.S.R. was the only test not showing improvement, there was a recurrence of disease within a short period. In these cases, therefore, although they are included in Group III, the E.S.R. proved to be correct, and the other tests were misleading. These cases will be reported briefly.

CASE 1.

A European male aged 24 years was admitted to hospital on the 7th September, 1942. He gave a history of cough and loss of weight for nine months. His weight was 118 pounds, his sputum was T.B. positive, and a radiogram of his chest showed extensive tuberculous infiltration in both lungs (Plate 1). He was afebrile and remained so throughout his stay in hospital. He was treated conservatively and showed rapid improvement. His weight increased steadily reaching 136 pounds after nine months and remaining at that level. Serial radiograms showed considerable clearing of the disease. Sputum became negative in December 1943 and was subsequently repeatedly negative. The E.S.R. showed little improvement, the monthly readings being as follows: 28, 28, 23, 27, 25, 26, 24, 25, 24, 22, 24, 26, 24, 23. In view of the remarkable clinical improvement, the results of the sedimentation test were ignored and he was discharged on the 14th May, 1944, after being in hospital for twenty months. He was instructed to have a period of convalescence before returning to work. The radiogram taken shortly before discharge showed the lungs almost clear of infiltration (Plate 2). Four months later he was readmitted to hospital with a severe recurrence. He was acutely ill, sputum was again T.B. positive, and a radiogram showed extensive infiltration throughout both lungs (Plate 3). He died three weeks after admission.

CASE 2.

An Indian female aged 21 years was admitted to hospital on the 18th October, 1941. She had previously been treated by right artificial pneumothorax for two years. This had been abandoned three months before, and shortly afterwards she was found to have new infiltration

at the apex of the left lung. On admission she was afebrile, weighed 100 pounds and her sputum was T.B. positive. Radiogram of her chest showed a little infiltration in both upper zones more marked on the left, and the right costo-phrenic angle was obscured (Plate 4). Her E.S.R. was 23 mm. Her condition improved steadily, weight went up to 115 pounds and sputum became T.B. negative after six months. Vague shadows remained in both lungs but never showed any tendency to spread. The E.S.R. was never less than 23 mm. during her stay in hospital and was usually between 25 and 28 mm. It was felt that this constantly high rate was sufficient reason for keeping her in hospital in spite of the other favourable findings. At one stage left pneumothorax was performed in an attempt to control whatever disease might be causing the high sedimentation rate but this had to be abandoned due to adhesions. She continued in hospital, clinically well and sputum negative, for over four years. It was then felt that it was not justifiable to keep her in hospital any longer and she was discharged on the 31st January, 1946. A radiogram of her chest still showed vague shadows in both upper zones (Plate 5), and her final E.S.R. was 25 mm. A routine radiogram on the 26th October, 1946, (Plate 6) showed a cavity and considerable infiltration in the upper half of the right lung.

CASE 8.

An Indian male aged 17 years was admitted to hospital on the 21st May, 1942, with a history of cough and fever for six weeks. On admission he had a temperature swinging up to 100°F. His weight was 105 pounds, and his sputum was T.B. positive. A radiogram of his chest showed scattered infiltration in the left subclavicular and mid zones, and infiltration with cavitation in the right

PLATE 1
(CASE 1)

PLATE 2
(CASE 1)

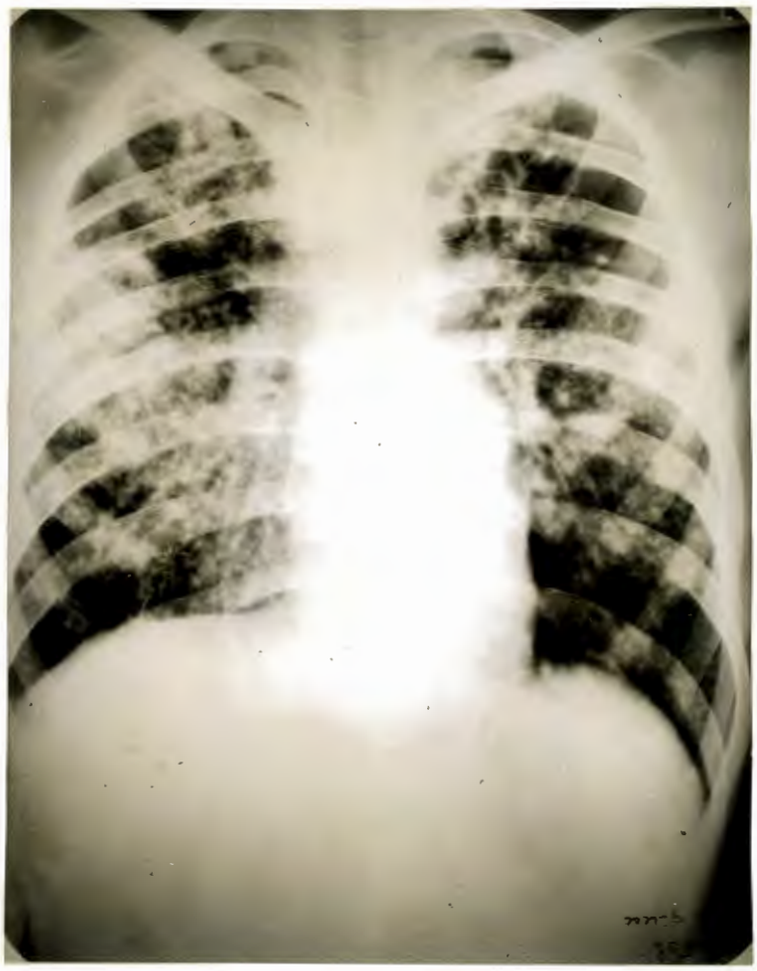


PLATE 3
(CASE 1)

PLATE 4
(CASE 2)

PLATE 5
(CASE 2)

PLATE 6
(CASE 2)

PLATE 7
(CASE 3)

PLATE 8
(CASE 3)

subclavicular zone (Plate 7). E.S.R. on admission was 25 mm. Right artificial pneumothorax was induced on the 8th June, 1942, and when the disease on the left side was found to be spreading this lung was also collapsed on the 11th August, 1942. Both pneumothoraces controlled the disease adequately and there were no adhesions. He soon became afebrile and by October the sputum was T.B. negative and remained so until his discharge. His weight gradually fell to 101 pounds, but as loss of weight is a common finding with bilateral pneumothorax this was not considered a bad sign. His sedimentation readings were as follows: 25, 22, 21, 19, 20, 22, 23, 22, 23. He was discharged from hospital on the 24th February, 1943, when a radiogram showed a very satisfactory bilateral pneumothorax (Plate 8). He attended regularly for refills and remained well for about six months when his condition began to deteriorate. The disease was found to be spreading and cavitating in the lungs in spite of the pneumothoraces. He was readmitted to hospital in October 1943 and died four months later.

CASE 4.

A European female aged 24 years was admitted to hospital on the 3rd July, 1940, with a history of cough and lassitude for two weeks and a small haemoptysis a week before. She was afebrile, weighed 134 pounds and her sputum was positive for tuberculosis. A radiogram showed infiltration in the upper zones of both lungs. E.S.R. on admission was 23 mm. She improved rapidly on conservative treatment. Sputum became negative one month after admission and remained so. Weight increased to 144 pounds after three months, and radiologically there was considerable clearing of the infiltration. Her sedimentation readings were: 23, 24, 24, 19, 22. She was discharged

from hospital on the 30th November, 1940, with the disease apparently quiescent. A routine radiogram in May 1941 showed fresh disease in the left lung and her sputum was again T.B. positive. She was readmitted for further treatment.

CASE 5.

A European female aged 28 years was admitted to hospital on the 25th February, 1941, with a history of cough and occasional streaking of the sputum for the past six months. She had a slight evening temperature up to 99.6°F. Her weight was 132 pounds and her sputum was T.B. positive. A radiogram of her chest showed infiltration in the left apex and subclavicular zone. E.S.R. was 13 mm. She appeared to respond to conservative therapy after a pneumothorax had been attempted unsuccessfully. She became afebrile and weight increased to 143 pounds. Sputum became T.B. negative in May and on serial radiograms the disease became progressively less. The E.S.R. was variable but on the whole showed no improvement, the readings being: 13, 20, 16, 9, 13. She was discharged from hospital on the 29th June, 1941. Seven months later it was found that a cavity had developed at the apex of the left lung. She was readmitted to hospital and had to undergo a thoracoplasty.

CASE 6.

A European boy aged 11 years was admitted to hospital on the 5th October, 1941. He had no symptoms, the disease having been found on routine X-ray as a contact of an elder brother with tuberculosis. He was afebrile and weighed 80 pounds. No sputum was obtained for examination. A radiogram showed typical primary tuberculosis in the right lung. E.S.R. on admission was 11 mm. He remained in

hospital for six months during which time there was great improvement. His weight increased to 95 pounds and a radiogram taken when he was discharged on the 31st March, 1941, showed both lung fields clear. His sedimentation readings were: 11, 10, 11, 9, 14, 9, 9 - a negligible improvement. He remained apparently well until January 1942 when he had an haemoptysis. Examination showed active tuberculosis in the upper lobe of the right lung. This subsequently extended and the sputum became T.B. positive.

CASE 7.

A European female aged 27 years was admitted to hospital on the 4th September, 1943. She had previously had a pneumothorax on the right side for three years which was abandoned in March 1943. She was readmitted to hospital because of new disease in the left lung. She was afebrile, weighed 116 pounds and a positive sputum was not obtained. A radiogram of the chest showed in the left subclavicular zone a large Assman focus which was cavitating in the centre. There was no evidence of active disease in the right lung. E.S.R. was 7 mm. The lesion in the left lung cleared rapidly and when she was discharged on the 1st February, 1944, a radiogram showed only a slight trace of infiltration remaining. Her weight was then 122 pounds and she had no sputum. The sedimentation rate showed a definite tendency to increase while she was in hospital: 7, 8, 9, 11. Three weeks after her discharge from hospital she had a sudden large haemoptysis. There was a recurrence of the disease in the left lung, and pneumothorax had to be induced as an emergency measure.

CASE 8.

A European female aged 24 years was admitted to hospital on the 8th June, 1939. A left artificial

pneumothorax had been induced three years before and was still being maintained. A radiogram showed the lesions in the left lung were completely healed and calcified, but there was recent infiltration in the upper zone of the right lung. She was afebrile, weighed 94 pounds and sputum was T.B. positive. E.S.R. was 15 mm. She was kept in hospital for four months. Her sputum was then T.B. negative, she weighed 105 pounds and a radiogram showed the disease in the right lung practically cleared. The sedimentation readings were 15, 22, 15, 23. As in the previous case the unfavourable prognostic indication is well defined even though the series is short. However, she was discharged from hospital. Four months later she had a severe haemoptysis due to a recurrence of the disease in the right lung, and pneumothorax had to be induced to control it. This case is of particular interest because of its similarity to Case 7.

CASE 9.

A Coloured male aged 18 years was admitted to hospital on the 4th July, 1939, with a history of cough and general malaise for six months. He was having an haemoptysis when admitted, but this quickly subsided and did not recur. He was afebrile, he weighed 92 pounds, and his sputum was positive for tuberculosis. A radiogram showed infiltration and a cavity in the upper half of the left lung, and minimal infiltration in the right subclavicular zone. His E.S.R. was 12 mm. He improved steadily with general treatment. His sputum became negative in January 1940 and his weight increased to 98 pounds. The radiogram showed definite clearing, and the cavitation was no longer apparent. The E.S.R. showed a tendency to become worse: 12, 22, 17, 24, 21, 21, 23, 24. He was discharged from hospital on

the 1st April, 1940, when the disease appeared quiescent. Six weeks later he was readmitted to hospital with a considerable extension of the disease and sputum again T.B. positive.

CASE 10.

A Coloured female aged 23 years was admitted to hospital on the 16th February, 1940, with a history of coughing and general malaise for five months. She was running an evening temperature up to 101°F. Her weight was 96 pounds and her sputum was T.B. positive. A radiogram showed infiltration and a cavity in the upper part of the left lung. E.S.R. was 29 mm. An attempt to induce a pneumothorax on the left side was unsuccessful. She was kept at rest in bed and at first appeared to improve. Later, although her general condition continued to improve, the cavity at the apex of the left lung increased in size. Thoracoplasty was recommended, but was at first refused. Eventually she agreed to undergo the operation. The first stage was performed on the 5th November, 1941, and the second on the 13th February, 1942. A radiogram showed the disease controlled, and she was discharged from hospital on the 14th April, 1942, with sputum T.B. negative and weight 104 pounds. The sedimentation rate was above 25 mm. throughout her stay in hospital including the final reading before discharge. She was kept under observation as an out-patient, and although she appeared to keep perfectly well, the E.S.R. remained high. In July 1943 she developed infiltration in the right lung, and was later readmitted to hospital with a pleural effusion on that side.

These case reports illustrate how the E.S.R. may sometimes be the only indication that the disease is not

quiescent. That there was activity at the time of discharge from hospital is shown by the subsequent recurrence. If this occurs soon, and without any precipitating cause, it is reasonable to assume that the disease process was in fact active all the time. In these ten cases the average time before relapse was only seven months. The shortest was three weeks, and the longest fifteen months.

Six of the cases in Group III in Table 3 were placed there because the E.S.R. showed a considerable improvement in a patient who was obviously getting worse and who died a short time later. Here the trend of the E.S.R. appears to have been quite erroneous. This anomaly, however, is a well recognised phenomenon and has been reported by Wintrobe,(106) Roche(83) and Muller.(66) The last author suggests that the decreasing sedimentation rate prior to death is due to liver damage causing a failure of plasma fibrinogen.

Altogether, then, 16 of the cases in Group III have had the apparent anomalies of their sedimentation rates satisfactorily explained. If this number is deducted, it leaves 42 patients (or 7.3%) in whom the E.S.R. was either useless or misleading. The test was reasonably accurate and to some extent useful in no less than 92.7% of 577 cases.

CHAPTER IV - PROGNOSIS.

In the previous chapter the E.S.R. was studied by comparing it with other methods of observation. Evaluation in this way is open to the criticism that the personal factor plays a large part. How closely the E.S.R. is correlated with the progress of the patient may be very much a matter of individual judgment. A more direct means of testing its significance is by observing the accuracy with which the E.S.R. can forecast the ultimate fate of the patient.

It is important to bear in mind that single sedimentation tests are of no use in prognosis. This is proved by the fact that the same sedimentation rate may be found in one person with extensive disease and another who is in perfect health. It is from the changes occurring in a series of tests that prognosis must be deduced. For example, two tuberculous patients may each have an E.S.R. of 15 mm., but in one it may recently have increased from 5 to 15 mm., and in the other decreased from 30 to 15 mm. Obviously, the prognosis is not the same in both cases.

This simple fact has been overlooked in some studies of the prognostic value of the E.S.R. De Cecio and Elwood (24) followed a series of 182 cases to determine whether the E.S.R. gave an accurate prognosis, but based their findings on a single test done just before discharge from hospital. Ringer and Roach (82) state: "No tuberculous patient should be discharged until the E.S.R. is normal". The limit of normal for the method they used (Cutler's) is 10 mm. In a case with a normal reading, therefore, the E.S.R. might have increased from 1 mm. to 10 mm. or decreased from 30 mm. to 10 mm. Hurford (46) in assessing cases before thoracoplasty bases his conclusions entirely

on a single reading. Lewis-Fanning and Myers (57) studied the significance of the E.S.R. in two ways: Firstly using only the last reading prior to leaving hospital; secondly using the difference between the first and last readings. They concluded that the prognostic value was not proved. Their approach to the problem cannot be considered satisfactory. Proper deductions are not possible even from their second method, for they use only two tests instead of studying the trend of all the tests done while the patient was in hospital.

In order to simplify this study of prognostic significance, a method has been devised of expressing as a single figure the information obtained from a whole series of sedimentation tests. The series is first examined in order to determine the general trend. Two readings are then selected which fit well into the general trend - one from near the beginning and one from near the end of the series. Usually these will be the first and last readings, but sometimes one or both of these are distorted due to intercurrent infection or for no obvious reason. It is only by examining the whole series that this distortion becomes apparent.

The two readings selected reflect accurately the actual change which has occurred in the E.S.R., and this may be expressed as a percentage of improvement or deterioration. For example, a change from 20 mm. to 5 mm. is 75% better, and a change from 20 mm. to 25 mm. is 25% worse. In some patients who are in hospital for a long period there may be a considerable fluctuation of the disease process. Thus the E.S.R. may at first steadily increase and later steadily decrease. Where these changes occur, the general trend over the last few months in hospital is regarded as significant.

Using the Cutler 50 mm. tube, where the E.S.R. is seldom above 30 mm., it is convenient to divide cases according to prognosis into five groups:

1. With 75% or greater improvement.
2. From 50% to 75% improvement.
3. From 25% to 50% improvement.
4. With the change in the E.S.R. less than 25% either way. Cases in this group are regarded as being in status quo.
5. With 25% or greater deterioration.

This grouping would have to be modified if applied to a method with a longer tube and consequently higher sedimentation readings. (This device for expressing sedimentation results is for statistical purposes only. It is not suggested that it should be added to the already too numerous methods of expressing sedimentation rates).

Of the 577 cases reviewed in the previous chapter a large number died in hospital, and a few were lost sight of shortly after they were discharged. There is a balance left of 362 cases who had at least four sedimentation tests while in hospital and were observed for not less than one year after their discharge. The period of follow-up varies from one year to six years. The numbers of cases followed for different periods of time are set out below. (If a patient was discharged six years ago and died after two years or so, he is still regarded as having a six-year follow-up. However, if he has been lost and his ultimate fate is unknown, he is counted as having been followed only for the number of years that he was actually under observation).

One year	- 51
Two years	- 44
Three years	- 50
Four years	- 71
Five years	- 78
Six years	- 68
Total	- 362

The series of sedimentation tests in each of these

cases has been studied to determine what change has occurred, and they have been divided into the groups described. At the end of each year after leaving hospital each patient is traced and classified as being either fit, unfit, or dead. The term "unfit" implies that there has been a recurrence of tuberculous disease. For the purpose of this study, if a patient is once classed as unfit, he is kept in this class while he remains alive, even though the disease may subsequently become inactive again.

In comparing the follow-up records of tuberculous patients, there are of course many factors which should be taken into account. The fate of the patient may be affected by his working conditions, his economic circumstances, by the various complications of pneumothorax treatment, or by death from accident or intercurrent disease. It is impossible to make allowance for all these variable factors, but the number of cases under review should be large enough to prevent the average result being affected by individual variations.

The relationship between the E.S.R. and prognosis is shown in Tables 4 to 9. These are arranged in cumulative form. Thus in Table 4 the cases followed for six years are classed according to their condition at the end of that period. In Table 5 cases followed for five or six years are included and classed according to their condition at the end of five years. In Table 6 cases followed for four, five or six years are included and classed according to their condition at the end of four years. The number of cases increases in this way until finally in Table 9 all the cases are shown as they were after being followed for one year.

It is clear from these tables that with any period of follow-up there is a direct relationship between the E.S.R.

TABLE 4 - SIX YEARS FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	5	1	1	7	71
50% better	6	3	5	14	43
25% better	4	3	5	12	33
I.S.Q.	4	3	22	29	14
25% worse	-	2	4	6	0
Total	19	12	37	68	

TABLE 5 - FIVE YEARS FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	14	5	1	20	70
50% better	11	8	8	27	41
25% better	6	8	12	26	23
I.S.Q.	8	6	47	61	13
25% worse	-	2	10	12	0
Total	39	29	78	146	

TABLE 6 - FOUR YEARS FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	23	7	1	31	74
50% better	22	9	10	41	54
25% better	11	10	13	34	32
I.S.Q.	11	19	62	92	12
25% worse	-	3	16	19	0
Total	67	48	102	217	

TABLE 7 - THREE YEARS FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	27	10	4	41	66
50% better	29	13	10	52	56
25% better	20	11	10	41	49
I.S.Q.	16	26	71	113	14
25% worse	1	5	14	20	5
Total	93	65	109	267	

TABLE 8 - TWO YEARS FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	34	9	1	44	77
50% better	36	13	8	57	63
25% better	26	23	4	53	49
I.S.Q.	24	38	73	135	18
25% worse	2	8	12	22	9
Total	122	91	98	311	

TABLE 9 - ONE YEAR FOLLOW-UP.

Change in E.S.R.	Fit	Unfit	Dead	Total	Percent Fit
75% better	50	4	1	55	91
50% better	57	16	1	74	77
25% better	37	24	2	63	59
I.S.Q.	38	65	43	146	26
25% worse	5	12	7	24	21
Total	187	121	54	362	

and the fate of the patient. The better the prognostic indication of the E.S.R., the greater is the chance both of remaining alive and of avoiding a relapse. This is shown particularly well in the final column where the number of patients remaining fit is expressed as a percentage of the total. In all six tables this percentage becomes progressively less as the prognostic indication of the E.S.R. becomes worse.

This method of analysis does not merely show that a relationship exists between the E.S.R. and the prognosis - this could have been demonstrated in a less complicated manner. The importance of these tables lies in the fact that they show in precise figures the degree of accuracy with which the E.S.R. can be expected to forecast the fate of the patient. For example, a patient with a 75% improvement in the E.S.R. has a 91% chance of remaining fit for one year (Table 9) and a 71% chance of remaining fit

for six years (Table 4). In comparison, a patient showing no appreciable change in the E.S.R. has a 26% chance of being fit at the end of one year (Table 9) and a 14% chance of remaining fit for six years (Table 4). This exact assessment of the prognostic accuracy of the E.S.R. provides valuable information as to how much significance should be attached to the test. The general conclusion is that it is unwise to discharge a patient from hospital when the improvement in the E.S.R. is less than 75%. (The improvement would have to be greater with a longer sedimentation tube).

Before the deductions drawn from Tables 4 to 9 can be accepted as valid, it is necessary to decide whether the figures are statistically significant. To determine whether the apparent association between E.S.R. and prognosis could be the result of chance sampling fluctuations, the χ^2 test has been applied to each table. The contribution to χ^2 calculated for each cell, and the total value of χ^2 for each table are shown in Table 10. The degrees of freedom in each table = 8. On plotting the degrees of freedom and the value of χ^2 on Yule and Kendall's chart,(109) the following results are obtained: For Table 4 the probability that the value of χ^2 is the result of chance sampling fluctuations is slightly less than 1 in 20. For the other tables (5 to 9) the probability is considerably less than 1 in 10,000. It may therefore be concluded that the results obtained from these tables are statistically significant.

The prognostic significance of the E.S.R. can be demonstrated in a different way by constructing follow-up tables to show what happened to the patients year by year. Such a table is not very instructive unless it covers a period of at least four years. Only those cases which

TABLE 10 - χ^2 TEST.

	Table 4	Table 5	Table 6	Table 7	Table 8	Table 9
Fit						
75%	4.74	14.05	18.85	11.31	16.24	16.40
50%	1.12	1.99	6.89	6.55	8.31	9.23
25%	0.13	0.13	0.02	2.28	1.31	0.61
I.S.Q.	2.08	4.22	10.66	13.88	15.83	18.57
25%	1.68	3.21	5.87	5.11	5.10	4.42
Unfit						
75%	0.05	0.27	0.00	0.00	1.16	11.26
50%	0.11	1.30	0.00	0.00	0.81	3.09
25%	0.37	1.56	0.82	0.10	3.62	0.41
I.S.Q.	0.88	3.09	0.09	0.08	0.06	5.37
25%	0.84	0.06	0.34	0.00	0.38	1.98
Dead						
75%	2.07	8.77	12.64	9.70	11.94	6.33
50%	0.90	2.86	4.46	5.93	5.52	9.13
25%	0.36	0.26	0.56	2.71	9.66	5.83
I.S.Q.	2.45	6.38	8.14	13.41	21.83	20.66
25%	0.04	2.00	5.60	4.18	3.71	3.27
Value of χ^2	17.82	50.15	74.94	75.24	105.48	116.56

have been followed for four years or more have been used for compiling the follow-up record. The cases are separated into groups as before according to the percentage change in the E.S.R., the numbers being:-

75% better	31
50% better	41
25% better	34
I.S.Q.	92
25% worse	19
Total	217

In Tables 11 and 12 the number in each group is expressed as 100, and the rest of the figures are altered in proportion. This is in order to facilitate comparison of the groups.

In Table 11 the number of cases surviving at the end of each year is recorded. This shows that patients die off far more rapidly in the groups where the E.S.R. gives a poor prognosis. In Table 12 the number remaining fit at the end of each year is recorded. The relationship

between the E.S.R. and the relapse rate is clearly seen. These follow-up records merely illustrate from a different angle what has already been demonstrated earlier in the chapter.

TABLE 11 - FOLLOW-UP RECORD SHOWING DEATHS.

Change in E.S.R.	Total Discharged	No. Alive After Years 1	2	3	4	Dead After 4 Years
75% better	100	100	100	97	97	3
50% better	100	100	85	83	76	24
25% better	100	94	91	74	62	38
I.S.Q.	100	66	43	36	33	67
25% worse	100	68	42	32	16	84

TABLE 12 - FOLLOW-UP RECORD SHOWING RELAPSES.

Change in E.S.R.	Total Discharged	No. Fit After Years 1	2	3	4	Unfit After 4 Years
75% better	100	93	77	74	74	26
50% better	100	85	68	59	54	46
25% better	100	65	56	50	32	68
I.S.Q.	100	27	16	14	12	88
25% worse	100	26	11	5	0	100

CHAPTER V - METHODS.

In this chapter an attempt will be made to sort out some basic facts from the confusion which exists in regard to methods of estimation and technical considerations. Details of the six methods in general use will not be given as they are described in numerous text-books, but they may be summarised briefly.

Two methods use a tube 50 mm. long and 5 mm. in diameter, namely, Cutler and Linzenmeier. Both use Sodium Citrate as the anticoagulant. (Cutler also has a wider tube 1 cm. in diameter). Two methods use a tube 100 mm. long, namely, Wintrobe and Rourke-Ernstene. The former has a tube 2.5 mm. in diameter and uses a mixture of Potassium and Ammonium Oxalate as anticoagulant. The latter has a tube 4 mm. in diameter and uses Heparin. The fifth method is the Westergren with a tube 200 mm. long, 2.5 mm. in diameter and using Sodium Citrate as anti-coagulant. Finally there are several variations of the micro-method all of which have a tube 1 mm. in diameter and are used chiefly in children.

A variety of other methods of estimating the E.S.R. have been suggested. Basu (9) claims that more sensitive results can be obtained by diluting the blood 1 in 50 in saline. Mori (65) states that the E.S.R. is directly related to the thymonucleic acid in the blood and uses a quantitative test for this substance to estimate the activity of disease. Goldberger (34) suggests a rapid method of determination merely by watching the pattern of a drop of blood drying on a slide. Whittington (103) uses a simultaneous estimation of sedimentation rate and plasma viscosity plotted on a two-dimensional chart which, he claims gives more consistent results than conventional

methods. Recently Weingarten (102) has reported that important information can be obtained by duplicate tests on every specimen - one in the incubator and one at 44°C. Certain diseases have a more rapid sedimentation rate in the hot specimen and others more rapid in the cold. None of these suggestions have as yet met with general acceptance.

TECHNICAL FACTORS.

There are a number of technical factors which are of considerable importance in estimating the E.S.R. The only one about which there is universal agreement is the position of the tube. If it is not absolutely vertical, the sedimentation rate is accelerated. This is noticable with an angle of only 3° according to Wintrobe. (106)

A narrow tube causes a slowing of the rate. Ham and Curtis (40) state that a diameter of 2.5 mm. has this effect. Muller (66) says the effect is noticed only if the diameter is less than 2.5 mm. This is of some importance for the popular Westergren tube is 2.5 mm. in diameter. In the micromethods the tube must obviously have a considerable retarding effect.

The anticoagulant has some effect on the rate and different authors give preference to different substances. Schuster (90) and Day, (21) report that Sodium Citrate gives more consistent results than Heparin or Oxalate. Muller (66) much prefers Heparin or Oxalate and states that Sodium Citrate retards the rate. Ham and Curtis (40) are in agreement with this, and estimate the slowing as 23% with dry Citrate and 33% with Citrate solution. Hambleton (41) states that Oxalate or Citrate solutions are better than dry Oxalate or Citrate. Thomas (96) finds that the retarding effect of sodium citrate varies with the pH of the solution, and Rogers (85) further complicates the issue by a statement

that the retarding effect of Citrate differs in different parts of the sedimentation curve. In view of these conflicting views it seems safe to assume that the choice of anticoagulant is unimportant provided the same one is used throughout. However, when it is intended to measure the cell volume in the same specimen of blood as is used for the E.S.R., the mixture of Potassium and Ammonium Oxalate is preferable as it causes no change in the size of the red cells.

With Sodium Citrate solution it is preferable to use it in the proportion of 1 to 9 (as with the Cutler method) rather than 1 to 4 (as with the Westergren method). Apart from the effect of the Citrate the dilution of the blood retards the sedimentation rate, so the less it is diluted the better. The slowing effect of dilution per se can easily be demonstrated by doing two tests with the same specimen and diluting with saline in one of them. (Dilution with plasma, of course, has the opposite effect).

Too long a delay between collecting the blood and starting the test causes a slowing of the sedimentation rate. Ham and Curtis (40) consider that a delay of 2 hours has no effect, but 3 hours causes slowing. Wintrobe (106) states that there is no change up to 4 hours. Vida (100) goes one better with 5 hours, while Muller (66) outbids them all with 6 hours. In practice, the test is so simple that there should be no difficulty in starting to read the test within the shortest time quoted.

There are conflicting views as to whether the effect of external temperature is of practical importance. Wintrobe (106) considers the variation negligible with temperatures from 22° to 27°C. Scott (91) states that the effect of room temperature can be disregarded in practice. Muller (66) ignores changes between 20° and 25°C. but avoids

colder rooms. She also advises letting the blood cool to room temperature before commencing the test.(36) Gordon thinks that seasonal variations in temperature should be taken into account.(75) Penman finds that 10° of cooling causes 10 to 20% slowing.(84) Rodgers goes so far as to recommend that all tests should be read with the sedimentation tubes immersed in a constant temperature water bath. The work of Weingarten (quoted above) on incubator and refrigerator temperatures is of great importance in this respect, but it has yet to be confirmed. A reasonable conclusion is that temperature can be ignored provided that the test is done in a room which is not subject to great extremes of temperature.

A factor which must be mentioned, although it is not a technical one, is menstruation. It is very widely accepted that the E.S.R. is increased during menstruation, and this has recently been reiterated by Obermer(70) and by reports from Safad hospital.(88) Yet Muller(66) says categorically that menstruation has no significant effect, and quotes several authors in support of this statement. It seems probable that the E.S.R. is affected in some women and not in others.

CORRECTION FOR ANAEMIA.

Correction of the sedimentation rate for anaemia has been the cause of much dispute. There is no doubt that anaemia does increase the rate but whether this is of sufficient importance to need correction is another matter. The large number of workers who consider it important to correct for anaemia is shown by the great variety of methods of correction and the arguments as to which is the best. Eight methods will be mentioned here.

Vida(100) uses a formula based on the cell volume.

Schuster(90) corrects by adjusting the cell count to a

- standard -

standard concentration before reading the E.S.R., although he considers that this is only necessary for research purposes. Walton (101) uses a table constructed experimentally and based on the cell count. There are four different correction charts based on the cell volume: Gram, Hynes and Whitby, Rourke and Ernstene, and Wintrobe. These are all described in detail by Muller. (66) Finally Muller herself has constructed an elaborate correction table using a mathematical formula based on the cell volume.

Despite these numerous methods at their disposal, there are many authors who prefer not to correct for anaemia. Hambleton and Christianson (41) regard it as theoretically advisable but unnecessary in practice. Scott (91) states that degrees of anaemia with a haemoglobin of not less than 80% are not of material importance. Ringer and Roach (82) find the test "clinically satisfactory" without correction. De Cecio and Elwood (24) state that correction for anaemia more often than not leads to erroneous results. Peters (78) suggests that the only sound solution to the problem is to discard all correction charts and evaluate the E.S.R. by comparison with the observed clinical picture. Even Wintrobe (106) who published a correction chart admits that correction for anaemia may mask a raised E.S.R.

Many authors adopt the attitude that the E.S.R. is a crude test in which accurate measurement is impossible and therefore such refinements as anaemia correction are out of place and unreasonable. The sedimentation rate is affected by so many variable factors besides the cell volume that it seems pointless to select this single item for special attention. Kayne, Pagel and O'Shaughnessy (52) state: "Great refinements of execution may even have the disadvantage of causing too much importance to be attached

to small variations". Edwards and Cuttrill[28] say: "The assumption of clinical changes from such mathematical data is unsound. Variable factors in the blood itself have still to be differentiated by clinical acumen".

Certain objections may also be raised against the validity of the correction charts. Davis[20] points out that clinical anaemia does not necessarily affect the sedimentation rate in the same way as the artificial anaemia used for constructing the chart. McFarlane and O'Brien[60] illustrate the fallacy of correction charts by the fact that they sometimes produce a negative value for the E.S.R.! Some of the strongest supporters of anaemia correction are those who use either the Wintrobe or the Hynes and Whitby charts.[66] Yet it has been shown conclusively by Muller that both these charts are based on erroneous data. Muller's own chart which in theory is a mathematical masterpiece actually reduces anaemia correction to an absurdity. Although the E.S.R. obviously cannot be read more accurately than to 0.5 mm., Muller's chart gives the corrected rate to two decimal places - a completely unscientific procedure.

In the series of cases reported here the E.S.R. was not corrected for anaemia. All refinements were avoided, and only big changes in the rate were regarded as having significance. This attitude seems to have been justified by the results reported in Chapter II, III and IV which show that the uncorrected sedimentation rate is a reliable test.

METHODS OF READING.

There are several methods of reading or expressing the sedimentation rate. Linzenmeier's method of recording the time when the red cells fall to the 18 mm. mark is far too prolonged when the rate is slow. Day's logarithmic

sedimentin index (22) is claimed to have special advantages, but it has never been satisfactorily explained why the complication of logarithms should be introduced. It has been suggested that the index is proportional to the amount of "sedimentin" in the blood, but what this mythical substance may be is uncertain in view of the numerous factors in the blood which influence the sedimentation rate. It is of interest to note that an index of 0,5 which Day claims will exclude active tuberculosis corresponds to a one-hour reading of about 2 mm. Day quotes case reports (23) illustrating incidents which were more accurately shown by the index than by the one-hour reading, but most of these incidents were in any case clinically obvious without any special tests.

For practical purposes the choice of a method of expressing the E.S.R. lies between the one-hour reading and the maximum velocity in mm. per minute. The latter entails charting the reading every five or ten minutes in order to find the rate during the phase of constant fall. The initial phase of rouleaux formation and the final phase of packing are thus excluded and the rate during the fastest period is expressed in mm. per minute. Theoretically there can be no doubt that mm. per minute is a more accurate reflection of the sedimentation rate than the one-hour reading which includes all three phases. In practice, however, two questions arise: Is the increased accuracy sufficient to make the extra labour worth while? Is the whole test not of such a crude nature that great accuracy in expressing the results is out of place and in fact meaningless?

The Rourke-Ernstene method is the only one that specifically uses mm. per minute, but other tubes have been used for the same purpose by various authors.

Muller [66] is an ardent supporter of this method, and of special interest is the fact that Cutler who originally recommended a one-hour reading has recently been converted to using mm. per minute. [19] On the other hand Penman [75] states: "The correlation between the single reading and the maximum velocity is near enough for practical purposes". Other authors who consider the one-hour reading sufficiently accurate for clinical work are Hambleton and Christianson, [41] Roche [83] and Peters [78] who says: "Recording at frequent intervals gives no more information than a one hour reading". The comments on excessive refinements quoted in connection with anaemia correction are also applicable here, but need not be repeated.

In the 1000 cases which have been reported in earlier chapters the one hour reading was taken as the significant figure. All sedimentation rates, however, were recorded on the Cutler chart at five minute intervals. It is therefore possible to find the maximum velocity in mm. per minute for every test and compare it with the one hour reading to determine which was the more useful method. This comparison will be made under three different headings - diagnosis, control and prognosis - corresponding to Chapters II, III and IV.

DIAGNOSIS.

The sedimentation rate in mm. per minute will in every case be calculated to the nearest .05 mm. In Table 13 the total of 1000 cases are analysed according to the stage of the disease and the E.S.R. in mm. per minute.

This table should be compared with Table 1. It was decided in Chapter II that a one-hour reading of 3 mm. is the highest that can be regarded as a

- significant -

significant negative result. A study of sedimentation charts shows that a one-hour reading of 3 mm. usually corresponds to .05 or .1 mm. per minute. If the latter figure is taken as the significant upper limit it is seen that the number of cases within this limit in Table 13 is almost the same as the number falling within the 3 mm. limit in Table 1. The two methods therefore give much the same result. It is clear also that the use of any higher limit than .1 mm. per minute (such as those quoted on page 3) would lead to a high percentage of errors.

TABLE 13.

E.S.R. (mm. per minute)	Group I	Group II	Group III	Total
.05	2	1	1	4
.1	1	4	0	5
.15	7	6	0	13
.2	13	23	12	48
.25	4	5	1	10
.3	14	18	16	48
.35	2	6	6	14
.4 or over	23	93	742	858
Total	66	156	778	1000

When dealing with these low sedimentation rates, this discussion is more of academic than practical value. In practice, when the red cells fall only 3 mm. in an hour, it is impossible to observe accurately at what stage they fall most rapidly, and the measurement of mm. per minute is really guess-work. There seems to be little point in using the method of mm. per minute for very low sedimentation rates.

CONTROL.

The 577 cases analysed in Table 3 were studied a second time using the E.S.R. in mm. per minute. As

before, the changes in the E.S.R. were compared in each case with the actual progress of the patient as observed by clinical and radiological methods. In Table 14 the cases are classified into the same three groups: close correlation, useful correlation and useless or misleading. Comparison with Table 3 shows only a slight difference between the two methods.

TABLE 14.

	Group	No. of Cases	Percentage
I	Close correlation	349	60
II	Useful correlation	173	30
III	Useless or misleading	55	10
	Total	577	100

In most cases the E.S.R. in mm. per minutes gave the same information as the one-hour reading, but in 36 cases there was sufficient difference in the degree of correlation to place them in another group. These cases were studied further to determine which readings followed the progress of the patient more accurately. In 19 cases the one-hour readings showed closer correlation, and in 17 cases the readings in mm. per minute were more correct. The two methods therefore appear to be equally useful.

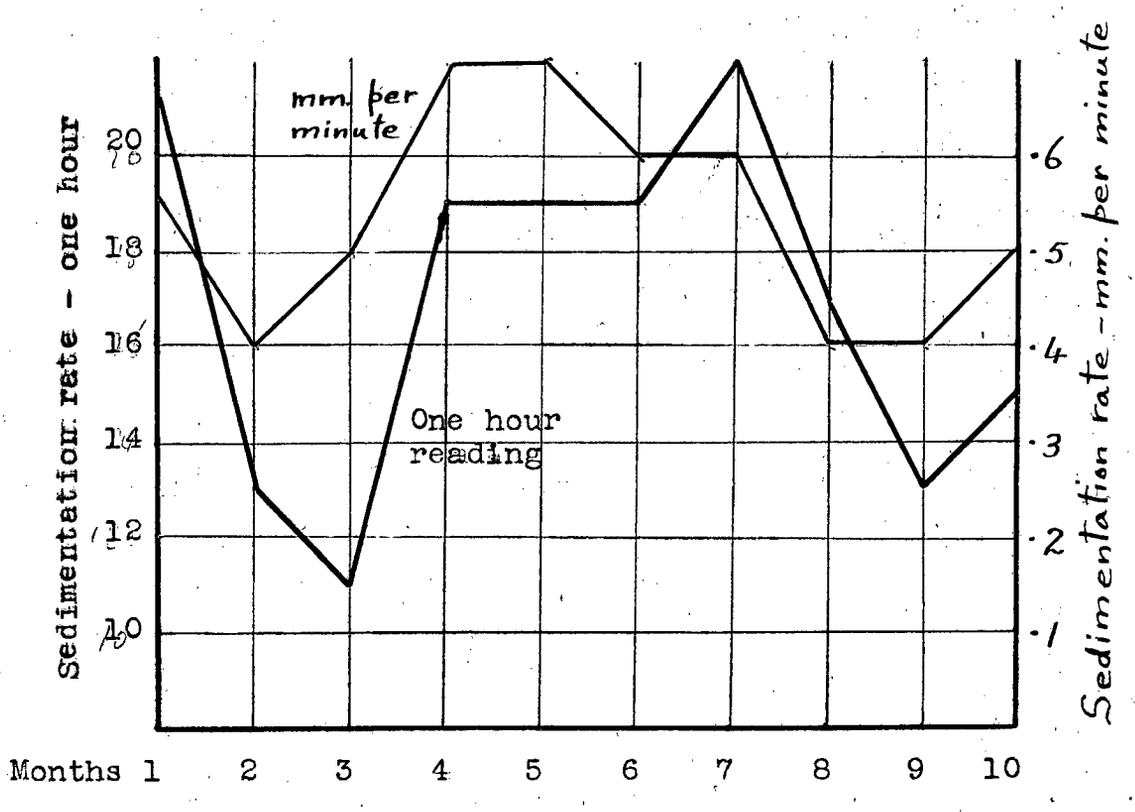
PROGNOSIS.

It is not possible to construct tables based on the mm. per minute reading that could be compared with the prognosis tables in Chapter IV. The percentage change in mm. per minute does not necessarily correspond to the percentage change in the one-hour reading. This is because the more rapid one-hour readings (say over 20 mm.) are retarded by the packing of cells in the lower part of the tube. The mm. per minute reading therefore tends to

show a much greater improvement than the one-hour reading. In the absence of compatible tables, it has been necessary to study individually each of the 362 cases dealt with in Chapter IV to see which method of reading gives the more accurate prognostic indication.

This study has revealed not a single case in which the prognostic indication of the two methods differed appreciably. Frequently there were variations here and there in a series of sedimentation tests. This accounts for the 36 cases mentioned above in which one or other method seemed to reflect more accurately the ups and downs of the patients' condition. In every case, however, when the series of tests was taken as a whole, the general trend from which prognosis is deduced was practically the same with both methods.

One example will suffice to illustrate how the general impression overrides individual variations. In the accompanying diagram a series of ten monthly sedimentation tests is shown, the one-hour reading and the mm. per minute reading being charted together. The two readings do not follow each other closely throughout, and the peaks and valleys of the two curves do not exactly correspond. Moreover the final one-hour reading is an improvement on the first, but the first and last mm. per minute readings hardly differ. The general trend of each curve is the same, however, and the general impression given by each curve is of a fluctuating sedimentation rate without any tendency to improve steadily. Each curve therefore indicates that the prognosis is unfavourable and the patient is unfit for discharge from hospital. This particular example was chosen because it was the case in which there was least similarity between the prognostic indications of the two methods.



It seems reasonable to conclude that expressing the E.S.R. in mm. per minute has no advantage over the one-hour reading.

CHAPTER VI - NON-TUBERCULOUS DISEASE.

An attempt will be made to summarise from the literature the numerous conditions in which the E.S.R. may be of use. These will be classified in such a way as to indicate especially where the E.S.R. may be helpful in differential diagnosis.

1. GENERALISED INFECTION OR INFLAMMATION.

The E.S.R. is increased in acute general infections, (106) including septicaemia. (20) It is normal in mumps except when there is a complicating orchitis. The E.S.R. may prove useful in predicting the onset of orchitis in mumps. (14) It is normal in pertussis. (20) It is low in cholera due to haemoconcentration. (104)

The sedimentation rate is increased in chronic infections. Tuberculosis has already been dealt with at length. (106, 18) The rate is high in syphilitic conditions including gummata, (70) syphilis of the heart or aorta, (106) liver and the central nervous system. (12) (20) It is high in leprosy, (30) and Kala Azar. (20) In malaria it is usually raised from the beginning of the illness. (108)

2. LOCALISED INFECTION OR INFLAMMATION.

The E.S.R. is increased when there is local suppuration (106) but the increase may be slight when the inflammatory process is walled off. (70) The change in the E.S.R. caused by a local infection depends on the site and the extent of the infection. Sometimes it is greatly increased; in other cases it may be normal. (106, 18)

In tonsillitis the rate is often normal. Kotyza (55) found a normal E.S.R. in 80% of tonsillectomy cases prior to operation. In children with an increased rate it may remain elevated after removal of

the tonsils, or it may fall to normal.[6] If it falls, it shows that a focus of infection has been removed.[55]

Opinions about the E.S.R. in appendicitis differ. Several authors report that it is usually normal in the early or acute catarrhal stage.[13, 106, 18] On the other hand, Lintgen and Fry[59] found an E.S.R. above 10 mm. in 52 out of 100 cases of acute catarrhal appendicitis in the absence of abscess formation. They conclude from this that the E.S.R. is of no value in differentiating between appendicitis and acute salpingitis. However, as the sedimentation rate is nearly always increased with pelvic inflammation and usually markedly so, a low rate will be of use in that it points to appendicitis. It would obviously be dangerous to regard an increased rate as excluding appendicitis.

The E.S.R. is increased with suppuration in the gall bladder.[18]

In acute otitis media the E.S.R. is normal during the early stage before pus is formed. It is greatly increased when there is tissue destruction or necrosis of bone. It is normal with chronic otitis media except during an acute exacerbation.[45] It is raised with acute mastoiditis.[106]

With sinusitis it is raised during an acute infection[106] or when there is suppuration.[18] Otherwise it is normal.

The E.S.R. is not increased by apical dental infection,[13, 18] or by superficial ulcerative conditions.[20] It is normal with anterior urethritis, but is increased when there is posterior urethritis or prostatitis.[20]

With nephritis there seems to be general agreement that the E.S.R. is a useful prognostic indication, a

decreasing rate being reliable evidence that the lesion is healing. (67, 68, 87) As regards diagnosis of activity, there is some difference of opinion. Some authors state that the rate is always increased with nephritis (40, 106) whereas Murphy and Rostetter (67) say that it may be normal in the presence of active disease. (56) Landau probably sums the matter up best by saying that the E.S.R. is nearly always increased in acute nephritis, but may be low or high in chronic nephritis.

3. NEOPLASTIC DISEASES.

The E.S.R. is not increased with uninfected benign neoplasms (106, 12, 18) and may therefore be useful in distinguishing these from malignant neoplasms which almost always caused an increased rate. (70, 13, 40) This increase depends on the vascularity and tendency of the tumour to break down, (106) and the E.S.R. is not always raised with an early scirrhous carcinoma. (20) If a malignant growth is completely removed, the E.S.R. should return to normal within six weeks, and if it later increases again there is probably local recurrence or metastasis. (43) There is a close correlation between metastatic involvement of bone and increase of sedimentation rate. (51)

The E.S.R. is very rapid in myelomatosis. (40, 60) It is moderately increased in leukaemia. (40) In Hodgkin's disease and other reticuloses it is increased during the active phase, but tends to become normal during periods of inactivity. It is therefore a useful guide to X-ray therapy. (20)

4. CARDIOVASCULAR DISEASE.

There seems to be universal agreement that the E.S.R.

is of great value in rheumatic fever, both in the diagnosis of activity and in the management and prognosis of the disease. (13, 10, 49, 106, 56, 50) The position is concisely stated by Dry: (27) In atypical cases of rheumatic fever in which "the symptoms often seem innocuous on superficial examination ..... studies of the E.S.R. are especially helpful in establishing a diagnosis..... The E.S.R. is probably the best guide in determining the length of complete rest in bed". A systolic murmur in a child can be ignored if the sedimentation rate is normal. (89) A decreasing rate is often a good prognostic sign that rheumatic nodules are about to disappear. (89)

The E.S.R. is useful in differentiating infective cardiac disease from congestive conditions (13) and from functional conditions. (12) It is increased with such lesions as endocarditis (18) and syphilitic aortitis. (106) It is usually normal with hypertension, angina pectoris and chronic valvular disease. (106) (18)

The E.S.R. is nearly always increased in the early stages of coronary thrombosis. (13, 40, 106) Shillito (93) states that it usually becomes increased about the third day, reaches a maximum between the fourth and eighth days and then gradually returns to normal. It is a valuable guide to the rate of healing of the cardiac infarct.

With varicose veins the E.S.R. remains normal when there is a simple thrombosis, but is increased when there is a septic phlebitis. (39) It is, therefore, a useful guide to treatment.

5. <u>RESPIRATORY DISEASE</u>.

The effect on the E.S.R. of simple catarrhal

inflammations such as the common cold is variable. (106, 18, 20) Some authors find the rate usually normal. Others state that it is sometimes normal but not infrequently raised. (100, 98) It is important to remember that after upper respiratory infections the E.S.R. may remain elevated for as long as two or three weeks. (49)

In acute bronchitis the rate is usually increased, but may be normal. (18, 20) (106) It is not increased in chronic bronchitis (39) or emphysema. (40)

The E.S.R. is raised in lobar pneumonia and returns to normal only when resolution is complete. (18, 20) (26) In atypical pneumonia it is increased and is useful in following the course of the illness. (73) Ravenswaay (80) goes so far as to say that the progress of the patient can be followed as accurately by the E.S.R. as by serial chest X-rays. It is especially useful in showing recurrences.

All pleural effusions, whether transudates or exudates, cause an increase in the sedimentation rate. (70) The test may be of use in deciding whether a spontaneous pneumothorax is of tuberculous origin or benign. If the latter, the E.S.R. is always normal. (66) Uncomplicated pneumonoconiosis does not affect the rate. (39)

Malignant disease of the lung may cause an increase of the E.S.R. before it shows any signs on the X-ray plate. (63)

6. ARTHRITIS AND ALLIED CONDITIONS.

Under this heading will be included several diseases which although not all arthritic, are linked together from the point of view of differential diagnosis. (10, 49)

In acute rheumatism the E.S.R. is always raised. A patient with vague joint pains should be kept under

close observation if the E.S.R. is abnormal.(56) The value of the test in observing the progress of the disease has already been mentioned.

The E.S.R. is increased in infective arthritis(13) and gonococcal joint infections.(106) It is also raised in gout,(13, 38) although in some cases only slightly so,(3) and it usually becomes normal between attacks.(33)

In rheumatoid arthritis the rate is rapid,(13, 95, 3,106) but it is of doubtful value in prognosis.(35, 15) In view of the frequent use of chrysotherapy for this disease, it is important to note that the E.S.R. does not give any warning of the onset of toxic effects of gold.(35)

In osteoarthritis the E.S.R. is always normal.(13, 3, 106, 33) This is an important point in distinguishing this condition from rheumatoid arthritis. The rate is rapid in ankylosing spondylitis.(33) Tuberculous joints cause an increase of the sedimentation rate, and this may be of value in differentiating a tuberculous hip from Perthe's disease which does not affect the rate.(69)

The E.S.R. is normal in fibrositis(39, 3) and in static causes of back pain.(33) In sciatica it is normal if the condition is a true neuritis or due to pressure of an intervertebral disc.(39, 33) If sciatic pain occurs with an increased E.S.R., a pelvic neoplasm should be suspected.

7. GASTRO-INTESTINAL DISEASE.

This section will deal especially with two common symptoms which often present difficulties in diagnosis: dyspepsia and diarrhoea.

With dyspepsia there is often doubt as to whether the cause is carcinoma or peptic ulcer. It has already

been mentioned that the E.S.R. is increased with carcinoma, except sometimes in the early stages of the scirrhous type. An ordinary gastric ulcer does not increase the sedimentation rate, (40, 18) nor does a duodenal ulcer. (95) However, if a peptic ulcer is very large and complicated the rate may be increased. (25) Thus the E.S.R. cannot distinguish between ulcer and carcinoma with absolute certainty, but the exceptions are sufficiently rare to give the test considerable weight. Certainly any patient with dyspepsia and an increased E.S.R. requires thorough investigation.

The E.S.R. is of great help in differentiating between functional diarrhoea and diarrhoea with organic disease in the bowel - dysentery, ulcerative colitis, tuberculosis or cancer. In the former it is low while with organic disease it is almost certainly high. (4)

8. LIVER DISEASE.

The E.S.R. is difficult to interpret in some diseases of the liver, due to certain complicating factors. In some cases jaundice seems to have a slowing effect on the sedimentation rate. In one series of tuberculous patients the rate was reduced during complicating hepatitis with jaundice. (76) It has also been suggested that in some cases with liver disease the E.S.R. is kept low due to reduced plasma fibrinogen. (106, 66) In view of these variable factors it is not surprising that there are conflicting views on the E.S.R. in infective hepatitis. Wood (108) found the rate was usually normal during the first ten days - in 30 out of 35 cases it was below 10 mm. - and he therefore considers the test useful in differential diagnosis. Miles (64) found the

rate low during the icteric phase but often raised before and after. (40) Ham and Curtis found it "moderately abnormal" in liver diseases with jaundice. (12) Briskman states that it is decreased in catarhal jaundice. (56) The safest attitude is to accept Landau's statement that the E.S.R. in infective hepatitis is very variable and not to be relied on.

The E.S.R. is increased with liver abscess, (106) cirrhosis, syphilis and malignant tumours of the liver. (12)

9. CENTRAL NERVOUS SYSTEM.

In acute poliomyelitis the E.S.R. is usually less than 10 mm. and this may help to distinguish it from meningitis. (56) The rate is normal in chorea when other manifestations of rheumatic fever are absent. (48, 39)

The E.S.R. is increased in disseminated sclerosis, amyotrophic lateral sclerosis and Parkinson's disease. (12) The test may be useful in the last-named condition, for it differentiates it from Parkinson's syndrome in which the rate is normal. It is increased with syphilis of the nervous system. (106) It is normal in schizophrenia. (18)

The most important point about the E.S.R. in nervous disease is that it is unaffected by psychological factors and is therefore normal in purely psychiatric conditions. (18, 20) It is therefore, of value in differentiating functional from organic disorders. It also helps to exclude organic disease in hypochondriacal patients with neurotic symptoms.

10. PELVIC DISEASE.

The E.S.R. may assist in the diagnosis of diseases of the female pelvis. It is normal with a Bartholin's cyst if this is not infected and with simple displacements of the uterus. (58) It is normal with fibroids of

the uterus and benign ovarian cysts,[58] but may increase if the cyst undergoes tortion.[106] It is, therefore, useful in distinguishing these conditions from malignant tumours in the pelvis which always increase the sedimentation rate. It is also raised with inflammatory disease in the pelvis including acute salpingitis.[58, 59, 106] The diagnosis between this condition and appendicitis has already been discussed. Finally, the E.S.R. is increased in pregnancy but usually not before the 10th or 12th week[106, 66] so it is of little use as a negative test for pregnancy. It returns to normal about the 4th week of the puerperium.[91]

11. ENDOCRINE DISEASE.

In diabetes the E.S.R. has been found normal[56, 18] but has also been reported to vary considerably.[20] It has been suggested that a raised sedimentation rate in diabetes indicates obscure septic complications.[66] The blood sugar level per se has no effect.[12]

In thyrotoxicosis the rate has been reported both as increased[18] and as variable.[20] The only other endocrinopathy in which the E.S.R. is increased is Addison's disease.[12]

12. NUTRITIONAL DISEASES.

Vitamin deficiencies do not affect the sedimentation rate,[40, 56] although it has been suggested that there is a correlation between the E.S.R. and the plasma ascorbic acid.[32]

In theory the E.S.R. should be affected by protein deficiency. The first protein to be reduced in the plasma when a loss of protein occurs is albumen. As albumen decreases the sedimentation rate, protein deficiency would be expected to increase the rate, and

this result has been reported.[32] However, as there has to be a considerable protein deficiency before a measurable hypoalbuminaemia occurs[17, 94] this does not seem to be of much practical importance.

13. ALLERGY.

The E.S.R. is not affected by allergic conditions.[39, 40] It is therefore normal in asthma,[18] hayfever, urticaria and uncomplicated eczema.[56]

14. THERAPY.

Certain forms of therapy influence the sedimentation rate, and these should be kept in mind if errors are to be avoided. It is increased by injections of vaccines, foreign protein and colloidal metals.[70, 13] It is also raised in serum sickness[37] and following irradiation.[13]

15. MISCELLANEOUS.

The E.S.R. is increased in any condition where there is tissue necrosis[70] or tissue damage.[40] It is increased with any severe trauma - operations, fractures and when there is extravasated blood.[70, 13] It is increased with acute intoxications such as lead or arsenic poisoning.[18]

There is some difference of opinion about the E.S.R. in erythema nodosum, presumably because the condition is not an entity, but may have many causes.[98] Ustvedt states that the rate is nearly always rapid in erythema nodosum, sometimes very rapid, and may remain so long after the rash is gone. He probably refers only to tuberculous erythema nodosum.[56] Landau considers that the E.S.R. is not affected by the rash per se, and Vanni[99] reports that it is only slightly raised. It may be assumed that the sedimentation rate in erythema nodosum depends on the underlying cause.

CHAPTER VII - CONCLUSION.

Before summarising the work which has been presented it is necessary to place in its proper perspective the importance that should be attached to the E.S.R. in Pulmonary Tuberculosis. In forming an opinion either as to diagnosis or prognosis in a suspected or known case of pulmonary tuberculosis there are several sources of information. These may be tabulated as follows:-

1. History. Symptoms.
2. Radiological examination.
3. Bacteriological examination.
4. E.S.R.
5. Total and differential leucocyte counts.
6. Tuberculin Test.
7. Physical examination.
8. Weight.

It is not possible to place these in order of importance, for many of them are complementary and several are indispensable. In general, however, it may be said that the first three are more important than the last five, and the E.S.R. is the most important of the last five. (The tuberculin test is important only when negative, and its application is limited entirely to diagnosis).

Much criticism of the E.S.R. has come from the authors who have expected too great a degree of accuracy from the test, and have condemned it when it was found to be not infallible. There is no single test for diagnosis or prognosis in Pulmonary Tuberculosis which is 100% accurate. Fishberg (31) states that the E.S.R. merely confirms the opinion gained by an evaluation of physical and radiological signs which give "ample information on the problems of prognosis". In practice the problem of prognosis is often obscure and every available test may be required for its elucidation. In many cases the sputum test and radiogram

alone are sufficiently conclusive. In many others an opinion can only be formed by weighing all the factors and striking a balance of probability. In this assessment of a case the E.S.R. frequently plays a useful and important part.

Several authors have stressed this attitude to the sedimentation rate. Muller (66) remarks that any one factor taken by itself may be grossly misleading - it is the combination of the various factors that is important. Kelman (54) states: "It is possible to get useful information from this test when it is used as one link in the chain of evidence on which diagnosis or prognosis may be founded". Walton (101) sums the matter up: "The sedimentation test, if correctly interpreted, will often weigh down the scales of differential diagnosis".

SUMMARY.

In 1000 cases of pulmonary tuberculosis the E.S.R. was increased sufficiently often for the test to be of use in excluding this disease. This statement holds good only if a one-hour reading of 3 mm. is regarded as the highest which excludes activity. If any higher limit is used the proportion of errors will be large enough to make the test valueless.

In 577 cases serial sedimentation tests showed a useful correlation with the actual progress of the disease in 92.7%. In 362 cases a close association was found between the prognostic indication of the sedimentation rate and the eventual fate of the patient. An attempt has been made to assess the reliability of the E.S.R. in exact numerical terms.

A comparison of methods of expressing the sedimentation rate showed that measuring the maximum velocity in mm. per

minute has no advantage over the one-hour reading.

An outline is given of diseases in which the E.S.R. may be of use.

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