PROGNOSTIC BLOOD TESTS IN TUBERCULOSIS

A COMPARISON OF THE RELIABILITY OF FOUR METHODS, BASED ON CLINICAL AND RADIOLOGICAL FINDINGS

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Introduction

It is generally accepted that periodical examination of the blood is of definite value in assessing the prognosis in tuberculosis. At Southfield Sanatorium Colony it has been a routine procedure to examine the blood of each patient every month. This examination consists of the estimation of the blood sedimentation rate, the total white count, and differential count, and for a time the Weltmann serum reaction was also practised.

For the purpose of this paper, a correlation of these tests has been made on the results obtained on 30 patients, in order to determine their reliability as compared with the clinical and radiological findings. Of these 30 cases, 28 were being treated for pulmonary tuberculosis, one for tuberculous disease of the hip-joint, and the other for renal tuberculosis. The cases have not been selected. The number of examinations has been stated in each case, and the reliability of the tests has been determined by referring to the clinical examination and to the radiological evidence. The standard adopted for each test and the method employed will be given in the appropriate section.

The Blood Sedimentation Rate.—It is usually considered that the test depends on the amount of cellular destruction taking place in the body. In healthy individuals there is always a certain amount of cellular destruction, but this keeps within definite limits, though it varies in amount from week to week. This variation was estimated by Greisheimer, who made repeated observations on a group of healthy men and women, and found that the blood sedimentation rate varied from week to week within normal limits. When the amount of tissue destruction passes beyond the normal, then the red blood corpuscles settle out quickly from the plasma.

The test is non-specific and cannot be used to diagnose any particular condition, but it indicates the presence of disease.
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Regardless of the disease present, whether it be active tuberculosis, pelvic inflammation, etc., the rapidity of the fall of the red blood corpuscles is in direct proportion to the severity of the disease. In pregnancy there is a rapid rise in the blood sedimentation rate and this is regarded as normal, but in every other case an increased blood sedimentation rate denotes the presence of disease.

Method.—The technique employed at Southfield Sanatorium for a considerable time is a modification of the Westergren method. The sedimentation of the blood takes place in a glass tube 15 cm. long and 2 mm. in diameter; this capillary tube is marked with a file at a distance of 10 cm. One cubic centimetre of blood is withdrawn from a vein and is mixed with 0·25 c.c. of sodium citrate solution (3·8 per cent.) in a small test-tube. A stand for the tube is made by fixing a strip of plasticine on a microscopic slide. The blood with sodium citrate solution is thoroughly mixed by rotating the test-tube, care being taken not to form air-bubbles. The blood is now withdrawn from the test-tube into the capillary tube to the 10 cm. mark. Before placing the capillary tube in the plasticine bed the column of blood is sucked up for half an inch, otherwise a small quantity of the mixture will be lost while fixing the tube into plasticine. The sedimentation tube must be kept perpendicular and in a sheltered place at room temperature, as cold currents of air retard the reaction. At the end of one hour the supernatant fluid is measured in millimetres, and the figure obtained is expressed as a percentage. A reading of from one to five is regarded as normal; from six to fifteen as moderately accelerated; and sixteen and over as a rapid fall.

Trail investigated the B.S.R. in a follow-up of 5000 cases over periods of from two to six years after discharge from the sanatorium in order to find out the value of this test as a factor in estimating ultimate prognosis. His results showed that patients who enter hospital with a figure of over 20, and who leave with a figure over 10, have a grave prognosis; this applied to all cases of clinical tuberculosis “open” and “closed”; and while the gravity increases with open cases, and in particular with those who remain so in spite of treatment, it appears that it is better to remain positive and secure a fall in the B.S.R. to under 10 than to be a closed case with a discharge figure of over 10.

Ten years ago Hilary Roche stressed the value of rest and exercise in tuberculosis, and he preferred to wait until the B.S.R.
had reached single figures before he allowed a patient to undertake exercise, particularly if the other factors suggested prudence. He found that a rise in the B.S.R. sometimes occurs before the onset of fever, haemoptysis, pleurisy, etc., and may be the first warning sign of increased activity.

**Weltmann Serum Reaction.**—This reaction was introduced by Weltmann in 1930, and like the B.S.R. has been used, though not to the same extent, in tuberculosis work. Like the B.S.R. it is a non-specific reaction, but when Weltmann introduced the method he claimed that it indicated either a fibrotic or exudative process according to the result obtained, and that the reaction would be of great value in determining changes taking place in the development of the tuberculous process.

**Method.**—From a stock solution of 10 per cent. calcium chloride (CaCl₂·6H₂O) ten dilutions consisting of 0·1 per cent., 0·09 per cent., 0·08 per cent., 0·07 per cent., 0·06 per cent., 0·05 per cent., 0·04 per cent., 0·03 per cent., 0·02 per cent., and 0·01 per cent. are made up. These dilutions are numbered from 1 to 10, beginning with the strongest concentration. Ten small test-tubes are placed in a metal rack and numbered. Into each tube is placed 5 c.c. of one of the calcium chloride solutions and 0·1 c.c. of unhaemolysed serum. The tubes are shaken so that the contents are well mixed and they are placed in boiling water for fifteen minutes. They are then removed, and the reaction can be immediately determined. The contents of the tubes may be clear, faintly opalescent, turbid, or there may be floculation. There is usually a sharp and easily noted difference between floculation and turbidity.

The number of tubes in which coagulation occurs is designated by Weltmann as the coagulation band (or C.B.) of that particular serum. If there is very slight or doubtful floculation in one tube, the reaction is interpreted as being intermediate between that tube and the one before it. With normal serum the first six tubes usually show floculation. Sometimes there is a doubtful floculation in the seventh tube. The normal coagulation band is therefore 6-6½ and is remarkably constant. This means that normal human serum diluted fifty times with calcium chloride solution and heated to 100° C. in a water-bath for fifteen minutes will not coagulate or flocculate if the concentration of the calcium chloride is less than 0·04 per cent. If the coagulation band is less than 6 Weltmann speaks of the reaction as showing a shift to the left, whereas, if the coagulation band is 7 or greater, the
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reaction indicates a shift to the right. In exudative conditions, such as lobar pneumonia, miliary tuberculosis, exudative tuberculosis, peritoneal tuberculosis, cholangitis and acute rheumatic conditions, there is a shift of the coagulation band towards the left. In cirrhosis of the liver, peritoneal carcinoma, chronic endocarditis, fibrotic tuberculosis and sepsis, there is a shift towards the right.

Leucocytic Examination.—The differential count has no definite value in the diagnosis of tuberculosis, because like the other tests mentioned in this paper the results of the count are non-specific. When, however, the diagnosis of tuberculosis has been established the interpretation of the results of the differential count gives a most reliable and accurate picture of the pathological changes taking place in the body, and it also helps in assessing the prognosis. In 1925 Cunningham et al. found that the course of a tuberculous lesion could be quite accurately followed by noting the relative number of monocytes and lymphocytes in the circulating blood of rabbits. It was found that when the monocyte-lymphocyte ratio was high, autopsy consistently showed an attenuated or arrested lesion. In 1926 Medlar began an extensive study of the leucocyte reaction in tuberculosis. From his studies he arrived at the conclusion that there are three leucocyte types which are produced by tuberculous lesions at different stages of the pathological process. The neutrophils, he says, predominate in the phase of abscess formation, of cavitation and ulceration. The lymphocytes are the chief cells concerned in the healing process, and the monocytes increase when extension of the tuberculous lesion takes place. In Edinburgh, Medlar’s work was corroborated in 1929 by Dunlop, who found that the proper interpretation of the leucocyte reaction was of definite prognostic value in tuberculosis. This interpretation of the pathological picture, however, must be on general lines, since in tuberculous individuals there will be lesions representing all stages of the development. Broadly speaking, the differential count will represent the predominant phase of the pathological process.

The tests which have been described are of inestimable value to the physician in charge of tuberculous patients. When a diagnosis has been made by physical and X-ray examination, and by demonstrating tubercle bacilli in the sputum, the examination of the blood will indicate the amount of constitutional or systemic disturbance. It is sometimes extremely difficult to assess the amount of activity by physical examination alone, and the
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laboratory tests described will estimate activity or quiescence in an accurate manner.

Of the 30 patients used in these tests, 16 had active pulmonary tuberculous lesions with cavitation. The remaining 14 had pulmonary lesions which were more or less quiescent. The total number of tests performed was 178. All the specimens of blood were withdrawn between 10.30 a.m. and 11 a.m. on the day of examination, and all the examinations were performed by the same individual, at approximately monthly intervals.

In order to determine the reliability of the tests, the following values were regarded as normal:

The Blood Sedimentation Rate: a fall of from 1 to 5 per cent. in one hour.
Total White Count: 8500 cells per cmm.
Weltmann Reaction: 6.

The interpretation of the differential count requires more explanation, and the standards adopted by Medlar to describe the abnormal counts were employed.

The Septic Leucocyte Picture

(a) The total leucocyte count is usually above normal.
(b) May be normal or below.
(c) Neutrophils are always above 65 per cent., usually 70 per cent. or more.
(d) Lymphocytes never above 25 per cent., usually below 20 per cent.
(e) Monocytes are usually above 8 per cent. New tubercle formation is indicated if above 9 per cent.

This type indicates that the main tuberculous process is undergoing abscess formation or ulceration and that healing is not occurring.

The Hyperplastic Picture

(a) Total count within normal limits usually or slightly increased.
(b) Mononuclear leucocytes always more than 10 per cent.
(c) Lymphocytes more than 25 per cent.
(d) Neutrophils below 60 per cent.

This indicates that new tubercles are being formed, but that the tubercles are not undergoing abscess formation. If the lymphocytes are above 30 per cent. the progress tends towards a healing stage.
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The above tables are based on the normal "mode" which allows the following limits as a normal blood picture:

- Total leucocytes per c.mm.: 6000 to 9000
- Polymorphonuclear leucocytes: 50 to 65 per cent.
- Lymphocytes (large and small): 25%, 39%
- Mononuclear leucocytes: 6%, 9%

It was found that the "cells per cubic millimetre" of each type was a more accurate index on which to base the interpretation than the percentages, except in leucopenic counts.

Results

Table of Results

| Case no. | No. of Tests performed. | No. of Tests proved reliable. | Clinical Examination. |
|----------|-------------------------|-------------------------------|-----------------------|
|          | B.S.R. | Welt. | Total W.B. | M/L ratio. | Bilateral: progressing |
| 1        | 11     | 8     | 11         | 1          | Bilateral: cavitation  |
| 2        | 9      | 3     | 4          | 8          | Bilateral: progressing |
| 3        | 4      | 2     | 2          | 4          | Bilateral: extensive cavitation. T.B. larynx |
| 4        | 5      | 5     | 5          | 2          | Bilateral: cavitation  |
| 5        | 5      | 5     | 4          | 3          | Bilateral: cavitation  |
| 6        | 6      | 5     | 5          | 4          | Bilateral: small cavity right apex |
| 7        | 5      | 5     | 4          | 1          | Unilateral: left side |
| 8        | 6      | 6     | 6          | 2          | Bilateral: cavitation  |
| 9        | 5      | 5     | 4          | 5          | Bilateral: right upper lobe cavity |
| 10       | 5      | 1     | 6          | 0          | Unilateral: left upper lobe quiescent |
| 11       | 5      | 1     | 6          | 0          | Bilateral: quiescent |
| 12       | 7      | 0     | 1          | 0          | Renal tuberculosis and T.B. epididymis |
| 13       | 5      | 5     | 2          | 1          | Bilateral: cavitation  |
| 14       | 5      | 4     | 3          | 4          | Bilateral: apical fibrosis left side |
| 15       | 4      | 3     | 3          | 2          | Bilateral: cavity right side |
| 16       | 5      | 5     | 5          | 2          | Bilateral: right mid zone |
| 17       | 5      | 1     | 1          | 1          | Tuberculosis right hip joint |
| 18       | 4      | 4     | 6          | 2          | Bilateral: renal involvement |
| 19       | 8      | 6     | 6          | 3          | Bilateral: left upper lobe fibrosis |
| 20       | 6      | 6     | 6          | 3          | Bilateral: progressing |
| 21       | 7      | 7     | 7          | 1          | Bilateral: with cavitation |
| 22       | 7      | 7     | 7          | 1          | Unilateral: right side |
| 23       | 7      | 7     | 7          | 0          | Unilateral: thoracoplasty |
| 24       | 7      | 5     | 3          | 3          | Bilateral: cavity left side |
| 25       | 7      | 3     | 3          | 3          | Bilateral: progressing |
| 26       | 8      | 8     | 10         | 1          | Unilateral: quiescent |
| 27       | 10     | 8     | 1        | 1          | Unilateral: quiescent |
| 28       | 3      | 2     | 3          | 3          | Bilateral and diabetes mellitus |
| 29       | 3      | 3     | 3          | 3          | Bilateral and diabetes mellitus |
| 30       | 3      | 2     | 3          | 3          | Bilateral and diabetes mellitus |

Total: 178, 144, 112, 129, 82
The complete data may be consulted in the table of results. In general, however, the findings may be stated as follows:—

**Blood Sedimentation Rate.**—The result in any test was deemed correct when it agreed with the prognosis as based on continued clinical and radiological findings. On this basis the series of 178 tests the blood sedimentation rate gave the expected results correctly 144 times, or 80 per cent. This result is slightly lower than that of Cutler and Cohen, who found that the test scored an average accuracy of 94 per cent. in 500 cases.

In a study of the results obtained on 1000 sedimentation rates, Volk found that there was a definite parallelism between the clinical findings and sedimentation rates. He found an agreement to the extent of 85 per cent. to 99 per cent., and concluded that this result was as close a check as anyone can hope for in a non-specific reaction.

**The Weltmann Serum Reaction** showed the expected results accurately 112 times out of the total of 178 tests performed, or 68.5 per cent.

This test has not become popular in this country and very few articles have been written about it. Makitra and Tyndel determined the Weltmann reaction in 200 patients with tuberculosis, and their results indicated that in cases of the exudative type the coagulation band gave more reliable results than did the sedimentation rate. These authors believed that in chronic tuberculosis the Weltmann reaction has prognostic value.

**Leucocytic Count.**—The total white count showed the expected results accurately 129 times out of the total of 178 tests, or 72.4 per cent. The total white counts exhibited a close relationship to the B.S.R. throughout the tests. When the B.S.R. was increased the total white count was also increased in 162 tests, or 90 per cent. Of the remainder the B.S.R. was increased twelve times when the white count was within normal limits, and the white count was increased on three occasions when the B.S.R. was normal.

Reference has already been made to the importance of the monocyte-lymphocyte ratio in the blood picture in tuberculosis. The course of the disease can be followed quite accurately by the relative numbers of these cells. When the disease is progressing the M/L ratio is low, *i.e.* the monocytes were increased and the lymphocytes decreased, and the ratio tends to rise gradually in cases which are improving, and remains high in quiescent cases.
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The M/L ratio, however, ignores entirely two very important variables, the total white count and the neutrophils, and because of these omissions the index cannot be accurate.

In 1935 Crawford and Medlar\textsuperscript{11} reported on a leucocyte index which included all the four variables in tuberculosis, namely, total white cells per unit, neutrophils, monocytes and lymphocytes. The purpose was to obtain a single index. In order to simplify the procedure a calculator was devised, but we have been unable to procure one in this country.

In the series of cases under observation the M/L ratio (4 : 1) gave the expected results correctly 81 times, or 45 per cent.

Summary.—The results in the material studied may be summarised as follows:

- B.S.R.: 80 per cent. accurate.
- Total Count: 72.4 per cent. accurate.
- Weltmann Serum Reaction: 68.5 per cent. accurate.
- Medlar Count: 45 per cent. accurate.

Conclusions.—Of the four tests investigated, the B.S.R. has proved the most reliable in aiding the assessment of the prognosis in pulmonary tuberculosis.

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