OBSERVATIONS

on the

ERYTHROCYTE SEDIMENTATION RATE

in

INFANCY AND CHILDHOOD:

with special reference to the use of

LANDAU'S MODIFICATION

of the

LINZENMEIER-RAUNERT MICROMETHOD.

Thesis for the Degree of M.D.,
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INTRODUCTION.

Within the last two decades, considerable attention has been directed, by observers in many countries, to the value of the sedimentation test in disease. This test depends on the observation that, in a column of blood which has been prevented from clotting by the addition of citrate or other anticoagulant, the red cells sediment more rapidly in disease than in health. Owing mainly to the methods in general use, which demand venipuncture, this attention has been principally directed to disease as it occurs in the adult, and only a relatively small amount of investigation has been carried out in children.

The present study, performed during a period of one year in Wards 5 and 6 of the Royal Hospital for Sick Children, Glasgow, was undertaken with the following objects:-

(1) To investigate the methods applicable to children, and to discover, if possible, a method which would be at once simple and efficient.

(2) To determine the value of the test as an aid to diagnosis and prognosis in the diseases of childhood.

I should like to express my indebtedness to Dr. Stanley Graham for permission to make observations on cases in his wards, and for much kindly advice, and patient and helpful criticism.

HISTORICAL SURVEY.

By the universal consent of the innumerable observers in all countries, the credit of introducing the phenomenon of red cell sedimentation as a modern clinical test is given to Robin FAHRAEUS,[23] of Sweden, whose first paper was published in 1918. As Fahraeus himself, however, has pointed out, in an admirable historical survey, the fact that the red cells of the blood sediment more rapidly in disease than in health was known to the Ancients.

The Grecian Haematology considered that the blood was divided into four different layers:-

I. A lowermost dark portion - MELANCHOLIA, (composed of red cells deprived of oxygen).

II. A bright red layer - SANGUIS - above this (formed by aërated red cells).

III. A greyish-white layer - PHLEGMA, (comprised of leucocytes and platelets).

IV. A yellow fluid, the blood serum, - CHOLERA.

The Greeks noted that, in disease, the third layer, the PHLEGMA, was greatly increased, and it was one of the main features of their pathology - the HUMORAL PATHOLOGY. In this, diseases were considered to have arisen from the cessation of the normal mixture of the four fluids of the blood as a result of chills, faulty diet, etc.; the usual fault being increase of phlegm. Nature was supposed to heal by causing the phlegm

to be expelled as pus, expectoration, etc., and it was noted that frequently the amount of this secretion was in proportion to the size of the phlegm in the venesected blood.

To quote HIPPOCRATES[55] (460-377 B.C.) "The human body contains blood phlegm, yellow bile, and black bile, and it is these which constitute her bodily nature, and which are the origin of sickness and health. The human being is healthiest when these elements with respect to combination, strength and quantity stand in well-proportioned relationship to one another, and are as much as possible intimately mixed; whereas she suffers when any one of these matters is present in too small or too great a quantity, or has separated and is not combined with all the rest."

This PHLEGM attracted the attention, not only of the Greeks, but of physicians for many centuries after the humoral theory had been discarded. Under such names as the "CRUSTA INFLAMMATORIA," "SIZE," and "BUFFY COAT" this grey layer was an index of disease up to the middle of the eighteenth century. The existence of anaemia was, of course, not then known.

GALEN[33] (129-201 A.D.) gave the earliest description of the buffy coat which has been preserved up to our times. He developed and elaborated the four-fluid theory.

Up till the end of the sixteenth century the ancient humoral pathology was considered to explain satisfactorily the

nature of disease, as far as the majority of physicians and the general public were concerned, although there were one or two more advanced thinkers who opposed the traditional doctrine of the four fluids, and considered that the changes in the blood in disease were the result of that disease, and not the cause.

A reform in the general conception of disease resulted from the discovery of the circulation of the blood by HARVEY in 1628, and the verification of the capillary circulation by MALPIGHI in 1661. The latter also discovered the red blood corpuscles, thus ushering in the NEW HUMORAL PATHOLOGY, in which the blood was held to consist of two layers, corpuscles and serum; and the "buffy coat" to be a converted product of blood corpuscles or of serum.

In the works of Thomas SYDENHAM[123] (1753) the "buffy coat" held a central place as a sign of inflammation of the blood. BOERHAAVE,[7] on the continent, was a great admirer of Sydenham, and considered nearly all diseases as disturbances in the circulation which arose from the blood becoming thicker and congealed; but he made the mistake of inferring from the consistency of the coagulated blood that of the flowing blood.

The first suggestion that the "buffy coat" was an expression of the preventive reaction of the organism in the modern sense of the term came from John HUNTER[61] (1728-1793), and both HEWSON[54] (1771) and he proved that a "buffy coat"

on the blood appeared when the sedimentation of the corpuscles, or the time of coagulation was increased.

The close of the eighteenth and the beginning of the nineteenth centuries marked a strong decline in the humoral pathology, this being mainly due to the discarding of blood letting as a therapeutic measure. About the middle of the last century the "buffy coat" again engaged the attention of observers, such as John ASHHURST[3] of Philadelphia, who wrote:-
"The slowness of coagulation and the increased cohesiveness of red corpuscles allow the separation of the fibrin and white corpuscles to take place before the process of clotting is completed, and this gives rise to the peculiar appearance which is known as the 'BUFFY COAT.'" The observation of the "buffy coat" was not, however, a practical measure in clinical diagnosis, as such a large quantity of blood (100 c.c.) was required for conditions to be favourable.

BIERNACKI,[5] at the end of last century, has the merit of being the first to call attention to a practical method of measuring in blood tests, in which coagulation has been prevented, the sinking rapidity of the corpuscles; or rather, the sedimentation speed. He determined how many cubic centimetres of clear plasma had collected above the red sediment after half and one hour, and stated in numbers per cent. how great a share these volumes formed of the plasma volume collected at the end of the sedimentation, the definitive plasma volume

being obtained at the end of twenty-four hours.

In 1918, FAHRAEUS[23] wrote the paper on what he called the "Suspension Stability of the Blood," which introduced the modern sedimentation test.

THEORY.

Introductory. A vast amount of literature has accumulated since Fahraeus' original paper on the causes of the phenomenon of sedimentation, but the explanations continue to be mainly theoretical, and no definite proof has yet been adduced to explain it satisfactorily.

1. Mechanism of Sedimentation.

The corpuscles of the blood are in suspension in the plasma, and the stability of such a suspension depends on the length of time during which the particles keep evenly distributed in the medium (WESTERGREN[129]). In suspensions in which the suspended particles are of higher specific gravity than the suspension medium (as with blood) the stability may be said to be inversely proportional to the speed with which the particles subside. The suspension stability of the blood is subjected to considerable, and constitutional changes (FAHRAEUS[23]).

Stokes' Law. This is the hydrodynamical equation which governs the velocity with which particles descend in a fluid, owing to gravity. According to this law the speed of sedimentation, "V", is directly proportional to "F", the force of gravity; and inversely proportional to "η", the viscosity of the dispersion medium, as well as to "r", the radius of the particle, in accordance with the formula,

$$V = \frac{F}{6\pi\eta r}$$

One or more of these factors may be much altered in different disease conditions. For example, in anaemias of the Addisonian type "r", the radius of the sedimenting red blood cell, is very considerably altered, and consequently "F" also will be affected; while in anaemias of the chlorotic type where the haemoglobin is much reduced and the plasma much increased, it is reasonable to expect that the viscosity of that medium will be considerably altered, as also will the force of gravity, "F", of the cells. It may also be supposed that the factors "F", "η", and "r" will, in certain disease conditions, be altered in such proportions as materially to affect "V" but little (NEWHAM[85]).

It is interesting to note here that PONDER,[103] in an exhaustive investigation of sedimentation and rouleaux formation, considered that "the sedimentation of red cells may be described by certain simple hydrodynamical equations;" (such as Stokes' Law) "provided that the cells are discrete - a condition which precludes the application of the equations to the fall of cells in plasma and serum, in which rouleaux formation occurs."

From a consideration of Stokes' Law, FAHRAEUS[23] stated that the causes of increased sinking velocity must be among the following:-

I. The specific gravity of the corpuscles is increased.

II. The specific gravity of the plasma is diminished.

III. The size of the corpuscles is increased.

IV. The corpuscles are aggregated.

Specific Gravity. By experiment he found that variations in the specific gravity of the corpuscles and the plasma are of very little, or no account with respect to the sinking speed of the corpuscles. NEWHAM and MARTIN's[86] findings were similar.

Plasma Viscosity. Fahraeus demonstrated also that increased sinking speed did not depend on a reduction of the viscosity of the plasma. Newham and Martin, working on tropical diseases, believed that, in general, the viscosity of the plasma showed no diminution in bloods with rapid sedimentation. In one disease associated with rapid sedimentation, namely Kala Azar, they found increased viscosity of the plasma. POPPER and KREINDLER[105] thought that the sedimentation rate was in inverse proportion to the viscosity of the plasma, and that increase of viscosity acted as an inhibitory factor on the rate, by preventing agglutination of the cells.

Size of the Corpuscles. Fahraeus considered that the only cases in which the increased size of the corpuscles could be imagined to increase the sinking velocity were those diseases of the blood where megalocytes made their appearance.

Agglutination. Having eliminated these factors, Fahraeus concluded that the explanation of the sedimentation phenomenon

lay in the differing degree of aggregate formation of the red corpuscles, and he found a complete parallelism between the degree of aggregate formation and the sinking speed. As an example he instanced De HAAN's[21] observation that in horses there was an extraordinarily great sinking speed associated with a very high degree of agglutination.

All authors are agreed on the fundamental importance of agglutination, but there is a wide difference of opinion when the question arises as to what causes acceleration of this agglutination and thus an increased sedimentation rate. (Acceleration of agglutination causes increase in the sedimentation rate because, according to simple physico-chemical rules, corpuscle aggregates sink more easily in the plasma than non-agglutinated corpuscles, the plasma streams flowing through the narrow interstices between the aggregates, and thus a layer, free from blood corpuscles and consisting of clear plasma, appears at the top of the blood mass. WESTERGREN[129], LUNDGREN[76]).

2. Causes of the Agglutination of the Red Corpuscles.

The first question which arises is whether it is the agglutinability of the corpuscles, or the agglutination capacity of the plasma which is increased in diseases associated with increased sedimentation.

Fahraeus performed the experiment of transferring the red corpuscles from a healthy man to the plasma of a pregnant

woman, and found that the male corpuscles sank much more rapidly in the "gravid plasma" than in the male plasma, but not so rapidly as the "gravid corpuscles" in the "gravid plasma." The corpuscles of the pregnant woman sank less rapidly in male plasma than in "gravid plasma," but not so slowly as male corpuscles in male plasma (see Table 1).

Table 1.

Mixture	Rapidity of Sedimentation
"Gravid corpuscles" + "gravid plasma"	++++
Male corpuscles + "gravid plasma"	+++
"Gravid corpuscles" + male plasma	++
Male corpuscles + male plasma	+

PAYNE[92] also found that the same red cells (washed) will sediment rapidly in plasma obtained from a diseased person, and normally in normal plasma. Experiments in transferring corpuscles from a rapidly sedimenting blood to plasma from a slowly sedimenting blood, and vice versa, with similar results to the above, have been carried out by HUNT,[59] FROSCH,[32] CHERRY,[11] PETERMAN and SEEGAR,[96] and by HADEN and ORR,[48] all of whom concluded that the rate of sedimentation was dependent on some constituent in the plasma, rather than the

red cells.

Several observers have carried out sedimentation in fluids other than the blood plasma. GARNIER and OUMANSKY,[34] working with pleural and ascitic fluids, found that, in general, red cells from different sources, placed in the same fluid, sediment in times appreciably equal. RADOSSAVLIEVITCH[106] found that cells taken from a healthy subject, with a normal value in their own plasma, always have a sedimentation rate in pleural and peritoneal exudates greater than the normal. HERMAN and HALBER[53] studied the rate with which red cells sediment in cerebro-spinal fluid, and found it to be very much slower than in serum.

In this volume of evidence in favour of the plasma, there is only one dissentient voice. NEWHAM[85] added the plasma of a rapidly sedimenting blood to the corpuscles of a normally sedimenting blood, and found practically no difference in the sedimentation rate; but on adding rapidly sedimenting blood corpuscles to the plasma of the slowly sedimenting blood, a distinctly enhanced sedimentation rate was noted. He therefore concluded that the factor influencing abnormal sedimentation resided in some property of the corpuscles.

Personal observations, which agree with the majority, are given later.

(a) Fibrinogen Content.

The next question which arises is in regard to the factor in the plasma responsible for accelerating agglutination; and the first and most popular suggestion is increase in the fibrinogen content.

This is far from being a new discovery. HEWSON[40] (1739-1774) believed that the "buffy coat" was composed of fibrin. The Englishman SCUDAMORE[119] was probably the first who by quantitative analysis really established that the fibrin was, as a rule, increased in "sizy" blood; while the Frenchmen ANDRAL and GAVARRET[2] in 1840 conducted comprehensive experiments in various diseases, and found that the presence of a "buffy coat" meant an increase in fibrin. The German, Hermann NASSE,[84] in the same century, however, pointed out two objections to the theory that increase of fibrin led to increased agglutination and thus to increased rate of sinking. The first of these was that, although corpuscles certainly sank more slowly in defibrinated than in fresh blood, they sank much more quickly in the defibrinated "buffy" blood than in the defibrinated normal blood. The other objection was founded on the circumstance that there were too many exceptions to the rule that increased quantity of fibrin and the "buffy coat" accompanied each other. A "buffy" coat was sometimes found in blood which, on analysis, was found to contain a normal percentage of fibrin. BIERNACKI,[5] in 1897, ascertained that the sedimentation speed was less in serum than

in plasma, and drew the conclusion that the fibrinogen must play a chief part in the increased speed of sedimentation.

FAHRAEUS[23] (1918 et seq.) divided the protein substances of the plasma into two chief groups:-

I. Albumin.

II. Globulins (Serum Globulin.
(Fibrinogen.

He tested the sinking velocity of horse corpuscles in albumin, serum globulin and fibrinogen solutions, and found that sedimentation was very much more rapid in the fibrinogen than in the globulin solutions, and in the latter much more rapid than in the albumin solutions. The degree of agglutination paralleled these findings.

In a comprehensive survey of the literature, he found evidence that the fibrinogen or the serum globulin, or both fractions were increased under those conditions where it was known, or might be expected, that the sinking velocity of the red corpuscles was increased. Fahraeus believed that there was an "undeniable correspondence" between the amount of fibrinogen and the sinking velocity; and that as a rule the plasma of the rapidly settling blood had an increased amount of serum globulin. Finally, he considered that the only other possible explanation of the facts would be the postulation of a "hypothetic agglutinin," but that, for many reasons, this was exceedingly unlikely.

Since Fahraeus' observations, a vast amount of work on

this subject has been published by observers in many countries, as the following representative survey, arranged in chronological order, will show:-

In 1921 FRISCH and STARLINGER[31] emphasised the importance of the fibrinogen content of the blood in causing accelerated sedimentation rates. The latter author added Kaolin, which absorbs fibrinogen, to a blood whose sedimentation rate was greatly increased; and showed that this procedure led to a marked decrease in the rate.

WESTERGREN[129] found in pulmonary tuberculosis that an increased sedimentation rate was associated with an increase of the fibrinogen content, and that sedimentation was about ten times greater in non-defibrinated blood.

Working on several hundred cases of different diseases, GRAM[40] concluded that one of the most important factors on which the sedimentation of the corpuscles depended was the fibrinogen percentage in the plasma, the sedimentation being accelerated by a rise in this value, and vice versa.

Writing in 1923 LINZENMEIER[74] also believed in the importance of the fibrinogen content as a cause of increased sedimentation.

In 1924 MURAKAMI and YAMAGUCHI[83] found the fibrinogen content greater in women than in men. (Note:- The normal sedimentation rate is more rapid in women than in men).

The toxaemias of pregnancy, and lobar pneumonia were

considered by FOSTER[26] to be associated with an elevated blood fibrin, while the occurrence of empyema in the latter disease caused a subsequent fibrin rise.

In 1925 determinations of the plasma fibrinogen in 125 cases of different diseases were carried out by ZECKWER and GOODELL,[136] who found that, in general, high values of fibrinogen were coincident with increased rate of sedimentation.

COOPER[16] found that a blood with a rapid sedimentation rate when drawn, showed a slow normal rate when defibrinated.

POPPER and KREINDLER,[105] quoting 17 cases, discovered an "indiscutable relation" between the sedimentation rate and the quantity of fibrinogen, "sans pouvoir toutefois affirmer l'existence d'en parallelisme absolu." They repeated Starlinger's experiment of adding Kaolin to the blood to absorb some of the fibrinogen, and found, as he did, a decrease in the sedimentation rate.

In 1926 NEWHAM[85] estimated the fibrinogen content in 14 cases, of which 5 showed marked rapidity of the sedimentation rate, while the others were normal. In none of these cases was the figure of 0.3-0.4 gramme of fibrinogen per 100 cubic centimetres of blood exceeded. To further test the influence of fibrinogen, the plasma from a rapidly sedimenting blood was pipetted off and heated to 59°C. for twenty minutes to coagulate this protein. It was then filtered, and added again to the corpuscles, but no difference in the sedimentation rate was noted.

In 1927 RHODIN,[111] working on scarlet fever, found that the globulin content sometimes showed a marked agreement with the sedimentation rate, but in other cases there was not such marked agreement, though always a recognisable relation.

In 1928 PINNER, KNOWLTON and KELLY,[100] in 218 blood samples, could not find a "lawful" relation between the sedimentation rate and the fibrinogen content, either in normal or tuberculous patients. They criticised Starlinger's experiment (see above) on the grounds that Kaolin absorbs other substances besides fibrinogen, and brings about decided changes in the electric potential of the plasma.

In 1929 GREISHEIMER, JOHNSTONE and RYAN[45] found that the sedimentation rate was faster in women than in men, while the fibrin content was lower in women than in men. For this reason, although they found that as the fibrin content increased the sedimentation rate became more rapid, they were not convinced that the fibrin content was the causal factor of increased sedimentation rate. One of the authors, GREISHEIMER, working on this occasion with WARWICK and WALTON,[47] on a series of 100 boys and girls between seven and seventeen years of age, found the correlation coefficient between the fibrin content and the sedimentation index (fall in one hour) "significant."

In 1930 ERNSTENE,[22] working on cases of rheumatic infection, observed a general parallelism throughout the course of the disease between the plasma fibrinogen content and the

sedimentation rate, corrected for cell volume.

ROCHE,[112] in 1932, working on pulmonary tuberculosis, considered that increase of fibrinogen and serum globulin in the blood plasma was probably the most important factor in the production of an increased rate.

In 1933 REES-WALTON[108] observed a slow sedimentation rate in certain cases of liver disease; but in other identical cases, a rapid rate. The slow rate was suggested to be due to deficient fibrinogen formation, but he did not get any diminution in the blood fibrinogen in his cases.

In 1934 CHERRY[11] found an increase of the plasma fibrin and globulin in rapidly sedimenting bloods, and GILLIGAN and ERNSTENE[38] found a striking correlation between the quantity of plasma fibrinogen and the sedimentation rate in rheumatic fever.

ALDRED-BROWN and MUNRO,[1] in 1935, compared a group of subjects suffering from chronic rheumatic disorders with a group of healthy young adults, and found that in the former group there were a large percentage of cases with an albumin value below the minimum value in the latter group; and a large percentage of cases with fibrinogen and globulin values above the maximum value in the latter group.

In 1936 COBURN and KAPP,[15] following experiments in which they modified normal plasma by adding protein fractions isolated from the blood of normal individuals and patients with rheumatism, concluded that the increased sedimentation rate in

acute rheumatism was caused by an increase in plasma fibrinogen and globulin. They also suggested that the increase of fibrinogen might be a direct response of the reticulo-endothelial cells to stimulation.

(b) The Influence of the ELECTRIC CHARGE of the Red Cells.

That the electric charge of the corpuscles must be taken into account with regard to the stability of their suspensions is proved by the fact that corpuscles migrate in an electric field (FAHRAEUS).[23] As this migration in plasma or serum takes place towards the anode, the corpuscles are considered to be charged with negative electricity, and so repel eachother. The maintenance of the electric charge is thus the principal stabilising factor (HADEN and ORR[48]). Agglutination of the corpuscles occurs when the difference in potential between them and the medium in which they are suspended falls to a certain point (NORTHROP and FREUND;[88] OLIVER and BARNARD[89]). PONDER,[104] however, showed that there was an exception to this ruling in the case of magnesium and calcium chlorides, which reduce the potential difference, and yet do not cause agglutination. In general, however, it may be said that anything which allows the cells to lose their electric charge will lead to agglutination, and thus to an increased rate of sedimentation (PAYNE[92]).

HOBER and MOND,[56] in 1922, found that the negative

charge of the red blood cells was greater in a solution of albumin, less in serum globulin, and still less in fibrinogen. Since then, several observers (e.g. FROSCH,[32] POPPER and KREINDLER,[105] HADEN and ORR[48]) have observed that the plasma fibrinogen and, to a lesser extent, the plasma globulin, allow the red cells to lose their electric charge; and in this way lead to more rapid agglutination, and thus to an increased rate of sedimentation. Frosch, Popper and Kreindler, and also ZUNZ[137] considered that the increase in fibrinogen and globulin was accompanied by a lowering of the surface tension of the plasma, but on the other hand, CLARK,[14] and REYNER,[110] from their experiments, believed that the surface tension was higher with a slow sedimentation rate than with a rapid one.

Other Factors suggested as having an Influence on Sedimentation.

(c) Blood Chloresterol.

KÜRTEN[67] in 1920 suggested increase in the blood chloresterol as a cause of increased sedimentation rate, and LASCH,[71] COOPER,[16] and POPPER and KREINDLER[105] have since found increased rates of sedimentation associated with hyper-chloresterolaemia. PINNER, KNOWLTON and KELLY[100] performed 140 simultaneous tests of chloresterol content and rate of sedimentation on 29 persons, and found a relationship in only 10 cases. NEWHAM,[85] in 15 cases with a rapid sedimentation rate, found an increased blood chloresterol in only one case;

and NITZESCU and GAVRILA,[87] in 32 cases of diabetes, discovered no relation between hyperchloresterolaemia and the sedimentation rate.

(d) Blood Sugar.

CHERRY[11] observed that the glucose tolerance test showed a decreased sedimentation rate with increase in the blood sugar percentage in controls, while the reverse appeared to occur in diabetics. Van ANTWERP[125] added a solution of dextrose to blood in process of sedimentation, but this was not productive of results.

(e) Serum Calcium.

MURAKAMI and YAMAGUCHI[83] found a certain relationship between the rapidity of the sedimentation rate and the serum calcium - when the sedimentation was rapid the serum calcium was relatively low, and vice versa.

(f) Blood Carbon Dioxide.

MORA and GAULT[81] observed that the sedimentation rate was reduced by bubbling carbon dioxide through citrated blood prior to placing it in the sedimentation tube, whereas by using oxygen the rate was increased. In congestive heart failure, where there is an excess of carbon dioxide in the blood, many observers (e.g. WOOD,[135] PAYNE and SCHLESINGER[93])

have found a slowing of the sedimentation rate.

3. Summary.

It would appear that the most generally accepted theory as to the causation of an increased rate of sedimentation is as follows:-

The rate of sedimentation depends largely on the size of the particles involved, and therefore it will be increased by any factor which causes the cells to agglutinate and form larger units. Broadly speaking, anything which allows the red cells to lose their electric charge will allow them to agglutinate. The plasma fibrinogen and globulin are both proteins which tend to allow the cells to discharge their electricity, whereas the plasma albumin acts in an opposite manner. An increase in the fibrinogen or a decrease in the albumin-globulin ratio will therefore tend to increase the sedimentation rate, and one or both of these changes are commonly found in practice when the rate is increased.

The question of the influence of anaemia on the rate is discussed later.

METHODS.

One of the most unfortunate features of the Sedimentation Reaction is the lack of any one generally accepted method of performing it. Thus the observer is faced with a wide variety of methods, for each of which its sponsor makes high claims. It is true that all these methods have a common basis, namely, a column of blood which has been prevented from clotting; but it has been found impossible to correlate exactly the findings by one method with those by another.

The methods fall into two main groups, according to whether venepuncture is necessary, or whether a drop of blood obtained from the ear or the finger is sufficient. The former are known as the MACROMETHODS, and the latter as the MICROMETHODS; and it is now proposed to give a short summary of the better known methods in each group.

A. THE MACROMETHODS.

1. The Fahraeus Macromethod.[23]

In this, the original "modern" method, blood is obtained from one of the arm veins by means of a puncture needle, and is taken up directly in test tubes, to which 2 c.c. of a 2 per cent. sodium citrate solution has been added. These tubes are 17 centimetres in length, and about 9 millimetres in internal diameter; and are marked for 10 c.c. of contents, the mark lying at about 2 centimetres from the tube

mouth. Blood-letting is stopped as soon as the fluid has reached the 10 cm. mark; therefore the ratio of citrate solution to blood is as $\frac{1}{4}$, and the height of the citrate-blood mixture about 150 millimetres. After inverting the tube several times, to obtain thorough mixing, it is placed in a vertical position. The sinking speed is obtained through measuring after a certain time the height of the clear plasma layer. Fahraeus read his results at the end of one hour.

The normal values are given by Fahraeus as follows:-

Table 2.

	MEN mm.in one hour	WOMEN mm.in one hour
Maximum	9.0	29.0
Minimum	0.5	2.0
Average	3.3	7.4
No. of subjects	82	61

2. The Westergren Macromethod.(129)

This technique is based on Fahraeus', but is modified to cause less interference with the patient.

A record syringe, holding about 1.2 c.c., is supplied with a little catch, effective on the piston. Into this syringe a solution of sodium citrate (3.8 per cent.) is drawn up, the needle put on, and the piston then pushed out till the

catch clasps, the citrate solution now filling one-fifth of the whole volume. A vein is now punctured, and the syringe filled with blood. When the piston is entirely extended, the contents are immediately emptied into a little test tube holding about 2 c.c., which is at once reversed a few times. The blood is then sucked up into the glass pipette where the sedimentation is to take place. These glass tubes, well cleaned and dried, are 30 cm. long, with an internal diameter of about 2.5 mm., and have the lower end drawn out to a very narrow point, as short as possible. 200 mm. from the bottom there is a mark - when filled up to this the pipette holds about 1 c.c. The blood is sucked up from the test-tube and allowed to run back at least five times. Finally, the blood is sucked up to the mark, and the filled tube is placed vertically into a stand, where a steel spring presses the pipette with the lower end against a pad of indiarubber. The time is noted.

Readings of the height of the layer of plasma, in millimetres, are taken at the end of one, two, and twenty-four hours.

Fahraeus himself pointed out the advantage of this method - that a high blood column is obtained with a relatively small amount of blood, and thus "daily tests are possible." The method has been used by a large number of investigators of different nationalities, most of whom considered it necessary

to make slight modifications. A modification popular in this country has been described by CROCKET,[17] and also by GRAY-HILL,[43] and, as it is the macromethod in use at the Royal Hospital for Sick Children, Glasgow, it will be described in full.

Into a 2 c.c. record syringe is drawn 0.4 c.c. of 3.8 per cent. sodium citrate solution, followed by 1.6 c.c. of blood, thus reaching the 2 c.c. mark. The contents of the syringe are discharged into an ordinary Wassermann tube, and there mixed. The citrated blood is then sucked up into a 1 c.c. pipette, of 2-3 mm. internal diameter, and graduated in hundredths, until the top of the blood column reaches the "0" mark. The top of the pipette is now sealed by means of a cork or plasticene, and the pipette is placed vertically in a rack. The height of the plasma column is read, in percentage, at the end of one, two, four and twenty-four hours.

Normal values, as given by various authors, are as follow:-

Table 3.

	POPPER & KREINDLER[105]	WOOD[135]	ROCHE[112]	CROCKET[17]
Men	3-6 mm.	1-7 mm.	Up to 4 mm.	1-5%
Women	4-8 mm.		Up to 6 mm.	5-10%

Note:- All these figures are for the values at the end of one hour, the question of readings at other intervals being considered later.

3. The Linzenmeier Macromethod. (74)

This method uses small tubes of 5 mm. diameter, and 6.5 cm. in height; with two marks, one at the level of 1 c.c., and the other 18 mm. below this. 0.2 c.c. of 3.8 per cent. sodium citrate solution and 0.8 c.c. of blood are aspirated into a syringe and then poured into one of the tubes up to the 1 c.c. mark. The time required for the upper level of the red cells to reach the 18 mm. mark is determined, and the results are expressed in minutes.

The normal value in men is 1,200-1,400 minutes, and in women 800-1,000 minutes.

4. Cutler's Graphic Method. (18)

This method, which is in use mainly in America, requires sedimentation tubes of at least 5 c.c. capacity, graduated in one-tenths of a cubic centimetre, each one centimetre in height, and marked in millimetres. 0.5 c.c. of a 3 per cent. sodium citrate solution is aspirated into a 5 c.c. syringe, following which blood is taken from an arm vein up to the 5 c.c. mark. Mixing is effected in the syringe, and the contents are then poured into the sedimentation tube. Before reading, the tube is inverted once or twice. The total sedimentation of the red blood cells at the end of one hour, expressed in millimetres, is called by Cutler the "Sedimentation Index," and the normal values for this are:-

In men - 2-8 mm. (average 3-4 mm.).

In women - 2-10 mm. (average 5-6 mm.).

The feature of this method, however, is that the readings are taken every five minutes during the first hour, and the results graphed. Cutler quotes ROTHE[114] as dividing the sedimentation reaction into three distinct phases:-

1. Preagglutination Period, with slow sedimentation.

2. Agglutination Period, with rapid sedimentation.

3. Period of Packing, when the sedimentation slows again and finally ceases, because the erythrocytes become packed in the bottom of the tube as closely as possible. The number of minutes before this "period of packing" sets in Cutler calls the "Sedimentation Time." The normal is always a matter of hours.

Cutler used his method mainly in cases of pulmonary tuberculosis, and, in graphing his results, recognised four main types of curve:-

I. A Horizontal Line, found in normal cases or in the absolutely quiescent.

II. A Diagonal Line, where the disease was quiescent.

III. A Diagonal Curve in slightly to moderately active cases.

IV. A Vertical Curve in the moderately to markedly active cases.

(Chart 1 shows examples of these curves, not necessarily from cases of tuberculosis, and obtained by Landau's microsedimentation method).

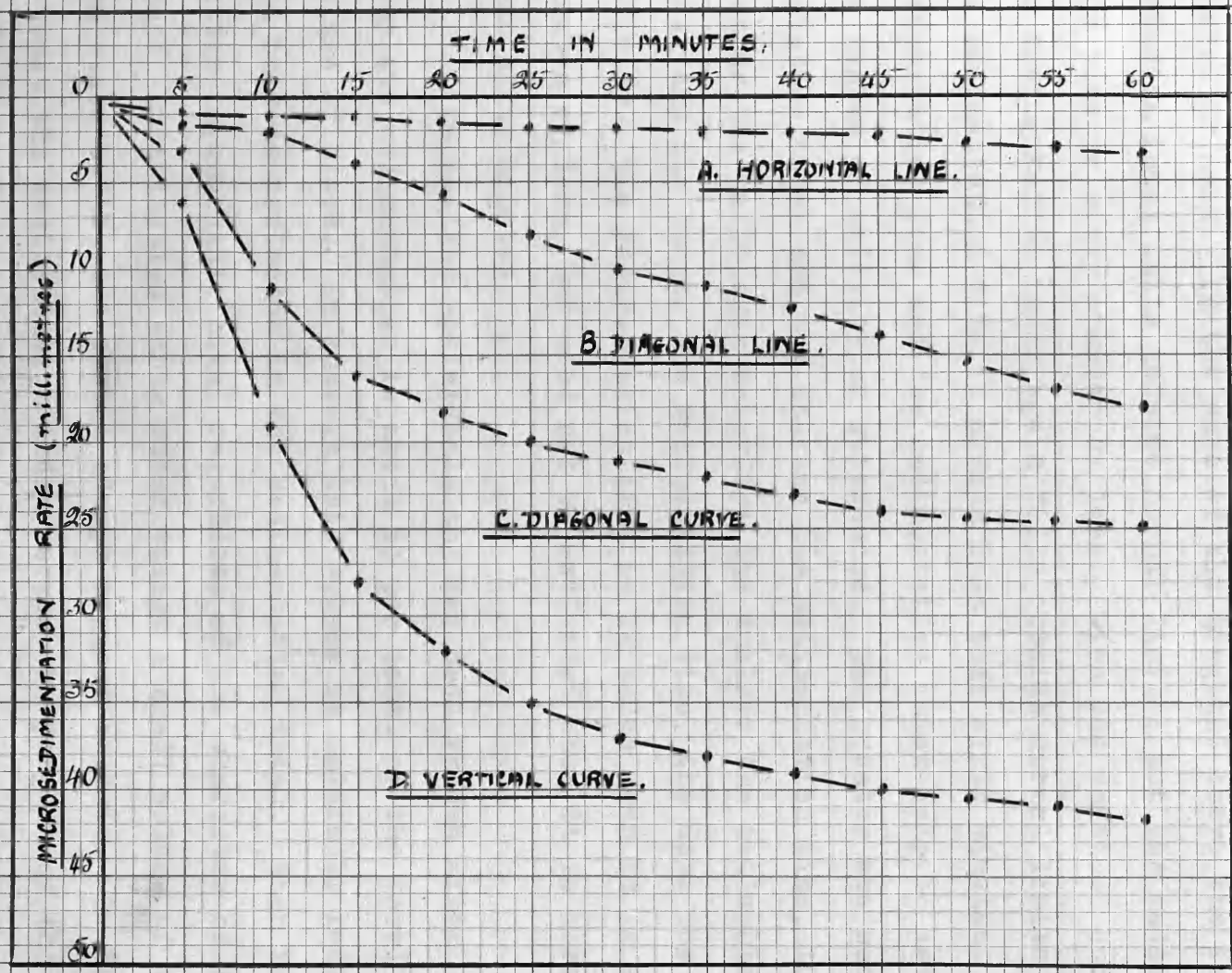


CHART 1. – CUTLER'S GRAPHIC METHOD.

The diagonal line has a sedimentation index falling outside of normal limits, and a sedimentation time of sixty minutes or more. In the case of the diagonal curve the sedimentation index falls outside normal limits, but the sedimentation time is sixty minutes or less. With the vertical curve the sedimentation index again falls outside normal limits, and the sedimentation time is always less than sixty minutes. The sedimentation time and the sedimentation index help to determine the degree of activity or quiescence. The greater the sedimentation index and the shorter the sedimentation time, the greater the pathologic activity; the smaller the sedimentation index and the longer the sedimentation time, the less the activity. The sedimentation time is of value when it is sixty minutes or less, but need not be estimated when it is more than sixty minutes.

In healthy individuals the red cell volume after complete sedimentation is about 50 per cent. of the total volume of blood. In anaemia this volume is naturally reduced, and this is reflected in the sedimentation index. When the latter is unusually high, regardless of the character of the graph, it indicates among other things a small volume of the red blood cells, and should always suggest anaemia. In this respect the sedimentation index serves the purpose of the haematocrit.

This method of Cutler's has been used by a number of observers in the United States (e.g. KILDUFFE,[66] GREISHEIMER[44]),

most of whom have reported favourably on it. Cutler himself found a very close resemblance between the clinical findings and the curve obtained. He has no doubt about the value of his method, and concludes modestly that "the 'Graphic Method' is the most informative method that has yet been proposed for the study of the blood sedimentation test, and should be the method of choice in all future investigations." PINNER, KNOWLTON and KELLY,[100] however, in a review of the sedimentation test, especially deride Cutler's method, consider it "unreliable and misleading," and say that the transition from a vertical curve to a horizontal, as the patient improves, is nonsense!

A somewhat similar graphic method, which helped to influence Cutler, has been used in France by GILBERT, TZANCK and CABANIS.[37]

Personal observations with the graphic method are recorded later.

5. The Haematocrit Method.

This is another method in use in the United States, but apparently mainly confined to that country. It was introduced by WINTROBE.[132]

The haematocrit is a graduated tube, somewhat less than 11 cm. in length, with a uniform bore of about 2.5 mm., and a flat inside bottom. On this tube a centimetre-millimetre scale 10 cm. in length is etched. Along the right side of the scale

the numbers 1, 2 ---- 10 are marked, commonly from below up, while on the left side of the scale the numbers 0 ---- 9 are etched from above down.

Venous blood is used, with 10 milligrams of dry potassium oxalate for every 5 c.c. of blood, as the anti-coagulant. A pipette with rubber bulb is used to fill the haematocrit, and the amount of blood required is 0.7 c.c. The tube is filled to the "0" mark, and the rate of fall read at the end of one hour, or as desired.

A self-recording photographic apparatus for use with this method has been described by SULKOWITCH.(122)

Wintrobe claims that the advantage of his method is that the haematocrit can be used to determine other factors as well as the sedimentation rate, i.e. the "volume of packed red corpuscles," which he believes to be the most useful criterion of the degree of anaemia at present available; and the "volume of packed leucocytes and platelets," which gives a rough idea of the number of these cells in the blood tested. He advocates the use of the haematocrit in routine diagnostic studies, as giving a clear, comprehensive and accurate macroscopic picture of the state of the blood.

MILLER,(80) however, in a report of his observations on the haematocrit method, was doubtful about the accuracy with which the "volume of packed red cells" can be measured with the haematocrit, as uncertainty is always present as to the amount of the suspending medium contained in the interstices between

the cells in the deposit.

Normal values for this method are not given.

6. Forman's Method.

This is another method of combining the sedimentation test with other tests, in this case the corpuscle volume and the icterus index. FORMAN[25] uses the ordinary Sahli haemoglobinometer as follows:-

A 5 per cent. sodium citrate solution is run into a Sahli haemoglobinometer up to the "30" mark, following which the tube is filled to the "100" mark with the patient's blood, and inverted several times. Readings of the height of the red cells are made at half and one hour. A reading at the end of 24 hours is made to get the corpuscle volume, and the supernatant serum is then used to estimate the amount of bilirubin in the blood.

Remarks on the Macromethods.

The above gives particulars of only a few of the more widely differing macromethods, but it will be seen that the choice is wide and varied. GREISHEIMER, TRELOAR and RYAN,[46] in an attempt to draw up transformation tables for the various methods, took simultaneous sedimentation tests of 200 patients by means of the Cutler, Westergren and Linzenmeier techniques, which three methods they considered to have the greatest

following. They found that the Linzenmeier technique gave, on the average, indices of a lower magnitude than those by the other two methods, while the Westergren gave indices of the highest average value. Blood sedimented relatively faster in the first hour by the Cutler method than by the Linzenmeier method, while it was much slower in the long, narrow Westergren pipette. They concluded that the average sedimentation in one hour for "normal" subjects appeared to be reasonably concordant for the three methods, but it was clear that sedimentation measures for human blood are, in part, specific for the technique employed.

TOWNSEND and ROGERS,[124] in a similar study of the same three methods, early discarded the Linzenmeier method on the ground of inconvenience. The Westergren method required far less time and gave more satisfactory results, while the Cutler method took more time, but gave the best results, especially in tuberculosis.

It may be said that the Westergren method has an immeasurably greater popularity in all countries than any of the other macromethods, and has the undoubted advantages of being relatively easy and simple to perform, and giving a high column of blood for the relatively small quantity required. Its accuracy would appear to be at least equal to that of the other methods.

B. THE MICROMETHODS.

1. The Fahraeus' Micromethod.

As with the macromethods, so with the micromethods, Robin FAHRAEUS[23] has the credit of describing the first micromethod.

His apparatus consists of a very small glass syringe, with a metal piston, which can be pushed out on a level with the mouth of the syringe. Sodium citrate solution is first drawn into the syringe to one-fifth of its volume, following which the mouth of the syringe is dipped in blood from a pricked finger, and the piston drawn fully up. Mixing is performed by pushing up and down the piston some few times. The syringe is then hung up vertically, mouth downwards, the blood-column obtained having a height of 25 mm. The reading-off is effected at the end of twenty minutes by the aid of a millimeter measure to be found on the outside of the glass tube.

Normal values for the method are not given.

2. The Langer-Schmidt Micromethod.[70]

In this method sedimentation tubes of 2.5 mm. diameter, and with a blood column 25 mm. in height, are used. A 5 per cent. solution of sodium citrate is sucked up the tube to a certain mark, and blood (0.12 c.c.) taken from the lobe of the ear is added. The mixture is blown out on to a small porcelain dish, thoroughly mixed, and then sucked up into the sedimentation

tube to the mark "0". The tube is now placed in a little test tube with some mercury at the bottom, and this is set in a rack. The result is read in one hour.

Values:-

Normal	0-10 mm.
High	12-15 mm.
Very high	15-25 mm.

3. The Ström Micromethod. (121)

This is another micromethod of Scandinavian origin, and is mentioned because figures are given comparing its values with those obtained by the Westergren method. In it, pipettes are used 200 mm. in length, and with an internal diameter of 1 mm. The normal values are given as 1-3 mm. for men, and 4-8 mm. for women and children.

4. The Cutler Micromethod. (19)

This micromethod is intended for use with graphs, as described in the same author's macromethod (above).

A 1 c.c. storage tube is first filled with 3 per cent. sodium citrate solution and then emptied, the citrate solution left on the walls of the tube being sufficient to prevent clotting. Blood is then collected in the storage tube, from a finger-puncture, until the tube is half-filled (about 0.5 c.c.). A pipette, of 2.5 mm. internal diameter and having graduations

from 0 to 50 mm. engraved on its stem, is now filled to the "0" mark from the blood-citrate mixture in the storage tube. A spring-clip is applied to the pipette, closing the lower end, and the pipette is then fixed in a rack.

Readings, as with Cutler's macromethod, are taken of the position of the sedimenting column of red cells every five minutes up to one hour, and conclusions as to the normality of the sedimentation rate drawn from the resulting graphs.

A photographic method of recording results by this method has recently been described by LEE.(72)

5. Payne's Micromethod.(92)

This is the micromethod devised and used by the biochemist to the Royal Hospital for Sick Children, London. His apparatus consists of a 1 c.c. pipette graduated in 0.01 c.cs.; a block of wood with plasticene on it, and thin capillary tubing with an internal bore of between 1.6 mm. and 1.9 mm., cut into lengths of about 12 cm., with a mark at exactly 10 cm. from one end.

Into the pipette is drawn 0.1 c.c. of 3.8 per cent. sodium citrate solution, followed by blood from the finger or ear to 0.5 c.c. The blood and citrate are discharged on to a glass capsule, mixed, and drawn up into the pipette again. One of the capillary tubes is now placed horizontally on the plasticene, and blood run into it up to the 10 cm. mark. Still horizontal, the capillary tube is pushed into the

plasticene and raised into a vertical position. The height of the plasma layer above the blood-cell column is measured in millimetres at the end of one hour. The normal reading lies between 3 mm. and 6 mm., while readings over 10 mm. are considered abnormal.

In using this method, Bruce PERRY[45] found difficulty in obtaining 0.5 c.c. of blood from the finger-tip, and made the following modifications:-

0.03 c.c. of isotonic sodium citrate solution is drawn into a 0.2 c.c. pipette, followed by 0.12 c.c. of blood, making 0.15 c.c. of blood and citrate mixture. The mixture is ejected into a small glass bottle and well shaken. Capillary tubing of 0.5 mm. bore is used as a sedimentation tube, as described by Payne.

A similar method has been recently described by HARVEY and HAMILTON[49] of Edinburgh, who use capillary vaccine lymph tubes of standard and uniform bore (1.1 mm.) with a blood column 7 cm. in length. After recording the sedimentation rate in millimetres at the end of one hour, they place the capillary tubes in an ordinary centrifuge tube, and centrifuge to a constant volume, in order to correct for cell volume in cases of anaemia.

6. The Linzenmeier-Raunert Micromethod.[75]

This method employs capillary tubes having a length of 27 cm., and a breadth of 1 mm., with an ampulla at the

upper end. Five per cent. sodium citrate solution is sucked up to the first mark on the tube; then the tube is laid flat on the table and blood is admitted to a second mark, giving a column of fluid 62.5 mm. in length. Mixing is performed by drawing the column of fluid into the ampulla three times, after which the tube is placed in a rack and sedimentation allowed to proceed. The height of the plasma is read off in millimetres at the end of one hour. The authors recommend reduction of the discovered height of the plasma to a value corresponding to a blood column 50 mm. in height, in order to be independent of variations in the height of the real column, - thus:-

Height of the real column = 60 mm.

Discovered height of plasma = 12 mm.

Unknown value = x mm.

$$\frac{x}{50} = \frac{12}{60}$$

$$\therefore \quad x = 10 \text{ mm.}$$

Landau's Modification.

The method which I have personally adopted is a modification of the above introduced by Albin LANDAU(68) of Sweden. His apparatus consists of capillary tubes 12 cm. in length and 1 mm. in internal diameter; with two marks, one at 12.5 mm. and the other at 62.5 mm. from the point. Above the upper mark there is an ampulla. A metal check syringe

with a screw piston is used for drawing up and mixing the blood. At the end of the metal cylinder of the syringe is a perforated rubber plug, the opening in which can be varied slightly by means of a screw collar.

Method of Testing.

1. Fit the capillary tube into the check syringe.

2. Draw up 5 per cent. sodium citrate solution by screwing the piston rod till the lower mark is reached.

3. Puncture the ear, finger or heel for blood.

4. Screw up blood until the upper meniscus of the column corresponds with the upper mark on the tube. (Approximately 0.2 c.c. of blood is required).

   This is easily done with one hand, grasping the syringe like a dagger, and manipulating the screw with the thumb and forefinger.

5. After washing the mouthpiece of the capillary tube, screw the citrated blood up into the ampulla, but not completely.

6. Mix by screwing the blood slowly down into the capillary tube, and drawing it up twice into the ampulla.

7. Screw the column down again into the capillary tube, close the opening of the tube with a finger, remove the tube from the syringe, and place it in the rack. Rubber packings at the base of this rack are fitted into strongly elastic ground-in metal cylinders, which slide easily and press the tubes firmly against the packings at the top of the rack, which are adjustable. This ensures that the tubes are securely fastened and cannot slip out in transport.

   The result is read off in millimetres after one hour.

In employing the check syringe very little citrated blood adheres, as a rule, to the glass sides, and therefore the

reduction of values as recommended by Linzenmeier for his method is unnecessary.

Table 4.

Classification of Readings.

	Linzenmeier-Raunert.	Landau.
Normal values (children under 2 yrs.)	1-5 mm.	1-6 mm.
" (children over 2 yrs.)	1-8 mm.	1-9 mm.
Slightly increased	6-14 mm.	10-15 mm.
Fairly high	15-25 mm.	16-30 mm.
High	Over 25 mm.	Over 30 mm.

A feature of Landau's modification is the ease with which the blood can be transported, and the test set up, within a period of six hours, at the operator's convenience. In order to do this, the blood is mixed as usual and the tube set in the rack. When it is wished to carry out the sedimentation the following procedure is followed:-

1. Remove the capillary tube from the rack, a finger placed over the upper end preventing the blood from escaping.
2. Hold the upper end of the tube between the thumb and the forefinger; while rapidly rotating it around its longitudinal axis, keep inclining it, so that the column of blood slides backward and forward in it ten times in each direction.

3. Open the valve on the check syringe (this is a small hole in the side of the syringe, normally closed by a rubber ring), fix the tube in the syringe and close the valve.

4. Mix in the ampulla by three suctions as described already, place the tube in the rack, and read off after an hour.

Remarks on the Micromethods.

As was the case with the macromethods, the micromethods described above are only a representative selection, the actual number in use being much greater. The amount of work done with the micromethods, however, is infinitesimal compared with that done with the macromethods, and each micromethod worker tends to have a method, or a modification of a method, of his own. As will be seen from the table, the micromethods differ widely in the height of the column of blood used, the internal diameter (to a lesser extent), and in the amount of blood required (see Table 5). It will be noted, however, that the normal values for practically all the micromethods resemble one another closely. The abnormal values are rather more affected by the choice of method.

The question of the influence of the height of the blood column and the internal diameter will be discussed later, but a practical point of great importance in choosing a micromethod lies in the amount of blood required. To obtain 0.5 c.c. from the ear, finger or heel of the average child, as required

Table 5.

Comparison of Micromethods.

Method.	Height of column.	Internal diameter	Amount of blood required	Normal reading
Fahraeus	25 mm.	-	-	-
Langer-Schmidt	25 mm.	2.5 mm.	0.12 c.c.	0-10 mm.
Ström	100 mm.	1 mm.	-	1-8 mm.
Cutler	50 mm.	2.5 mm.	0.5 c.c.	Graphic.
Payne	100 mm.	1.6-1.9 mm.	0.5 c.c.	0-10 mm.
Perry	100 mm.	0.5 mm.	0.12 c.c.	0-10 mm.
Harvey & Hamilton	70 mm.	1.1 mm.	-	-
Linzenmeier-Raunert	50 mm.	1 mm.	0.2 c.c.	1-8 mm.
Landau	60 mm.	1 mm.	0.2 c.c.	1-9 mm.

by the Cutler and Payne methods, is a matter of some difficulty. PERRY,[95] whose work was done on rheumatic children, modified Payne's method for this reason. To be of real value, a method must be capable of use in practically every case, irrespective of age; and this, to my mind, rules out the Cutler and Payne methods. The Fahraeus method is mainly of interest as being the first micromethod described.

The Langer-Schmidt, Perry and Hamilton and Harvey methods all require practice and dexterity to perform, and their accuracy is largely dependent on the operator. The Linzenmeier-Raunert method has also this disadvantage, which,

however, is almost completely overcome by the introduction of the check syringe by Landau.

It is my opinion that the method described by Landau is the micromethod of choice, for the following reasons:-

1. The information given by it would appear to be at least as reliable as that given by any other micromethod.
2. It is simple to perform.
3. Readings need not be taken immediately, but the sedimentation tubes may be transported, set up, and read later.

The apparatus can be obtained from "Rudolph Grave, Malmskillnadsgatan 48 C., Stockholm," at a cost of approximately £2.

The Optimum Time for Reading the Sedimentation.

This, again, is a point on which opinions differ. FAHRAEUS[23] pointed out that, if the sedimentation tubes were of unlimited length, the velocity of sedimentation would be retained for an unlimited period of time, but since, for practical reasons, we must confine ourselves to shorter tubes, there came a moment when the red cells were packed at the bottom of the tube. Long before this, however, a decrease, varying in different blood tests, in the sinking velocity took place; and it was not possible to take a reading at any time, and thereafter transfer the values obtained to a certain period of time, by means of a simple calculation. The most

detailed representation was obtained from readings at intervals during the sinking, but the trouble involved did not give commensurate results, and therefore Fahraeus fixed the time of ONE HOUR, since, at the end of that time, sedimentation had in every case proceeded sufficiently far to give readable results, but was never finished.

WESTERGREN,[129] in his study of the sedimentation test, found good reasons for the contention of Fahraeus that the study of the sedimentation while still proceeding was the most valuable; and considered that the observation at the end of one hour gave a fairly good idea of the stability. His conclusion, however, was that "when stating the height of the layer of plasma at the end of one, two and twenty-four hours, the suspension stability is expressed with sufficient precision."

Several observers, e.g. ZECKWER and GOODELL,[136] CARVALHO and FERREIRA de MIRA fils,[10] consider the twenty-four hour reading to be of no practical value. Some authors, such as GRAY-HILL,[43] and HUNT[59] consider that the important readings are those taken at the end of one and two hours, and the latter author has evolved a graph for obtaining the correct sedimentation rate from these readings. Another way of obtaining the latter is afforded by KATZ[64] formula:-

$$\frac{S1 + \frac{S2}{2}}{2} = \text{The Sedimentation Rate}$$

(where S1 = sedimentation at the end of 1 hour,
S2 = sedimentation at the end of 2 hours).

Certain American authors, e.g. KILDUFFE,[66] HASKINS[50] et alia., consider that one hour is too long, and advocate periods varying from 15 to 45 minutes. In Germany, HENKEL[52] suggested that the blood be centrifuged for five minutes at 1,100 revolutions per minute, and the degree of sedimentation then noted, thus eliminating the time factor.

The vast majority of authors, however, have accepted the one hour reading, and no convincing proof has been brought forward that readings taken after the hour give further information.

Immediate and Delayed Readings.

The advantage of a method which would enable a test to be set up and read a few hours after blood has been taken, without altering the result, is obvious. Very few authors have considered this point, although without it the test would have little practical value outside of a hospital. WESTERGREN[129] noted that in his test-tubes the citrated blood could be kept for some time, before the capacity for sedimentation was tried. He considered that to keep the blood for a period up to five or six hours was without consequence, but that, after about twenty-four hours, the power of sedimentation was, as a rule, obviously reduced. CUTLER[18] said that his tubes could be allowed to stand for ten hours without any significant change

or alteration in the character of the graph. HARVEY and HAMILTON[49] found that one difficulty which they found impossible to surmount was the necessity for the test to be carried through at the bedside. Their capillary tubes could not be carried about, although they believed that this would make no difference in the reading. They considered that preservation of the citrated blood seemed to have the effect of slowing the sedimentation rate. LANDAU[68] performed a series of 134 tests immediately, and again after 6 hours, and found, at the most, a difference of 2-3 mm. In 90 per cent. of the cases the difference did not exceed 2 mm.

Certain personal observations regarding this are recorded later.

Macromethod versus Micromethod.

The question arises as to whether the macromethod or the micromethod is the best, from all points of view, for general use. This again is a matter on which opinions differ widely. Many of those who use a macromethod dismiss micromethods with a word. FAHRAEUS, for example, when describing his micromethod, said that he was unable to recommend it, as its fault, which he believed would probably make every micromethod inferior, was that the blood column did not become sufficiently high. Similarly, KATZ and LEFFKOWITZ,[64] in their survey of the sedimentation test, considered that the micro-

methods were inferior to the macromethods.

Few of those who dislike the micromethods appear to have had much practical experience of them, and their objections are mainly based on theoretical reasoning. The advocates of the micromethods, on the other hand, have, in many cases, compared both types of method.

MORRISS and RUBIN[82] made a series of tests using tubes of various diameters such as 0.2 c.c., 0.1 c.c., pipettes, and capillary tubing. They found that the smaller tubes gave a slightly higher percentage reading than the standard method, the differences increasing with the decrease in diameter of the tube - capillary tubes being unsatisfactory. With regard to the latter point, PERRY[95] pointed out that one objection to the use of capillary tubing of small bore was that, if the sedimentation rate was rapid, the boundary line between the clear supernatant plasma and the sedimented red cells was in some cases blurred. This, however, occurred only in the minority of cases, and solely in those in which the rate was rapid, and where accuracy of reading to 2-3 mm. was not essential.

Morriss and Rubin concluded that, while on the whole the micromethod was not as reliable as the standard macromethod, it was sufficiently so to be employed with confidence for clinical purposes.

CUTLER[19] compared his macro- with his micromethod, found the results were very close, and concluded therefore that

the latter was as reliable as the former.

BEAUMONT and MAYCOCK[4] performed simultaneous tests with the Westergren, and Zeckwer and Goodell techniques, and also with an unspecified micromethod, which involved the use of a capillary pipette graduated from 1-100 mm., with a bore of 1.13 mm. No constant discrepancy was discovered between the readings of the three methods, but the technique of the micromethod was complicated, and difficulty was found in obtaining sufficient blood to carry it out.

Comparing his micromethod with Westergren's macromethod STRÖM[121] found that the results were roughly comparable in the following relation:-

$$\frac{\text{Westergren}}{\text{Ström}} = \frac{3}{2}$$

Below 35 mm. the readings were close, but over 35 mm. the micromethod tended to lag behind Westergren's (see Table 6).

Table 6.

Comparison of Values by the Westergren and Ström Techniques.

Sedimentation Rate (Westergren).	Sedimentation Rate (Ström).
0-35 mm.	0-35 mm.
35-50 mm.	35-45 mm.
50-60 mm.	45-50 mm.
60-75 mm.	50.55 mm.
75-95 mm.	55-60 mm.
> 95 mm.	> 60 mm.

FRIEDLANDER,[30] working with the Langer-Schmidt technique, found that the values with this method were proportionate to the Westergren macromethod values.

PETERMAN and SEEGAR,[96] working on children, used the Westergren method, and found that the great difficulty was to obtain blood for even one sedimentation test in really ill children.

LANDAU[68] pointed out the disadvantage of venipuncture in corpulent people, young children, and babies; and emphasised another important factor in children, namely apprehension, which was very marked in venipuncture. He conducted simultaneous tests by his method and by Westergren's, on the same patient, in 300 cases. The lower values corresponded fairly well, but the higher values showed greater differences, and it was found impossible to reduce the different methods to common values.

Personal observations, recorded later, agree with those of Landau.

The conclusion, therefore, would appear to be that the macromethods are more effective for the higher values than the micromethods, but that for practical purposes the micromethod values are sufficient.

Necessity for Repeated Tests.

Several observers have emphasised the fallacy of drawing deductions from a single observation of the sedimentation rate, which is of "little value in diagnosis and of no value in prognosis" (PETERMAN and SEEGAR[96]). Both LANDAU[68] and van ANTWERP[125] pointed out that a repeated test will usually give the correct reading, but that occasionally such repeated tests show a consistently raised reading, where a normal reading was expected, and that in these cases a careful search should be made for some underlying cause.

WESTERGREN[129] has observed isolated cases with occasional unexpectedly small values, and suggests here the possibility of a technical fault, as yet unknown.

FACTORS INFLUENCING THE SEDIMENTATION RATE.

1. Age.

The blood of the new-born infant shows the least sedimenting properties (FAHRAEUS,[23] REES-WALTON,[108] REICHEL[107]). LEVY-SOLAL,[73] working with blood from the mother's vein and from the infant's cord respectively, found, in 78 cases, that the average maternal sedimentation rate was 65 compared with an average foetal rate of 1.5.

After birth the rate gradually increases until adult life, as is illustrated by the accompanying table (Table 7) given by LANDAU.[68]

Average Normal Values in Children (Landau).

AGE	AVERAGE S.R.
Birth to 1 week old	1 mm.
2 weeks to 3 weeks old	2 mm.
One month to 1 year old	3 mm.
1 year to 5 years old	3 mm.
Over 5 years old	3-4 mm.

2. Sex.

In adults the rate is usually slightly higher in women than in men, a difference which is more marked when pregnancy is present (FAHRAEUS,[23] REES-WALTON,[108] GREISHEIMER[44]). In children, however, there is no such difference between the sexes (REICHEL,[107] GREISHEIMER, WARWICK and WALTON[47]). The last-named authors consider that apparently some change occurs at the age of puberty or shortly thereafter, which is responsible for the sexual differentiation in the case of adults.

3. Climate.

Climate is not considered by many observers to have any effect upon the sedimentation rate, but HOVERSON and PETERSEN[58] in America have suggested that daily variations in the sedimentation rate, found by them in twelve patients suffering from general paralysis of the insane, were due to meteorologic conditions.

ROCHE,[112] working with cases of pulmonary tuberculosis, found that altitude had the effect of slowing the sedimentation rate, and considered that this was due to the diminution in the total mass of blood leading to an apparent increase of the red cells.

4. Height of the Sedimentation Tube.

The longer the sedimentation tube, the greater is the distance traversed by the sedimenting red corpuscles, and therefore the higher are the values obtained in rapidly sedimenting bloods (FAHRAEUS,[23] WESTERGREN,[129] WINTROBE and LANDSBERG[133]). Practical requirements, however, limit the size of the sedimentation tube, and the scale required has to be regarded as an empirical one. A reading of, say, 35 mm. with a Landau tube, would be many times greater with a tube of twice the height. MAIA,[77] working with tubes of varying heights, found considerable differences in the sedimentation rate, which did not occur when tubes of uniform height were used. His findings are in accordance with those of other observers, and it would seem advisable that the height of the blood column used should be uniform.

5. Bore of the Sedimentation Tube.

Most observers consider that tubes of more than 2 mm. internal diameter are suitable for the test, but there is a difference of opinion as to whether tubes of less than this diameter are sufficiently reliable. WINTROBE and LANDSBERG[133] considered that tubes less than 2 mm. in internal diameter were unsatisfactory because of uneven sedimentation; and MAIA[77] found marked differences in the sedimentation rate with tubes of 1 mm. internal diameter or less. HARVEY and

HAMILTON,[49] however, pointed out that the test was one of relative rather than absolute fall, and that the calibre of the tubes was therefore unimportant. They found that sedimentation was more rapid and easier in capillary tubes. LANDAU,[68] in about 9,000 tests, found only a small number where the sedimentation was uneven, and, by his method, the test could be repeated with the same sample of blood and a correct reading obtained. The same author performed simultaneous double tests on the same person in 100 cases, and found that in values between 1 mm. and 8 mm. the differences did not exceed 1 mm. in 94 per cent., or 2 mm. in the remaining 6 per cent.; in values between 9 mm. and 25 mm. the difference in 92 per cent. did not exceed 2 mm. (4 per cent. showed a difference of 3 mm., and 4 per cent. a difference of 4 mm.); and lastly in values over 25 mm. the differences in 94 per cent. were not above 2 mm., and in 6 per cent., 3 mm. These differences in no way affected the clinical deductions from the reading obtained.

6. Inclination of the Sedimentation Tube.

Sedimentation takes place much more rapidly in tubes inclined from the vertical, than in vertical tubes (LUNDGREN,[76] MAIA,[78] PONDER[103]). LANDAU[68] performed double tests in 160 cases, one being set up vertically, and the other at an angle of 45 degrees. He wished to discover whether, by

inclining the tube from the vertical, a more speedy reading could be taken, but discovered that the results in the case of the obliquely inclined tubes were unsatisfactory. As even a slight variation from the vertical will cause a difference in the rate, all these authors emphasised that, to obtain uniform results, sedimentation must take place in strictly vertical tubes.

7. Anticoagulant.

Sodium citrate solution, in the proportion of one part of the solution to four parts of blood, is the anti-coagulant in most common use, but there is some disagreement as to the optimum percentage. REES-WALTON[108] considered that the "usual" sodium citrate concentration of 5 per cent. was much higher than required, and might exercise osmotic influence on the erythrocytes; and he therefore suggested 3.8 per cent. as being more nearly isotonic with the blood. WESTERGREN[129] also used 3.8 per cent., but considered that variations beteen about 2 per cent. and 5 per cent. had a very unimportant influence on the sedimentation. PEYRE[97] used concentrations of 3.5 per cent. and 5 per cent. in a number of double tests, and found that the sedimentation rate and the blood volume were, for all practical purposes, equal in both cases.

Some authors are opposed to the dilution with sodium

citrate, and ERNSTENE,[22] for example, considered that such dilution made accurate measurements impossible. Other anticoagulants which have been advocated are hirudin (RUBIN and SMITH[117]), and oxalate (ZUNZ[138]). PETERMAN and SEEGAR,[96] in their review of the sedimentation reaction, found wide variations between the anticoagulants used; which were difficult to interpret, and did not parallel any other observations.

The position would appear to be that sodium citrate is the favourite anticoagulant, and that its concentration, provided that it is uniform for the method used, is unimportant.

8. Temperature.

Most authors agree that increase of temperature has the effect of increasing the sedimentation rate (MAIA,[78] ROCHE[112]), but that variations in the usual room temperature do not play any practical part (WESTERGREN,[129] REES-WALTON,[108] WINTROBE and LANDSBERG,[133] NEWHAM[85]). HENDERSON,[51] however, found that rise of temperature did not always cause an acceleration of the sedimentation rate in pathological cases, and concluded that where it was desired to trace the variations in the sedimentation index of the blood of any particular case over a period of time, it was desirable that the successive observations should be made at constant temperatures.

9. Digestion.

It is agreed by those authors who have investigated the subject, e.g. REES-WALTON,[108] WINTROBE and LANDSBERG,[133] POPPER and KREINDLER,[105] that the ingestion of food has no influence on the sedimentation rate. LANDAU[68] investigated the daily variations in the sedimentation rate in 15 cases, at 2-hourly intervals, and found only a slight variation, which was insignificant. There appeared to be a tendency to get a slightly higher reading in the evening than in the morning.

10. Source of Blood.

Both WINTROBE and LANDSBERG,[133] and LANDAU[68] found no appreciable difference in the sedimentation rate of blood taken from a vein, and that taken from a capillary.

11. Exercise.

FAHRAEUS[23] and WESTERGREN[129] both considered that violent exercise might lead to a slight increase of rate, but WINTROBE and LANDSBERG[133] thought its influence negligible.

12. Emotion.

Van ANTWERP[125] found an exceptional rate with the first test in tuberculous children, while the second test gave a much lower rate. He considered that this might be

due to excitement, and suggested that the latter influenced the rate either by the outpouring of epinephrine, or by an increase in the blood sugar. He endeavoured to prove this theory by adding epinephrine or dextrose to a blood specimen, and comparing the sedimentation rate obtained with that of a control blood specimen. Neither experiment was productive of results.

13. The Red Cell Count.

That a pronounced reduction in the number of red cells would lead to an increase of the sedimentation rate was recognised by FAHRAEUS,(23) but since then many varying opinions have been expressed as to the extent of this influence.

The strongest advocate in favour of the importance of the red cell count was REES-WALTON,(108) who believed that correction of the sedimentation rate for anaemia was essential. He supported his contention by taking five tubes of 1 c.c. of blood each, in which he contrived, by means of the addition or subtraction of plasma, to obtain concentrations of 5, 4, 3, 2, and 1 million of red cells respectively. He found the sedimentation rate greatly increased as the red cell count decreased, with a constant rate in the 1,000,000 tube. He therefore used the 5,000,000 tube as a routine basis for comparison of sedimentation rates.

WINTROBE and LANDSBERG(133) also believed that the sedimentation rate should be corrected for the degree of dilution

(anaemia) or concentration (polycythaemia) of the blood, and advocated the haematocrit method for this purpose. CHUNG,[12] also using the haematocrit method to correct the cell volume percentage, required from 3 c.c. to 5 c.c. of blood. HARVEY and HAMILTON[49] used the erythrocyte volume, obtained by centrifuging their tubes after reading the sedimentation, to correct the rate for anaemia. ERNSTENE[22] also gave a method for correcting the rate to eliminate the accelerating effect of anaemia, and believed such correction to be necessary in rheumatic fever.

On the other hand, many observers (e.g. RHODIN,[111] GREISHEIMER,[44] HUNT[59]), have found that there is no constant relation between the sedimentation rate and the number of red cells. ZECKWER and GOODELL[136] considered that the factor of cell volume was less important than might be supposed, and WESTERGREN[129] believed it inconsiderable compared with other factors such as the plasma protein. RUBIN[115] made over 100 complete blood counts in conjunction with the sedimentation rate, and found no relation between the number and haemoglobin content of the red blood cells and the sedimentation rate. He considered that with a red cell count between 4 and 5½ millions and a haemoglobin percentage of from 70 to 80, the factor was of no appreciable importance; while in cases of severe anaemia the blood picture would probably be of more importance than the sedimentation rate. WOOD,[135] in a survey of the sedimentation reaction in heart disease, did not find that polycythaemia was of importance in slowing the rate.

BOERNER and FLIPPIN,[8] working with the Westergren method, made corrections for anaemia as recommended by Walton. They found that the differences between corrected and uncorrected bloods were not in any way proportional to the degree of anaemia, while 8 c.c. to 10 c.c. of blood were required for the correction. PAYNE and SCHLESINGER[93] considered Walton's procedure too cumbersome for general use, and attempted to verify his results with their own method. Their findings did not confirm Walton's, and the sedimentation readings gave the most divergent results in the region of 3 to 5 millions, where the red cell count would naturally fall in the majority of cases. Similarly PERRY,[95] working on rheumatism in children, did not find it necessary to correct the sedimentation rate for the number of red cells, as suggested by Ernstene.

Personal observations are recorded later.

14. The Size of the Individual Red Cell.

The size of the individual red cell does not appear to have any influence on the sedimentation rate (NEWHAM and MARTIN,[86] WINTROBE and LANDSBERG[133]).

15. The Haemoglobin Percentage.

GRAM[42] believed that the difference in the sedimentation rate between the sexes might be due to difference in the haemoglobin percentage, and suggested a correction to 100 per cent. PEYRE,[98] however, did not find any constant relationship between the haemoglobin percentage and the sedimentation rate; and REICHEL[107] reported a normal rate in secondary anaemias with 50 per cent. haemoglobin.

A. PERSONAL OBSERVATIONS OF THE LANDAU MICROSEDIMENTATION METHOD.

Ease of Performance.

Considerable practice is not necessary in order to become proficient in the use of this method. The introduction of the check-syringe makes it possible for the citrate solution, and later the blood, to be drawn up accurately to the correct levels and then mixed. The syringe with the tube attached can easily be held in the right hand, while the piston-rod is screwed, as required, by the thumb and index finger of that hand. This leaves the left hand free to hold the ear or heel, and the procedure can therefore easily be carried out without the assistance of a second person.

Obtaining of Blood.

The blood required for the test was obtained in older children from the ear, and in infants from the heel. The apparatus, as recommended by Landau, contains a guarded Hagedorn needle, with a spring and catch. The extent of the needle which will enter the skin can be altered by adjusting the guard. This needle was found to be satisfactory in obtaining a suitable quantity of blood, and was preferred by the patients to the use of the ordinary Hagedorn needle, or a splinter of glass.

A fairly free flow of blood was found to be essential, as delay in obtaining the requisite amount tended to produce

clotting of the column of blood in the sedimentation tube, and rendered the reading valueless.

Attitude of the Patient.

Children of from about four years upwards very soon became accustomed to the method, and in many cases actually asked for a "jag". This attitude is naturally of great value where a routine test is concerned, and means that the possible effect of emotional disturbance can be practically ruled out.

Breakages.

The only fragile part of the apparatus is the tubes. Some of these inevitably suffer damage in the course of time; a particularly susceptible part being the tip. It was found that fresh tubes, of identical structure, could be made locally at a moderate figure.

Cleaning of Tubes.

The sedimentation tubes were easily cleaned by rinsing with water, methylated spirit and ether, in that order; and dried by blowing a stream of air through the tube by means of a rubber-bulb. An absolutely dry tube was necessary for accurate readings.

Readings with Venous and Capillary Blood.

Microsedimentation rates taken with blood from veni-

puncture, and, at the same time, with blood from the ear, gave practically identical results. Table 8 shows 10 cases in which the two readings were performed.

Table 8.

Microsedimentation Rates with Venous and Capillary Blood.

No.	Capillary.	Venous.	Difference
1	36 mm.	37 mm.	1 mm.
2	12 mm.	11 mm.	1 mm.
3	41 mm.	50.5 mm.	0.5 mm.
4	9 mm.	9 mm.	0 mm.
5	31 mm.	32 mm.	1 mm.
6	4.5 mm.	4 mm.	0.5 mm.
7	39 mm.	40 mm.	1 mm.
8	2 mm.	1.5 mm.	0.5 mm.
9	32 mm.	32 mm.	0 mm.
10	13 mm.	13 mm.	0 mm.

Time of Reading.

The extent of fall at the end of one hour was taken, as this is the most common practice. In many acute cases equal information could be obtained from a reading taken at the end of half-an-hour, as Table 9 shows, but this reading would not be so satisfactory in less severe cases.

Table 9.

Readings at the end of ½ hour and 1 hour.

ACUTE CASES.

	M.-S.R.	
	½ hour	1 hour
Rheumatism	23	29
Tuberculosis	27	32
Pericarditis	34	40
Rheumatism	37	41
Rheumatism	30	35
Pyuria	30	36
Pyuria	37	42

SUB-ACUTE and QUIESCENT CASES.

	M.-S.R.	
	½ hour	1 hour
Diabetes	10	18
Icterus	8	22
Rheumatism	10	18
Rheumatism	5	15
Chorea	2	8
Tuberculosis	10	19
Tuberculosis	12	22

Changing Plasma and Corpuscles.

The experiment of substituting the corpuscles of a rapidly sedimenting blood for those of a slowly sedimenting blood, and vice versa, was performed in twelve cases, six of whom had a high micro-sedimentation rate, and the other six a normal rate. The blood used was the surplus of the previously citrated blood from modified Westergren tests, and was contained in Wassermann tubes. These tubes were centrifuged, and the corpuscles from one tube screwed up into a Landau tube to fill one-half of the usual column, while the plasma from the second tube was screwed up to form the remaining one-half. A second Landau tube was filled in a reverse manner. Mixing was performed in the usual way, and readings made at the end of one hour. The initial micro-sedimentation rates were obtained with the same

previously citrated blood, in order to facilitate comparison. Table 10 gives the results.

It will be seen that, although the experiment was only a rough one, the sedimenting property appeared to be contained, without doubt, in the plasma, and not in the corpuscles.

X

Initial Micro-sedimentation Rate		"Rapid" corpuscles + "slow" plasma.	"Slow" corpuscles + "rapid" plasma.
Rapid	Slow		
39 mm.	5 mm.	3 mm.	39 mm.
38.5 mm.	8 mm.	5 mm.	36 mm.
32 mm.	1.5 mm.	3 mm.	35 mm.
32 mm.	14 mm.	9 mm.	36 mm.
28 mm.	4.5 mm.	5 mm.	26 mm.
38 mm.	10 mm.	6 mm.	35 mm.

Application of CUTLER'S GRAPHIC METHOD to the Micro-sedimentation Rate.

As a matter of interest, readings were taken in a number of cases at 5-minute intervals up to 1 hour. The resulting graphs were found to agree with Cutler's description to a certain extent.

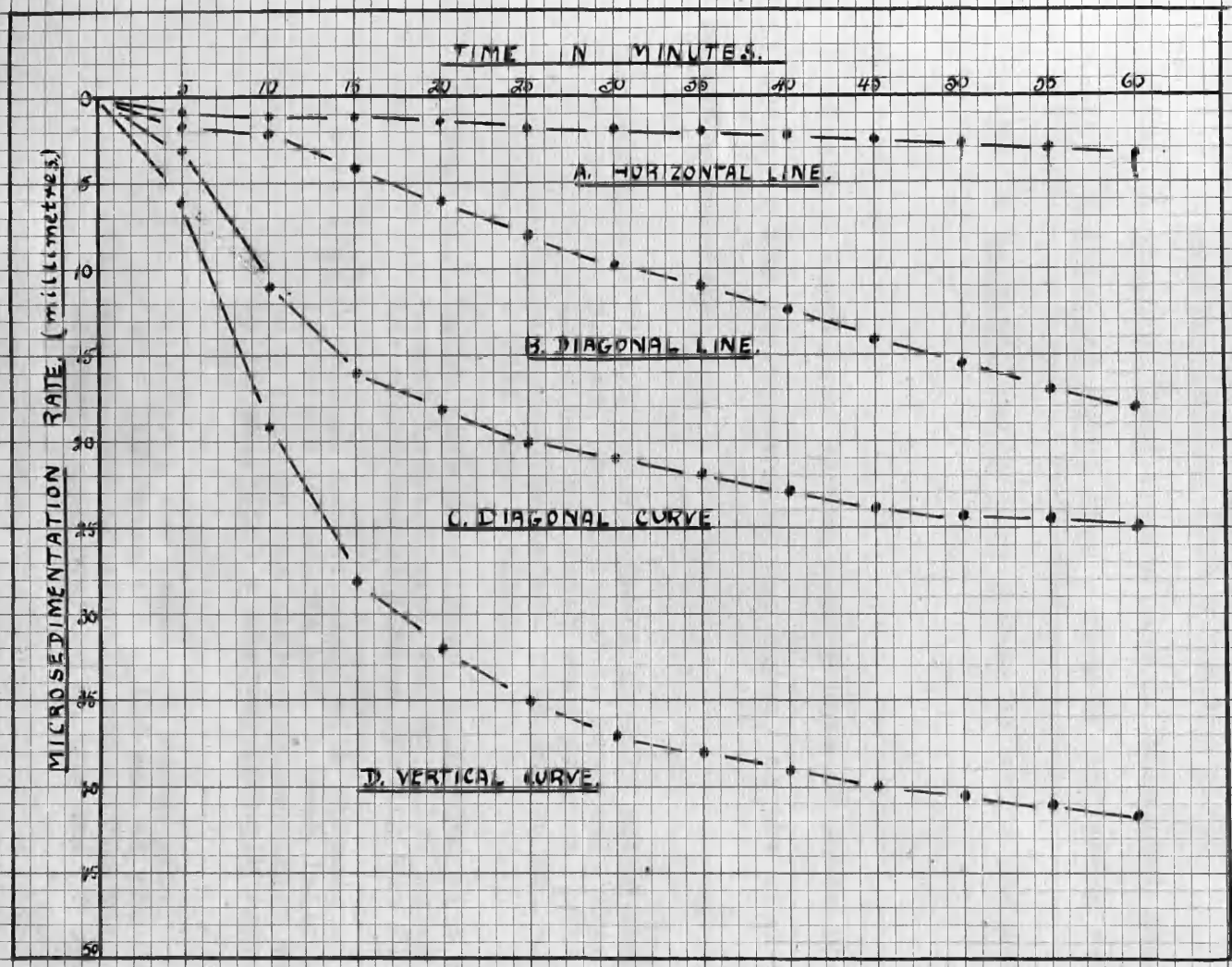


CHART 2. - GRAPHIC METHOD of recording MICROSEDIMENTATION RATE.

Chart 2 shows:-

(A) A horizontal line from a healthy girl.

(B) A diagonal line from a case of quiescent rheumatism.

(C) A diagonal curve from a case of improving broncho-pneumonia.

(D) A vertical curve from a case of acute rheumatism.

Chart 3 shows four curves from a case of acute rheumatism, and illustrates the improvement in the curve, as the condition of the patient improved.

Curve I: This curve was taken shortly after the patient was admitted to hospital, when arthritis and fever were present. The micro-sedimentation rate was 40 mm. - a very high reading.

Curve II, taken five days later, coincided with a normal temperature, and no joint pains. The micro-sedimentation reading was 35 mm.

Curve III: Continued improvement, with absence of fever and arthritis led, a week later, to a fall in the micro-sedimentation rate to 18 mm., with a correspondingly improved curve.

Curve IV: This curve was taken one month after Curve III, when the child was at the Country Branch, and apparently well. The micro-sedimentation reading at the end of one hour was now 6 mm.

It will be seen that the curves represent the improvement in the sedimentation rate very vividly, but the information given by the reading at the end of one hour would appear to be

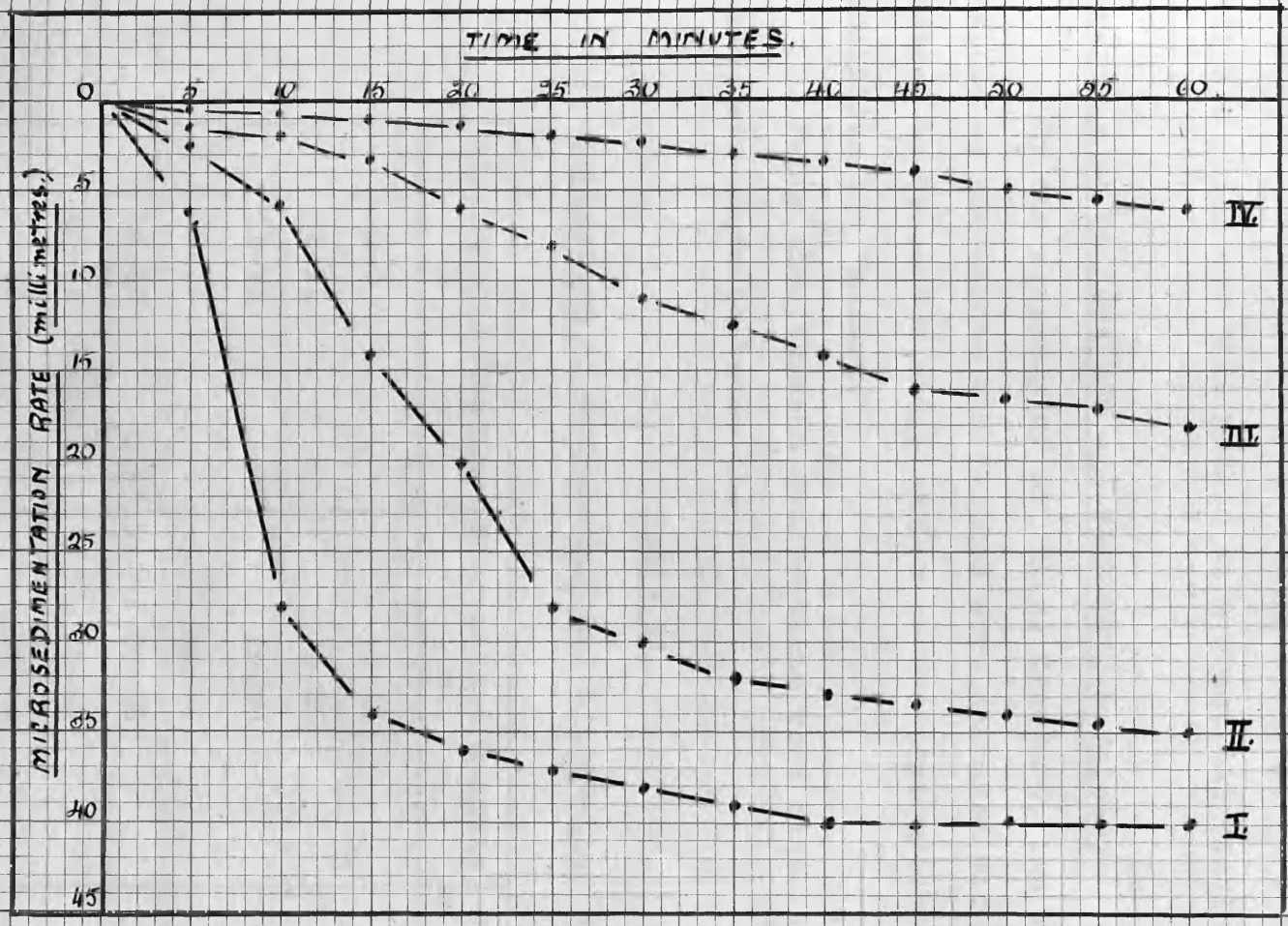


CHART 3. - CUTLER CURVES from a Case of ACUTE RHEUMATISM.

quite sufficient indication of the clinical progress, if less picturesque. The necessity of taking readings at 5-minute intervals rules out this method as a practical routine procedure.

Comparison of MACROMETHOD and MICROMETHOD Values.

By the courtesy of Dr. Ethel Crawford, the values obtained by the Landau micromethod were compared with those obtained by Crocket's modification of Westergren's method (for description see "Methods").

Fifty simultaneous observations were made, and the results are shown in Table 11.

Table 11.

Comparison of Macromethod and Micromethod Values.

Macromethod Reading. %	Micromethod Reading. mm.	Number of cases
0-5	0-11	12
5-15	8-25	15
15-25	25-39	6
25-35	30-40	6
35-45	30-35	3
45-55	35-40	3
55-65	39-42	5

It was not found possible to make direct comparisons between the values by the two methods, as sedimentation in the

large Westergren tube does not take place proportionately to sedimentation in the small Landau tube.

Macromethod values between 0 per cent. and 5 per cent. are considered to be normal, and the table shows that the corresponding micromethod values also fell within the normal limits, 0-10 mm. With a moderate increase in the sedimentation rate the values by the two methods again agreed fairly well, a macro-value of 15 per cent. corresponding with a micro-value of not more than 25 mm. When the macro-values were greater than 15 per cent. the micro-values were always high, i.e. over 25 mm., but there was no similarity between the values. The highest value recorded by the micromethod was 42 mm., but the macromethod readings rose as high as 65 per cent.

It is probable that in the acutely ill cases the macromethod would more accurately represent the variation in the clinical condition, but this is of doubtful value, and it is questionable whether the results obtained would justify the necessity for venipuncture in a seriously ill child. Of much more importance is the finding that normal readings were obtained in the same cases by both methods. This suggests that the micromethod is of equal value to the macromethod in denoting the cessation of activity of infection.

Immediate and Delayed Readings.

One of the advantages claimed for Landau's method is the ability to repeat readings after an interval of a few hours.

In order to find out whether such repeated readings would give sufficiently accurate results, 97 readings were repeated at intervals varying from 1 to 24 hours. In many cases the repeat reading was taken after the tubes had been carried in a horizontal position in a motor-car, thus reproducing the conditions under which the microsedimentation test would be carried out in general practice.

Tables are given to show the difference in the micro-sedimentation rate read immediately, and

(A) after a period of 1-6 hours (Table 12);

(B) after a period of 19-24 hours (Table 13).

From the first table it will be seen that readings taken up to 6 hours after the blood was withdrawn show a difference of 1 mm. or less in 60 per cent. of the cases. 92.9 per cent. did not differ by more than 2 mm., and no case showed a difference greater than 3 mm. In the lower values, 0-20 mm., a difference not greater than 0.5 mm. was found in 50 per cent. of the cases.

The deduction as to the clinical state of the patient drawn from the delayed reading in no case differed from that drawn from the immediate reading.

The second table (Table 13) shows that micro-sedimentation readings, repeated after a period of 18-24 hours has elapsed, are much less reliable, 55.6 per cent. showing a difference of 4 mm. or more.

Table 12.

Immediate Readings compared with Readings taken after a period of 1-6 hours.

M.-S.Reading	No.of Cases	Difference between Immediate and Delayed Reading - millimetres -				
		0-0.5	0.5-1	1-2	2-3	3-4
0-10 mm.	30	15	9	6	0	0
10-20 mm.	24	12	2	9	1	0
20-30 mm.	9	1	1	5	2	0
30-40 mm.	7	1	1	3	2	0
TOTALS:	70	29	13	23	5	0
PERCENTAGE:		41.5	18.5	32.9	7.1	0

Table 13.

Immediate Readings compared with Readings after a Period of 18-24 hours.

M.-S.Reading	No.of Cases	Difference between Immediate and Delayed Reading - millimetres -			
		0-1	2-4	4-8	Over 8
0-10 mm.	12	3	6	3	0
10-20 mm.	7	0	1	3	3
20-30 mm.	4	0	2	1	1
30-40 mm.	4	0	0	0	4
TOTALS:	27	3	9	7	8
PERCENTAGE:		11.1	33.3	26	29.6

Out of the total of 97 cases, 18 showed a delayed reading exactly the same as the immediate reading; 63 showed a delayed reading slower than the immediate reading, and the remaining 16 showed a delayed reading more rapid than the immediate. These last 16 were all cases in which the M.-S.R. was below 10 mm. This suggests that storage of the citrated blood tends to cause a slowing of the micro-sedimentation rate, except in cases which have a normal value.

B. PERSONAL OBSERVATIONS ON THE INFLUENCE OF THE RED CELL COUNT AND HAEMOGLOBIN PERCENTAGE ON THE MICROSEDIMENTATION RATE.

Twenty-eight blood counts were performed simultaneously with the microsedimentation test in a variety of diseases. Tables have been given to show the microsedimentation rates in association with a red cell count of over 5 millions; between 4 and 5 millions; between 3 and 4 millions; and below 3 millions; together with the disease present, and the clinical condition of the patient.

No attempt was made to correct for anaemia.

I. Red Cell Count over 5 Millions:

Table 14.

	Disease	Condition of Patient	Red Cells	Haemo-globin %	M.-S.R. mm.
1	Hypochromic anaemia	Well	5,000,000	55	3
2	Gastro-enteritis	Improving	5,200,000	80	23
3	Icterus neonatorum	Slight jaundice	5,680,000	112	2
4	Icterus neonatorum	Slight jaundice	8,000,000	120	2.5
5	Prematurity	Marasmic	5,530,000	110	2.5
6	Pink Disease	Much improved	5,000,000	80	10.5
7	Tumour of thymus	Dying	7,250,000	84	10
8	Congenital heart	Not seriously ill	6,910,000	95	18

Eight cases are included in this section (Table 14).
The first case shows a hypochromic anaemia with a red cell count of 5 millions, but a marked diminution in the haemoglobin percentage, 55 per cent., which however did not affect the M.-S.R., which was normal.
The second case had a M.-S.R. of 23 mm., while the blood count was normal. The cause for the increased rate was doubtful, but the child, who appeared fairly well and whose stools were normal, developed discharging ears shortly afterwards.

The next two cases were cases of icterus neonatorum, who were practically recovered. The M.-S.R. was almost identical in both, although in one the red cells numbered $5\frac{1}{2}$ millions, and in the other 8 millions.

The case of pink disease showed no fever, and the weight was going up at the time when the observations were made.

Case 7 was the one case in this series where the M.-S.R. markedly did not reflect the seriously ill condition of the patient. Here the red cell count was high, $7\frac{1}{4}$ millions, while the M.-S.R. was only 10 mm., and the patient died that evening. The red cell count could not, however, be held solely responsible for the low M.-S.R., as cardiac failure with oedema was present. The last case provides a contrast, as here a red count of almost 7 millions was associated with an increased M.-S.R. (18 mm.).

Polycythaemia, therefore, would not appear to exercise a slowing effect on the microsedimentation rate.

II. Red Cell Count between 4 and 5 Millions:

Table 15.

	Disease	Condition of Patient	Red Cells	Haemo-globin %	M.-S.R. mm.
1	Pericarditis	Improving	4,650,000	75	25.5
2	Rheumatic V.D.H.	Seriously ill	4,430,000	91	8.5
2a	Rheumatic V.D.H.	Improving	4,280,000	80	25
3	Chorea	No carditis	4,800,000	95	6
4	Pulmonary Tubercle(?)	Moderately ill	4,440,000	55	20.5
5	Catarrhal Jaundice	Jaundice - no fever	4,110,000	65	15
6	Gastro-enteritis	Slight fever - loose stools	4,080,000	78	13
7	Congenital Heart	No cyanosis or fever	4,010,000	81	14

Seven cases fall under this heading and are given in Table 15.

In the first case in this series, the child had been seriously ill and the condition was improving slowly. The M.-S.R. reading agreed with the clinical condition.

The second case was one in which, at the first observation, cardiac failure with oedema was present and was probably responsible for the low M.-S.R. When the oedema had disappeared the M.-S.R. rose, although the blood count was hardly changed.

In the third case the blood count and the M.-S.R. were both within the limits of normal.

The fourth case was not seriously ill, but the question of pulmonary tuberculosis arose, as the radiograph showed a dense

shadow on the right side, suggesting cavity. The skin-tests were negative, and the actual diagnosis remained in doubt. The M.-S.R. was moderately rapid, and did not disagree with the clinical findings.

In the case of catarrhal jaundice the degree of anaemia (4 millions) might be considered to be responsible for the M.-S.R. being slightly over the normal upper limit, as jaundice without anaemia does not appear to be associated with increase in the sedimentation rate.

Similarly, in the next case, gastro-enteritis, a count of 4 million red cells was associated with a slight increase in the M.-S.R., while a slight degree of fever was present, and the stools were loose. A later blood count, however, was over the 5 million mark, while the M.-S.R. had risen to 23 mm., showing that the increase in M.-S.R. was evidently not due to the anaemia.

In the last case, congenital heart disease, the child had had a cough for one week, but there was no cyanosis or fever. Here again a slightly increased M.-S.R. was associated with a blood count of 4 millions.

III. Red Cell Count between 3 and 4 Millions:

Eight cases fall within this group, and are given in Table 16.

The first case had an abscess of the shoulder joint, with fever. The blood count of 3,800,000 followed a blood transfusion; the count before the transfusion having been close on $2\frac{1}{2}$ million.

Table 16.

	Disease	Condition of Patient	Red Cell Count	Haemo-globin %	M.-S.R. mm.
1	Abscess	Fevered and ill	3,830,000	65	20
2	Broncho-pneumonia	Dying	3,740,000	85	1.5
3	Gastro-enteritis	Improving	3,800,000	58	17
4	Lymphadenoma	Seriously ill	3,290,000	45	38
	Lymphadenoma	Seriously ill	3,260,000	45	42
	Lymphadenoma	Seriously ill	3,660,000	45	42
5	Microcephalus	Loose stools	3,400,000	65	9
6	Rheumatic V.D.H.	Seriously ill	3,700,000	70	40.5
7	Septicaemia	Seriously ill	3,290,000	70	18
8	Empyema	Seriously ill	3,340,000	60	32

The M.-S.R. was 41 mm. before the transfusion, and 20 mm. after it, and the difference might be considered to have been due to the change in the red cell count, except for the fact that the shoulder-joint was aspirated in between the two counts.

Case 2 shows a red cell count of $3\frac{3}{4}$ millions with a low M.-S.R. of 1.5 mm. This child was "in extremis," with a subnormal temperature, and died shortly afterwards.

Case 3 was admitted with a history of convulsions, and had slight fever and a moderate gastro-enteritis. A red cell count of 2.9 millions on admission coincided with a M.-S.R. of 25 mm. Two days later the fever had disappeared, the stools

were practically normal, and the blood count was 3,800,000. The M.-S.R., meantime, had fallen to 17 mm.

In the fourth case, lymphadenoma, the disease was in an advanced stage, and the patient gravely ill. It will be noticed that the M.-S.R. rose from 38 mm. to 42 mm., in spite of an increase in the red cell count of 300,000. The high M.-S. value agreed with the clinical findings.

The case of microcephaly showed a slight degree of enteritis, without fever, but, without the anaemia, the M.-S.R. would probably have been lower than 9 mm., as the patient was a baby of three months.

In case 6 the girl was apparently recovering from an attack of rheumatism with moderate carditis, when she suddenly developed a high irregular fever with dilatation of the heart. The M.-S.R. rose from 15 mm. before the fever to 40.5 mm. after it, while the red cell count coinciding with the second reading was 3.7 millions. She died two days later. The sharp rise in the M.-S.R. in this case was again entirely justified by the clinical condition, apart from the anaemia.

The case of septicaemia was an acutely ill infant of six weeks old, who died two days after the M.-S.R. and the blood count were done. The M.-S.R. here was rather lower than might have been expected, in spite of a count of rather over $3\frac{1}{4}$ millions.

Case 8 was acutely ill with fever and, on the day on which the M.-S.R. and the blood-count were performed, 115 c.c.

of pus were removed from the chest. A high M.-S.R. was to be expected in this case.

IV. Red Cell Count below 3 Millions:

Table 17.

	Disease	Condition of Patient	Red Cell Count	Haemo-globin %	M.-S.R. mm.
1	Abscess	Fevered and ill	2,470,000	30	41
2	Gastro-enteritis	Fever and diarrhoea	2,290,000	44	25
3	Icterus gravis	Seriously ill	2,560,000	47	19
4	Prematurity	Seriously ill	2,250,000	46	34
5	Lymphatic leukaemia	Dying	930,000	25	1

Table 17 shows the findings in the five cases in this group. The first two cases have already been considered in the previous group (Cases 1 and 3), as the blood count rose above 3 millions on subsequent examination.

In the 3rd case, icterus gravis, the increase in the M.-S.R. was probably partly due to the anaemia of $2\frac{1}{2}$ millions, but the child died that same evening.

The fourth case was an extremely emaciated and wasted child, with a pustular eruption on the back and the chest, discharge from both eyes, and an enlarged spleen. The M.-S.R. was high, with a red cell count of $2\frac{1}{4}$ millions. The child died next day.

The last case is the only one to show a red cell count of under one million. The patient, a girl of 8 years, was in a dying condition on admission. The M.-S.R. and the blood count were done just before a blood transfusion was given, but unfortunately the child died while the latter was in progress. The very low M.-S.R. found in this case is a not uncommon phenomenon immediately before death.

Summary of Findings.

A red cell count of between 4 and 5 millions did not appear to exercise any appreciable effect on the M.-S.R.

Red cell counts below 4 millions probably tended to accelerate the M.-S.R. but this influence was inconstant, and the M.-S. value as a rule gave a result which agreed with the clinical condition.

The question of the influence of anaemia on the sedimentation rate is discussed later.

C. PERSONAL OBSERVATIONS ON THE RELATION OF THE BLOOD CHLORESTEROL TO THE MICROSEDIMENTATION RATE.

In order to investigate the suggestion that the blood chloresterol was a factor influencing the M.-S.R., a number of simultaneous observations were performed through the kind co-operation of Dr. V. Stark. Dr. Stark considers as normal readings of the blood chloresterol falling between one hundred and one hundred-and-forty milligrams per cent., but these limits are arbitrary. In a series of twenty-one surgical cases, readings were performed before and after operation, in order to observe whether any difference in the chloresterol reading was paralleled by a difference in the microsedimentation reading (Table 18). The nature of the operations was varied, as was also the difference between the pre-operative and the post-operative readings. Table 19 summarises the behaviour of the chloresterol and the M.-S.R. in these cases. It will be seen that in eleven out of the twenty-one cases (approximately fifty per cent.) a fall in the blood chloresterol after operation was associated with a rise in the M.-S.R., but, in the other fifty per cent., the results varied considerably. It would appear that the blood chloresterol commonly falls after an operation, while the M.-S.R. as a rule rises; but the relation between the chloresterol and the M.-S.R. is not at all close. This conclusion is further supported by the findings given in

Table 18.

Blood Chloresterol and Microsedimentation Rate Before and After Operation.

No.	Initials	Age yrs.	Nature of Operation	Before Operation		After Operation		Result	
				Blood Chlor-esterol	M.-S.R.	Blood Chlor-esterol	M.-S.R.	Blood Chlor-esterol	M.-S.R.
1	C.P.	8½	Appendicectomy	131.0	4.5	117.2	14	Fall	Rise
2	D.M.	4	Sympathectomy	111.5	1.5	98.9	2	Fall	No change
3	A.B.	7	Appendicectomy	108.5	8.5	98.9	10	Fall	Rise
4	H.F.	2½	Repair of inguinal hernia	98.9	4.5	102.3	9	Rise	Rise
5	P.O'N.	3	Repair of inguinal hernia	102.3	11.5	90.7	15	Fall	Rise
6	C.McI.	1	Reduction of bladder prolapse	93.1	20	90.7	19	Fall	No change
7	D.M.	11/12	Repair of inguinal hernia	98.9	7	93.1	7	Fall	No change
8	C.S.	7	Tenotomy	98.9	6.5	93.1	11.5	Fall	Rise
9	J.L.	11/12	Repair of inguinal hernia	111.5	1.5	87.3	3	Fall	Slight rise
10	A.W.	1 2/12	Appendicectomy	93.1	30	70	39	Fall	Rise
11	J.C.	3	Tenotomy	131	14	105.7	14	Fall	No change
12	J.R.	11	Empyema (drainage)	96	33	87.3	30	Fall	Fall
13	C.H.	2	Manipulation of dislocated hip	120.6	5	102.3	9	Fall	Rise
14	D.McI.	12	Tenotomy	96	11.5	93.1	20	Fall	Rise
15	J.M.	7	Tenotomy	98.9	17	105.7	18	Rise	Slight rise
16	J.M.	7	Osteotomy	111.5	17	102.3	22	Fall	Rise
17	R.S.	7	Repair of hypo-spadias	108.5	4.5	98.9	11.5	Fall	Rise
18	J.H.	6	Manipulation of dislocated hip	111.5	5	117.2	7.5	Rise	Rise
19	C.L.	4/12	Evacuation of abscess	90.7	37.5	81.6	33	Fall	Fall
20	J.H.	2	Manipulation of talipes	117.2	2	105.7	1.5	Fall	No change
21	D.B.	1 4/12	Repair of inguinal hernia	105.7	10.5	98.9	12.5	Fall	Rise

Note:- The figures given for the blood chloresterol are in milligrams per cent., while those for the microsedimentation are in millimetres.

Table 19.

Summary of Surgical Cases.

Effect of Operation on:-		Number of Cases
Blood Chloresterol	Microsedimentation Rate	
Fall	Rise	11
Fall	Fall	2
Rise	Rise	3
Fall	No change	5

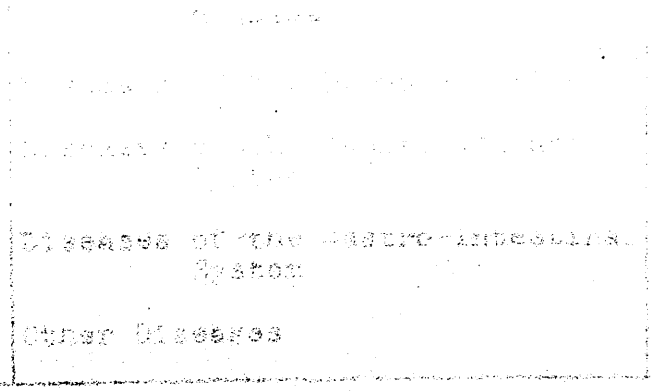
Table 20.

Blood Chloresterol and Microsedimentation Rate - Single Readings.

No.	Initials	Age (yrs.)	Condition	Blood Chloresterol (mgm.%)	M.-S.R. (mm.)
22	A.McK.	6	Lymphatic leukaemia	105.7	39
23	K.O'N.	12	Acute nephritis	433.3	41
24	W.S.	7	Hypospadias	98.9	7
25	M.C.	3	Double talipes	102.3	8.5
26	J.L.	$1\frac{4}{12}$	Cleft palate	105.7	12.5
27	W.B.	11	Undiagnosed	70	42.5
28	T.D.	10	Diabetes	117.2	8.5
29	P.D.	11	Diabetes	131.0	6
30	J.L.	12	Diabetes	127.6	14
31	W.D.	11	Diabetes	131.0	7
32	M.G.	14	Diabetes	171.2	23

Table 20. In this small group the two highest microsedimentation values were found in cases 23 and 27, namely 41 mm. and 42.5 mm., while the corresponding blood chloresterol readings were the highest, 433.3 milligrams per cent., and the lowest, 70 milligrams per cent., in the group. Among the five cases of diabetes (cases 28-32), case 32 showed the highest chloresterol and the highest microsedimentation readings, but cases 29 and 30, with a slight difference of 3.4 milligrams in the chloresterol, showed a difference of 8 millimetres in the microsedimentation rate.

From these findings, the conclusion is drawn that there would not appear to be any relationship between the level of the blood chloresterol and the rate of sedimentation of the red cells.



D. THE MICROSEDIMENTATION RATE IN DISEASES OF CHILDREN.

Introductory.

Under this heading are given the results of personal observations on a variety of diseases, which are divided into the following groups (Table 21):-

Table 21.

Groups

Group		Pages
I	Rheumatism	85
II	Tuberculosis	113
III	Non-tuberculous Respiratory Disease	130
IV	Diseases of the Nervous System	140
V	Diseases of the Genito-urinary System	151
VI	Diseases of the Gastro-intestinal System	160
VII	Other Diseases	171

The last group, Group VII, is made up of those conditions which do not come under any of the previous groups. Where references in the literature have been found, they are included at the beginning of each group.

Table 22 is given to show what is meant when a micro-sedimentation reading is spoken of as "normal," "slightly increased," "moderately increased," "high," and "very high."

Table 22.

Reading, in millimetres.	Classification
0-10	Normal
10-15	Slightly increased
15-25	Moderately increased
25-35	High
35-42	Very high

In order to avoid constant repetition, the words "Micro-sedimentation Rate" are abbreviated to "M-S.R." in the text.

I. MICROSEDIMENTATION IN RHEUMATIC DISEASE.

Review of Literature.

Of recent years, the question of the value of the sedimentation test in connection with rheumatic disease in children has received considerable attention. The following is a brief survey of the literature, arranged in chronological order:-

In 1926, KAHLMETER,(63) using Westergren's method, made observations on sixty cases of acute rheumatic fever, and found a high rate of sedimentation in all those cases during the acute stage, with regression paralleling the clinical symptoms. He considered that the sedimentation test was a better index of the activity than were the clinical symptoms, such as fever, leucocytosis and arthritis. Many cases who were clinically considered to be recovered still had a high sedimentation value, and these patients, if allowed to return to their ordinary lives, showed a relapse, frequently preceded by a further rise in the sedimentation rate. He therefore concluded that acute polyarthritis should never be regarded as cured until the sedimentation rate gave normal readings.

WESTERGREN,(130) in 1927, published observations on acute rheumatic polyarthritis which agreed with those of KAHLMETER. He found the fall in the sedimentation rate in this disease to be more slow and irregular than in other diseases of an infective nature, and considered that the test gave more clear information than the leucocyte count.

In 1930 ERNSTENE,(22) using a method which corrected the sedimentation rate for anaemia, performed simultaneous leucocyte counts and sedimentation estimations on a number of cases. He discovered that, in all types of the disease, the sedimentation rate, with few exceptions, remained elevated for several days to a few weeks after the leucocyte curve had become normal; and concluded that the infection could not be

considered arrested until the sedimentation rate had become, and remained, normal.

In 1932, PAYNE,[92] working at the Great Ormond Street Hospital, found a very close relationship existing between the clinical findings and the sedimentation rate, and considered that the test afforded a reliable numerical index to the progress enabling a more certain valuation to be made of the efficacy of any line of treatment. He also suggested that the sedimentation rate would prove a useful guide in determining the presence or absence of an active cardiac lesion.

LANDAU'S[68] paper on "Microsedimentation" appeared in 1933, and he recorded observations on seventy children suffering from acute polyarthritis, with and without cardiac complications. The high initial rate in these cases was, he considered, of no value in prognosis, although useful in diagnosing true rheumatism from "growing pains"; but repeated tests gave a valuable picture of the course of the disease, and were a guide to prognosis. He did not allow rheumatic children up from bed, until repeated tests had shown normal values. By observation after dismissal, he discovered that most of the children with normal rates when discharged continued well, while some of those with increased rates returned in a short time with a relapse. When cardiac decompensation and a condition of stasis set in, a decreasing rate with low values most often occurred. From observations on twenty-five cases of chorea, he considered that, where chorea was the sole rheumatic manifestation, the

microsedimentation values were within normal limits; whereas, with other manifestations present, the rate was increased. In the light of these findings, he suggested that the view of chorea as a metarheumatic disease - an intoxication of the cerebral cortex - might have some justification.

In 1934, PERRY,[95] using a modification of Payne's micromethod, believed that acute rheumatic carditis was always associated with a high sedimentation rate, and that the latter was an accurate index of active infection. As with previous observers, he reported a normal rate in chorea uncomplicated by carditis; and, with the onset of congestive cardiac failure, a frequent return of the rate to normal.

In the same year, WARNER[128] called attention to the possibility of a biochemical and dietetic factor which might predispose to juvenile rheumatic disease, and suggested that some of the manifestations of rheumatism, particularly uncomplicated chorea, might not be of an infective nature at all. He pointed out that in uncomplicated chorea there is no rise of temperature, no tachycardia, no change in the leucocyte count, and a normal sedimentation rate; and put the question why, if chorea is an infective disease, is there no rise in the rate of sedimentation until carditis supervenes.

In 1935, PAYNE and SCHLESINGER,[93] using Payne's micromethod, made a series of observations on two hundred and twenty-nine cases of juvenile rheumatism. One hundred and forty cases showed no evidence of active rheumatism during the observation

period; and, of these, seventy-four had no signs of cardiac involvement and, with three exceptions, showed no rise in the sedimentation rate apart from intercurrent infections. The rate in sixty-six children, who had had cardiac involvement at some time or another, was normal in fifty-six and raised in ten. In five of the latter this rise was transitory. In eighty-nine cases of active rheumatism the sedimentation rate closely paralleled the clinical condition in all but seven, in which latter it was either higher or lower than was to be expected. Seven fatal cases occurred, in all but one of which there was a raised rate; in this one case cardiac failure was prominent. When subcutaneous nodules were present, Payne and Schlesinger believed that the test was of considerable value, as a gradual return of the rate to normal showed that the nodules were about to vanish. Conversely, a persistently raised rate indicated continuation of the acute stage, and that the nodules would be present for an indefinite period. From these results, they considered that the test was a valuable one, which allowed observation of the progress of rheumatic children to be made with great accuracy. In twenty-eight out of fifty cases of uncomplicated chorea the sedimentation rate was raised for a short time only, after admission to hospital; while in twenty-two it was never above normal. They did not find that an increase of the rate in chorea was any guide to the after-development of cardiac disease.

WOOD,[135] in 1936, was of the opinion that a normal sedimentation rate was important evidence against the activity of rheumatic carditis; while COBURN and KAPP,[15] in the same year, stated that the rate was regularly elevated in patients with rheumatic carditis; and that, except when associated with congestive heart failure, a decreasing rate almost always reflected diminishing activity of the rheumatic process.

Personal Observations.

Observations were made on forty-eight cases of the rheumatic infection, and these will be considered in some detail, as the writer feels that, apart from tuberculosis, juvenile rheumatism is the disease in which the M.-S.R. is probably of most value. If, as is suggested by the majority of writers, the estimation of the sedimentation rate is a guide to the activity of the rheumatic process, it is a very valuable addition to the clinician's equipment. It is well known how great the difficulty is, in certain children, to obtain sufficient evidence of the extent of the rheumatic infection, and to assess the degree of activity. The temperature and pulse-rate afford only a moderate amount of information; and the suggestion made is that the sedimentation test is, in such instances, of decided value both as regards diagnosis and prognosis.

The cases considered in the following pages have been divided for purposes of classification according to the principal

rheumatic manifestation which was present on admission, although this was not necessarily the only manifestation.

ARTHRITIS.

Only six of the cases were admitted to hospital with acute arthritis. A table is given to show the M.-S.R. on admission and discharge (Table 23), and brief case histories follow.

Table 23.

Microsedimentation Values on Admission and Discharge of Cases of Arthritis.

Case	Initials	Age (years)	Admission M.-S.R. (mm.)	Discharge M.-S.R. (mm.)
1	H.H.	9	17.5	10
2	M.M.	6½	41	5
3	R.M.	4	32.5	6
4	J.W.	6	42	12.5
5	R.McE.	9	25	8
6	W.L.	9	39	11.5

Case 1. H.H. Boy, aged 9 years: first attack of acute rheumatism in 1933-34; chorea in January, 1935; arthritis for two months before present admission in March, 1936; no fever; M.-S.R. 17.5 mm. initially, fell to normal within two weeks, and was not subsequently over normal limits; no evidence of cardiac involvement.

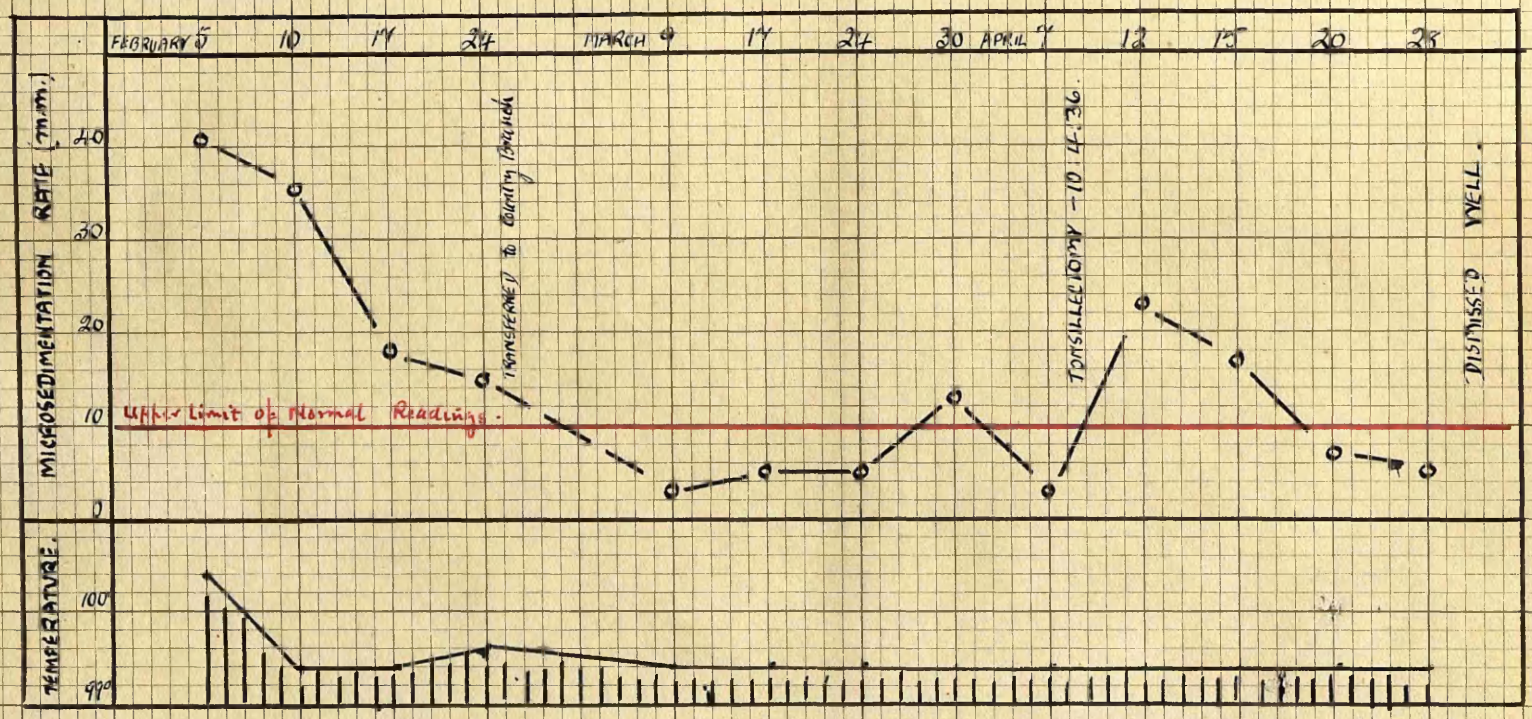


CHART 4 - M.M. - ACUTE ARTHRITIS.

Case 2. M.M. Girl, aged 6½ years: tonsillitis with fever for three weeks; arthritis for three days before being admitted to hospital (2.2.36); short systolic murmur at the apex on admission: fever subsided within one week, but M.-S.R. did not reach normal value until one month, but thereafter, except on one occasion, remained within normal limits apart from a short rise due to tonsillectomy (See Chart 4). The single raised value mentioned was not high (13 mm.), and was not due to any discoverable reason.

Case 3. R.M. Boy, aged 4 years: scarlet fever from 23.11.35 to 18.1.36; onset of arthritis 25.1.36; admitted to hospital on 28.1.36; cervical glands enlarged and tender; short apical systolic murmur; irregular fever which persisted for one month; M.-S.R. reached normal value at the same time as the temperature, and remained so, except for an elevation partly due to tonsillectomy (See Chart 5). No evidence of rheumatic carditis on dismissal, other than a short apical systolic murmur, slightly conducted.

Case 4. J.W. Boy, aged 6 years: no previous rheumatic history; arthritis for one week before admission (22.4.36); faint basal systolic murmur; no fever on admission, but M.-S.R. very high (42 mm.); arthritis subsided after one week on salicylates; slight irregular fever present during second and third weeks in hospital, and systolic murmur now heard at all areas, conducted to the axilla; M.-S.R. fell slowly and irregularly; approached normal limits when the temperature had been settled for two weeks, but was still very slightly raised on dismissal (1.6.36); readmitted after one month for period of convalescence, but was found to have diphtheria, the M.-S.R. being raised (21 mm.); transferred to Fever Hospital, but has since reported well in September and October, 1936.

Case 5. R.McE. Boy, aged 9 years: no previous rheumatism; intermittent pains in legs for six weeks; swelling of right knee for two days before admission on 18.6.36; on admission, no fever, arthritis or nodules; apical systolic murmur conducted to the axilla; M.-S.R. high (25 mm.); sent to Country Branch for two months, during which he kept well; on readmission

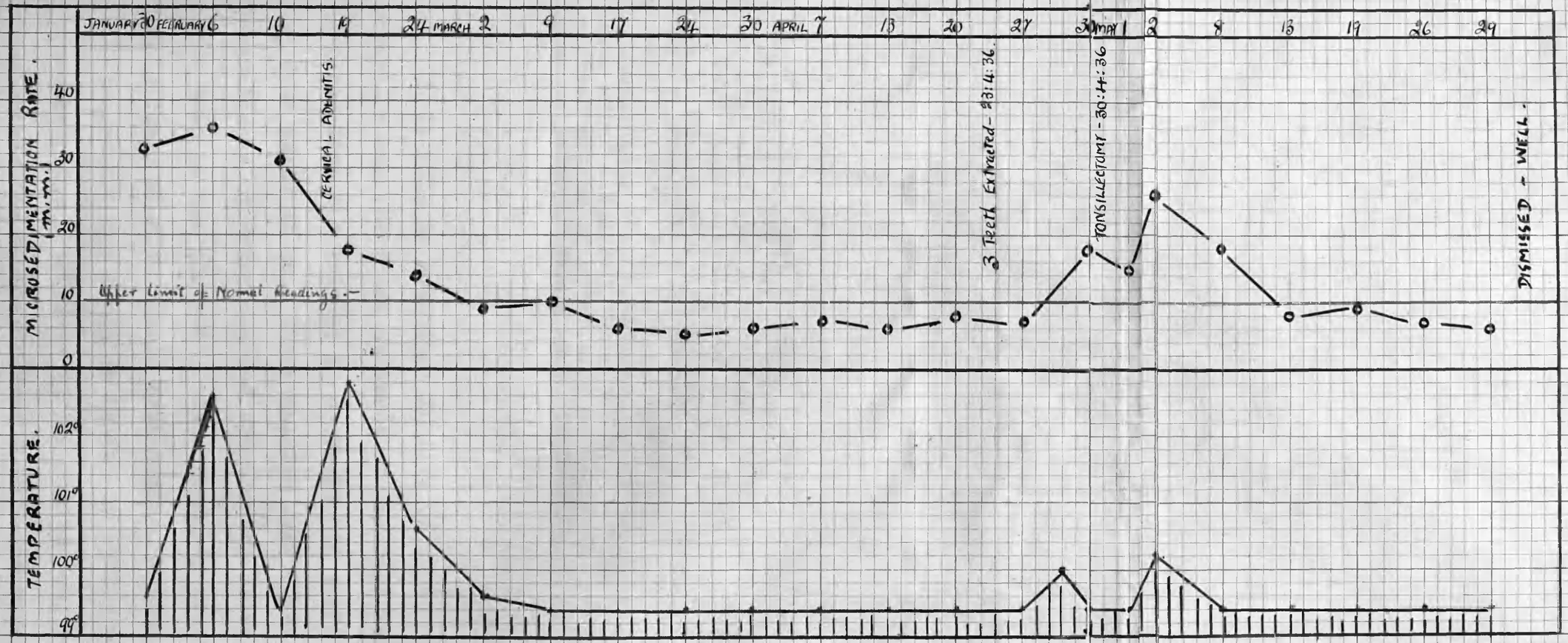


CHART 5 - R.M. - ACUTE ARTHRITIS.

Case 5 (contd.):

M.-S.R. was 4 mm., rising to 15.5 mm. after tonsillectomy, but falling again to 8 mm. within two weeks, when he was dismissed.

Case 6. W.L. Boy, aged 9 years: tonsillitis five weeks, and arthritis one week before admission on 16.7.36; no fever on admission; faint systolic murmur heard at all areas; M.-S.R. very high initially (39 mm.), but fell within a fortnight to 12 mm.; readmitted to Yorkhill after two months at the Country Branch; M.-S.R. normal (5 mm.), rising to 18 mm. after tonsillectomy, but falling again to 11.5 mm. a fortnight later, immediately before dismissal. At the time of writing, one month after dismissal, this boy has just been readmitted with a fresh attack of arthritis; no fever, and the cardiac condition as before. The M.-S.R. is 25.5 mm.

It will be seen that in five of these six cases the arthritis was the first evidence of the rheumatic infection, and in these five the initial M.-S. value was consistently high, ranging from 25 to 42 mm. The remaining case (Case 1) had had previous attacks of arthritis and chorea respectively, and was improving when he was admitted, which probably accounts for the relatively lower M.-S.R. This high initial M.-S.R. has no value in prognosis, but would be useful in distinguishing true rheumatic arthritis from cases of indefinite body pains of non-rheumatic origin, in which a normal M.-S.R. is generally found.

Four cases had reached a normal value of the M.-S.R. before they were dismissed, and two cases (Cases 4 and 6) still had a M.-S. reading slightly over the upper limit of normal.

One of these latter (Case 6) was readmitted one month later with a fresh attack of arthritis, while in the other (Case 4) the condition was complicated by the development of diphtheria, which was responsible for a sharp rise in the M.-S.R.

In all the cases, except Case 3, the elevated M.-S.R. persisted for some weeks after fever had disappeared. Case 3 is of interest as in this patient there was a slight rise of temperature twenty-four hours before tonsillectomy, associated with a M.-S.R. of 17.5 mm. (See Chart 5). No cause was found to account for this, and tonsillectomy was not, therefore, postponed. On the day following tonsillectomy the rate was actually lower - 15 mm. - but had risen to 26.5 mm. next day, when there was a slight degree of fever. This rise in the M.-S.R. might be taken as a contra-indication for tonsillectomy, and it is interesting in this connection to note that tonsillectomy had apparently no adverse effect, as the rate fell to a normal value within fourteen days.

CARDITIS.

This group of fourteen cases includes the serious cases with badly damaged hearts, in which one would welcome help in assessing the activity of the disease. As was pointed out, however, in the chapter dealing with "Methods," the limitations of the microsedimentation test are found when the really high values are reached. The maximum reading possible with the microsedimentation test falls at about 42 millimetres, whereas

the corresponding macromethod value might be as high as 65 per cent., or even 70 per cent. These high macromethod values were, however, found in only a very small proportion of the cases at present under discussion, and did not appear to afford more reliable information than the corresponding microvalue.

A table (Table 24) is given of all the cases in the group, showing the principal lesion, the degree of activity, and the initial and final M.-S.R's.

Table 24.

Carditis.

Case	Initials	Age (yrs.)	Principal Lesion	State of the Disease	Initial M.-S.R. (mm.)	Final M.-S.R. (mm.)
7	E.L.	$7\frac{1}{2}$	Pericarditis	Active	35.5	18
8	M.S.	$6\frac{1}{2}$	Pericarditis	Active	38	25.5
9	M.F.	$9\frac{1}{2}$	Pericarditis	Active	45	9
10	B.S.	8	Pericarditis	Active	32	40.5
11	M.W.	$8\frac{6}{12}$	Pericarditis	Active	37	20
12	J.D.	$8\frac{5}{12}$	Pericarditis	Active	39	31
13	M.C.	9	Endocarditis	Active	1.5	18
14	P.H.	8	Endocarditis	Active	32	9
15	A.C.	7	Endocarditis	Active	22.5	19
16	J.W.	11	Endocarditis	Quiescent	12	3
17	J.M.	6	Endocarditis	Quiescent	6	5
18	I.W.	12	Endocarditis	Quiescent	5.5	3.5
19	U.K.	$11\frac{1}{12}$	? Functional	No activity	2	2
20	C.B.	9	Subacute bacterial endocarditis	Active	31.5	37

Note: In Case 20 the subacute bacterial endocarditis followed upon a rheumatic carditis, and the case is therefore included in this group, although M.-S. readings were commenced after the onset of the subacute bacterial endocarditis.

PERICARDITIS.

Brief summaries of the six cases of pericarditis (Cases 7-12, Table 24) are as follow:-

Case 7. E.L. Girl, aged 7½ years: first evidence of the rheumatic infection - precordial pain and breathlessness in November, 1935; kept in bed three weeks; admitted to hospital on 23.4.36 with history of breathlessness for ten weeks; examination revealed pericarditis; slight fever; M.-S.R. high (35.5 mm.). Onset of cardiac failure with enlarged liver and oedema was associated with a fall in M.-S.R. to 18 mm.; death took place rather over three weeks from the date of admission (See Chart 6).

Case 8. M.S. Girl, aged 6½ years: acute arthritis with cardiac involvement in August, 1935; kept in bed till November, 1935; continued to be easily tired, appetite poor; dyspnoea, precordial pain and cough for five days before admission on 4.5.36; pericarditis present on admission; nodules on wrist and elbows; M.-S.R. very high (38 mm.), fell irregularly, reaching 25.5 mm. on 2.6.36; dismissed after two months' convalescence at the Country Branch, with heart still enlarged, and double murmur heard at the apex.

Case 9. M.F. Girl, aged 9½ years: no previous rheumatism; precordial pain and breathlessness for ten days; admitted on 19.4.36 with pericarditis; M.-S.R. very high (45 mm.), but fell within ten days to 38 mm; sent to Country Branch for five weeks, but readmitted because of a return of fever and breathlessness; M.-S.R. had risen again to 42 mm.; thereafter steady improvement in general condition; M.-S.R. reaching normal value before dismissed on 6.7.36 at her parents' request;(See Chart 7), on dismissal, heart still enlarged; double apical murmur; no nodules.

CHART 6.

E. L.

PERICARDITIS.

CHART 7 - M.F. - PERICARDITIS.

Case 10. B.S. Girl, aged 8 years: no previous rheumatic manifestations; lassitude, breathlessness and "growing pains" for three weeks; no fever; heart enlarged, with musical systolic murmur at apex; M.-S.R. high (32 mm.), falling within two months to 15 mm., when the condition was apparently quiescent; one week later, while still in hospital, there was a relapse, with irregular fever, enlargement of the heart, dyspnoea; and death occurred within seven days, the M.-S.R. rising to 40.5 mm. three days before the end; post-mortem examination showed pericarditis with marked stenosis and incompetence of all the valves.

Case 11. M.W. Girl, aged 8½ years: had been in hospital for two months, following an attack of arthritis, when present investigation was commenced; no history of rheumatic infection prior to this; gravely ill; pericarditis, endocarditis, and nodules; for two months M.-S.R. varied between 35 and 40 mm., the clinical condition remaining much the same; fall in M.-S.R. to 23 mm. coincided with slight clinical improvement, which continued, and the nodules disappeared; M.-S.R. reached its lowest value (11 mm.) one month later, and patient was transferred home ten days subsequently (i.e. five and a half months after admission), bedridden, but undoubtedly improved from her previous condition; the M.-S.R. having again risen to 20 mm. (See Chart 8).

Case 12. J.D. Boy, aged 8½ years: rheumatic fever with cardiac involvement at 5 years; precordial pain for ten days before admission on 10.12.35; seriously ill, with pericarditis and double apical murmur; M.-S.R. very high (35-44 mm.) for about two months, in association with irregular fever; sudden fall of 9 mm. in the M.-S.R., in spite of condition being apparently unchanged and fever slight, preceded death by three days; post-mortem examination showed greatly enlarged heart with vegetations on all valves (See Chart 9).

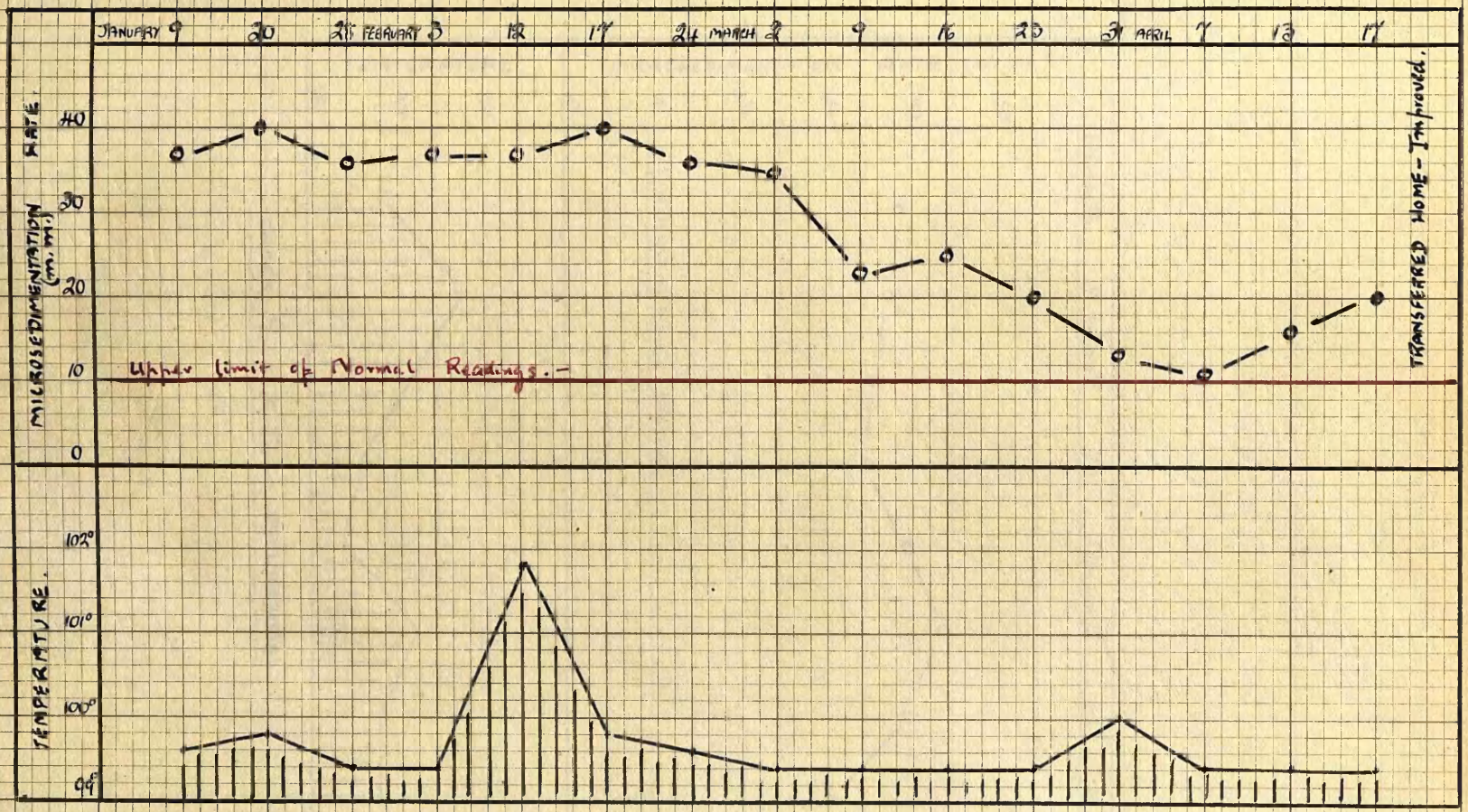


CHART 8. - M.W. - PERICARDITIS.

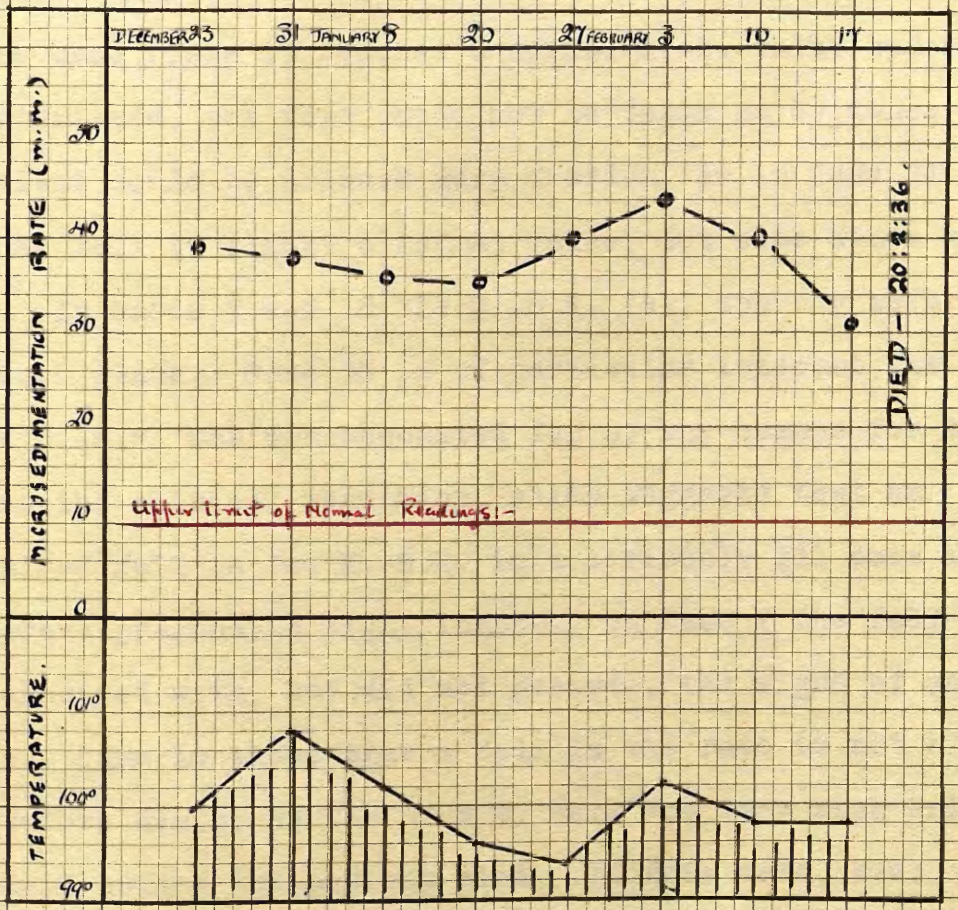


CHART 9. - J. D. - PERICARDITIS.

It cannot be claimed that estimation of the M.-S.R. was of great value in these cases. In all six the rate on admission was very high, but this finding did not convey more information than was to be obtained from clinical examination. Only one case (Case 9) reached a normal M.-S. value before being dismissed, but this could not be taken as evidence that the patient could be allowed more freedom, as in Case 11 the rate also fell to almost a normal value, but rose again within a week. In Cases 7 and 12 the M.-S.R. fell shortly before death took place. Case 12 is of particular interest, as the fall in M.-S.R. was not accounted for by any change for the worse in the clinical condition, which suggests that an unexplained fall in the M.-S.R. in a seriously ill case may be of grave prognostic significance. In Case 7 the fall in rate coincided with, but did not precede, the signs of cardiac failure. Case 10 shows that a fall in the rate is not always found before death, as the M.-S.R. here was very high only three days before the patient died. In this case, also, warning of the impending relapse was not given by the M.-S.R., which was only slightly raised before the relapse occurred. Case 11 illustrates how clinical improvement was paralleled by a dip in the curve of sedimentation readings, while the temporary nature of the dip showed the need for continued rest.

ENDOCARDITIS.

Summaries of the eight cases falling under this heading are as follow:-

Case 13. M.C. Girl, aged 9 years: "growing pains" at 5 years; acute arthritis in October, 1935; admitted in April, 1936, with oedema of the face and ankles; cardiac enlargement; double murmur; nodules, and abundant albuminuria; initial M.-S.R. showed a very low value (1.5 mm.), and the rate remained persistently below 10 mm. so long as oedema was present (See Chart 10); on the disappearance of oedema after salyrgan, M.-S.R. rose in an intermittent manner, reaching highest value when consolidation of lung with fever was present; return of oedema was associated with fall in M.-S.R., but latter did not rise when salyrgan injections again dispersed oedema; on her transfer home on 27.8.36 the heart was still markedly enlarged; no fever, nodules, or oedema; lungs practically clear; and the M.-S.R. 18 mm.

Case 14. P.H. Girl, aged 8 years: pericarditis in 1931; breathlessness and vomiting for one month before admission in April, 1936; heart enlarged to left with double apical murmur; no fever or nodules; M.-S.R. high (32 mm.); kept in hospital for over three months, with steady clinical improvement, apart from one temporary rise in temperature associated with headache; first normal M.-S.R. obtained ten weeks after admission, but rate again slightly raised for two weeks; normal reading before dismissal on 27.7.36, when she was apparently well (See Chart 11).

Case 15. A.C. Boy, aged 7 years: "growing pains" in July, 1935; admitted in January, 1936; heart enlarged with double mitral murmur; no fever; M.-S.R. moderately increased (22.5 mm.), but reached normal value within a fortnight; rate again slightly raised (15.5 mm.) on 9.3.36, and continued to rise in spite of normal temperature and no signs of activity; on 30.3.36 pulse rate rose slightly, and on 6.4.36 there was fever, the M.-S.R. being now very high (36 mm.); fever subsided after ten days on aspirin, but M.-S.R. fell slowly, showing moderately increased rate (19 mm.) on 18.5.36, before patient was sent to a Convalescent Home (Chart 12).

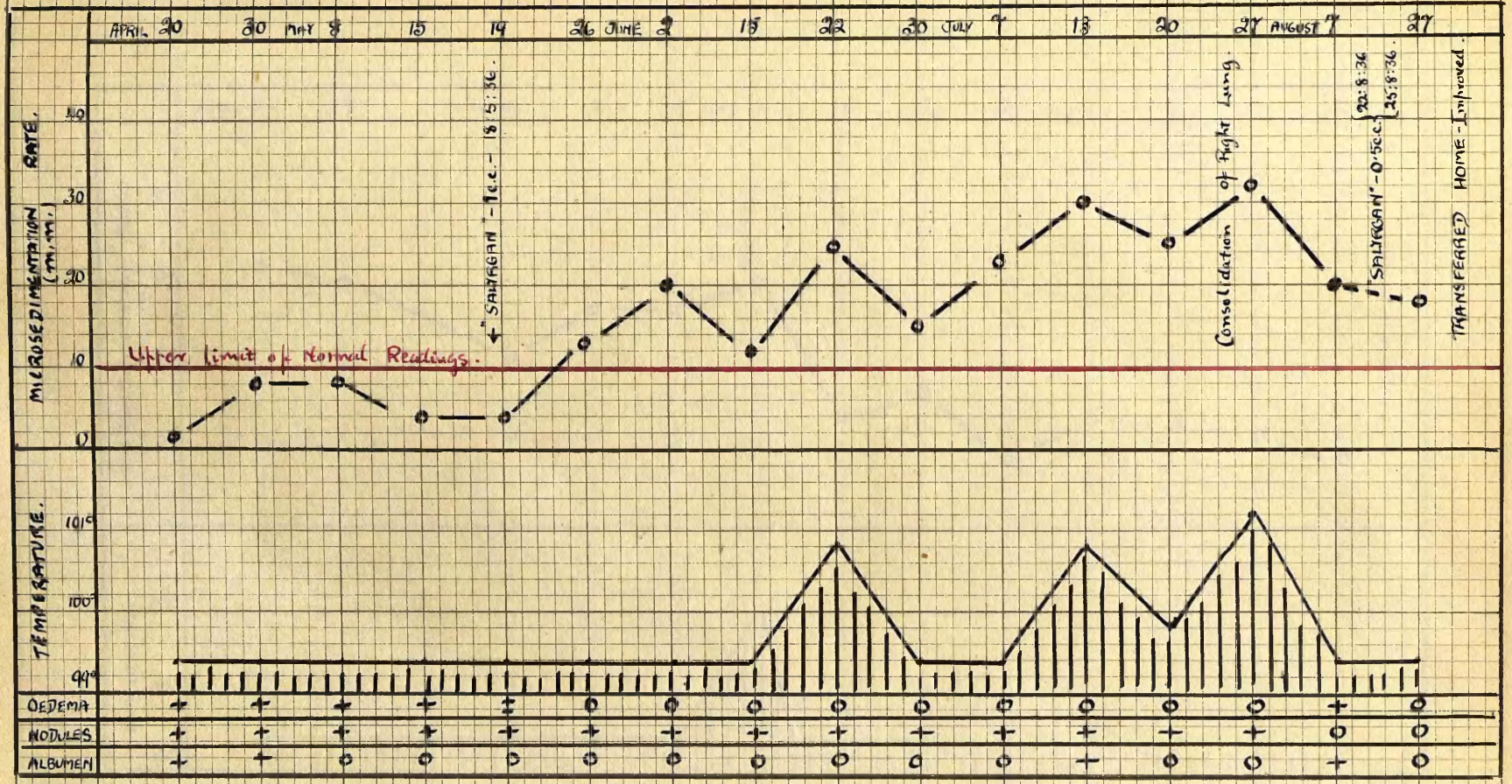


CHART 10. - M.C. - CONGESTIVE CARDIAC FAILURE.

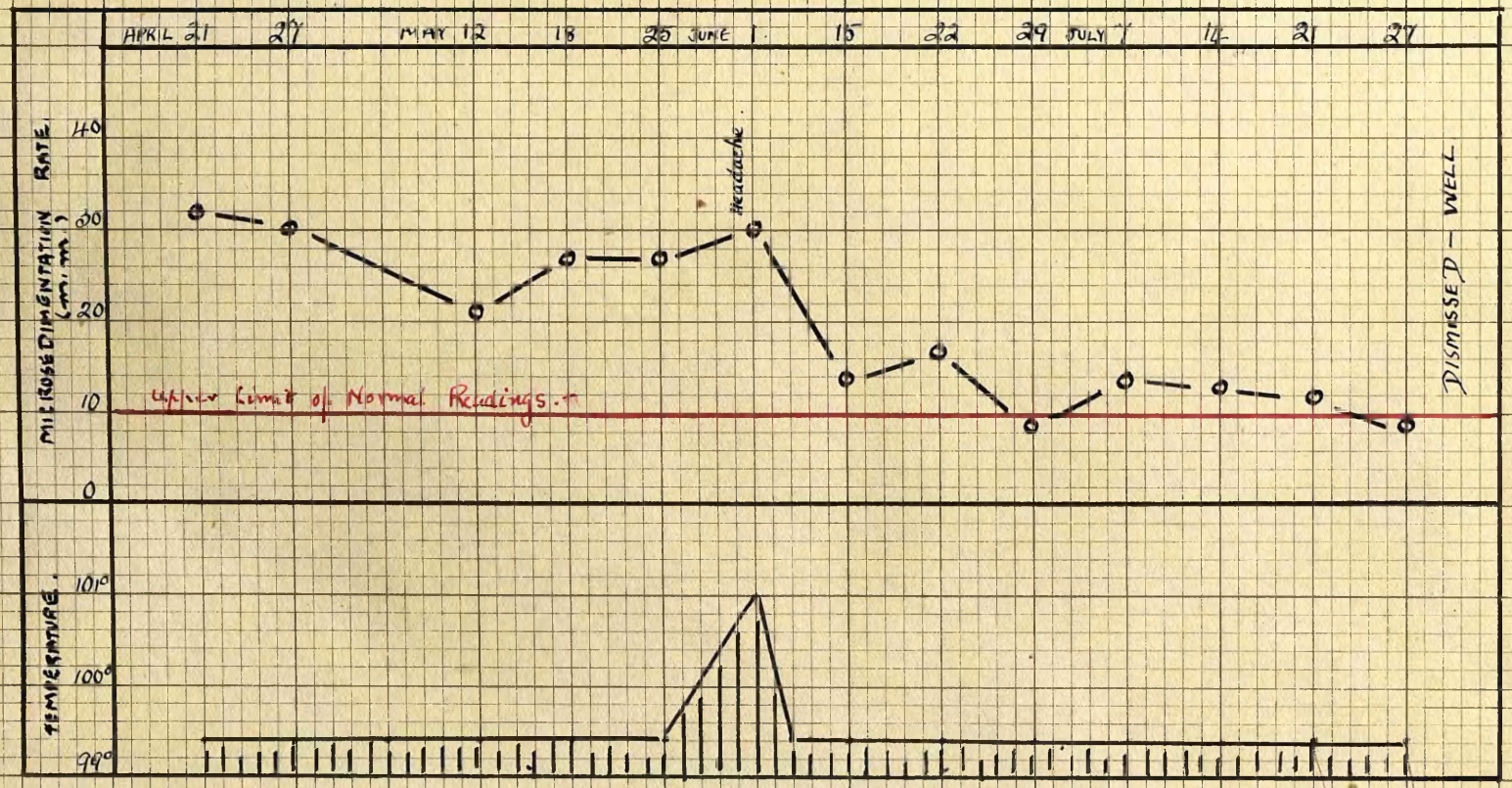


CHART 11. - P.H. - ENDOCARDITIS.

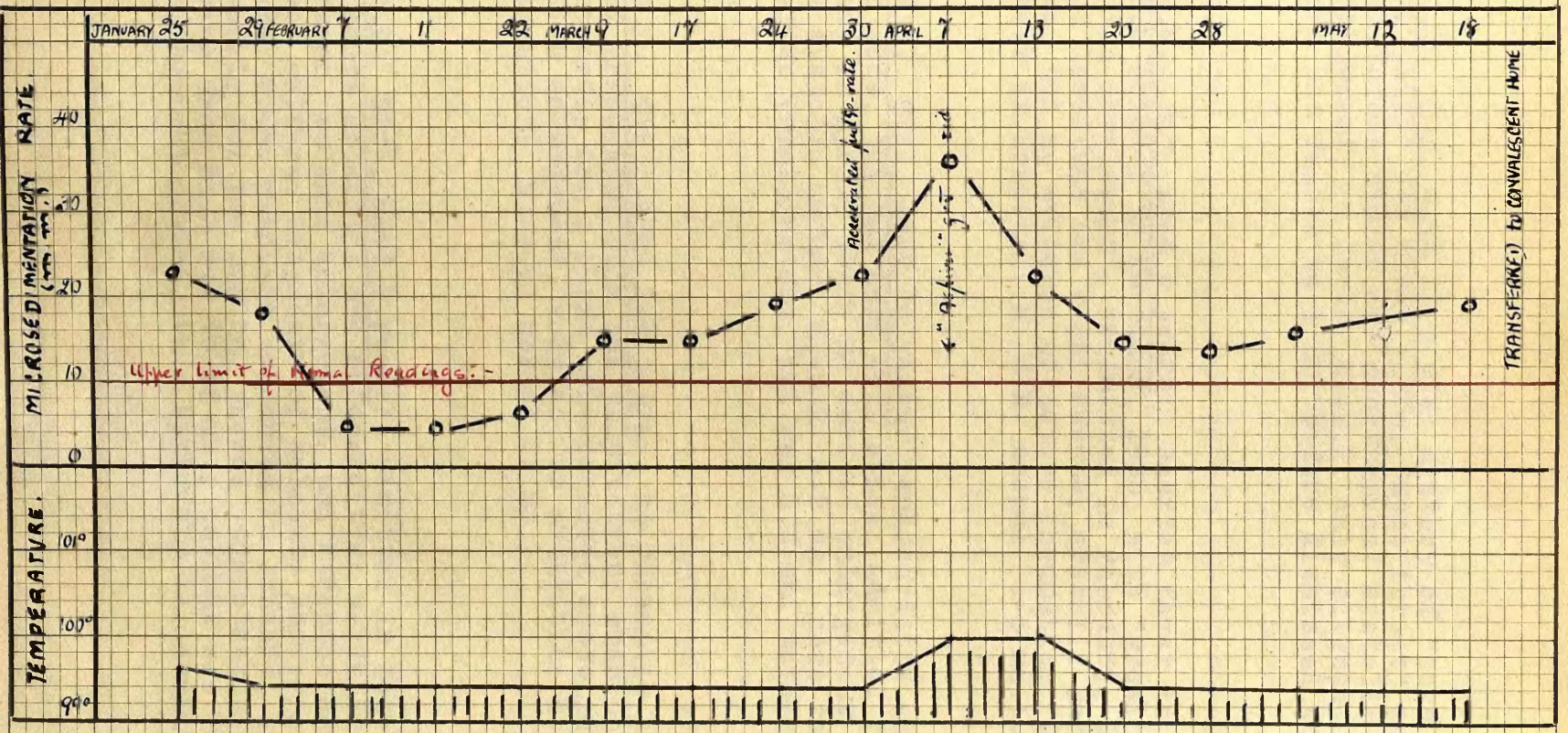


CHART 12. - A.C. - ENDOCARDITIS.

Case 16. J.W. Boy, aged 11 years: history of "sore throats" and "growing pains" for three years; "sore throat" and headache for one week before admission; short apical systolic but no cardiac enlargement; no fever; M.-S.R. only slightly increased (12 mm.), and had fallen to 3 mm. before dismissal one month later.

Case 17. J.M. Boy, aged 6 years: scarlet fever in 1933; in hospital from October to November, 1935, with "growing pains," but no cardiac involvement; readmitted in February, 1936, with complaint of lassitude and night sweats; systolic murmur heard at all areas, but no evidence of active rheumatism; dismissed after one week in hospital; M.-S.R. normal (5-6 mm.).

Case 18. I.W. Girl, aged 12 years: endocarditis and pericarditis in 1934, but had kept well since; admitted for tonsillectomy in April, 1936; no cardiac enlargement or nodules; soft mitral systolic murmur; M.-S.R. 5.5 mm., rose to 7.5 mm. four days after tonsillectomy, and was 3.5 mm. before dismissal.

Case 19. U.K. Girl, aged 11½ years: no rheumatic history; complaint of precordial pain and palpitation; examination showed tachycardia and a short non-conducted systolic murmur, but no cardiac enlargement, nodules, or arthritis; dismissed as "non-rheumatic"; M.-S.R. normal (2 mm.).

Case 20. C.B. Girl, aged 9 years: admitted in October, 1935, with acute arthritis and endocarditis; while in hospital, irregular fever, splenic enlargement, and streptococcus isolated on blood culture; diagnosis of subacute bacterial endocarditis made; M.-S. readings commenced in January, 1936, and performed weekly for two months, showed consistently high value, varying from 31.5 mm. to 38 mm.; patient was removed by her parents, against advice, in a seriously ill condition.

Case 13 illustrates well the effect of congestive heart failure on the M.-S.R. So long as oedema was present, the M.-S.R. remained below the upper limit of normal readings, but when the oedema was dispersed by the use of Salyrgan, there was an immediate rise in the rate. Thus in congestive heart failure the M.-S.R. would appear to behave in a contrary manner to that found in the ordinary case of endocarditis, as clinical improvement is at first associated with a rise in the rate instead of a fall. Case 14 shows the slow fall in the rate as the patient improves, a normal reading being obtained when fever has been absent for some weeks. Case 15 is of particular interest, as a steady rise in the M.-S.R. was present for a month before a relapse occurred, showing that the apparent clinical improvement was only temporary. The M.-S.R. could be said to have had a definite value in this case. In Cases 16 to 18 the M.-S.R. was useful in confirming the clinical finding of quiescence of the rheumatic infection. In Case 18 the rate was normal even after tonsillectomy, which, as far as my observations go, causes a rise of M.-S.R. in the majority of rheumatic subjects. Case 19 is included to show the use of the M.-S.R. in helping to disprove a diagnosis of rheumatism in a doubtful case. In Case 20, subacute bacterial endocarditis had followed the original rheumatic infection, and the M.-S.R. was, as might be expected, high, but did not give information of any greater value than could be discovered by ordinary clinical examination.

CHOREA.

This group comprises twenty-eight cases in which chorea was the principal manifestation of the rheumatic infection. Approximately one-half of these cases showed no evidence of rheumatic activity other than chorea (Table 25), while the other half showed signs suggestive of other forms of rheumatism, such as carditis (Table 26). Summaries are given of certain illustrative cases in each group.

Table 25.

Uncomplicated Chorea.

M.-S.R. never exceeded	No. of Cases
5 mm.	5
10 mm.	8
15 mm.	2
Total:	15

Illustrative Cases:-

Case 21. J.S. Boy, aged 10 years: chorea in June, 1935, and again in October, 1935; return of chorea in January, 1936; admitted in February, 1936; no evidence of cardiac involvement; signs of chorea had disappeared within a fortnight; M.-S.R., performed at weekly intervals till 21.4.36, did not exceed 5 mm.

Case 22. A.McG. Girl, aged $5^{10}/12$ years: chorea for one month before admission; no previous attacks; no cardiac involvement; chorea persisted for almost three months; M.-S.R. at no time rose above 10 mm., even following tonsillectomy (See Chart 13).

Case 23. D.H. Boy, aged $5^{9}/12$ years: scarlet fever in October, 1935; admitted in March, 1936, with severe chorea, which had developed suddenly; no cardiac involvement; M.-S.R. did not exceed 10 mm., except after tonsillectomy, when it rose to 15 mm., falling to a normal value eighteen days after the operation.

Case 24. E.B. Girl, aged $7^{8}/12$ years: scarlet fever in 1934; chorea in May, 1935; admitted in June, 1936, with history of chorea for two months; no cardiac involvement; M.-S.R. 12 mm., but fell to 6 mm. within one week, and was not subsequently raised above normal.

A normal microsedimentation rate is therefore the usual finding in cases of chorea, where there is no evidence of the presence of any other rheumatic manifestation. Cases 23 and 24 are given to show exceptions to this rule. In Case 23 tonsillectomy was responsible for raising the rate above normal, and the rise was slight and transitory. This finding differs from that in Case 22, as in the latter there was no rise in rate after tonsillectomy. In Case 24 the first M.-S. reading fell slightly over the upper limit of normal, but subsequent readings were within it.

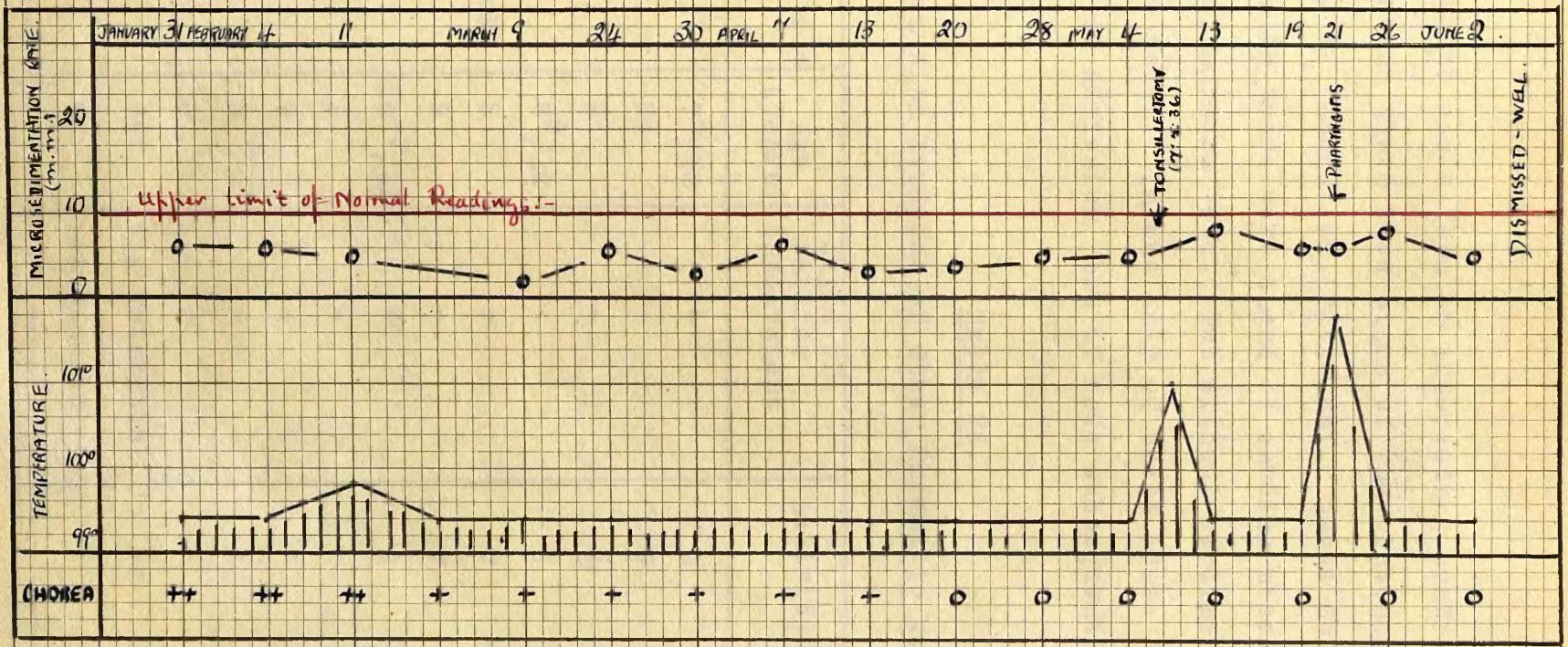


CHART 13 - A. M^c G. - UNCOMPLICATED CHOREA.

These cases form an interesting contrast to the next group, in which there were signs of the presence of one of the other forms of rheumatism (Table 26). Cases 25 to 31 were all cases in which there were signs of cardiac mischief such as tachycardia, murmurs, etc., but without cardiac enlargement, nodules, or fever. In one only of these (Case 25) the M.-S.R. was normal on admission, but it rose subsequently on one occasion.

Table 26.

Chorea with Evidence of Other Rheumatic Manifestations.

Case	Initials	Age (years)	Signs of cardiac involvement	Activity	M.-S. Rate	
					Initial	Highest Value
25	P.T.	$7^{6}/12$	+	0	7	15
26	L.L.	$8\frac{1}{2}$	+	0	13.5	13.5
27	M.T.	8	+	0	15.5	20.5
28	M.M.	$7^{8}/12$	+	0	14	14
29	M.McN.	8	+	0	10.5	18
30	E.B.	9	+	0	11	31
31	E.S.	$10^{10}/12$	+	0	13	13
32	S.T.	6	+	+	28	28
33	E.P.	9	+	+	20	20
34	D.D.	8	+	+	39	39
35	M.D.	10	+	+	28	28
36	J.G.	$7\frac{1}{2}$	+(& arthritis)	++	30.5	34
37	C.B.	9	+(& nodules)	+	10	14

Case 25. P.T. Boy, aged $7^{6}/12$ years: chorea present on admission (3.12.35) also apical systolic murmur; no fever, cardiac enlargement, or nodules; M.-S.R. within limits of normal, except on 23.1.36 (See Chart 14), when there was no chorea, no fever, and a normal pulse-rate.

The initial M.-S. value in Cases 26, 28 and 31 was also the highest value recorded. The rate in all three cases had fallen to normal within a fortnight, and did not subsequently rise. Case 26 is typical:-

Case 26. L.L. Girl, aged 8½ years: arthritis in February, 1936; chorea commenced at the end of March, 1936; admitted on 14.4.36; soft systolic murmur at all areas; no arthritis, nodules, or fever; M.-S.R. slightly raised on admission (13.5 mm.), but fell to normal five days later.

Three cases, Cases 27, 29 and 30, showed their highest M.-S. value following tonsillectomy, prior to which the rate had been normal. Case 30 is given as an illustration of this:-

Case 30. E.B. Girl, aged 9 years: chorea in January, 1936, lasting six weeks, systolic murmur noted; second attack of chorea in May, 1936; admitted in June, 1936; chorea very slight; loud systolic murmur all areas, conducted to axilla; no cardiac enlargement or fever; M.-S.R. 11 mm. on admission, fell below upper limit of normal in five days, thereafter tending to vary within the limits of normal, or slightly over it; sharp rise in rate after tonsillectomy, with gradual fall, taking three weeks to reach normal (See Chart 19).

Cases 32 to 37 were all cases in which the cardiac involvement accompanying the chorea was considered clinically

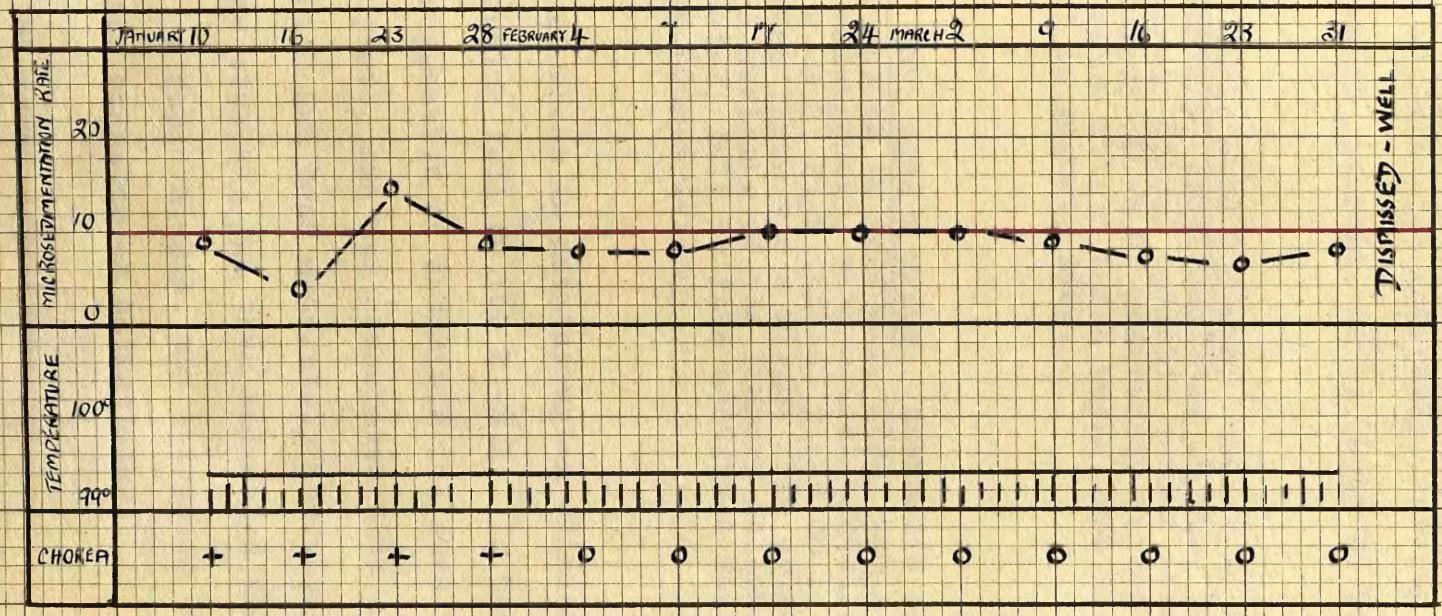


CHART 14. - P. T. - CHOREA with CARDIAC INVOLVEMENT (non-active)

to show signs of activity. The M.-S.R. in all these cases, with one exception, was high initially, falling gradually as clinical improvement occurred, as is shown by Cases 33 and 34.

Case 33. E.P. Girl, aged 9 years: chorea in September, 1935, and again in February, 1936; admitted in May, 1936, with moderately severe chorea; mitral systolic murmur conducted to axilla; no fever or nodules; M.-S.R. moderately raised at first; reached normal value within three weeks, and did not again rise before dismissal in August, 1936.

Case 34. D.D. Boy, aged 8 years: rheumatic carditis in the summer of 1935; chorea in February, 1936; admitted on 13.3.36; slight cardiac enlargement, with mitral systolic murmur and triple rhythm; M.-S.R. high initially (39 mm.); fell gradually till 28.4.36, when there was a slight rise coinciding with slight fever and swelling of the fingers following the stopping of salicylates; fall in rate continued when salicylates were again given (Chart 15).

Case 33 shows an uninterrupted clinical improvement, with a corresponding fall in the M.-S.R. In Case 34, on the other hand, a suggestion of arthritis followed the stopping of sodium salicylate, and was associated with a slight rise in the M.-S.R., which had been moderately increased when the salicylates were stopped, and thus indicated that activity was still present. A rapid M.-S.R. may therefore be a contra-indication to the stopping of salicylates.

Case 37 is of some interest:-

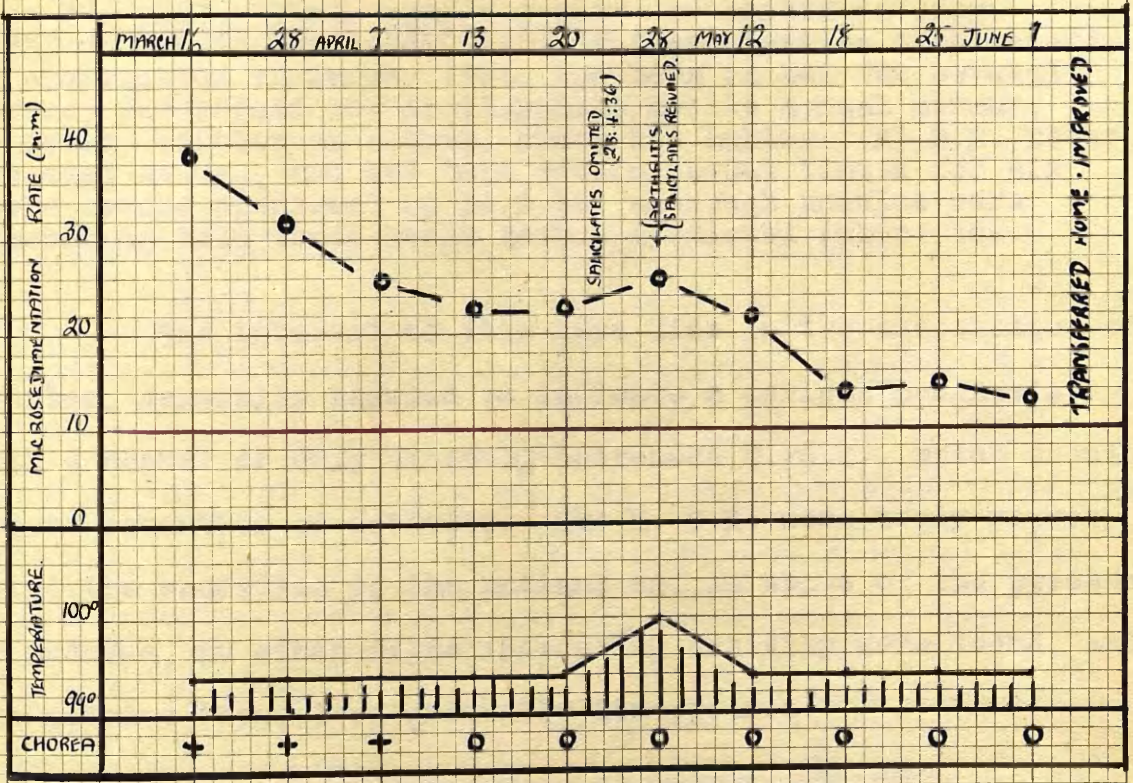


CHART 15 - D.D. - CHOREA with CARDIAC INVOLVEMENT (Active).

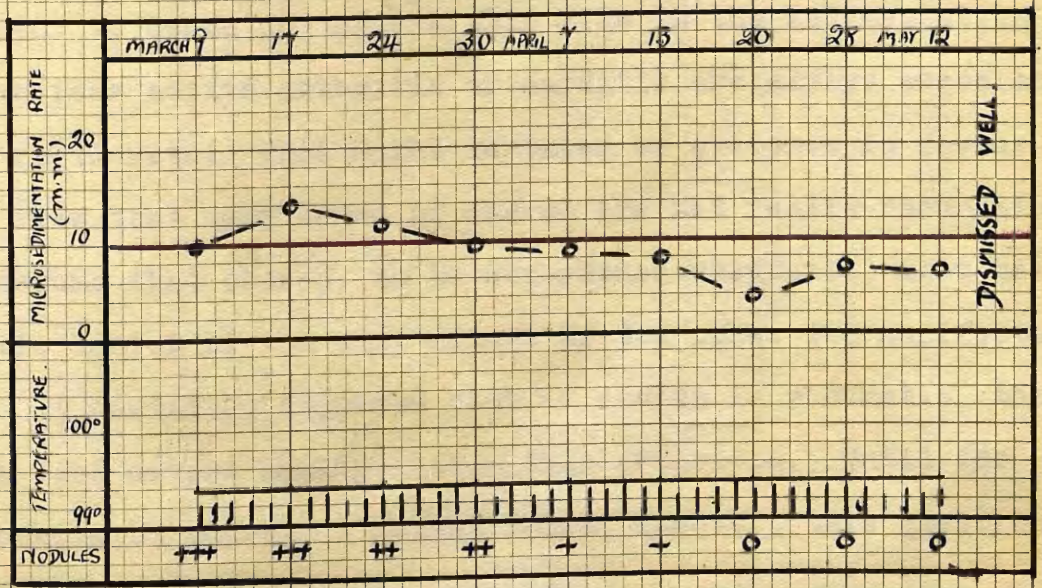


CHART 16. - C.B. - SUBCUTANEOUS RHEUMATIC NODULES.

Case 37. C.B. Girl, aged 9 years: arthritis in July, 1935; chorea in September, 1935, without cardiac involvement; on examination in March, 1936, had been in bed for several months; pulse-rate not accelerated; double apical murmur; no fever; nodules on elbows, knees and ankles; M.-S.R. never exceeded 14 mm., and had been within normal limits for six weeks before dismissal on 15.5.36, although nodules were present up till three weeks before dismissal (Chart 16).

The interest of this case lies in the association of nodules, generally assumed to indicate a serious prognosis, with a normal or only slightly increased M.-S.R., which should denote cessation of activity. The M.-S.R. more truly represented the condition of the patient as, in spite of the presence of nodules, no other signs indicating activity were found, and the nodules themselves gradually disappeared.

General Remarks on Chorea.

It is interesting to find that chorea by itself does not appear to cause any appreciable rise in the sedimentation rate, whereas active arthritis or carditis are always associated with a rapid rate. This might be taken as evidence in favour of the view that many cases of chorea are not really rheumatic, if we assume that chorea, to be considered rheumatic, must be a rheumatic lesion of the same nature as the other two manifestations. It certainly suggests that if chorea is rheumatic, then it is a less severe manifestation than arthritis. Until the pathogenesis of chorea is better known, however, this question is unlikely to be definitely settled.

The practical value of the microsedimentation rate in

chorea is to indicate when other manifestations of the rheumatic infection, which may be associated with the chorea, are active, and when their quiescence can safely be assumed.

The Effect of Tonsillectomy in Rheumatic Patients.

Mention has already been made in the foregoing pages of cases in which the M.-S.R. rose following removal of the tonsils and adenoids. Particulars of twelve such cases are given in Table 27, showing the rate before and after tonsillectomy, and the time taken for it to return to a normal value. As the subject is of some interest, short notes on each case will also be given.

Table 27.

Tonsillectomy in Rheumatic Subjects.

No.	Initials	Type of Rheumatism	M.-S.R. (mm.).		Time taken to return to normal
			Before T.& A.	After T.& A.	
I	R.M.	Arthritis	17.5	26.5	2 weeks
II	M.M.	Arthritis	2.5	23	2 weeks
III	R.McE.	Arthritis	4	15.5	2 weeks
IV	W.L.	Arthritis	5	18	2 weeks
V	W.A.	Chorea	9	14	2 weeks
VI	D.H.	Chorea	4	15	2 weeks
VII	E.B.	Chorea	7	31	3 weeks
VIII	M.McN.	Chorea	5	18	3 weeks
IX	M.T.	Chorea	10	20.5	(see footnote *)
X	A.McG.	Chorea	5	8	-
XI	J.D.	Chorea	10	10	-
XII	I.W.	Carditis	5.5	7.5	-

(*Note:- No. IX was dismissed one week after tonsillectomy, on account of an outbreak of measles in the ward).

No. I. R.M. Boy, aged 4 years. This case has already been considered on page 94, and was the only instance of the M.-S.R. being over normal values before tonsillectomy. The raised value was isolated, associated with a slight degree of fever, and did not appear to be a contra-indication to the operation, as the rate fell to normal within the average time.

No. II. M.M. Girl, aged 6½ years. The M.-S.R. had given normal readings for one month before tonsillectomy. The rise after the operation was associated with slight fever, and temporary acceleration of the pulse-rate (Chart 17).

No. III. R.McE. Boy, aged 9 years. Definite evidence of cardiac involvement. No fever after tonsillectomy, and rise in M.-S.R. slight and temporary.

No. IV. W.L. Boy, aged 9 years. Soft systolic murmur, but no enlargement of the heart. Slight rise of temperature following the operation, associated with the slight rise in M.-S.R.

No. V. W.A. Boy, aged $5^{7}/12$ years. No evidence of rheumatic manifestations other than chorea; consistently normal M.-S.R. before tonsillectomy, with only very slight rise after the operation, associated with slight fever.

No. VI. D.H. Boy, aged $5^{9}/12$ years. As with No. V, there was no evidence of rheumatism apart from the chorea, and the rise in M.-S.R. was slight and transient (Chart 18).

No. VII. E.B. Girl, aged 9 years. Apical systolic murmur in addition to the chorea, and the M.-S.R. showed slightly raised values on more than one occasion. Some fever after the operation,

TONSILLECTOMY in RHEUMATIC SUBJECTS.

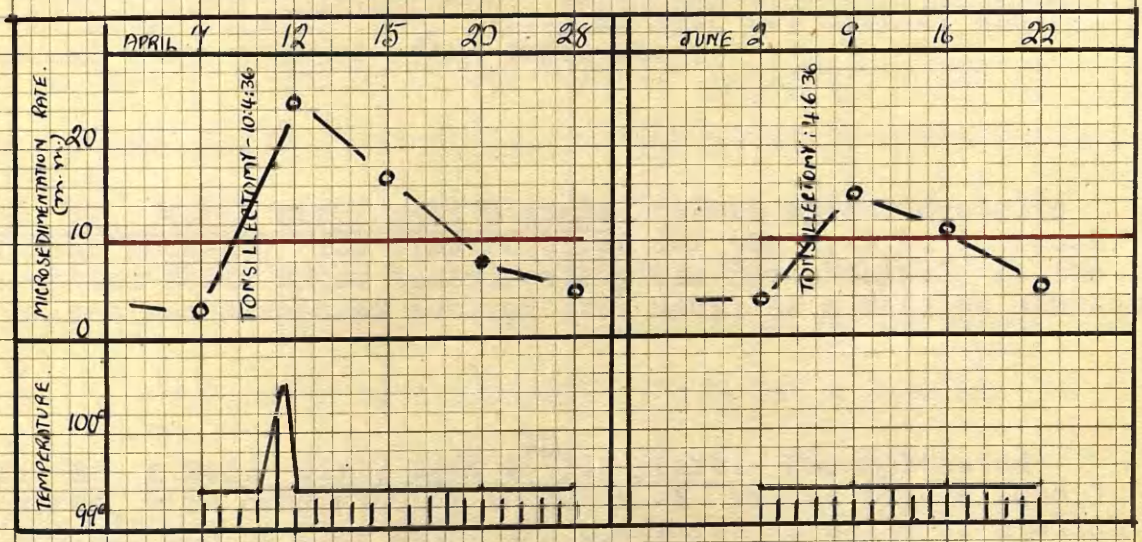


CHART 17 - M.M. - ARTHRITIS.

CHART 18. - D.H. - CHOREA.
(Uncomplicated)

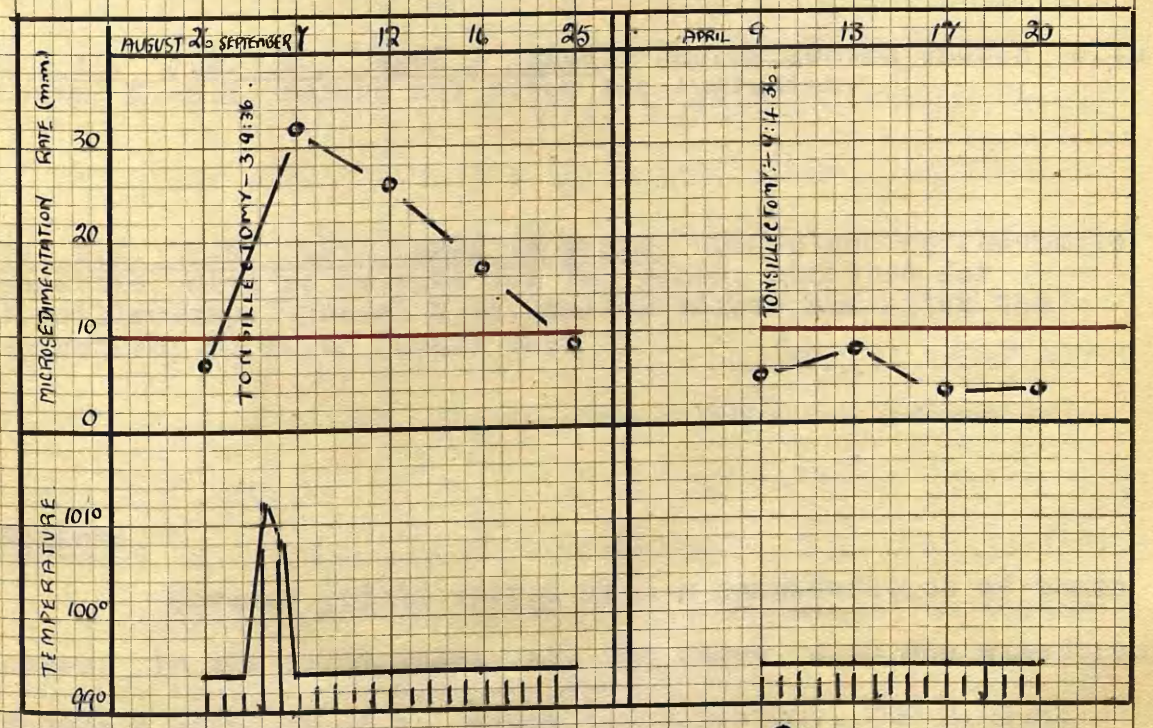


CHART 19 - E.B. - CHOREA.
(With Cardiac Involvement)

CHART 20 - I.W. - CARDITIS.
(Old-standing).

No. VIII. M.McN. Girl, aged 8 years. No evidence of rheumatism other than chorea. Fever and accelerated pulse-rate after tonsillectomy; M.-S.R. rise not marked, and normal value reached after three weeks.

No. IX. M.T. Girl, aged 8 years. Short apical systolic murmur present. The time required for the M.-S.R. to reach a normal value after tonsillectomy was not obtained, as the patient was dismissed earlier than usual as a measles contact.

No. X. A.McG. Girl, aged $5\frac{10}{12}$ years. Uncomplicated chorea, with consistently normal M.-S. values before tonsillectomy, and no rise after the operation in spite of a slight degree of fever.

No. XI. J.D. Boy, aged 7 years. Uncomplicated chorea, with normal M.-S.R. before and after the operation.

No. XII. I.W. Girl, aged 12 years. Old-standing rheumatic carditis, with no relapse for two years; admitted for tonsillectomy. Normal M.-S. values before and after the operation; no fever (Chart 20).

Remarks.

Several points emerge from a consideration of these cases. In the first place, all the cases, with one exception, showed a normal M.-S.R. before tonsillectomy, the M.-S.R. thus agreeing with the clinical finding that the rheumatic infection was quiescent. The exception (No. I) had shown a

normal M.-S.R. up to the day before operation, when there was a slight rise of temperature for no apparent cause, which had disappeared by the following morning. This upset was not considered to be sufficiently serious to require postponement of the operation, and no ill-effects were observed. The M.-S.R. rose after the operation to quite a high value, but returned to normal within the average time of two weeks.

Following tonsillectomy, there was a rise in the M.-S.R. in all patients who had a history of recent active rheumatic arthritis or carditis, but a normal value was recorded as a rule after two weeks, or, at the most, three weeks. Two cases of apparently uncomplicated chorea (Nos. V and VI) showed a rise after operation, but in both this rise was only slight, and in two other similar cases (Nos. X and XI) the rate remained within the normal range. Patient No. XII had suffered from endocarditis and pericarditis two years prior to the operation, but had kept well since then. In this case the absence of any post-operative rise in M.-S.R. might be regarded as a confirmation of the quiescence of rheumatic activity.

In all the cases in which the M.-S.R. rose following the operation there were associated signs of slight constitutional upset. Such signs were also found in one case of uncomplicated chorea, although the M.-S.R. did not exceed normal values. It would seem that the rise in rate in these

rheumatic patients was due rather to the trauma caused by the operation, than to any relapse of the rheumatic infection, as it is very unlikely that the latter would subside within such a short period as two to three weeks. It was hoped to include in this section figures for the M.-S.R. before and after tonsillectomy in non-rheumatic subjects. Unfortunately, the latter are not kept in hospital for more than forty-eight hours, and it was found that the full extent of the rise in M.-S.R. was not evident until some days after the operation.

It would appear reasonable to conclude that, in spite of Case No. I, normal M.-S. readings are advisable before the removal of tonsils and adenoids in a rheumatic patient; and that estimation of the rate after the operation gives an indication of the degree of traumatic upset, and of the time when the patient can be considered completely recovered.

SUMMARY OF FINDINGS.

In all cases of rheumatic arthritis and carditis, where the infection was believed to be clinically active, the M.-S.R. was markedly increased. As clinical improvement took place, the M.-S.R. fell slowly, but took longer to reach normal values than the other evidences of activity, such as the temperature and pulse-rate.

An increase in the M.-S.R., or a persistently raised M.-S.R., tended to indicate continued activity, in spite of the lack of signs and symptoms..

Low M.-S. values were found in the presence of congestive cardiac failure.

A M.-S.R. within normal limits was the customary finding in cases of uncomplicated chorea.

In most cases with a recent history of rheumatic arthritis or carditis, a temporary rise in the M.-S.R. was found following tonsillectomy.

II. TUBERCULOSIS.

Tuberculosis and rheumatism are the two diseases in which the estimation of the sedimentation rate gives the greatest promise of value. Of the two, tuberculosis has, as regards sedimentation, been the most studied, as the test is in routine use in many sanatoria, and thus observations have been made on tuberculous patients for considerable periods. The vast proportion of this work has, however, been performed on the disease as it occurs in adults, and relatively few observations on juvenile tuberculosis are available.

The following is a brief review of the literature, arranged in chronological order:-

In 1931, WESTERGREN,[129] in repeated observations on three hundred and sixty-nine male patients, found no single examination of an active case giving a value approximately normal, while the degree of increase of the sedimentation rate corresponded surprisingly well with the extent of activity which the process might be presumed to possess. He was of opinion that the sedimentation rate was a considerably more reliable measure of the activity of the tuberculous process than the temperature, and that, although not a specific reaction, it could very likely have a diagnostic value in tuberculosis. Thus, in a case where tuberculosis was suspected but no real fever present, and where certain diseases which, like tubercle, affected the sedimentation, could be left out, a pathological value of the sedimentation rate appeared strongly suggestive of tuberculosis. On the contrary, with a normal rate, active phthisis could probably be excluded. The test was valuable in prognosis, as real improvement led to a decrease in the rate, while improvement without decrease was, as a rule, temporary.

In 1925, COOPER,[16] ZECKWER and GOODELL,[136] POPPER and KREINDLER,[105] and BOCHNER and WASSING[6] all reported rapid sedimentation rates in pulmonary and other forms of tuberculosis, and considered the test of value in prognosis, but not to any extent in diagnosis. The last-named pair of observers spoke of the sedimentation as a state or

condition, like fever, and suggested that in chronic tuberculosis it played a similar part to that of the complement-fixation test in syphilis.

In 1926, CUTLER,[18] using his own "graphic" method, stated that the sedimentation rate was a more reliable index of the presence or absence of activity in tuberculosis than the temperature, pulse-rate, gain in weight, or physical signs. He noted a tendency for the rate to fall shortly before death in some cases.

In 1927, FLACK and SCHEFF,[24] comparing the differential white blood count, the skin sensitiveness and the sedimentation rate in twenty-eight cases, found that the last-named was more sensitive to the specific stimulation than was the focal reaction, and more adaptable in establishing certain rules concerning the reactions of the organism than the skin sensitiveness. The differential white blood picture was, however, more sensitive to specific stimulation than the temperature and the sedimentation rate.

In 1928, TOWNSEND and ROGERS,[124] working on cases of pulmonary tuberculosis, considered that there was a parallelism between the severity of the disease and the increase in the sedimentation rate, improvement in the patient's condition leading to a decrease in the rate, and vice versa. Like Cutler, they reported a fall in the rate in certain cases shortly before death.

On the other hand, PINNER, KNOWLTON and KELLY[100] obtained normal rates of sedimentation in five out of forty-two patients with active tuberculosis, from which they concluded that a considerable percentage of patients with active tuberculosis had a normal rate, and that, therefore, the test was diagnostically and prognostically almost without value.

In 1929, SCHLOSS and MILLER[118] used the sedimentation test in association with a serum reaction, the latter involving the use of a water-soluble extract of the tubercle bacillus called "Tubercumet." In one hundred and thirty-six out of one hundred and forty-seven cases the combination of the sedimentation rate and the serum reaction was found to give pictures closely approximating to those determinable by the usual methods of diagnosis.

In 1930, CROCKET[17] stated that the sedimentation rate was practically always increased pari passu with the toxaemia, and that it approached normal as the resistance improved and the disease became quiescent. A high reading in an individual with a previously good reading presaged an exacerbation.

In 1932, ROCHE[112] gave as his opinion that monthly sedimentation tests were as essential as repeated recording of the temperature and pulse-rate. Low rates could be generally regarded as of good prognostic significance, although, in emaciated patients with very advanced disease, relatively low readings were almost invariable. He considered that the test

was of proven value in the management of cases of pulmonary tuberculosis, and that strict limitation of the patient's activities until the sedimentation had fallen to "slightly increased" rates would greatly minimise the risk of relapse.

In 1933, LANDAU,[68] from observations made on two hundred children of all ages, suffering from various forms of tuberculosis, considered that the sedimentation rate materially affected the endeavour to fix the time when the activity of the tuberculous process ended. When another infective process supervened, the rate rose, and remained high for some time after the process had finished. He suggested that if the diminished activity in the tuberculous process, marked by the descending sedimentation curve, should prove to indicate a cessation of the bacillary secretion, the attainment of a normal rate would be a valuable indicator that danger of infection was terminated, and a much more convenient and rapid method than gastric lavage. In pleurisy he found high sedimentation values as a rule, the rate remaining high for a long period after the temperature had subsided; while in pulmonary tuberculosis he noted no rise, or only a slight rise in the cirrhotic processes, but a more decided rise in the exudative, pneumonic or cavernous conditions, according to activity. In miliary tubercle and tuberculous meningitis the rate varied considerably, rising in most cases, but in others showing low values. Ante-mortem, there was sometimes a rise, and sometimes

a fall. He concluded that the sedimentation test was of little value in the diagnosis of a tuberculous infection, but was of great assistance in judging the activity of such a process, once it had been diagnosed.

In the same year FRIEDLANDER[30] made observations on children by means of the Langer-Schmidt micromethod, finding a high rate in all cases of the exudative forms of tuberculosis. Out of forty-eight cases with tubercle bacilli in the stomach lavage, thirty-one gave high sedimentation values, and seventeen normal values, and he therefore advised caution in placing any great reliance on the test in diagnosis. Four cases of tuberculous meningitis showed strikingly low rates even on admission to hospital, and in all cases before the end the rate fell to normal, even if it had risen slightly during the course of the disease. In thirty-three children with positive tuberculin reactions, admitted for observation, all of whom were found clinically healthy, the sedimentation rate, repeated at regular intervals, showed normal values in all thirty-three, and was thus of use in confirming the other findings.

In 1934, REILLY[109] performed sedimentation tests on thirty-six tuberculous girls, aged between eight months and fourteen years. He found that thirty-one out of thirty-three of these patients who were considered clinically active had an increased rate; and believed that, compared with other laboratory tests for activity, the sedimentation rate indicated pathological

effects much more frequently. FREEDMAN,[27] from observations made on two hundred and fifty cases of pulmonary tuberculosis, considered that the test was of aid in the differential diagnosis of early and doubtful cases, giving normal values in all cases discharged as non-tuberculous.

In 1935, WALLGREN[126] emphasised that all other factors should be taken into consideration when judging the condition of a tuberculous lesion by the sedimentation test, as the latter was also affected by commonplace infections. He was of the opinion that a child with primary tuberculosis should generally be kept in bed until the sedimentation was normal, and that thereafter the amount of exercise to be allowed should be guided by its effect on the rate. In common with other observers, he noted that the raised rate was maintained for a month, or, in more severe cases, months after the fever had disappeared.

In 1936, REICHEL,[107] writing on the sedimentation test in juvenile tuberculosis, stated that in erythema nodosum very high readings were the rule, in tuberculosis generally the rate was over normal, and that a high rate was the customary finding in miliary tuberculosis and tuberculous meningitis. Later in the same year HOUGHTON,[57] from observations on two thousand cases of pulmonary tuberculosis, believed that the sedimentation rate was a valuable indication of disturbed metabolism and of the constitutional disturbance resulting from tuberculosis, and as such had a definite place in the blood picture.

Personal Observations.

The cases on which observations were made numbered in all twenty-eight, and were composed as follows:-

Glandular tuberculosis	-	Five cases.
Primary lung tuberculosis	-	Four cases.
Pleurisy with effusion	-	Two cases.
Renal tuberculosis	-	One case.
Miliary tuberculosis and tuberculous meningitis	-	Fourteen cases.
Erythema nodosum	-	Two cases.

Observations on these conditions were not sufficiently numerous to give satisfactory conclusions, because in the event of a definite diagnosis of tuberculosis being made the case was notified, and transferred to a Corporation hospital. Certain other cases were transferred to the surgical wards for operation, while many of the cases with miliary tuberculosis and meningitis were acutely ill when admitted to hospital, and died within a short time afterwards.

GLANDULAR TUBERCULOSIS.

The features of five cases of glandular tuberculosis are given in Table 28, while in Table 29 a series of ten cases with non-tuberculous glandular swellings is given to serve as a contrast.

Table 28.

Glandular Tuberculosis.

Case	Initials	Age (yrs.)	Glands enlarged in				Skin Tests	Range of M.-S.R. (mm.)	Result
			Neck	Abdomen	Axillae	Groins			
38	W.H.	5/12	++	0	+	++	++	30-35	Transferred to Corporation Hospital
39	D.C.	2½	++	++	++	+	+++	30-35	Transferred to Corporation Hospital
40	E.K.	1 1/12	+	+++	+	+	-	20-25	Transferred to Corporation Hospital
41	T.N.	3 4/12	+	++	0	0	+	20-25	Transferred to Surgical Ward
42	B.W.	2½	+	+++	0	0	++	25-30	Transferred to Surgical Ward

Cases 38, 39 and 40 were notified as "glandular tuberculosis," and in Cases 41 and 42 the diagnosis of tuberculous abdominal glands was confirmed at operation.

All the cases of glandular tuberculosis (Table 28) showed a markedly increased M.-S.R., the highest values being found in the three cases (Cases 38, 39 and 42) with the most definitely positive skin tests. Only one case, Case 40, had negative skin tests, but the clinical findings were strongly suggestive of abdominal tuberculosis. The question arises whether this rapid M.-S.R. in glandular tubercle would be of assistance in the differential diagnosis of glandular swellings.

Table 29.

Non-Tuberculous Glandular Swellings.

Case	Initials	Age (yrs.)	Glands enlarged in				Skin Tests	Range of M.-S.R. (mm.)	Disease
			Neck	Abdomen	Axillae	Groins			
I	N.I.	$6^{5}/12$	++	0	+	+	-	5-15	Anorexia
II	A.W.	$7^{6}/12$	++++	+	++++	+	-	38-42	Lymphadenoma
III	R.M.	4	++	0	0	0	-	30-40	Tonsillitis (acute)
IV	M.R.	11	++	0	0	0	+	20-30	Tonsillitis (acute)
V	P.B.	$2\frac{1}{2}$	++	0	0	+	-	5-10	Tonsillitis (quiescent)
VI	M.O.	$2\frac{1}{2}$	+	0	+	+	-	5-10	Tonsillitis (quiescent)
VII	A.C.	$^{7}/12$	+	0	+	+	-	5-15	Tetany
VIII	T.H.	$2^{9}/12$	++	0	0	0	-	15-30	Tonsillitis (acute)
IX	A.McK.	$4^{11}/12$	++	0	+	+	-	20-40	Lymphatic leukaemia
X	R.C.	$2^{8}/12$	0	++	0	+	-	25-35	Retroperitoneal abscess

Table 29, which has been given for purposes of comparison, includes various non-tuberculous cases, in which enlargement of the lymphatic glands was present. Cases II and IX in that table show two diseases, in which the differential diagnosis from tuberculosis often arises, namely lymphadenoma and lymphatic leukaemia. The M.-S.R. in both instances was high, and would not, therefore, have helped to

distinguish the conditions. This was also the case with acute tonsillitis (Cases III, IV, and VIII), and with Case X, where a palpable mass in the abdomen proved to be a retroperitoneal abscess. The other cases in Table 29 all showed a M.-S.R. lower than that found in glandular tuberculosis, and this finding might possibly be of use in confirming the absence of active tuberculous infection in enlarged glands.

It cannot be claimed, however, that the M.-S.R. is a means of differentiating glandular enlargement due to tuberculosis from that caused by other conditions, as any severe toxaemia would appear to cause an increase in the rate.

PRIMARY LUNG TUBERCULOSIS.

The four cases included under this heading are given in Table 30, followed by short summaries of the case history.

Table 30.

Primary Lung Tuberculosis.

Case	Initials	Age (years)	Skin Tests	Range of M.-S.R. (mm).	State on Dismissal
43	A.M.	$8\frac{3}{4}$	++	15-20	Improved
44	C.W.	6	+	5-20	Improved
45	M.D.	$6^{10}/12$	+	15-25	Improved
46	J.McM.	5/12	++	5-20	I.S.Q.

Case 43. A.M. Boy, aged $8^{3}/12$ years. History of incontinence of faeces from the age of four years; enlarged glands in neck, groins and axillae; positive skin tests; X-ray showed marked increase in the hilum shadows and enlarged mediastinal glands; M.-S.R. moderately increased during two months' stay in hospital.

Case 44. C.W. Girl, aged 6 years. Family history of tuberculosis; cough, night sweats and pain in the chest for two months; X-ray showed infiltration along the interlobar sulcus with increased mediastinal shadows; skin tests positive; no fever; M.-S.R. 18 mm., reached normal value after five weeks; but rose to 16 mm. one month subsequently, when X-ray showed fluid still present between the lobes of the lung; before dismissal, when the chest was apparently clear and the child well, the M.-S.R. had again fallen to a normal value (Chart 21).

Case 45. M.D. Girl, aged $6^{10}/12$ years. Mother died of phthisis while patient was in hospital; five months' history of anorexia; sweating and cough for a few days before admission; deficient breath sounds with rale in right lung; skin tests positive; no fever; M.-S.R. moderately increased during stay in hospital, without giving any reading higher than 22.5 mm., still raised (17 mm.) after two months' rest in bed.

Case 46. M.McM. Girl, aged 5/12 years. History of loss of weight and cough for one month; enlarged glands in neck and axillae; markedly positive skin tests; enlarged liver and spleen; impaired percussion note with rhonchi in right lung; radiologist reported "tuberculosis"; M.-S.R. initially 25 mm., fell to 19 mm. at the end of one week, and showed normal reading after three weeks, when child was notified as "pulmonary tuberculosis" and transferred to a Corporation hospital.

Remarks.

All four cases showed a raised M.S. value on admission to hospital. In two cases the rate fell to normal before dismissal, while in the other two it was still slightly raised. The data are insufficient to enable any conclusions to be drawn as to the value of M.-S. readings in this type of case.

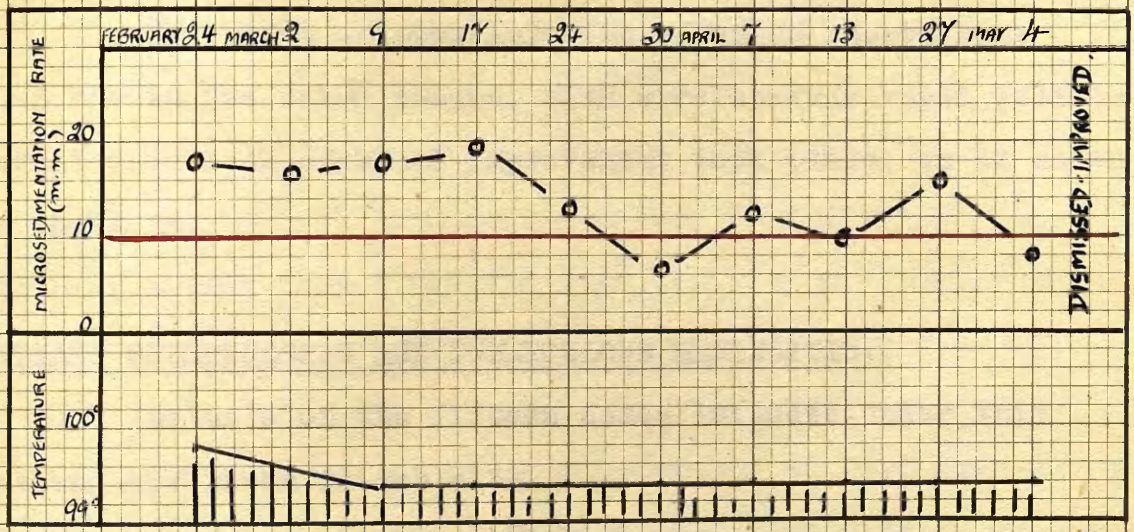


CHART 21 - C.W. - PRIMARY LUNG TUBERCULOSIS.

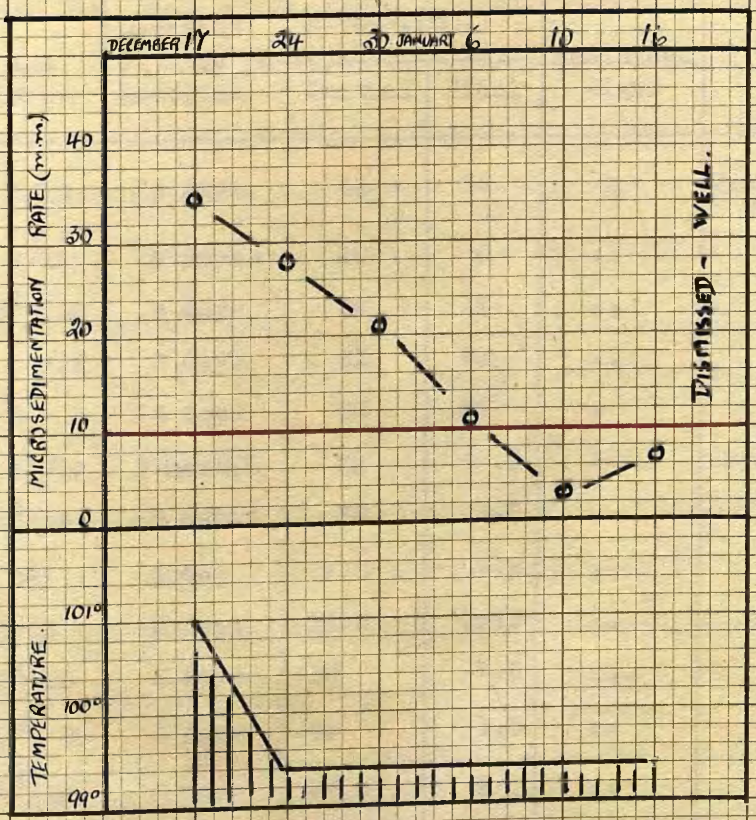


CHART 20. - I.E. - PLEURISY with EFFUSION.

PLEURISY WITH EFFUSION.

Two cases of pleurisy with effusion showed high M.-S.R's in the acute stages, with a relatively rapid fall to normal values as clinical improvement took place, as is shown in Chart 22.

MILIARY TUBERCULOSIS AND TUBERCULOUS MENINGITIS.

Details of the fifteen cases included under this heading are given in Table 31.

Table 31.

Miliary Tuberculosis and Tuberculous Meningitis.

Case	Initials	Age (yrs.)	Duration of stay in hospital	M.-S.R.(mm.)		Meningeal Signs	Result
				Initial	Final		
47	J.G.	7/12	14 days	40	34	+	Transferred to Corporation Hospital
48	H.R.	8/12	4 days	15	0	++	Died
49	R.V.	$5^{11}/12$	8 days	22	19	+++	Died
50	M.G.	4/12	3 days	21	21	++	Died
51	S.L.	5	14 days	32	28	+	Died
52	W.H	11/12	2 months	33	14.5	+	Irregular dismissal
53	W.McD.	$1^{9}/12$	8 days	20	1.5	++	Died
54	R.R.	$3\frac{1}{2}$	1 day	9.5	9.5	++	Died
55	N.A.	8/12	2 days	10.5	10.5	++	Died
56	J.S.	$2^{4}/12$	5 days	15	7.5	+++	Died
57	J.C.	$1^{11}/12$	5 days	26	1.5	++	Died
58	M.McA.	$1^{4}/12$	6 days	27	9	++	Died
59	R.C.	$2^{7}/12$	6 days	23	22	++	Died
60	M.W.	$8^{2}/12$	7 days	23	13	++	Died
61	I.B.	$1^{4}/12$	10 days	9	21.5	++	Died

The majority of these cases were seriously ill on admission, and their stay, therefore, short; one case only (Case 52) being in hospital for more than a fortnight. The latter was admitted with a tuberculous bronchopneumonia, and the M.-S.R. at this stage was high (i.e. over 30 mm.), but, with the gradual development of miliary tubercle, the rate commenced to fall, and was only slightly increased when he was irregularly dismissed. It is interesting to note that the only other cases in which the initial M.-S.R. was over 30 mm. were the two (Cases 47 and 51) with the next longest duration of stay in hospital; and that, also, these were the patients in whom the signs of meningeal involvement were least marked. In general, the initial M.-S.R. was not as rapid as might have been expected from the seriousness of the patients' condition; and, furthermore, the tendency was for the rate to <u>fall</u> as the condition became worse.

In two cases, in which a M.-S. reading was obtained within an hour or two of death (Cases 48 and 57), a very low value was recorded; Case 48 showing no sedimentation whatever at the end of an hour. This last finding was very exceptional, and was the only occasion on which a complete absence of sedimentation was observed. At the time when the reading was taken the child was "in articulo mortis," and it is possible that the power of sedimentation is lost in certain cases at this stage. Only one case, Case 61, showed a rise in the

M.-S.R. before death (from 7.5 mm. to 21.5 mm.); while in Case 59 the rate remained much the same. In both these patients the final reading was taken within twenty-four hours of death. In Cases 49, 50, 51, 54, 55, and 58, where the M.-S.R. was performed from two to four days before death, a fall from the previous value occurred in Cases 49, 51, and 58, while death occurred in the remainder before the reading was repeated.

RENAL TUBERCULOSIS.

Case 62. D.McL. Boy, $5^{6}/12$ years. Markedly undernourished and badly cared-for child; admitted in convulsions on 19.12.35, with fever and pyuria; initial M.-S.R. high, 35 mm., falling with clinical improvement to 20.5 mm. one month later, when child dismissed as a chicken-pox contact. Readmitted on 23.2.36 in convulsions; M.-S.R. 19.5 mm., rose slightly two days later, but fell thereafter in association with clinical improvement, reaching a value of 10 mm. at the end of three weeks; transferred to surgical side, where, on laparotomy, the left kidney was found to be the seat of advanced tuberculous disease.

This case showed no particular point of interest, and the M.-S.R. and the clinical condition were in fairly close agreement.

ERYTHEMA NODOSUM.

Of recent years much attention has been given in the Scandinavian countries to erythema nodosum, and paediatricians there are agreed that the association of this condition with tuberculosis is almost invariable, their opinion being shared by the Glasgow paediatricians. WALLGREN[126] of Sweden considers that erythema nodosum makes its appearance simultaneously with the first clinical manifestation of tuberculosis in the organism. One would therefore expect to find high sedimentation rates in this condition, and such have been recorded (REICHEL[107]). Wallgren, however, described a "post-primary erythema nodosum tuberculosum,"[127] which could occur in tuberculous persons who had never had any previous eruption; and which ran its course in a much shorter time than the primary form, the sedimentation test, in particular, becoming normal remarkably quickly. LANDORF,[69] also, described a small minority of children with erythema nodosum, in whom even relatively strong injections of tuberculin failed to produce a reaction, and believed that in such cases the erythema nodosum might be a non-specific allergic phenomenon. The sedimentation rate in these cases showed a rapid fall when compared with that in the tuberculin positive.

Personal observations were obtained in two cases only:-

Case 63. H.D. Girl, aged 4 years. History of swellings on both legs for ten days; on admission erythema not marked; slight fever; skin-tests positive; M.-S.R. 19 mm., normal value (5 mm.) before dismissal, one month subsequently.

Case 64. W.F. Boy, aged 8 years. History of erythema for one week; fairly well-marked eruption on admission; no fever; skin-tests positive; M.-S.R. 22 mm., four days later rash beginning to fade; M.-S.R. 7.5 mm., and did not again rise above upper normal limit.

No deductions can be made from such small material, but it is interesting to find that in both these cases the M.-S.R. was not high initially; and that it fell to normal within a short period. Possibly they were examples of Wallgren's "post-primary" type.

SUMMARY OF FINDINGS.

The M.-S.R. showed a moderately increased or high value in all cases of definite tuberculous infection, except in certain cases where a fatal issue was imminent, when the rate fell to a slightly increased or normal value. The latter finding was common in the inevitably fatal forms of tuberculosis, such as generalised tubercle and meningitis, but was not invariable.

As has been stated earlier, these cases were not under observation for a sufficiently long time to permit of discovering whether the M.-S.R. varied in accordance with the clinical picture.

III. RESPIRATORY SYSTEM - NON-TUBERCULOUS DISEASES.

Few references to respiratory diseases, other than tuberculosis, have been found in the literature. LANDAU[68] did not perform microsedimentation tests on acute cases, as he considered that the other clinical findings gave more reliable information than the sedimentation rate; while REICHEL[107] stated that catarrhal infections in general showed an increased rate of sedimentation, which was parallel to the severity of the infection.

WINGFIELD and GOODMAN[131] found increased sedimentation values in cases of lung disease other than pulmonary tuberculosis, and considered that this finding meant that the sedimentation test had no value in the differential diagnosis of the latter.

GALLAGHER[35] performed the test as a routine in the medical examination of six hundred and eighty-five preparatory schoolboys. He came to the conclusion that the estimation of the sedimentation rate was a definite aid in cases of broncho-pneumonia, a steady decrease in the rate giving assurance that the trouble was gradually subsiding; or a continued acceleration compelling investigation for some further complication.

Personal Observations.

Microsedimentation estimations were performed on thirty-seven cases, classified as follows:-

Broncho-pneumonia - Seventeen cases.

Lobar pneumonia - Four cases.

Empyema - Four cases.

Chronic pneumonia - Seven cases.

Bronchiectasis - Five cases.

BRONCHOPNEUMONIA.

Among the seventeen patients in this group there were eight deaths, a mortality of 47 per cent (See Table 33), while nine were dismissed "recovered" (Table 32).

Table 32.

Bronchopneumonia - Recoveries.

Case	Initials	Age (years)	Highest M.-S. Value (mm.)	M.-S.R. before Dismissal	Remarks
65	G.M.	4/12	17.5	3.5	Normal temp. for 3 wks. Chest clear.
66	I.McG.	10/12	38	22	No fever for 1 month; Weight up; chest clear.
67	A.P.	11/12	31	21	Normal temp. for 1 week; sent to Country Branch.
68	S.G.	$2^{5}/12$	25.5	15.5	Normal temp. for 2 wks. Chest clear.
69	R.S.	4/12	39.5	26.5	Normal temp. for 2 wks; sent to Country Branch.
70	M.D.	$2^{11}/12$	36	25	Normal temp. for 2 wks; chest clear; rheumatic arthritis.
71	S.L.	9/12	41	16.5	Chest clear; apparently well.
72	S.F.	3/12	-	18	Convalescent when M.-S.R. performed.
73	A.D.	8/12	-	22	Convalescent when M.-S.R. performed.

Table 33.

Bronchopneumonia - Fatal Cases.

Case	Initials	Age (yrs)	Time in hospital (days)	M.-S.R.		Time of last M.-S.R.
				Highest	Before death	
74	A.McL.	$1^{6}/12$	7	26	25	Day before death
75	J.G.	14/52	14	21.5	11	Day before death
76	D.McA.	7/52	5	14	5	Day before death
77	W.McC.	3/12	8	5.5	1	Day of death
78	T.W.	7/12	2	5	5	Day before death
79	W.M.	4/52	2	36	36	Day before death
80	J.S.	9/12	1	20	20	Day of death
81	G.C.	2/52	1	1.5	1.5	Day of death

Tables 32 and 33 provide an interesting contrast. All the cases which recovered, with the exception of Case 65, showed a raised M.-S.R. before dismissal, though clinical evidence of activity was absent. On the other hand, five of the fatal cases had a normal, or low reading before death (Cases 75, 76, 77, 78 and 81). In four fatal cases, who were in hospital for less than forty-eight hours, only one M.-S.R. was performed, this value being low in two of these patients (Cases 78 and 81), but rapid in the remaining two (Cases 79 and 80). In Case 81 the temperature was subnormal when the M.-S.R. was taken, but in Cases 78, 79 and 80 there was fever of from 100° to 105°Fahr. Thus the M.-S.R. did not prove of any value in forecasting the fatal issue in these cases, one

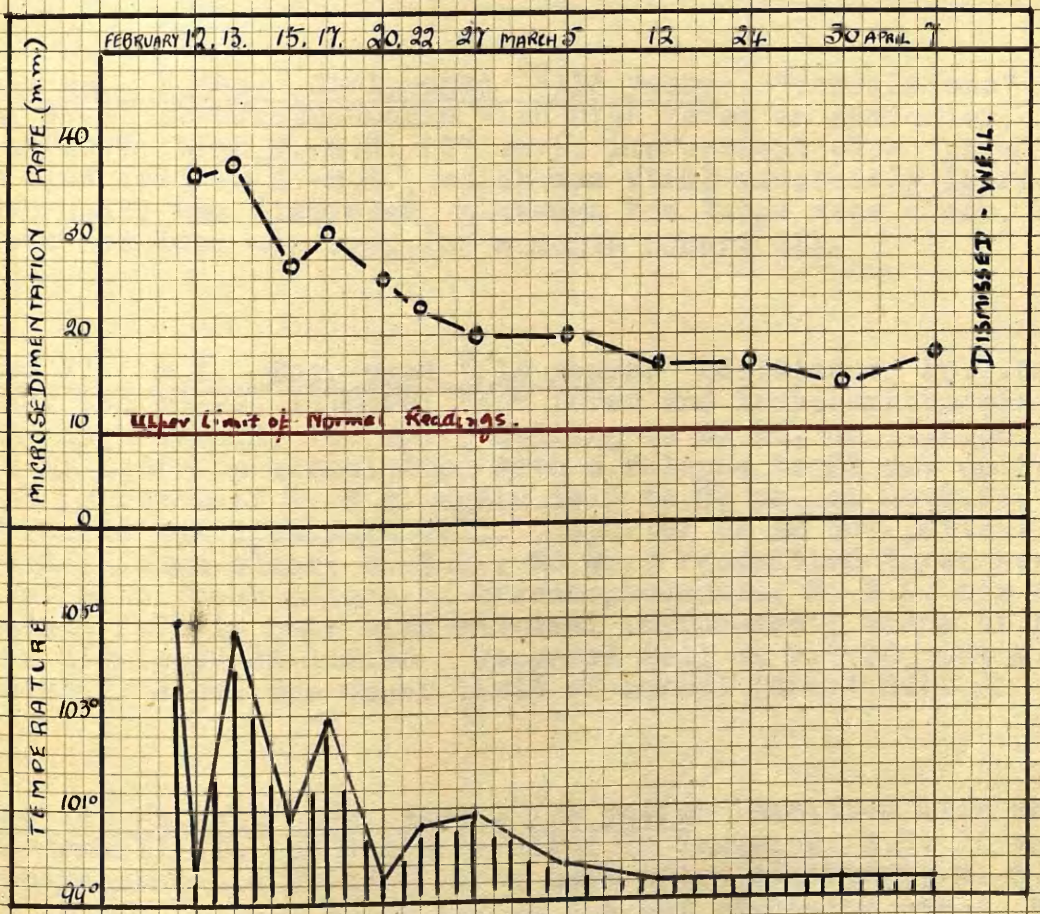


CHART 23. - I. McG. - BRONCHOPNEUMONIA.

patient showing a low value, and another, equally ill, a rapid one.

The following short case-histories illustrate the behaviour of the M.-S.R. in bronchopneumonia:-

Case 66. I.McG. Girl, aged $^{10}/_{12}$ years: "convulsions" for one week; bronchopneumonia with high fever on admission; diarrhoea; high M.-S.R. (37 mm.); improvement slow, paralleled by slow fall in M.-S.R., which was still moderately increased when child was dismissed, although the lungs were clear, and there had been no fever for a month (Chart 23).

Case 71. S.L. Boy, aged $^{9}/_{12}$ years: admitted on 30.1.36 after two weeks' illness; high fever and bronchopneumonia; very high M.-S.R. (38 mm.), falling to 25 mm. on 17.2.36, but rising again in association with a relapse to 33 mm. on 26.2.36; with improvement M.-S.R. again fell to 23 mm. on 24.3.36, when the child was dismissed well. Reported as an out-patient on 3.4.36; lungs clear; M.-S.R., 22 mm.; readmitted three weeks later with fresh attack of bronchopneumonia; M.-S.R. now 41 mm.; gradual fall in rate with clinical improvement; value of 21 mm. when dismissed on 1.6.36. Reported well on 9.7.36, but M.-S.R. was still above the upper limit of normal (Chart 24).

Case 74. A.McL. Boy, aged $1^{6}/_{12}$ years: admitted with fever and tonsillitis; no definite signs in lungs; M.-S.R. 15 mm., bronchopneumonia evident three days after admission; M.-S.R. now 20 mm., rising to 25 mm. on the day preceding death, which occurred when the child had been one week in hospital.

Case 75. J.G. Boy, aged $^{14}/_{52}$ years: admitted on 26.12.35 with bronchopneumonia, high fever, diarrhoea; M.-S.R. 21.5 mm., rising to highest value (25 mm.) on 7.1.36; but falling to 18 mm. on 8.1.36, and 11 mm. on 9.1.36, the day preceding death.

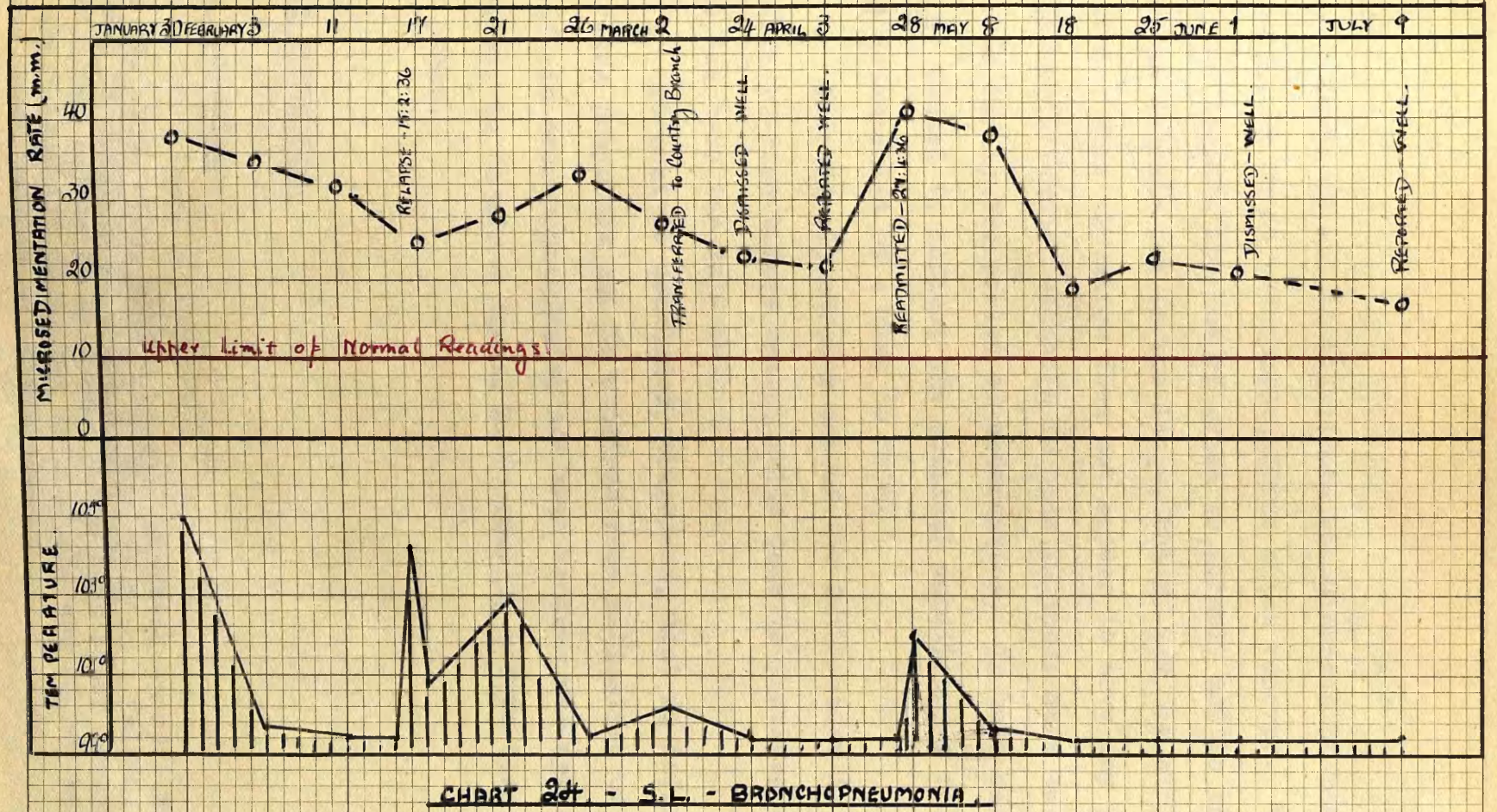


CHART 2d - S.L. - BRONCHOPNEUMONIA.

Remarks.

Cases 66 and 71 illustrate the slowness of the fall in M.-S.R. in those bronchopneumonias which recover. Weeks after the temperature has returned to normal, and no physical signs can be made out in the lungs, the M.-S.R. is still elevated. This elevation does not appear to have any prognostic significance, although in Case 71 there were two relapses during the period of observation. In both cases the M.-S.R. tended to reflect the clinical condition, a relapse being accompanied by a rise in rate.

Case 74 illustrates one of the fatal cases in which the M.-S.R. rose before death; while Case 75 provides a contrast, as here the rate fell.

It must be concluded, therefore, that no information regarding prognosis can be obtained from estimation of the M.-S.R. in bronchopneumonia; and that it does not appear to be necessary to obtain a normal M.-S. reading before dismissing such cases.

LOBAR PNEUMONIA.

Case Histories:-

Case 82. W.B. Boy, aged 8 years: admitted on 25.1.36 with history of onset on 23.1.36; M.-S.R. 36.5 mm., falling to 30 mm. on 29.1.36; crisis on 30.1.36. Three days after crisis M.-S.R. was still high (29 mm.), but fell at the end of one week to 15 mm., when patient was dismissed.

Case 83. C.S. Girl, aged 12 years: admitted on 30.3.36, with history of three days' illness; M.-S.R., 25 mm., rising to 32 mm. on 3.4.36, when crisis occurred; dismissed one week later, when M.-S.R. had fallen to 16 mm.

Case 84. C.W. Girl, aged 4 years: admitted on 28.3.36, with history of onset on 25.3.36; M.-S.R. 36.5 mm. on 31.3.36; crisis on 1.4.36; dismissed one week later, M.-S.R., 11 mm.

Case 85. M.G. Girl, aged 9 years: admitted on 18.5.36 after one day's illness; M.-S.R. 30.5 mm., temperature fell by lysis, reaching normal on 26.5.36, when M.-S.R. was 22 mm.; dismissed one week later with M.-S.R. now 12 mm.

Remarks.

All four cases behaved in a similar fashion. The M.-S.R. before the crisis was high, falling fairly rapidly after the crisis, but in no case reaching a normal value before the patient was dismissed. Thus again we find the sedimentation rate lagging behind the temperature and other signs in reaching normal, and this delay does not appear to have any untoward significance.

EMPYEMA.

Case Histories:-

Case 86. N.L. Boy, aged 5 years: lobar pneumonia with crisis on 9.2.36; return of fever five days later; admitted on 3.3.36 with right-sided empyema; 15 c.c. pus removed from chest on 5.3.36, when temperature was normal and M.-S.R. 9 mm.; four days later there was still no fever, but M.-S.R. had risen to 39 mm.; thereafter gradual improvement, although small amounts of pus were still obtained at intervals; M.-S.R. continued to give very high readings till 13.4.36, when reading was 20 mm.,

CHART 25 - N.L. - EMPYEMA.

a fortnight after the last quantity of pus (6 c.c.) had been removed from the chest. When dismissed on 20.4.36, patient was looking well and putting on weight, although there was still slight dulness at the right lung base; the M.-S.R. was now 16 mm. (Chart 25).

Case 87. E.K. Girl, aged 1 7/12 years: whooping cough in February, 1936; measles in May, 1936; admitted on June 24 with history of fever persisting since the attack of measles; empyema of right lung, pneumococcus isolated on culture; M.-S.R. rose from 32 mm. on 30.6.36 to 34 mm. on 14.7.36, fever continuing and pus still being removed from right lung; sharp rise of temperature to 104°F. on 25.7.36, with cyanosis and dyspnoea, indicated commencing pneumonia of left lung; M.-S.R. rose to 41 mm., and death took place six days later.

Case 88. A.H. Boy, aged 10/12 years: admitted with history of fever, dyspnoea and cough for three weeks; empyema of left lung, 115 c.c. pus removed; M.-S.R. high (30-35 mm.); transferred to surgical ward for operation, and further M.-S. readings not obtained.

Case 89. J.R. Boy, aged 11 years: history of pain in left chest, cough and fever for two weeks; admitted on 30.10.36; left-sided empyema, from which 100 c.c. of pus were removed; M.-S.R. 36.5 mm.; two days later still high fever, M.-S.R. rose to 39.5 mm., transferred to surgical ward where rib resection was performed; on 18.11.36 fever was still present, and discharge coming from the chest, but the M.-S.R. had fallen to 33 mm.; on 25.11.36 temperature had fallen to normal, and discharge stopped, but M.-S.R. was still high (30 mm.); at the time of writing the temperature has remained normal, and there is considerable improvement, but the M.-S.R. continues to show a high reading.

Remarks.

As might be expected, a very high M.-S. value is the rule in empyema. The gradual nature of the fall in M.-S.R., which is still rapid when fever has subsided, and discharge

has ceased, is shown by Cases 86 and 89. It is very interesting to find that in Case 86 the first reading was surprisingly low - 9 mm. - in spite of the presence of an indubitable empyema, which, however, was at first afebrile. This low value is difficult to explain, but the fact that the next reading, taken four days later, was very high, suggests that the first was for some reason abnormal. This finding is of value in showing that no significance can be attached to a single normal M.-S.R. in a doubtful case. In Case 87 a change for the worse in the patient's condition was paralleled by a sharp rise in the M.-S.R.

To sum up, in empyema the M.-S.R. does not appear to give more full information than can be obtained by the ordinary methods of examination.

CHRONIC PNEUMONIA.

The seven cases in this group were characterised by a history of respiratory trouble over a considerable period, without any evidence of tuberculosis. Four had a normal or only very slightly raised M.-S.R. during their stay in hospital, while the remaining three showed a moderately increased rate on admission (20-30 mm.), which in two cases had reached a normal value at the end of one week, and in one case took three weeks to reach normal. Two illustrative case histories are given

below, Case 90 being an example of the first type, and Case 91 of the second.

Case 90. M.M. Girl, aged $9^{5}/12$ years: patient in R.H.S.C. with "chronic pneumonia" in 1931; cough, spit and failure to gain weight since; admitted in June, 1936, with coarse rales in the right chest; tuberculin skin-tests negative; X-ray showing area of probable calcification in the right lung; temperature remained normal throughout her stay of three months in hospital, and M.-S.R. never exceeded normal values.

Case 91. J.W. Boy, aged $10^{5}/12$ years: in hospital from November, 1935, to January, 1936, with "chronic pneumonia"; readmitted in June, 1936, because of persistent cough and slight loss of weight; numerous rales in right lung, but no evidence to support diagnosis of tuberculosis; no fever; M.-S.R. 28 mm., but fell rapidly, reaching a normal value after three weeks.

BRONCHIECTASIS.

Five cases of bronchiectasis, in three of whom the diagnosis was confirmed by radiography after the injection of lipiodol, were all afebrile during their stay in hospital, and all showed increased M.-S. values, which tended to vary from week to week, but were never high. In none of these cases was the M.-S.R. below the upper limit of normal readings when the patient was dismissed.

It seems unlikely that estimation of the sedimentation rate in such cases will throw any light on the diagnosis or prognosis, or give an index for treatment.

SUMMARY OF FINDINGS.

A high M.-S.R., which fell slowly, and was commonly still above normal limits on dismissal of the patient, was found in those cases of bronchopneumonia which recovered. Thirty-eight per cent. of the fatal cases of bronchopneumonia showed a markedly increased M.-S.R. before death, while the other sixty-two per cent. showed normal or only slightly increased values. No explanation for this difference was discovered.

Cases of lobar pneumonia and empyema showed very high M.-S. values during the acute stages, with a gradual fall corresponding to the clinical findings, when recovery took place. A raised rate was generally found for a considerable period after clinical recovery, but had no prognostic significance.

In chronic pneumonia and bronchiectasis slightly or moderately increased values, with a tendency to vary, were the common finding.

Estimation of the M.-S.R. in this group of non-tuberculous respiratory diseases was not found to afford more valuable information as regards diagnosis, prognosis or clinical condition, than could be obtained by the ordinary methods of examination.

IV. DISEASES OF THE NERVOUS SYSTEM.

Few observations have been made on these forms of nervous disease which occur in children. LANDAU[68] recorded normal microsedimentation rates in epilepsy, and also in the acute stage of poliomyelitis, which latter finding he suggested might be of value in differential diagnosis. JUARROS and GALARIETA[62] considered that the sedimentation rate was useful in certain nervous affections, e.g. congenital syphilis and meningitis, as demonstrating the persistence or otherwise of an active inflammatory process.

As regards tumours, most observers record an increased rate in malignant tumours generally (ZECKWER and GOODELL,[136] COOPER,[16] HUNT,[60] GRAM[42]). KESSLER,[65] however, found that in fifty-three per cent. of cases of malignant tumour the rate of sedimentation was not sufficiently high to make the test of importance in the differential diagnosis between benign and malignant disease.

Personal Observations.

These were made on forty cases of nervous disease, classified as follows:-

Non-tuberculous Meningitis	-	Seven cases.
Poliomyelitis	-	Eight cases.
Epilepsy	-	Seven cases.
Other conditions	-	Eighteen cases.

NON-TUBERCULOUS MENINGITIS.

Table 34.

Non-tuberculous Meningitis.

Case	Initials	Age (yrs.)	Type of Meningitis	Range of M.-S.R. (mm.)	Result
92	B.McD.	4/12	Cerebrospinal fever	25-30	Transferred
93	S.G.	2½	Cerebrospinal fever	30-35	Transferred
94	D.McL.	4/12	Cerebrospinal fever	35-45	Transferred
95	S.C.	5/12	Cerebrospinal fever	35-45	Transferred
96	J.D.	1	Influenzal	20-30	Died
97	W.R.	7/12	Influenzal	15-45	Died
98	A.S.	5/12	Serous	5-20	Dismissed well.

Table 34 gives particulars of the seven cases in this section, four of which were cerebrospinal fever, two influenzal meningitis, and one serous meningitis.

Cerebrospinal Fever.

All four children were acutely ill when admitted, the diagnosis being confirmed by examination of the cerebrospinal fluid. In each the M.-S.R. was at a very high level, and in Case 95 a fall in the rate, from 41 mm. to 36.5 mm. in twelve hours, took place following the injection of antimeningococcal serum. These cases were transferred to a Fever Hospital as soon as possible after the diagnosis was confirmed.

Influenzal Meningitis.

Both cases had rapid M.-S. values on admission, and both were acutely ill. In Case 96 the M.-S.R. on admission was 22.5 mm., and rose within a week to 28 mm., death taking place some days later. The initial M.-S.R. in Case 97 was very high, 42 mm., and was associated with a high degree of fever, but two days later, with high fever still present, the M.-S.R. fell to 18 mm., and death occurred within twenty-four hours.

Serous Meningitis.

In this case there was a history of convulsions, and a moderate degree of fever was present on admission, with a M.-S.R. of 19.5 mm. On lumbar puncture a lymphocytic exudate was found, and the Pandy test was positive. The skin tests were negative. Five days after admission the temperature had become normal and the M.-S.R. had also reached a normal value, 9 mm., which fell to 5.5 mm. one week later, prior to dismissal.

Remarks.

High M.-S. values in the acute forms of meningitis were to be expected, and were in keeping with the clinical findings. As the cases of cerebrospinal fever were transferred to Fever Hospitals, it was not possible to discover whether a fall in the M.-S.R. sometimes preceded a fatal issue, as was found in one of the cases of influenzal meningitis. In the solitary case diagnosed as "serous" meningitis, the return of a slightly raised

M.-S.R. to normal agreed with the rapid clinical improvement.

POLIOMYELITIS.

It will be seen from Table 35 that, out of eight cases, only two (Cases 99 and 106) showed any rise of M.-S.R. above normal values. In both these cases the increase in rate, which did not exceed 15 mm., was found in the first reading after admission, and in both the next reading showed a normal value. (Chart 26, taken from Case 99, is given to illustrate this.)

Table 35.

Poliomyelitis.

Case	Initials	Age (years)	Range of M.-S.R.
99	G.R.	$4^{8}/12$	5-15
100	P.B.	$2\frac{1}{2}$	5-10
101	J.McD.	11	5-10
102	M.O.	$2\frac{1}{2}$	5-10
103	H.A.	$9\frac{1}{2}$	5-10
104	J.S.	$7\frac{1}{2}$	0-5
105	S.G.	$4^{9}/12$	5-10
106	R.B.	4	5-15

This normal M.-S.R. in poliomyelitis can be of use in the differential diagnosis of a doubtful case; as is shown by the following case-history:-

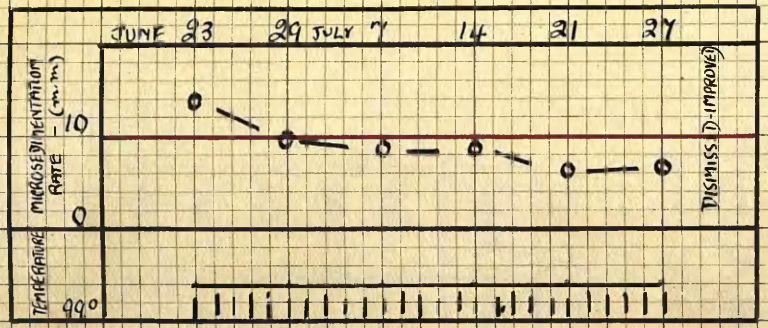


CHART 26. - G.R. - POLIOMYELITIS.

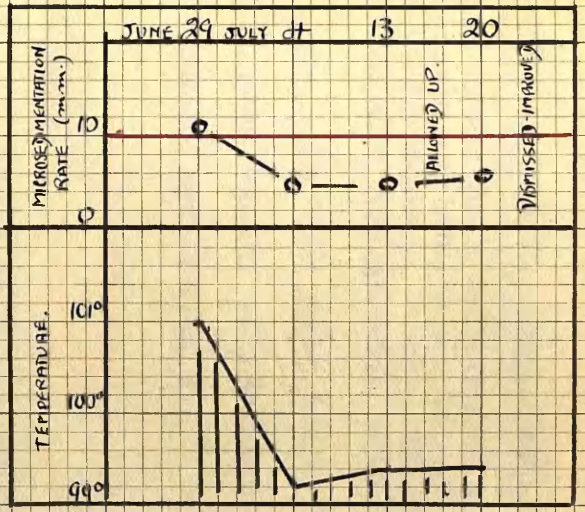


CHART 28. - D.McD. - ENCEPHALITIS.

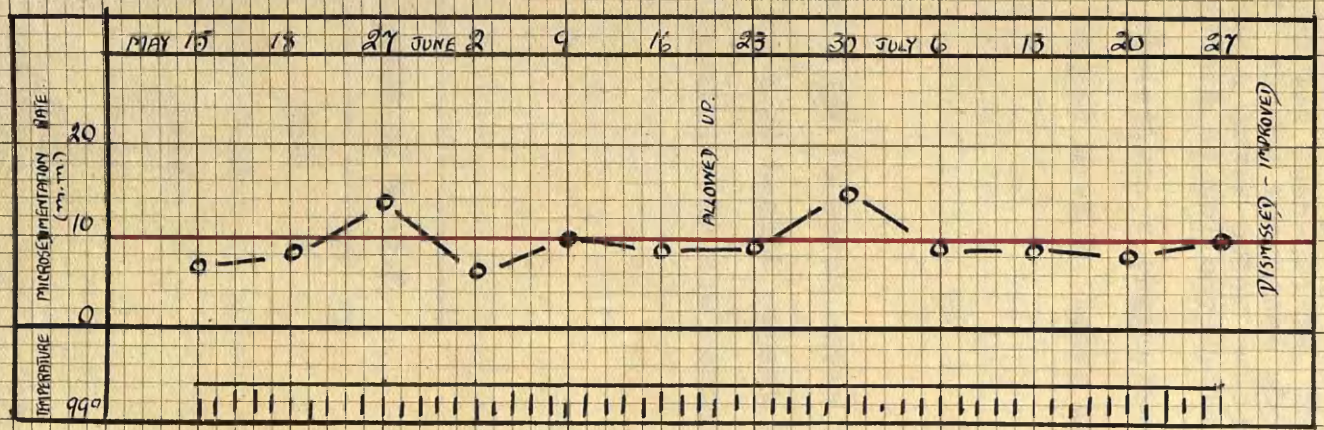


CHART 27. - A.G. - CEREBELLAR ATAXIA.

Case 103. H.A. Boy, aged 9½ years: admitted with obscure fever, and history of joint pains and inability to walk for one week; pain on passive movement of the knee-joints, but no redness or swelling; lumbar puncture showed increased globulin; M.-S.R. normal, 7 mm.; two days later a lower motor neurone paralysis was present, and the diagnosis of poliomyelitis made.

In this case there was, on admission, a suggestion of the possibility of rheumatism, the normal M.-S.R. being strong evidence against this.

EPILEPSY.

Table 36 gives the M.-S. readings in seven cases of epilepsy. All of these cases were in good health, apart from the epilepsy, and no case showed a reading over the normal limits while in hospital.

Table 36.

Epilepsy.

Case	Initials	Age (years)	Range of M.-S.R.
107	C.O.	11	0-5
108	W.N.	9	0-10
109	A.C.	5	0-10
110	H.McD.	4	0-10
111	A.B.	11	0-5
112	S.C.	8 9/12	0-5
113	S.W.	8	0-10

OTHER NERVOUS CONDITIONS.

Ataxia.

Readings were performed on two cases of cerebellar ataxia:-

Case 114. G.S. Boy, aged 4½ years: history of diarrhoea for five days, and ataxia for one day; slight Rombergism on admission, but no other positive findings; kept in hospital for a fortnight and discharged well; M.-S.R. did not rise over 6 mm.

Case 115. A.G. Girl, aged 12^{9}/12 years: history of backwardness and difficulty in walking; marked Rombergism on admission, with positive Babinski, ankle clonus, and absent abdominal reflexes; slight optic neuritis; increased globulin content and slight increase in cell count of the cerebrospinal fluid; condition appeared to be a familial form of cerebellar ataxia; M.-S.R. normal except on two occasions, when there was a slight rise, not accounted for by any change in the clinical symptoms (Chart 27).

The estimation of the M.-S.R. was not found of value in these cases.

Encephalitis.

Observations were made on three cases diagnosed as "encephalitis," short summaries of which follow:-

Case 116. D.McD. Boy, aged 8½ years: history of fall on head on 20.6.36; fevered on 25.6.36; admitted on 29.6.36 with characteristic polio-encephalitis with bulbar signs; fever; increased globulin content of cerebrospinal fluid and cell count of 106 per cubic centimetre (lymphocytes); skin tests negative; M.-S.R., 11 mm. By 4.7.36 there was general improvement, and M.-S.R. had fallen to 5 mm.; dismissed on 20.7.36; only remaining abnormal finding being slight degree of facial paralysis (Chart 28).

Case 117. J.McC. Boy, aged 7 years: condition appeared to be a lower motor neurone lesion as a sequel to an attack of measles immediately prior to admission; no fever; cerebro-spinal fluid negative; M.-S.R. slightly increased, 15 mm., but fell to 7 mm. in association with clinical improvement; dismissed after three weeks in hospital with diagnosis of "post-measles encephalitis"; M.-S.R. on dismissal being 12 mm.

Case 118. P.M. Girl, aged 6/12 years: history of fever, vomiting; diarrhoea and restlessness for two days; admitted with dehydration and marked craniotabes, but no abnormal signs in nervous system; high fever; M.-S.R. normal; died two days later, the pathologist reporting "polio-encephalitis" at the post-mortem.

Remarks.

These findings are similar to those in poliomyelitis, a normal or only slightly increased M.-S.R. being the rule in both conditions. In Case 116 this relatively low M.-S.R. contrasted in a marked degree with the apparently seriously ill condition of the patient on admission, but indicated, in this instance, a favourable prognosis.

Birth Injury.

Table 37.

Birth Injury.

Case	Initials	Age (years)	Condition	Range of M.-S.R. (mm.)	Result
119	Baby C.	1/365	Meningocele	0-5	Died
120	T.K.	4	Convulsions since birth.	0-5	Died
121	W.T.	4/52	Convulsions	0-5	Died
122	M.C.	2/52	Convulsions	0-5	Dismissed improved
123	A.C.	2/52	Deformity of skull	0-5	Dismissed improved

All five cases of birth injury showed M.-S. values of under 5 mm., as shown in Table 37, and only one case was over one month of age:-

Case 120. T.K. Boy, aged 5 years: history of periodic convulsions since birth; severe attack two days before admission; admitted unconscious, with right-sided flaccid paralysis; M.-S.R. 1.5 mm., died thirty-six hours later; no post-mortem allowed.

Normal M.-S. values were also found in two cases of mental deficiency, one of whom was a microcephalic.

Hysterical Paralysis.

In two cases, in which this diagnosis was made, the M.-S. readings were of interest:-

Case 124. I.G. Boy, aged 11 7/12 years: history of loss of power in both legs twelve hours before admission to hospital; stout, healthy, intelligent boy; good family history and no previous serious illness; indefinite paraplegia, with negative Babinski; small boil on neck, and history of several previous boils; M.-S.R. definitely raised (25 mm.), but had fallen to 11.5 mm. two days later, when the patient was able to walk and run without difficulty; dismissed well after one week in hospital; M.-S.R. being 12 mm.

In this case the initial M.-S. reading suggested that more than mere hysteria was present, and the question of the influence of the boil arises. (It is of interest to note that the M.-S.R. in a case of genuine hemiplegia in a boy of 9 years old was normal - 3 mm.). The rapid improvement in the boy's condition was paralleled by a fall in the M.-S.R., and it is

possible that there was some temporary organic cause for both the symptoms and the raised M.-S.R.

The second case will be given in some detail, as it presented special features of interest in connection with the sedimentation rate.

Case 125. W.B. Boy, aged 11 years: history of convulsions at nine months old, none since; backward, attends special school. On 30.8.36 developed "chill", with shivering and fever, but was able to go to see doctor on 14.9.36; after which he went to bed, and next day (15.9.36) complained of pain across the back and in the legs, with inability to move the latter. On admission on 19.9.36 body and legs were held stiffly, and boy appeared unable to walk; deep reflexes exaggerated, but no evidence of organic nervous disease, and on following day he declared voluntarily that he had been "kidding". At this point the paralysis was considered to be hysterical in origin, but the M.-S.R. was found to be high (28 mm.), and this cast doubt on such a diagnosis. For first three weeks in hospital there was loss of weight, accompanied by slight fever; M.-S.R. rose rapidly, reaching peak value of 42.5 mm. on 29.10.36, although definite clinical improvement present, and boy much brighter mentally and able to walk. Condition was fully investigated; lumbar puncture, Wassermann reaction, Widal test, blood culture, blood sugar curves, serum calcium, blood non-protein nitrogen, and blood cholesterol all giving normal findings, while a blood fibrinogen estimation on 4.11.36 gave a low normal result. The radiologist, however, reported "abnormality of the vertebral bodies" in an X-ray of the spine, and considered the appearances suggested "spondylitis ankylopoietica". On 2.12.36 transferred to Country Branch very much improved, able to walk; no fever, but still slight stiffness of the knees; M.-S.R. still high (34 mm.). Two months later (29.1.37) returned to Yorkhill prior to dismissal; mentally much brighter; walking easily; no stiffness of limbs; M.-S.R. now 12.5 mm. Reported as out-patient on 4.3.37; apparently very well; no pain or stiffness; but M.-S.R. still raised slightly - 14 mm. (See Chart 29).

Remarks.

In this case, on admission, a diagnosis of hysteria seemed permissible, but the high M.-S.R. suggested the presence of organic disease. Progressive lenticular degeneration

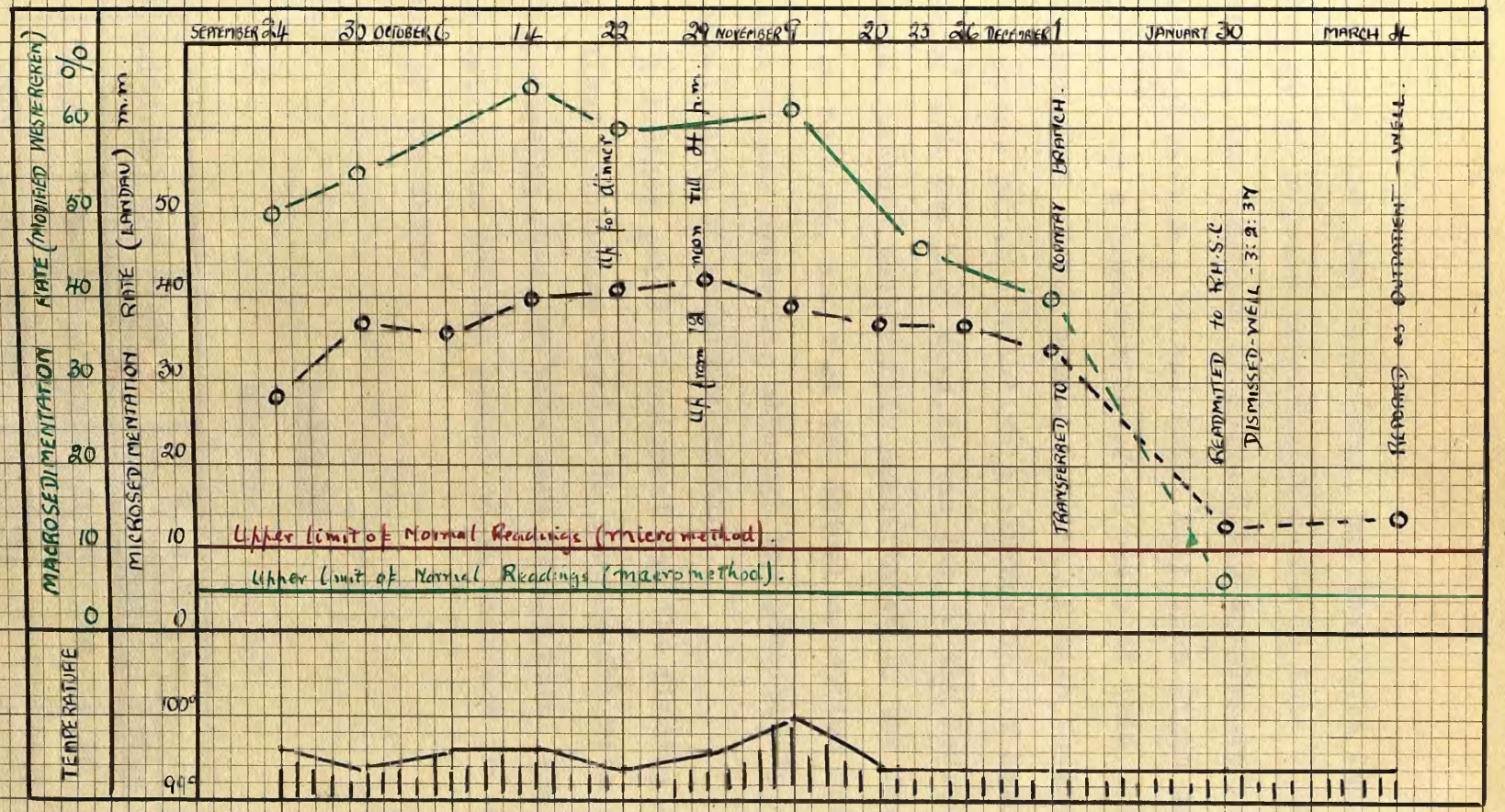


CHART 29. - W.B. - HYSTERIA and ANKYLOPOIETIC ARTHRITIS.

(Wilson's disease) was considered, but the rapid improvement and and absence of hepatic involvement rendered this unlikely. On considering the question of spondylitis ankylopoietica explaining the high M.-S.R., it was found that such might be the case. GOLDING[39], in a description of 91 cases of this unusual condition, remarked on the common finding of high sedimentation rates. As the paralysis entirely cleared up, it seems logical to assume that the high M.-S.R. was due to the lesion in the vertebrae, perhaps temporarily exacerbated by the feverish illness on 30.8.36, and that the actual condition for which he was admitted was hysteria, although the possibility of some undetected focus of infection remains.

A further point of interest was the finding of a low normal blood fibrinogen reading in association with a very high M.-S.R., showing that, in this case at any rate, the increased sedimentation was not the result of an increase in the fibrinogen content of the blood.

Tumours.

Table 38.

Tumours.

Case	Initials	Age (yrs)	Site of Tumour	M.-S.R. (mm.)			Result
				Range	Highest	Final	
126	M.N.	7	Cerebral	10-20	20	20	Dismissed improved
127	G.P.	1	Spinal	10-22.5	22.5	22.5	Died
128	H.B.	5	Pontine	0-11	11	4.5	Died
129	E.G.	3½	Pontine	0-32	32	32	Died

Table 38 gives particulars of the M.-S.R. in four cases diagnosed as tumour of the nervous system. In Cases 128 and 129 the diagnosis was confirmed by post-mortem examination. Brief notes on the cases are as follow:-

Case 126. M.N. Boy, aged 7 years: previously in hospital from April, 1935, to August, 1935, with diagnosis of cerebral tumour; decompression carried out; readmitted in May, 1936, on account of severe headache; M.-S.R. varied between 10 mm. and 15 mm. during one month's stay in hospital, with a reading of 20 mm. prior to dismissal. These readings did not appear to reflect the clinical condition.

Case 127. G.P. Boy, aged 1 year: seriously ill on admission, and died twelve days later; spinal tumour diagnosed from clinical findings, as no post-mortem was allowed; M.-S.R. rose before death.

Case 128. H.B. Boy, aged 5 years: inoperable pontine tumour, confirmed at post-mortem; M.-S.R. fell before death, which took place very suddenly from haemorrhage.

Case 129. E.G. Girl, aged 3½ years: inoperable pontine tumour, confirmed at post-mortem; gradual wasting before death; M.-S.R. rose gradually from 1.5 mm. on 25.9.36 to 32 mm. on 18.11.36, the day preceding death.

Remarks.

Case 129 was the only one of these patients who showed a high M.-S.R., contrary to what some observers have reported in malignant disease. The M.-S.R. did not parallel the clinical condition, and was of no value in prognosis, as it rose before

death in Cases 127 and 129, but fell in Case 128. It is interesting to find such a high M.-S. value in the closing stages of Case 129, as dehydration, which might be expected to slow the sedimentation by reason of the concentration of the blood, was very marked.

SUMMARY OF FINDINGS.

With the exception of acute infections of the meninges, such as cerebrospinal fever, normal or only slightly raised M.-S. values were commonly found in diseases of the nervous system. In the majority of cases estimation of the micro-sedimentation rate was not of value in either the diagnosis or prognosis, but in one or two cases the relatively low rate was useful in helping to differentiate a purely nervous condition from other diseases, such as rheumatism.

V. DISEASES OF THE GENITO-URINARY SYSTEM.

Review of Literature.

References to the sedimentation rate in diseases of the urinary tract in adults are not numerous, and in children, even less so. In chronic nephritis in adults POPPER and KREINDLER(105) reported normal, or slightly accelerated rates; and in acute nephritis, high values. GRAM(42) also stated that the sedimentation rate was generally increased in nephritis.

LANDAU[68] made observations on seven cases of nephritis in children, finding high microsedimentation values in the acute stages, which, as a rule, fell as the urine became clear. He did not consider that the test had any great value in nephritis.

As regards pyuria, OSMAN,[90] writing in 1936, stated that "as in many other acute infective diseases after the temperature has returned to normal, a weekly estimate of the sedimentation rate of the red blood corpuscles is a useful index of the general progress of the case."

Personal Observations.

The material in this section consisted of twenty-three cases, made up as follows:-

Acute Nephritis	-	Eleven cases.
Nephrosis	-	One case.
Pyuria	-	Eleven cases.

ACUTE NEPHRITIS.

Table 39 shows the condition of the urine, and the M.-S.R., on admission and discharge, of the eleven cases of nephritis. In all cases the condition of the urine had cleared up before dismissal. The M.-S.R. during the acute stages was rapid, falling gradually as the urine cleared. Readings did not, however, reach normal values until some time after the

Table 39.

Acute Nephritis.

Case	Initials	Age (yrs)	Admission.				Discharge				State on Dismissal
			Albumen	Blood	Oedema	M.-S.R.	Albumen	Blood	Oedema	M.-S.R.	
130	J.E.	11	+	+	0	23.5	0	0	0	15	Well
131	D.T.	5	++	+	+	36	0	0	0	23	Nephritis cured - chest condition ?
132	D.N.	5	++	+	0	41.5	0	0	0	10	Well
133	J.F.	8	++	+	++	21	0	0	0	16	Well
134	E.C.	10	+++	++	++	19	0	0	0	11	Well
135	D.McC.	3	++	+	+	37	0	0	0	21	Improved - transferred to Country Branch
136	M.McA.	$4\frac{1}{2}$	+	+	+	20	0	0	0	7	Well
137	M.D.	8	+++	++	+	35	0	0	0	25	Improved - transferred to Country Branch
138	G.H.	5	+	+	+	20	0	0	0	33	Well
139	C.S.	$8^3/12$	+	+	0	28	0	0	0	9	Well
140	A.B.	$7^3/12$	++	+	++	23.5	0	0	0	8.5	Well

urine was free from albumen, in the majority of cases.

In five cases, Cases 132, 136, 138, 139 and 140, the M.-S.R. showed a normal value before the child was dismissed, as is illustrated by the following case-history:-

Case 132. D.N. Boy, aged 5 years: history of discharging ears two weeks before admission; haematuria and albuminuria, but no oedema; M.-S.R. very high (41.5 mm.); no blood or albumen in the urine after one week in hospital, but M.-S.R. did not reach normal value till the fifth week (Chart 30).

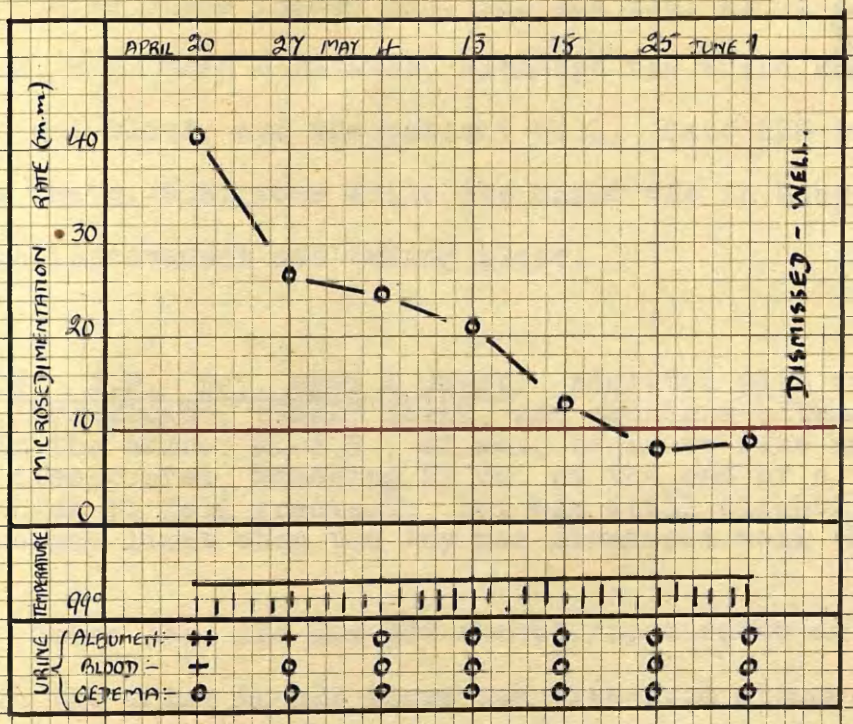


CHART 30. - D.N. - ACUTE NEPHRITIS.

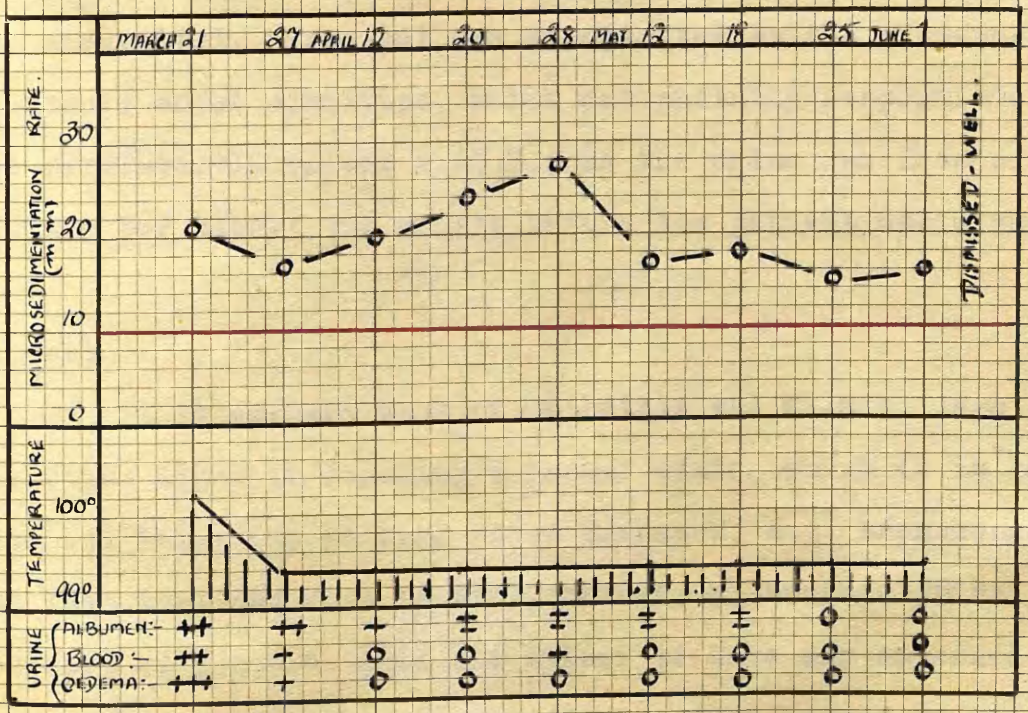


CHART 31. - J.F. - ACUTE NEPHRITIS.

Three cases (Cases 130, 133 and 134) still had a slightly raised M.-S.R. when dismissed, although the urine was free of albumen and blood, and the patient well. Case 133 is of interest, as the M.-S.R. rose while the child was in hospital, although improvement was taking place.

Case 133. J.F. Boy, aged 8 years: admitted with very marked oedema, drowsiness, slight fever, and abundant albumen and blood in the urine; M.-S.R., 21 mm., began to rise as the oedema disappeared, reaching 27 mm. at the end of a month, after which it fell gradually, but was still slightly over the upper normal limit when the boy was dismissed well (Chart 31).

Cases 131, 135 and 137 showed rapid rates on dismissal, although the urine in all three was free from albumen and blood, and there was no oedema. The latter two cases were sent to the Country Branch for a period of convalescence, which was uneventful. Case 131 was complicated by the presence of a chronic chest condition, which was probably responsible for the persistently raised M.-S.R., as the urine was free of albumen for almost two months before the patient was dismissed.

Remarks.

It is evident that in nephritis the M.-S.R. lags behind the other signs in reaching a normal state, which is in keeping with its behaviour in many other diseases, e.g. bronchopneumonia. The fact that the rate is still raised, although clinical recovery is present, does not appear to have any untoward significance. In association with a marked degree of oedema

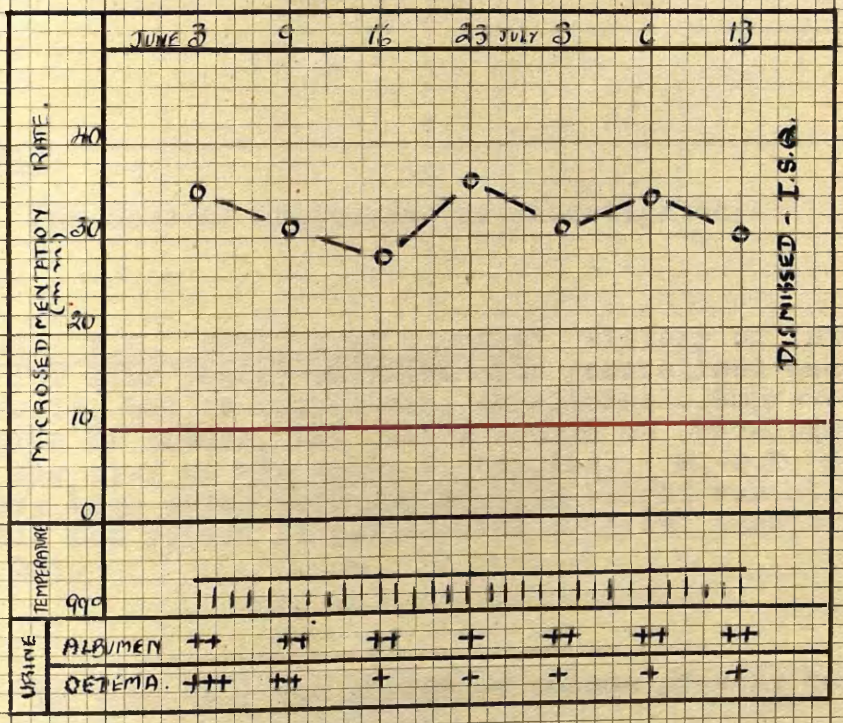


CHART 32. - F.D. - NEPHROSIS.

a somewhat lower M.-S.R. than would otherwise be the case is frequently found; disappearance of the oedema coinciding with a rise in the rate (Case 133). Apart from this, the M.-S.R. falls as the clinical condition improves, but has no advantage over the other signs in prognosis.

NEPHROSIS.

One case of nephrosis was investigated:-

Case 141. F.D. Girl, aged 8 years: history of intermittent oedema for four years; admitted with generalised oedema, albuminuria; but no haematuria; considerable improvement in the degree of oedema, but little change in the albuminuria, during her stay of six weeks in hospital; M.-S.R. remained at a very high level throughout, with slight variations, which did not appear to reflect the clinical condition (Chart 32).

In this case the amount of oedema present had no apparent relation to the M.-S.R., which remained at a high level.

PYURIA.

Table 40 gives the condition on admission and discharge of eleven cases of acute and chronic pyuria, together with the type of treatment given. Rapid M.-S. values on admission to hospital were found in all seven "acute" cases, but in two out

Table 40.

Pyuria

Case	Initials	Age (yrs.)	Type of Pyuria	Admission			Discharge			Treatment	Condition on Discharge
				Temp. °F.	Pus in urine	M.-S.R.	Temp. °F.	Pus in urine	M.-S.R.		
142	C.T.	2	Acute	100^{4}	++	37.5	99^{4}	0	9	Alkalies	Well
143	N.G.	$7^{10}/12$	Acute	99^{2}	++	20	99^{4}	0	6.5	1.Alkalies 2."Protosil"	Well
144	C.G.	1	Acute	101^{2}	++	30	99^{4}	±	13.5	Alkalies	Well
145	M.D.	10	Acute	100^{4}	+++	32	99^{4}	0	8	Alkalies	Well
146	J.B.	8	Acute	99^{4}	++	25	99^{4}	±	14	Hexamine	Well
147	K.G.	11/12	Acute	100^{4}	+++	38	99^{4}	0	25.5	1.Alkalies 2.Mandelic acid	Well
148	J.F.	7/12	Acute	103	++++	41.5	-	-	-	Alkalies	Died
149	M.M.	4/12	Chronic	101	++	10	99^{4}		10	Alkalies	Improved
150	J.McG.	6	Chronic	99^{6}	+++	40	99^{4}		25	-	Transferred to Surgical Ward
151	C.R.	$12^{6}/12$	Chronic	99^{4}	++	21.5	99^{4}		19	1.Hexamine 2.Mandelic acid	No change
152	J.D.	7	Chronic	99^{4}	++	10.5	99^{2}		7	Mandelic acid	Improved

Note:- The symbol ± indicates the presence of one or two pus cells per microscope field.

of four "chronic" cases this value was just at the upper limit of normal readings. As the condition of the patient improved, there was a corresponding fall in the M.-S.R., which, however, did not reach a normal reading before discharge in all cases. Brief summaries of certain illustrative cases will be given:-

Case 143. N.G. Girl, aged $7^{10}/12$ years: admitted with acute pyuria; no fever till third day after admission when temperature rose and remained elevated for ten days; corresponding rise in M.-S.R. from 20 mm. to 37.5 mm., treatment with alkalies failed to reduce amount of pus in urine; local treatment with "protosil" given, and urine cleared within one week, M.-S.R. showing simultaneous fall (Chart 33).

Cases 142 and 145 behaved in a similar fashion to Case 143, but in them the fall in the M.-S.R. was more gradual.

Case 147. K.G. Girl, aged $11/52$ years: admitted with acute pyuria, coliform in character; fever; M.-S.R. very high (38 mm.); alkaline treatment for one week, omitted in favour of mandelic acid; improvement in general condition and disappearance of pus associated with fall in M.-S.R., which was, however, slow; on dismissal urine was pus-free and culture sterile; but M.-S.R. still rapid (25.5 mm.). This child reported well one month later.

Cases 144 and 146 resembled Case 147, as both were clinically well when dismissed, with culture of the urine sterile, but with the M.-S.R. still slightly elevated.

Case 148 was admitted in a critically ill condition, with hyperpyrexia and profuse pyuria, and died two days later. The M.-S.R. was very high. Post-mortem examination revealed advanced pyelonephritis.

Cases 149 to 152 were all patients in whom the pyuria was chronic. In Case 150 the pyuria was not marked, and gastro-enteritis was present in addition; culture of the urine giving a growth of B. proteus. The M.-S.R. never rose above the upper limit of normal, and showed the same reading on admission and on discharge. Case 151 is of interest, as the M.-S.R. fell coinci-

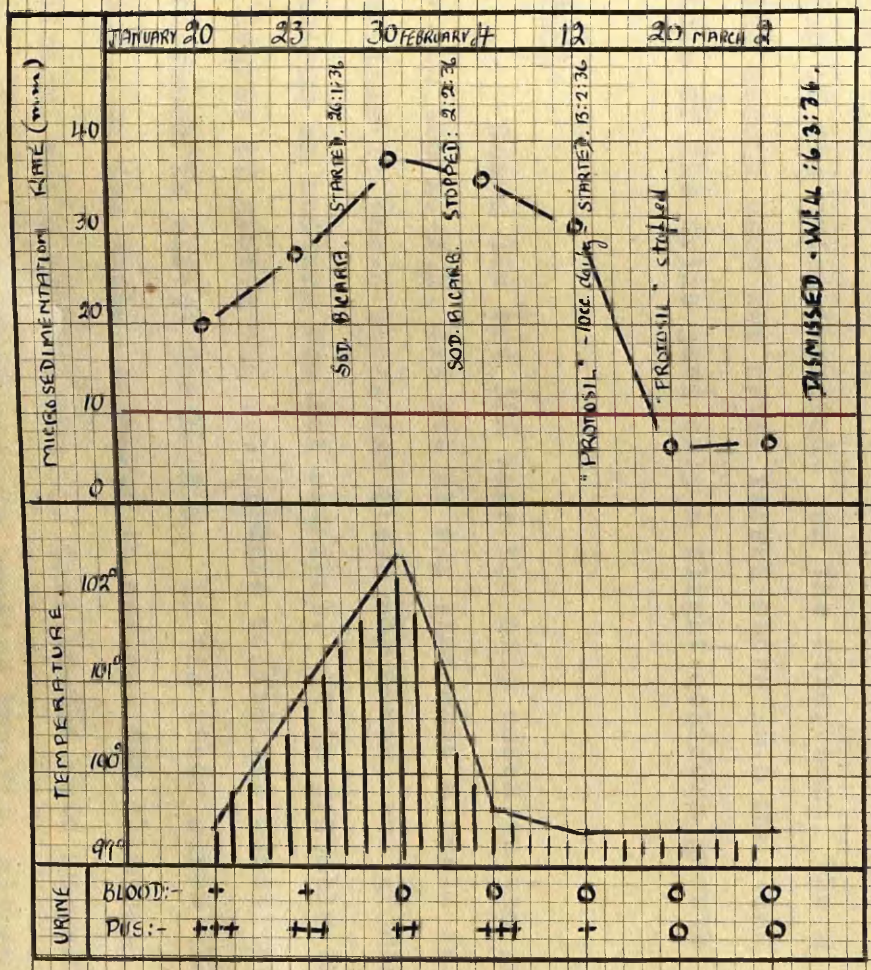


CHART 33. - N.G. - ACUTE PYURIA

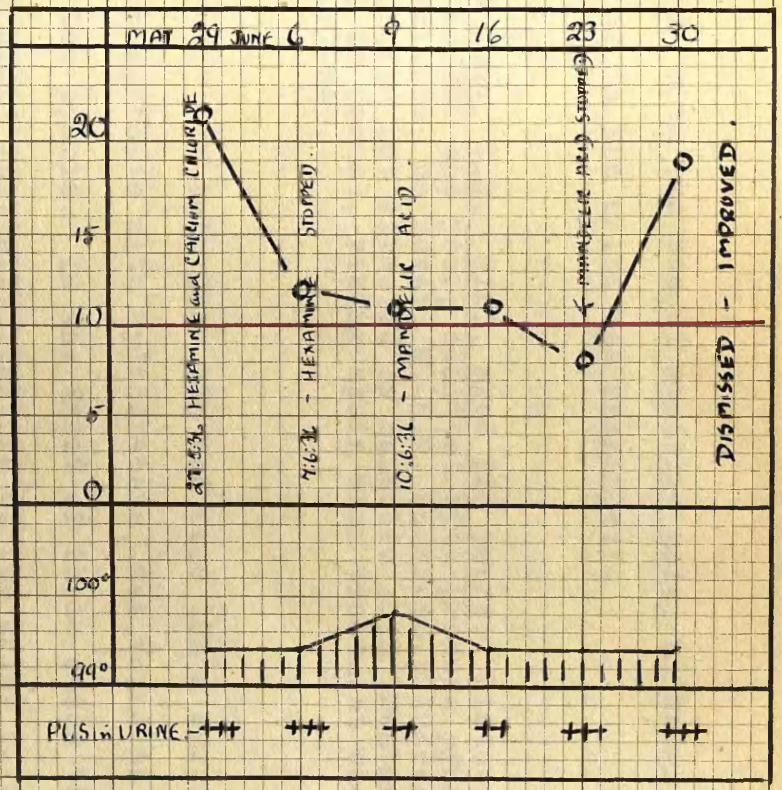


CHART 34. - E.R. - CHRONIC PYURIA.

dently with the use of mandelic acid, although the amount of pus in the urine was unchanged:-

Case 151. C.R. Girl, aged 12½ years: history of persistent pyuria for one year; admitted with profuse pyuria, coliform on culture; no fever; M.-S.R. moderately increased; degree of pyuria not affected by mandelic acid treatment, but M.-S.R. fell to normal, rising again when treatment was omitted (Chart 34).

In both Case 150 and Case 152 a surgical condition, hydronephrosis with hydroureters, was found to be responsible for the pyuria. In the first of these cases the M.-S.R. was very high initially, culture of the urine giving a heavy growth of bacillus coli, and it fell gradually as the condition of the urine improved. On the other hand, the M.-S.R. in the second case was never raised above 10.5 mm., and culture of the urine gave only a slight coliform growth.

Remarks.

Cases 149 and 152 were the only cases in the group in which the M.-S.R. did not at any time show a rapid value. In neither of these cases was there any fever, and growth of organisms on culture was not abundant. It is probable that the degree of pyuria did not produce sufficient constitutional disturbance to affect the M.-S.R. In the other cases the M.-S.R., on the whole, appeared to reflect the clinical condition; while in Case 150 the fall in the rate suggested that mandelic acid treatment was causing benefit, although the

degree of pyuria was unchanged. The delay in reaching normal values, as in Cases 144, 146 and 147, was apparently unimportant, when clinical recovery was present, and culture of the urine sterile.

SUMMARY OF FINDINGS.

Both in acute nephritis and acute pyuria the M.-S. readings were at first high, and tended to fall gradually towards normal as clinical improvement took place. In most cases this fall did not reach normal values until a variable time after the other findings. The significance of this delay is not apparent, unless it be due to the persistence of physico-chemical changes, which might be expected to reach their normal equilibrium some time after recovery from the causal infection is clinically apparent. Whatever the explanation, a raised M.-S.R. in the presence of clinical recovery did not appear to have any untoward significance.

In one case of nephrosis and two cases of chronic pyuria high M.-S. values were found; but in two other cases of chronic pyuria the M.-S.R. was not appreciably raised, and it is suggested that in such patients there is an absence of constitutional disturbance sufficient to affect the sedimentation.

It cannot be claimed that performance of the M.-S.R. on these cases of urinary tract disease gave more information than could be obtained by the usual careful clinical examination, and culture of the urine.

VI. DISEASES OF THE GASTRO-INTESTINAL SYSTEM.

Review of Literature.

Few references dealing with the behaviour of the sedimentation rate in gastro-intestinal disorders, either in children or adults, have been found in the literature. GRAM[42] considered that most diseases of the gastro-intestinal system showed normal sedimentation rates, apart from any increase which might be due to the effect of anaemia; while WESTERGREN[129] believed that irregular values occurring in some of his cases were caused by diarrhoea. REICHEL,[107] reviewing the work done on gastro-enteritis in children, stated that in this disease there was no hard and fast rule for the sedimentation rate, which varied without apparent relation to the other clinical findings. He suggested that the low values found in pyloric stenosis were probably due to dehydration. HADEN and ORR[48] investigated the sedimentation rate in dogs, in which an obstruction of the upper gastro-intestinal tract had been experimentally produced, and found that the rate rose rapidly after this operation, being affected much more quickly than were the level of the chlorides and the non-protein nitrogen.

In diseases of the liver, REES-WALTON[108] reported in certain cases a slow rate, but in other apparently identical cases, a rapid one. In an endeavour to explain these findings, he investigated the results of adding bile-salts to blood

"in vivo" and "in vitro", and considered that, when retention of the salts occurred in the blood stream, there were three phases:-

Phase I, when the concentration of bile-salts was not increased sufficiently to effect a slowing of the sedimentation rate, because the plasma proteins were able to absorb these salts.

Phase II, where the cholaemia surpassed the power of absorption of the proteins, with the result that the excess of bile-salts increased the suspension stability of the red cells, thereby diminishing the sedimentation rate to such an extent that it was difficult to attach importance to the employment of this reaction in the presence of inflammatory conditions or neoplasma.

Phase III, where the reactionary power of the organism was elevated and the effect of the bile-salts became nullified, when the sedimentation rate would again be influenced by the pathological process.

He suggested that this hypothesis would help to explain the paradoxical results.

LANDAU,[68] out of twenty cases of epidemic hepatitis, found an increased microsedimentation rate in eighteen, and a normal rate in two. He believed that a considerably increased rate pointed to a more seriously protracted process, while continued high values were an unfavourable prognostic sign.

Personal Observations.

Fifty-one cases in all were investigated, composed as follows:-

Gastro-enteritis	-	Thirty-four cases.
Ileo-colitis	-	Five cases.
Diseases of the Liver	-	Seven cases.
Miscellaneous	-	Five cases.

GASTRO-ENTERITIS.

Table 41 gives details of the thirty-four cases in this group. Many of them were complicated by the development of some other disease, such as bronchopneumonia, frequently a terminal event. In several cases, especially where dehydration was a prominent feature, difficulty was found in obtaining a sufficiently free flow of blood to perform sedimentation. The mortality of the entire group was 67.7 per cent., but, if the uncomplicated cases are considered separately, the mortality was exactly 50 per cent., which latter agrees with the hospital figures for gastro-enteritis occurring in the summer of 1935.

Recoveries.

Eleven cases were dismissed either "well" or "improved", and Table 42 is given to show the M.-S. reading before dismissal in these patients. The children who were

Table 41 - Gastro-enteritis - Review of Cases.

Case	Initials	Age (yrs.)	Complications	Range of M.-S.R. (mm.)	Result
153	P.N.	4/12	-	5-10	Dismissed well
154	G.B.	3/12	Bronchopneumonia	30-35	Died
155	D.B.	6/12	-	10-15	Died
156	A.S.	5/12	-	10-25	Dismissed well
157	G.W.	6/52	Tetany	0-10	Died
158	W.K.	7/52	-	0-10	Died
159	A.G.	3/366	Sub-dural haemorrhage	5-10	Died
160	E.C.	13/52	-	30-40	Died
161	J.McL.	4/12	Bronchopneumonia	0-5	Died
162	W.C.	6/12	-	10-15	Died
163	M.McC.	3/12	Mental defect	10-30	Died
164	J.D.	3/12	-	10-15	Dismissed well
165	J.L.	10/52	-	5-15	Dismissed improved
166	D.S.	1	-	10-15	Dismissed improved
167	S.D.	6/12	-	5-10	Died
168	C.F.	4/12	-	5-10	Dismissed improved
169	S.H.	14/52	-	5-15	Died
170	W.C.	4/12	-	0-5	Died
171	W.McC.	3/12	Bronchopneumonia	0-5	Died
172	M.R.	5/52	-	10-15	Dismissed improved
173	J.F.	7/52	Tetany	0-20	Died
174	I.B.	3/12	-	20-25	Died
175	D.C.	5/12	-	5-10	Dismissed well
176	C.M.	4/12	-	5-15	Dismissed improved
177	J.P.	6/52	Bronchopneumonia	10-25	Died
178	A.S.	6/12	-	0-5	Dismissed well
179	J.G.	14/52	-	10-25	Died
180	W.S.	10/365	Icterus gravis	0-5	Died
181	J.McF.	5/12	Tetany	0-5	Died
182	M.W.	6/52	Pachymeningitis haemorrhagica	5-20	Died
183	V.D.	10/12	Bronchopneumonia	0-15	Died
184	J.McK.	8/52	Sinus thrombosis	5-10	Died
185	C.M.	7/12	-	0-10	Dismissed well
186	T.W.	7/12	Bronchopneumonia	0-10	Died

dismissed as "improved" were not completely recovered, but were sufficiently so to be allowed home, owing to the danger of fresh infection if they had been kept in hospital.

Table 42.

Gastro-enteritis - Recoveries.

Case	Initials	Age (years)	M.-S.R. before dismissal (mm.)	State on dismissal
153	P.N.	4/12	7	Well
156	A.S.	5/12	15.5	Well
164	J.D.	3/12	10.5	Well
165	J.L.	10/52	11.5	Improved
166	D.S.	1	10.5	Improved
168	C.F.	4/12	7	Improved
172	M.R.	5/52	12	Improved
175	D.C.	5/12	9.5	Well
176	C.M.	4/12	7	Improved
178	A.S.	6/12	3.5	Well
185	C.M.	7/12	1.5	Well

It will be seen that all these cases were dismissed with a M.-S.R. either below the upper limit of normal readings, or only slightly above it. No case was complicated by the presence of another disease, and in none was a high M.-S. value recorded during their stay in hospital. In most, the readings varied between 0 mm. and 15 mm., and did not appear to reflect the clinical condition. The following case

illustrates the typical findings:-

Case 156. A.S. Boy, aged 5/12 years: history of diarrhoea and vomiting for one week; no dehydration; no fever; M.-S.R. slightly raised at first (13 mm.), but fell to normal within a week, rising again to 23 mm. three weeks later, although there was no diarrhoea, and child was apparently improving; rise not due to anaemia, as blood count was normal; M.-S.R. fell before dismissal, but not below upper normal limit (Chart 35).

In this case there may have been some focus of infection which was not discovered by clinical examination, and was responsible for causing the rise in the M.-S.R. If so, it was not sufficiently acute to affect the child's progress to recovery.

Fatal Cases.

Tables are given to show the M.-S. reading before death in fatal cases of uncomplicated gastro-enteritis (Table 42), and in gastro-enteritis complicated by inter-current disease (Table 43).

Table 42.

Gastro-enteritis - Uncomplicated Fatal Cases.

Case	Initials	Age (years)	M.-S.R. before death (mm.).	Time before death when M.-S. reading taken
155	D.B.	6/12	11	One day
158	W.K.	7/52	5	Four days
160	E.C.	13/52	36	Day of death
162	W.C.	6/12	12	Four days
167	S.D.	6/12	7	One day
169	S.H.	14/52	15	Two days
170	W.C.	4/12	3	Five days
174	I.B.	3/12	23	Two days
179	J.G.	14/52	11	One day

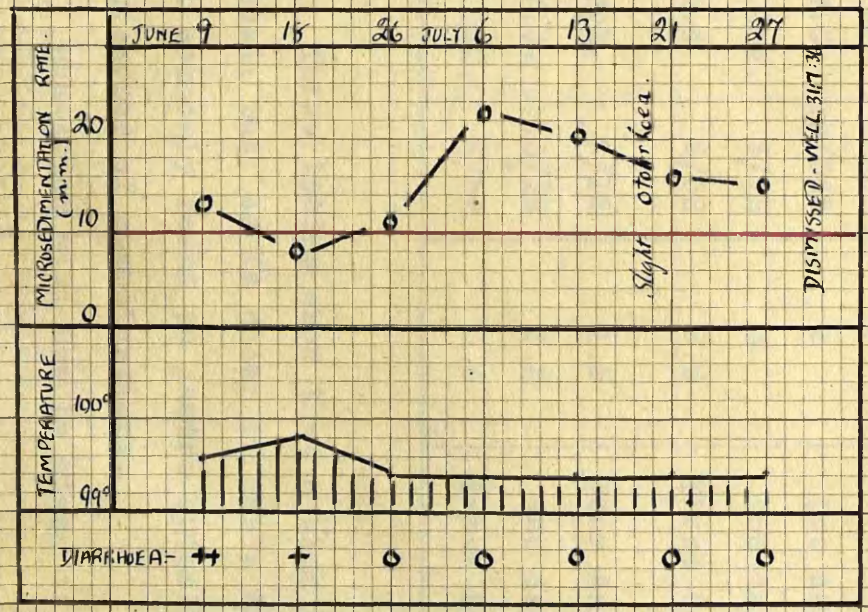


CHART 35 - A.S. - GASTROENTERITIS.

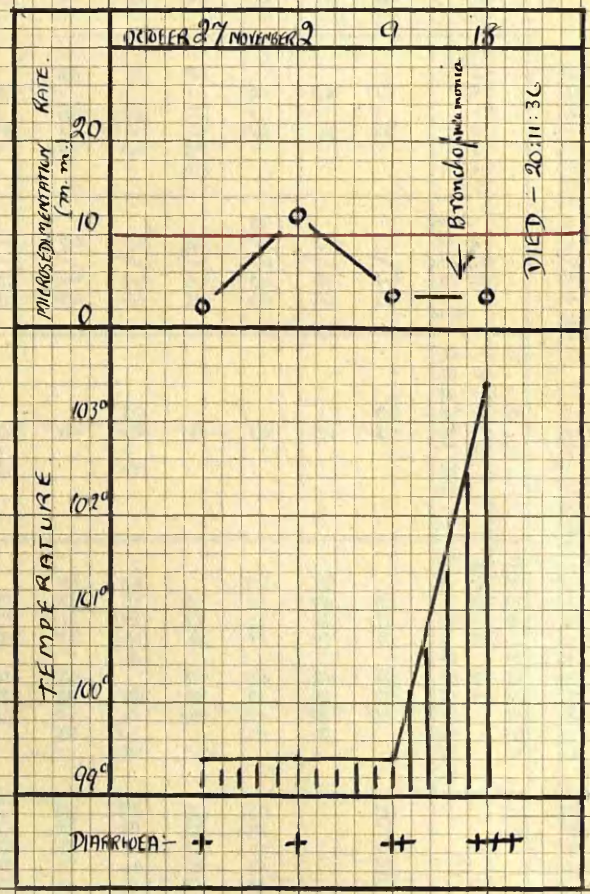


CHART 36. - V.D. - GASTROENTERITIS.

Table 43.

Gastro-enteritis with Complications - Fatal Cases.

Case	Initials	Age (yrs.)	M.-S.R. before death(mm.)	Time before death of M.-S.reading	Complication
154	G.B.	3/12	32	One day	Bronchopneumonia
157	G.W.	6/52	3	Four days	Tetany
159	A.G.	3/366	6	Four days	Subdural haemorrhage
161	J.McL.	4/12	4	One day	Bronchopneumonia
163	M.McC.	3/12	29.5	Three days	Mental defect
171	W.McC.	3/12	4	Four days	Bronchopneumonia
173	J.F.	7/52	3.5	One day	Convulsions
177	J.P.	6/52	10.5	Seven days	Bronchopneumonia
180	W.S.	10/365	2	Two days	Icterus gravis
181	J.McF.	5/12	5	One day	Tetany
182	M.W.	6/52	8.5	Three days	Pachymeningitis haemorrhagica
183	T.W.	7/12	1.5	Four days	Bronchopneumonia
184	V.D.	10/12	3.5	Two days	Bronchopneumonia
186	J.McK.	8/52	6.5	Three days	Sinus thrombosis

These tables show that a high M.-S.R. before death was unusual; but, as is shown in Table 41, high M.-S. readings were not commonly found in gastro-enteritis at any time, even in the presence of complications.

Summaries will now be given of three illustrative cases:-

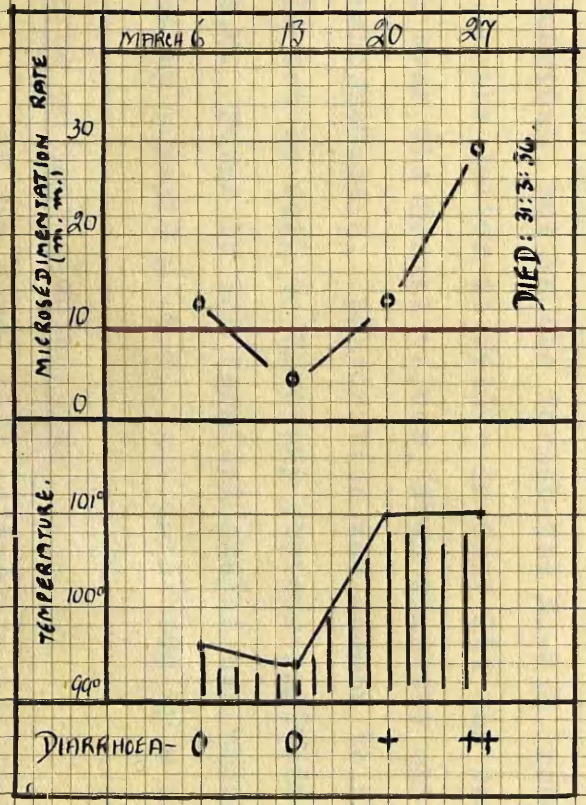


CHART 37 - M. MIC. - GASTRO-ENTERITIS.

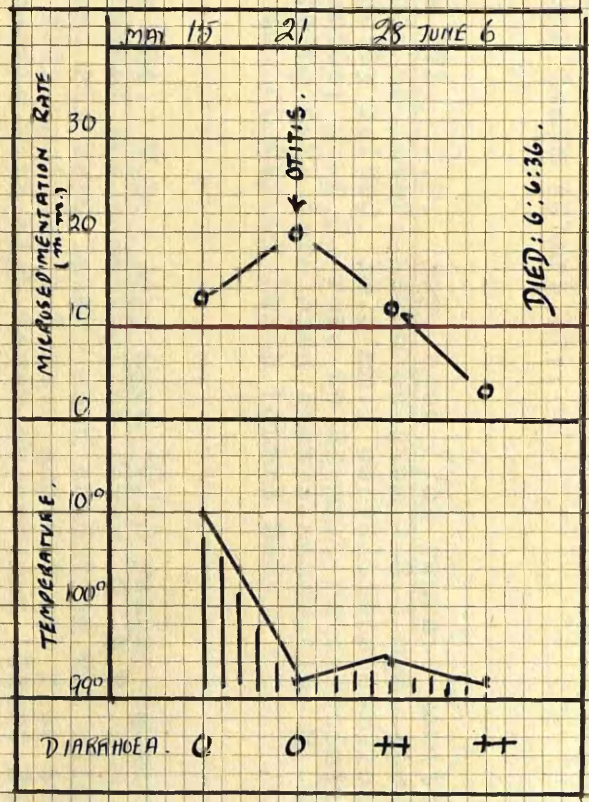


CHART 38.- J. F. - GASTROENTERITIS.

Case 163. M.McC. Girl, aged 3/12 years: admitted with nasal catarrh and convulsions; gastro-enteritis with fever developed; M.-S.R. rose from normal to a high value (29.5 mm.) before death (Chart 37).

Case 173. J.F. Boy, aged 7/52 years: admitted in convulsions; no fever; serum calcium - 8.0 mgm. per cent.; M.-S.R. slightly raised, 13.5 mm., convulsions controlled by calcium chloride; M.-S.R. rose to 20 mm., in association with discharging ear; developed gastro-enteritis; M.-S.R. fell to 3.5 mm. on day of death (Chart 38).

Case 184. V.D. Boy, aged 10/12 years: admitted with diarrhoea and vomiting; no fever; M.-S.R. 2.5 mm., rose to 12 mm. six days later, when condition was slightly improved, but fell again to 3.5 mm., and did not rise even when bronchopneumonia with high fever supervened (Chart 36).

These three cases illustrate the varying behaviour of the M.-S.R. in fatal cases of gastro-enteritis. In Cases 163 and 173 the gastro-enteritis developed while the child was in hospital, but in the former the M.-S.R. rose before death, and in the latter it fell. In Case 184 the rate was never much over the normal values, even when the child developed bronchopneumonia. Dehydration was common to all cases, and could not be said to have any obvious influence on the M.-S.R. Fever in the terminal stages was accompanied in some cases by a rapid M.-S.R., and in others by a normal rate.

Remarks on Gastro-enteritis.

It was hoped that estimation of the M.-S.R. in gastro-enteritis might give some information regarding the

prognosis of the disease, but this hope was not fulfilled. In general, M.-S. values were not much above the upper normal limit at any stage of the disease and, when rapid rates were found, there was often no clinical explanation discovered. LANDAU[68] also recorded variations of the M.-S.R. in infants while in hospital, which were not explained by any change in the clinical condition. He believed that these variations were due to occult nosocomial infections. Against this suggestion, however, is the finding of normal values in several cases where the enteritis was associated with a definite infection, such as bronchopneumonia. There was no uniformity of behaviour of the M.-S.R. in cases where a fatal issue was imminent. In some there was a fall in the rate, in others a rise, and in others still the rate continued relatively unchanged. No explanation for these variations, such as the presence of dehydration or fever, was found to be satisfactory.

ILEO-COLITIS.

In four cases of acute ileo-colitis a raised M.-S.R. was found during the acute stages, with a return to normal values when the patient recovered. One chronic case was followed for a period of two months, and is of interest, as the injection of anti-dysenteric serum was followed by a temporary rise in the M.-S.R.

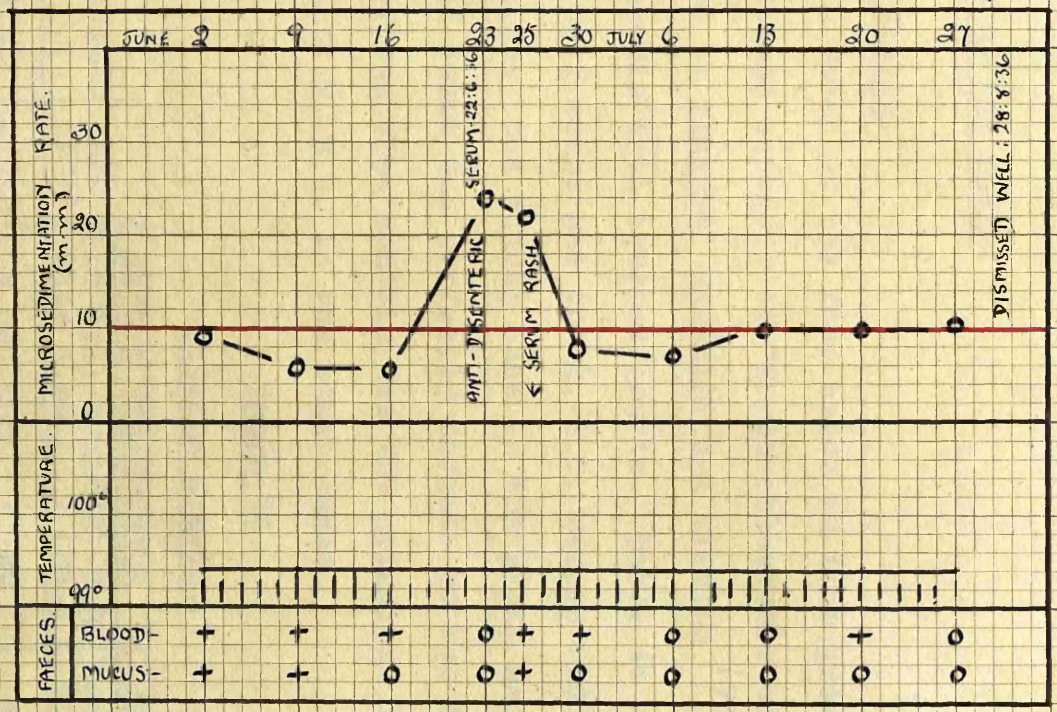


CHART 39. - A.S. - ILEO-COLITIS.

Case 187. A.S. Boy, aged $10\frac{3}{4}$ years: admitted with ileo-colitis which had persisted for six weeks; investigation by X-ray and sigmoidoscope, and stool culture all gave negative results; M.-S.R. kept within normal limits, apart from a sharp and temporary rise after the giving of anti-dysenteric serum (Chart 39).

DISEASES OF THE LIVER.

Icterus Gravis.

Three of the four cases in this group were examples of the second category of "Erythroblastosis of the New-born," described by PARSONS, HAWKSLEY and GITTINS,[91] namely, haemolytic anaemia with icterus gravis. Table 44 is given to show the red cell count and the M.-S.R. before and after blood transfusion. The fourth case in the group was jaundiced, but the blood count was perfectly normal, as was the M.-S.R., and it is obvious that anaemia was the principal factor responsible for a rapid M.-S.R. in the other cases.

Table 44.

Icterus Gravis.

Case	Initials	Age (yrs)	BEFORE TRANSFUSION		AFTER TRANSFUSION	
			Red Cell Count (per c.mm.)	M.-S.R. (mm.)	Red Cell Count (per c.mm.)	M.-S.R. (mm.)
188	W.S.	10/365	2,030,000	29	4,270,000	10
189	J.D.	13/365	1,200,000	32	2,560,000	19
190	McI.	5/365	3,400,000	14	5,670,000	2
191	M.R.	12/365	8,000,000	2.5	-	-

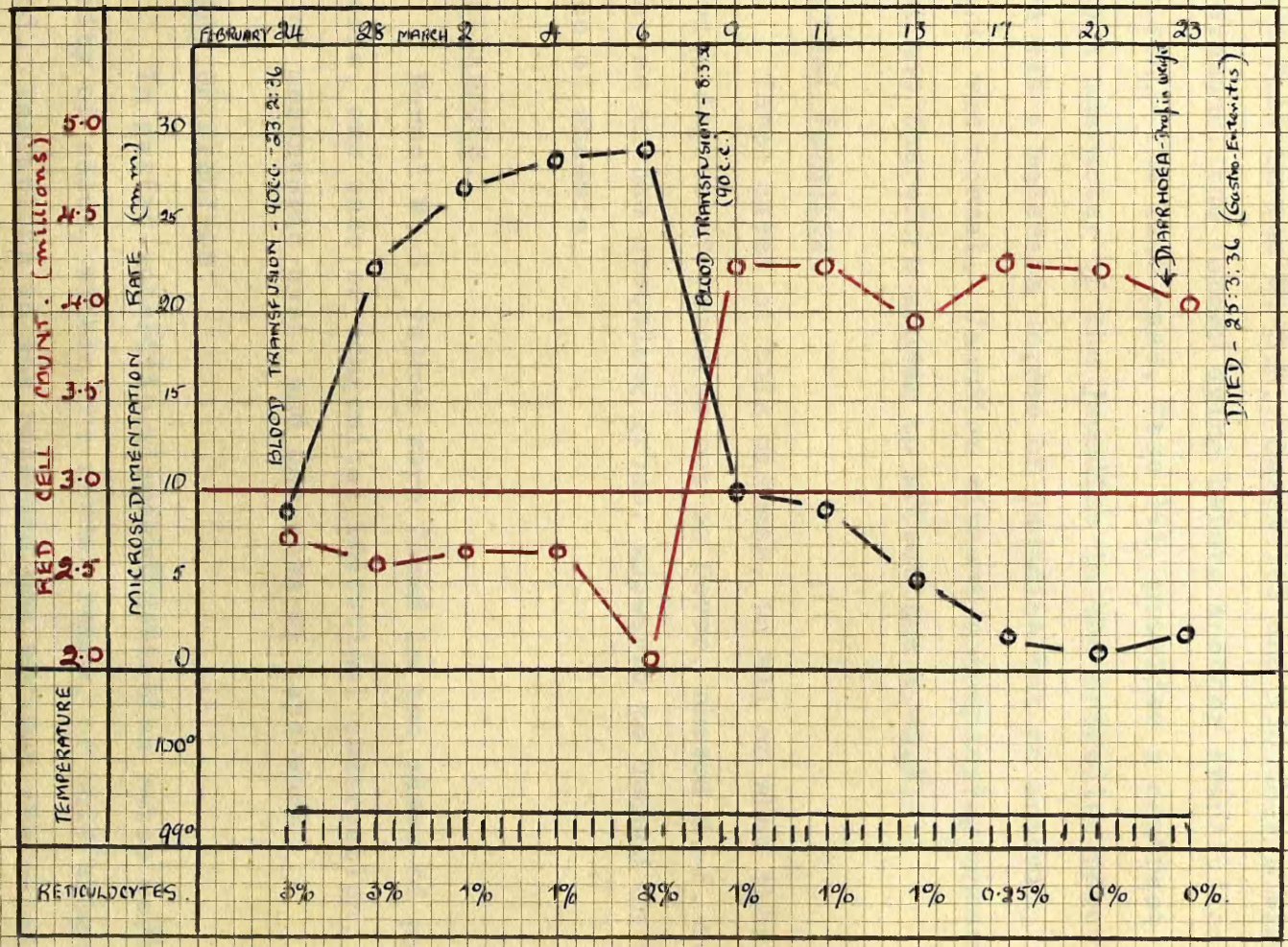


CHART #0. - W. S. - ICTERUS GRAVIS.

The chart of Case 188 is given (Chart 40) as it shows graphically how improvement in the red cell count is associated with a fall in the M.-S.R. Cases 189 and 190 show a similar improvement, the former dying before another transfusion could be given. The last case, Case 191, provides a contrast to the serious character of the jaundice in the preceding three cases. There was a moderate degree of jaundice but no anaemia, and the M.-S.R. was normal. Jaundice without accompanying anaemia would not therefore appear to affect the M.-S.R.

Catarrhal Jaundice.

Three cases of this disease, in all of whom there was a moderate degree of jaundice but no fever, showed M.-S. readings which, as in the preceding group, appeared to depend on the degree of anaemia.

MISCELLANEOUS.

Normal M.-S. values were found in two cases of pyloric stenosis, one case of congenital intestinal obstruction, one case of mesenteric cyst, and one case of tape-worm.

SUMMARY OF FINDINGS.

In gastro-enteritis microsedimentation rates were, in the majority of cases, within the normal range, or only slightly raised. Variations in the rate did not reflect the clinical condition. In cases with complications, a raised M.-S.R. was found in some, but in others the values were normal. A fatal issue was sometimes preceded by a fall in the M.-S.R., and sometimes by a rise, or no change. The conclusion arrived at was that the

estimation of the M.-S.R. was not of value in gastro-enteritis.

In ileo-colitis the M.-S.R. tended to parallel the clinical findings, being raised during the acute stage, with a fall to normal values on recovery.

Jaundice per se did not appear to affect the M.-S.R., raised values in cases with this symptom being usually accounted for by the degree of anaemia present.

Normal values were also found in a number of other gastro-intestinal diseases, which were non-inflammatory in type.

VII. OTHER DISEASES.

In this section are recorded observations on various diseases which were not included under the previous headings.

SEPTIC CONDITIONS.

A. Abscesses.

Observations were made on three children with abscesses. In two of these the abscess was present on admission to hospital; in one case being located in the shoulder-joint, and in the other retroperitoneal. Both cases showed high M.-S. values, between 30 mm. and 40 mm., and were transferred to a surgical ward for operation. In the third case the abscess developed while the child was in hospital, and a short summary will be given:-

Case 192. W.A. Male, aged 5/12 years: admitted with convulsions; serum calcium - 5.6 mgm. per cent.; intramuscular injections of calcium gluconate given; fever and a rise in M.-S.R. preceded by one week the appearance of an abscess in the right buttock; after evacuation of the abscess, clinical condition improved rapidly, and M.-S.R. fell to normal (Chart 41).

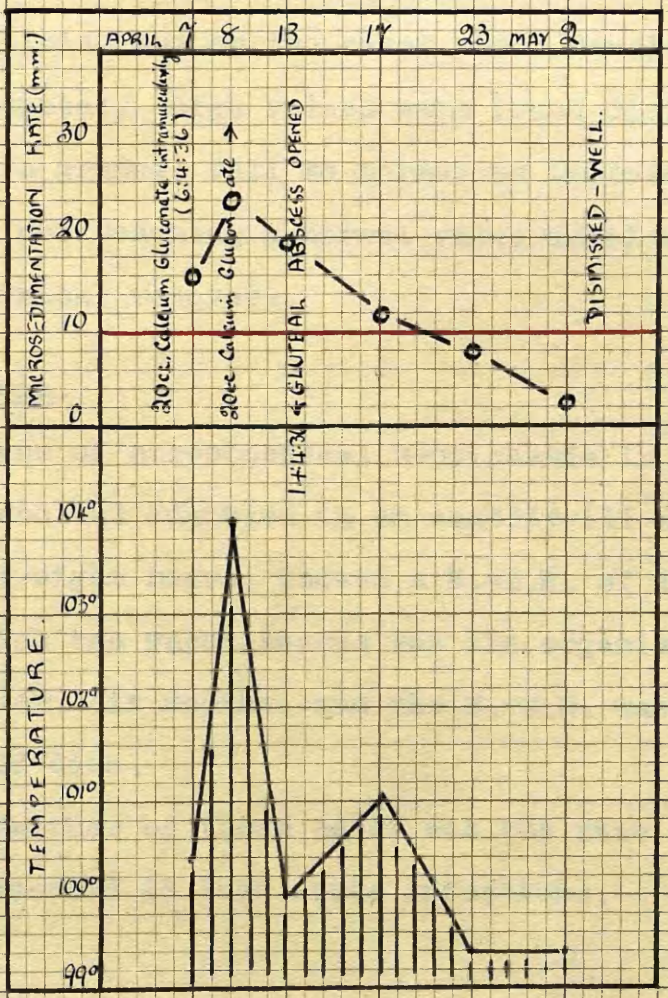


CHART #1 - W. A. - ABSCESS

This high M.-S.R. in the presence of pus might be of assistance in distinguishing an abscess from a non-inflammatory swelling, in doubtful cases.

B. Tonsillitis.

M.-S. readings were done on one case which was admitted with tonsillitis, and on two cases which developed tonsillitis while in hospital. High values were found during the acute stage, with a gradual fall to normal as improvement took place, the M.-S.R. not reaching a normal value until some days after apparent clinical recovery.

C. Septicaemia.

A case of streptococcal septicaemia in a baby of six weeks old, who was admitted in an acutely ill condition and died within forty-eight hours, showed a M.-S.R. of 18 mm. Another case, in which the pneumococcus was the organism responsible, was slightly older, six months, and the M.-S.R. was 28 mm. on the day the child died.

In neither of these cases was the rate as rapid as might have been expected in such acute infections.

CRETINISM.

Two cases of cretinism, in which there was no evidence of other forms of disease, showed normal M.-S. values. In two other cretins, in whom intercurrent disease, gastro-enteritis in one case and tetany in the other, was present, the M.-S.R. was slightly raised.

DIABETES.

References in the Literature. Neither REES-WALTON[108] nor LANDAU[68] found any increase in the sedimentation rate in diabetics. NITZESCU and GAVRILA,[87] however, from observations on thirty-two cases of diabetes of varying severity, considered that the rate was increased in clinical diabetes, the increase being in direct proportion to the severity of the disease. In three cases of severe diabetes, after long insulin treatment, although the other symptoms were improved to the verge of disappearance, the sedimentation rate was only slightly lowered, without returning to normal; and they believed that this indicated that the sedimentation depended on factors which were very little influenced by insulin. As regards this latter theory, PICO, FRANCESCHI and NEGRETE[99] estimated the sedimentation rate in horses before and after the intravenous injection of one hundred units of insulin, and obtained very inconstant results. They found, however, one interesting point - that the horse with a rapid rate before the injection of insulin showed a more marked hypoglycaemia after the injection than the horse with a slow rate.

Personal Observations.

Observations were made on four cases of diabetes in the wards. Two of these were admitted on account of an upset of the carbohydrate tolerance caused, apparently, by coryza; and in both the M.-S.R. was at first raised. In the other two cases, although sugar and acetone were present in the urine initially, the M.-S.R. was well within the normal limit. A summary is given of the following case, in which M.-S. readings were made for a period of almost four months:-

Case 193. W.D. Boy, aged 12 years: history of a previous admission to hospital in 1930; disturbance of carbohydrate tolerance for four weeks following a "cold in the head"; admitted on 7.2.36; von Pirquet and Mantoux tests, negative in 1930, now positive; sugar and acetone in the urine; X-ray showed increase in the mediastinal and hilum shadows; occasional rise in temperature during first fortnight in hospital; difficulty found in adjusting insulin requirement, which rose as high as 185 units on 27.4.36, but thereafter fell, reaching 115 units before dismissal on 2.6.36; M.-S.R. moderately increased at first, but fell slowly to normal values (see Chart 42). Readings taken on two occasions during hypoglycaemic coma were both normal.

In this case it appears reasonable to suggest that the upset of carbohydrate tolerance was possibly due to the patient passing through his primary tuberculous infection; the evidence being the slight degree of fever, and the fact that the cutaneous tuberculin reactions, previously negative, had become positive. The M.-S.R. was raised for a period of two months after admission, during which the insulin requirement steadily rose. After the M.-S.R. had reached, and kept, normal values, however, the insulin requirement began to fall rapidly, indicating a return to the original carbohydrate tolerance. Thus the M.-S.R. apparently reflected the activity of the underlying condition (primary tuberculous lesion ?). If this explanation is correct, the test would be of value in assessing the presence of, degree of activity, and response to treatment of intercurrent disease in diabetics.

Blood Sugar and M.-S.R.

Simultaneous estimations of the blood sugar and the

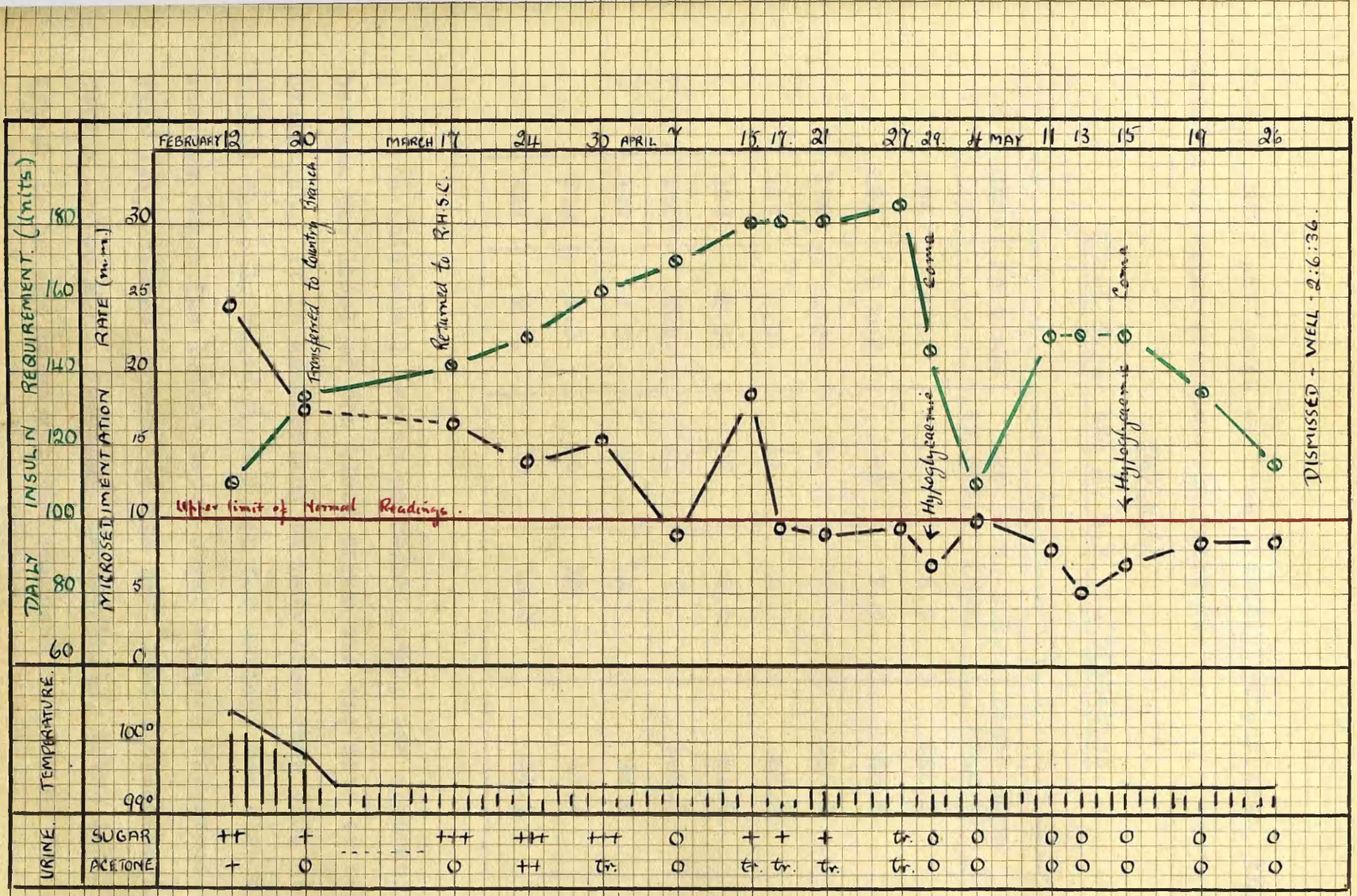


CHART #2. - W.D. - DIABETES.

M.-S.R. were performed on nine diabetic outpatients, the results of which are shown in Table 45.

Table 45.

Blood Sugar and M.-S.R. in Diabetics.

Case	Initials	Age (years)	M.-S.R. (mm.)	Blood Sugar (mgm.%)
194	T.D.	10	8.5	222.2
195	L.McB.	2½	7.5	50.5
196	A.G.	15	9	206.2
197	P.D.	11	6	67.7
193	W.D.	12	8.5	81.9
198	W.D.	11	7	108.1
199	J.L.	12	14	98.0
200	M.G.	14	23	45,4
201	M.C.	10	10.5	54.3

In this small series no relationship was apparent between the level of the blood sugar and the rate of sedimentation. It is interesting to note that Case 200, which showed the only rapid M.-S.R. in the series, was also the case in which the lowest blood-sugar reading was recorded. Case 195, however, which had the next lowest blood-sugar, gave a normal M.-S. reading. Incidentally, there did not appear to be any cause for the increase in M.-S.R. in Case 200 as the child was apparently well.

PINK DISEASE (Erythroedema polyneuritis).

Microsedimentation readings were done on three cases of this disease, short notes on which follow:-

Case 202. M.L. Girl, aged $1^{4}/12$ years: M.-S.R. normal, but this child died very suddenly from a bronchopneumonia lasting a few hours; M.-S. reading on the day before death was 10 mm.

Case 203. P.K. Boy, aged $10/12$ years: improved while in hospital, but dismissed before complete recovery, owing to risk of other infection; M.-S.R. varied between 10 mm. and 15 mm., and was 14.5 mm. prior to dismissal.

Case 204. F.F. Girl, aged $7/12$ years: admitted with nasal catarrh and conjunctivitis; no fever; M.-S.R., 18 mm., developed diarrhoea with fever one week later, and M.-S.R. rose to 26 mm.; removed by parents against advice.

Remarks.

As might be expected in a disease where the patient is particularly susceptible to various infections, the M.-S.R. was raised in two of these cases. In the third case, however, the normal M.-S. reading gave no indication of the approaching bronchopneumonia, which was to prove fatal.

CONGENITAL HEART DISEASE.

WOOD[135] reported that uncomplicated cases of congenital heart disease showed a normal sedimentation rate, where cyanosis was not a feature, while in two cases with cyanosis he found very low values.

Personal observations on two cases, one a boy of eight years and the other a boy of four years, showed a moderately increased M.-S.R., 18 mm. and 20 mm. respectively, on admission to hospital; slight cyanosis being present in the former. In both, the rate fell to a normal value before the child was dismissed. A third case, in a baby of three months, showed no cyanosis, and had a M.-S.R. varying between 10 mm. and 15 mm. In this case, however, there was a moderate degree of anaemia (four million erythrocytes per cubic millimetre), which was probably partly responsible for the slight increase of the M.-S.R. above the upper limit of normal.

MALIGNANT DISEASE.

Tumours of the nervous system have already been considered in that section. Notes are given here of two other cases of malignant disease:-

Case 205. A.W. Boy, aged $7^{6}/12$ years: advanced stage of Lymphadenoma, with large glandular masses in the neck and axillae, and a secondary anaemia of from three to three-and-a half million red cells per cubic millimetre. The M.-S.R., estimated at weekly intervals for a period of one month, gave readings varying between 38 mm. and 42 mm.

Case 206. J.B. Boy, aged 3½ years: admitted in seriously ill condition, with oedema of the face, hands, and feet; and enlargement of the heart, liver and spleen; M.-S.R., 10 mm. on the day following admission, and patient died next day; post-mortem examination showed a tumour of the thymus.

Remarks.

In Case 205 the very high M.-S.R. was undoubtedly due in part to the degree of anaemia; while in Case 206 the relatively low reading was probably a result of the cardiac failure.

RHEUMATOID ARTHRITIS.

Brief notes on three cases of this disease follow:-

Case 207. E.M. Girl, aged 3 years: history of arthritis for six months, following attack of scarlet fever; admitted with fever; M.-S.R. high, 30 mm.; three weeks later much improved and M.-S.R. 15 mm.; reported at the end of three months well, apart from slight thickening of both knee-joints; M.-S.R. now normal, 7 mm.

Case 208. C.C. Girl, aged $3^{8}/12$ years: history of arthritis for ten weeks; admitted with M.-S.R. of 24 mm. This child is still in hospital and improvement is slow; the M.-S.R. showing values between 22 mm. and 34 mm.

Case 209. W.D. Boy, aged 5½ years: time of onset not definitely known; wrist and ankle joints affected; admitted with M.-S.R. of 13 mm., which fell to a normal value at the end of three weeks; marked rise in M.-S.R. after tonsillectomy to 35 mm., remained at high level for five weeks; reached normal value two months after the operation (Chart 43).

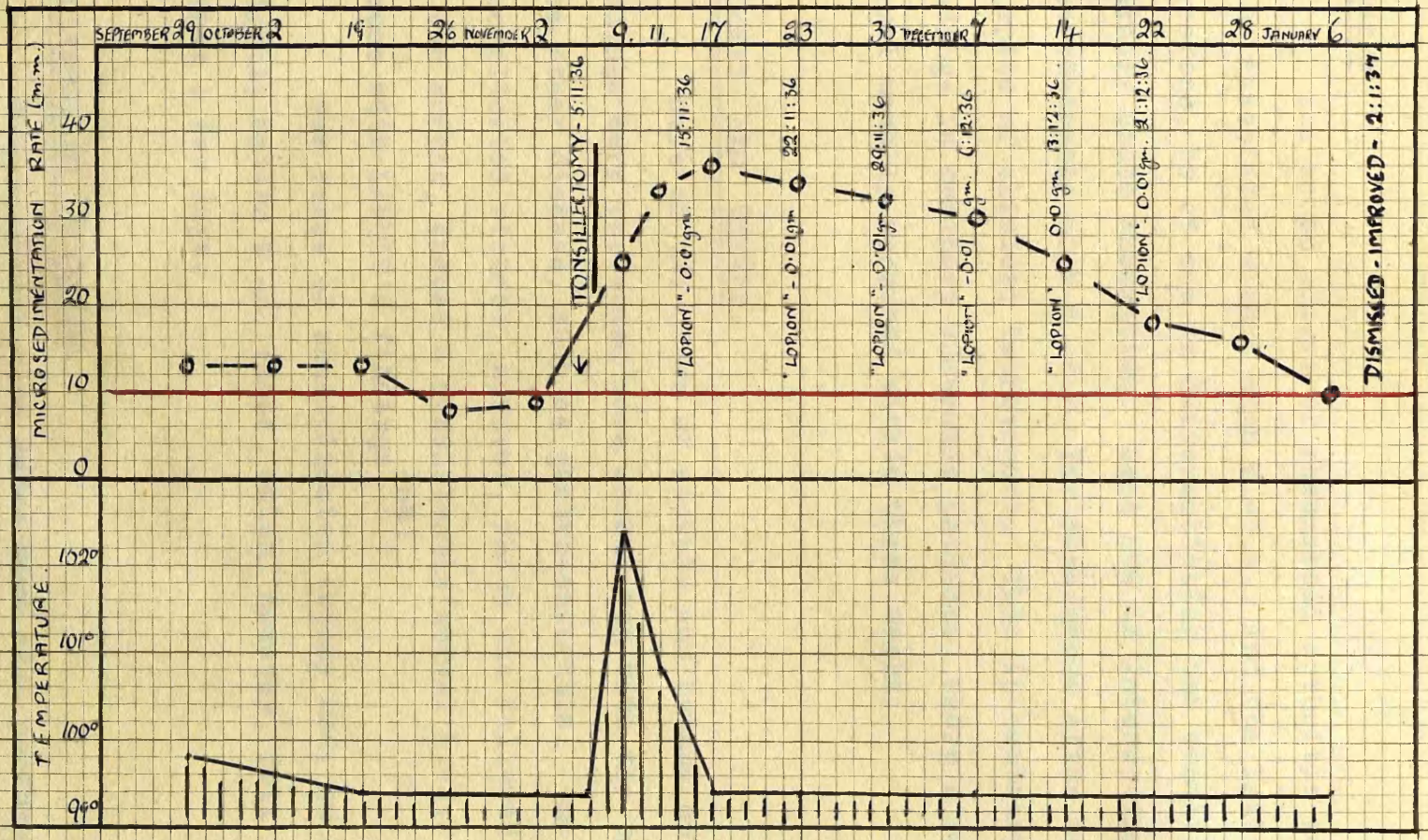


CHART #3. - W.D. - RHEUMATOID ARTHRITIS.

Remarks.

The acute stages of rheumatoid arthritis would appear to be associated with a high M.-S.R., and the latter would not, therefore, be of use in differentiating the condition from ordinary acute rheumatism. Case 209 is interesting, as showing a persistently high M.-S.R. for nine weeks after tonsillectomy, in spite of clinical improvement. This is contrary to the findings in ordinary rheumatic patients, where a return to normal usually occurred within three weeks.

RICKETS AND TETANY.

Most of the cases of rickets and tetany on which M.-S. readings were performed were associated with the presence of some other disease, such as gastro-enteritis. One case of uncomplicated rickets, however, which was followed for a period of two months, showed a consistently normal M.-S.R. (This agrees with LANDAU'S findings[68]).

Two cases of uncomplicated tetany had, on admission, slightly raised M.-S. rates, which, however, fell to normal within a few days.

UNCLASSIFIED DISEASES.

Microsedimentation rates were also performed on cases of coeliac disease, pseudohypertrophic muscular dystrophy, chronic parotitis, general debility and purpura. In all these

cases except the last-named the M.-S.R. was well within normal limits. The case of purpura haemorrhagica showed an increase in the M.-S.R. when the associated anaemia became severe, but a return to normal with improvement in the blood count.

DISCUSSION.

Causation of the Phenomenon. The first question which arises is whether it can be considered that the mechanism of sedimentation, and the factors responsible for its variations are definitely known. The mechanism of sedimentation appears undoubtedly to be related to the size of the particles involved, and the latter is dependent on the degree of agglutination of the red cells. It is a matter of speculation, however, as to what element or elements in the blood affect this agglutination. The most popular theory, which attributes the principal role to fibrinogen, has been already discussed, and is most attractive as an explanation. There does not seem to be any doubt that, in a large number of cases where the sedimentation rate is increased, the blood fibrinogen content is also raised. If this were the invariable finding, the theory would stand on a very sound basis. Several observers have, however, failed to find a definite relationship between the fibrinogen content and the sedimentation rate. PINNER, KNOWLTON and KELLY[100] quote BRIEGER[9] that "the only regularity of the serum protein curve in the healthy and still more in the tuberculous, is its irregularity," and they believe that the fibrinogen-sedimentation rate relationship may well be included in this statement. Personal observations on the blood fibrinogen were not made, as the subject has already

been most thoroughly investigated, and the information likely to be obtained did not therefore, in my opinion, justify the removal of the relatively large amount of blood required. It seems certain that fibrinogen increase is not the only cause of a rapid rate, although it may be one of the causes.

Other blood constituents which have been suggested as having an influence on sedimentation, such as the blood sugar and the blood chloresterol, stand on a much less secure basis than fibrinogen, and their opponents outnumber their advocates. My observations did not support the presence of any relationship between either the blood chloresterol or the blood sugar and the sedimentation rate.

One must conclude that the cause of increased sedimentation of the red cells in disease cannot be attributed to any single factor, but is probably the result of a number of changes, mainly physico-chemical in nature.

Influence of Anaemia. There is no doubt that an obvious degree of anaemia will result in a definite acceleration of the sedimentation rate, but difficulty arises in assessing the importance to be given to this factor. Many writers, such as REES-WALTON[108] and ERNSTENE,[22] consider that anaemia has a purely mechanical effect; the reduction in the number of the red cells enabling them to fall more rapidly. They therefore believe that, by adjusting the sedimentation reading to a

standard blood-count, the influence of anaemia will be eliminated, and the corrected reading give the true state of the disease process. The majority of observers, however, do not agree that the problem is as simple as this, for they find that no constant relationship between the degree of anaemia and the rate of sedimentation occurs in their cases. The results of personal observations incline me to agree with this view. If the exact nature of the phenomenon of sedimentation were known, it might be reasonable to exclude one of the symptoms of disease, such as anaemia, in order to estimate the activity underlying the other symptoms. So long, however, as this is obscure, it is surely better to allow the test to be judged on its clinical merits alone.

In the severe anaemias, such as pernicious anaemia, the very high sedimentation readings are in large measure probably due to the mechanical effect of the reduction in number of the cells, but it has not been suggested that the test is of value in these conditions. In a case of pernicious anaemia Rees-Walton,[108] by correction of the blood count of one-and-a-quarter millions to a standard of five millions, reduced the sedimentation reading from 27.5 to 0.0. It appears rather ridiculous to suggest that the latter reading was a better guide to the state of the patient than the former.

Apart from the question of the desirability of correction for anaemia, the amount of blood which would require

to be withdrawn in order to make the correction renders the procedure quite impracticable for routine use, at least in children. It is probably necessary in cases with a blood count of four millions and under to bear in mind the effect of anaemia when considering the sedimentation readings, but with counts of over four million the influence of anaemia would appear to be relatively negligible.

Choice of Method. In the chapter on "Methods" the question of whether a macromethod or a micromethod should be used was discussed. The conclusion drawn from the literature, and supported by personal observations, was that the macromethod gave the wider range of readings, but that the micromethod was sufficiently reliable for practical purposes. Granted this latter premise, the micromethods have an overwhelming advantage over the macromethods for use in children. Few children come to regard venepuncture with equanimity, whereas it may equally truly be said that few children continue for long to regard a prick in the ear, which gives a momentary sensation of pain, with any feeling of dread. I feel strongly that the sedimentation test does not afford information of sufficient value to justify the pain and discomfort caused by venepuncture. The use of the latter in hospital is possible, but in private practice it would be impracticable as a routine weekly measure.

Having decided on the use of a micromethod, the question arises as to which micromethod, and the apparatus devised by Landau appears to me to have considerable advantages over any other, and to possess no disadvantage peculiar to itself. It is simple to use, and promises greater accuracy than any of the other micromethods. It has also one great advantage, that the blood sample can be taken in the patient's home, and the result read within a period of six hours afterwards, at the doctor's convenience. This means that the method, unlike any other, is capable of use by the busy general practitioner. Comparison of this method with a modified Westergren macromethod showed that the clinical deductions from both methods were similar in the normal and moderately increased values, while discrepancies were found only when the high values were reached. In the majority of cases the micromethod readings were just as informative as the corresponding macromethod readings.

Accuracy of Readings. It cannot be claimed that readings can be made accurately to within one millimetre, and a certain degree of latitude must be allowed. It was remarkable, however, how constant, within two to three millimetres, readings taken weekly remained in, for example, a case of uncomplicated chorea. LANDAU[68] found that the M.-S.R. in his series of healthy "controls" did not exceed an upper limit of 9 mm., and there-

fore considered all readings between 0 mm. and 9 mm. as "normal". The M.-S.R. in a series of forty cases personally observed, who were considered clinically healthy when the M.-S.R. was performed (Table 46), varied between 1 mm. and 10 mm., which has been considered the "normal" range in the present investigation.

Table 46.

Normal Readings.

Age (years)	Number of Cases	Microsedimentation Rate (mm.).		
		1-5	5-10	Over 10
0-1	11	10	1	0
1-5	9	6	3	0
5-12	20	10	10	0

All but one of these children under one year of age showed a M.-S.R. of 5 mm. or less, and it is therefore probable that a M.-S.R. of, say, 9 mm. in an infant is abnormal, but this increase is hardly sufficient to be of value.

Influence of Various Factors. It seems to be established that the sedimentation rate increases slightly with age, and is relatively more rapid in women than in men, no difference between the sexes being found in childhood. The influence

of the length and bore of the tube used, and of the temperature at which readings are taken, is not great, provided that these factors are constant for the particular method used. In this connection it may be mentioned that Landau's tubes are uniform, and that all readings were made at ordinary room temperature. It is important that the tube in which sedimentation is taking place should be kept vertical, otherwise the reading will be affected.

Some writers have suggested that the use of sodium citrate solution as an anticoagulant, by its action in diluting the blood, introduces a serious fallacy into the test, and they advocate its replacement by powdered oxalate, or hirudin. It is not unlikely that this procedure would cause all readings to be rather lower than with citrate solution, but no proof has been offered that the value of the test would be in any way enhanced. Certainly the vast majority of observers are satisfied that citrate solution is sufficiently reliable, and continue to use it. The exact strength of the solution used does not appear to be important.

Other factors, such as ingestion of food, muscular exercise, and emotion do not appear to have any recognisable influence on the rate of sedimentation.

Time of Reading. Certain observers, e.g. WESTERGREN,(129) advocate readings of the sedimentation at two hours, four hours, and twenty-four hours, as well as at one hour, while CUTLER(18)

improves on this by strongly recommending five-minute readings up to the hour. Such readings may give a more composite picture of the sedimentation, but there does not seem to be any proof that they afford more valuable information regarding the patient's condition than does the one-hour reading. Few observers could afford the time necessary, and indeed the extended readings are usually made by a number of different persons, who are not as a rule punctilious in making the observation at the correct time.

It would certainly simplify the test if readings could be made at the end of a shorter period than one hour, but adoption of such a procedure, unless it could be made universal, would only render the comparison of results even more difficult than it is already.

Points in connection with the Landau Micromethod. One of the objections to the use of a micromethod put forward by certain writers is that, with tubes of such small bore, the level of the red cell column tends to be indefinite at the end of one hour. I have not found this to be the case in more than one or two instances where the M.-S.R. was very rapid; and it is quite simple to repeat the reading in the manner described earlier, the end-point of the second reading being almost invariably distinct. A difficulty much more commonly experienced was in obtaining a free flow of blood from the ear or

heel. If there was a delay in getting the requisite amount of blood, clotting was very apt to take place in the tube, and the reading was spoiled. In many of these cases a second "stab" provided a sufficient flow.

The tubes must, of course, be perfectly dry before use, and it was found to be advisable periodically to steep them in an ordinary cleaning solution overnight, in order to remove the slight film of blood which was apt to collect inside the ampulla. Impacted fragments of blood-clot in the bore of the tube were easily removed by the use of a piece of thin wire.

The Value of the Sedimentation Test.

In the absence of a definitely proved explanation of the phenomenon of sedimentation, the value of the test must necessarily be considered from an empirical standpoint. Opinions as to its general usefulness are varied, but most observers are agreed that the routine estimation of the sedimentation rate is of definite assistance in two important diseases, namely, rheumatism and tuberculosis.

Rheumatism. The great importance of this disease in childhood need not be stressed, and any aid to diagnosis or prognosis would be welcomed. Its seriousness depends on its tendency to affect the heart, and thus cause permanent dis-

ability; and one of the principal problems of its management is to know how long it is necessary to keep the patient at rest. No single symptom or sign can be absolutely relied on for this purpose, and the period of restraint has usually to be arbitrarily fixed. Now it is suggested that the sedimentation rate is a measure of the activity of the disease process, and that it is so sensitive that it reaches normal values only when all traces of this activity have disappeared. This suggestion can not be definitely proved, as there is no means at our disposal for measuring the degree of activity; and its likelihood rests upon the correlation of the sedimentation rate with the clinical findings.

With the important exception of uncomplicated chorea, and congestive cardiac failure, which will be discussed shortly, no case of rheumatism, in which the infection was considered, from careful clinical examination, to be active, showed a M.-S.R. within the normal limits. In most cases, in the early stages, very high rates were recorded, even in the absence of a marked degree of fever. In the presence of steady clinical improvement a slow fall in rate took place, normal readings being recorded many weeks after the other signs of activity, such as fever and an accelerated pulse-rate, had disappeared. If, during this period, there was a relapse of the symptoms, such as a rise of temperature with, perhaps, a return of arthritis, the M.-S.R. rose coincidently. In one case in which this occurred (Case 15), the rise in rate preceded the

clinical evidences, and thus gave warning of the relapse.

In those patients with the most seriously damaged hearts as, for example, the cases of pericarditis, the M.-S.R. during the acute stages gave the highest readings, as would be expected. The Landau micromethod cannot, however, as accurately reflect the variations in such patients' condition as would a macromethod, as it is limited to a maximum reading of about forty-two millimetres. Improvement is usually associated with a falling M.-S.R., but there is one important exception to this rule - congestive cardiac failure. The onset of the latter generally results in a well-marked fall in the M.-S.R., and such a fall in a seriously ill cardiac patient is a sign of grave omen. In one of my cases of pericarditis (Case 12) an unexplained drop in rate was one of the earliest signs that death was imminent. A low M.-S.R. in a patient with cardiac failure does not, however, always indicate a fatal prognosis. In another case (Case 13), admitted with a marked degree of congestive heart failure, the rate was at first very low, and rose gradually when the signs of failure began to disappear, eventually reaching a high value. Here the rising M.-S.R. was a good prognostic sign, as it indicated that the heart was recovering.

The presence of subcutaneous rheumatic nodules over bony prominences is commonly considered to indicate a more serious prognosis, but it has been found that, where such

nodules are associated with a falling sedimentation rate, the prognosis is good, and disappearance of the nodules within a short period can be expected (see Case 37).

In chorea, one finds an exception to the rule that the sedimentation rate is increased in the rheumatic infection, worthy of comment, normal readings being found in uncomplicated cases. The explanation of this is not apparent. It may be that certain cases of chorea are not of rheumatic origin, and for these the term "meta-rheumatic chorea" has been suggested. However, in any series of cases of chorea, other manifestations of rheumatism occur with such great regularity that it is impossible not to regard chorea as being, in the vast majority of cases, of rheumatic origin. The normal M.-S.R. would suggest that chorea is a less serious manifestation than arthritis, and there is a certain amount of clinical evidence in support of this view. It is also interesting to find that the M.-S.R. shows normal, or only slightly increased readings in other affections of the nervous system, such as anterior poliomyelitis. In those cases of chorea in which signs of cardiac involvement were present in addition to the chorea, the M.-S.R. was always raised, and did not show normal values until evidence of the activity of this complication had disappeared. Estimation of the M.-S.R. can thus be of value both in uncomplicated chorea, and in chorea associated with one of the other rheumatic manifestations. In the former a rise in

the rate will suggest, for example, the advent of carditis; while in the latter weekly readings will assist in assessing the progress of the patient towards recovery.

From these findings in rheumatic patients, I think it is reasonable to assume that there is a definite connection between the sedimentation rate and the activity of the infection. It may be that the former is increased as a result of physico-chemical changes in the blood produced by the toxins of rheumatism. If this is true, are such changes not present in uncomplicated chorea, or are they not sufficiently marked to produce increased sedimentation? Against the latter theory there is the extremely sensitive character of the sedimentation rate, which would appear to be affected by even trivial infections. Possibly, however, the rate <u>is</u> slightly raised in chorea, although not sufficiently so to show an abnormal reading. Table 25 showed that ten out of fifteen cases of uncomplicated chorea had a M.-S. reading at one time or another of over five millimetres, which may have been abnormal for these particular patients. Whatever the reason, chorea <u>per se</u> does not cause any appreciable effect on the sedimentation rate.

The importance of the test in rheumatism depends largely on the observation that the rate does not return to normal until some time after all evidence of activity is at an end, and the deduction from this that it reflects the continuance of activity, which cannot be detected clinically. As has been pointed out earlier, this theory can not be proved, but it appears suffi-

ciently likely to make it advisable that the sedimentation rate should be taken into account in deciding when the patient can be allowed more liberty. It is probably of advantage to continue rest in bed until the M.-S.R. reaches a normal value, and remains within normal limits for at least two weeks. The result of permitting more freedom can then be gauged by its effect on the rate. If no rise in the M.-S.R. occurs, further allowances can be made, but a rise will indicate the need for continued restriction. While the child is in hospital weekly estimations of the rate are recommended and, after dismissal, an occasional reading would help to confirm continued absence of activity. There is no doubt that the M.-S.R., taken in conjunction with the clinical findings, as all such tests should be, is of distinct value in the management of the rheumatic infection.

Tuberculosis. In the management of adult tuberculosis, this test has obtained a recognised place. In children, however, where the disease is much more often acute, it can be readily understood that there are not so many opportunities to study the test and, indeed, the necessity for such a test in children is probably not as great as in adults. In my small series of cases of glandular tuberculosis and primary lung tuberculosis, the M.-S.R. was always raised where activity was clinically considered to be present. As was mentioned in the section on "Tuberculosis," however, cases were transferred to a Corporation

Hospital when a definite diagnosis of tubercle was made, and thus readings were not obtained for sufficiently long periods to enable an opinion as to the value of the test to be made. Scandinavian writers have reported favourably on the use of the test in juvenile tuberculosis, being of opinion that it accurately reflects the activity of the process. In children passing through their primary infection it is customary to find a definitely raised sedimentation rate. An illustration of this is the case of diabetes (Case 193), where an upset of the carbohydrate tolerance seemed difficult to explain until, on admission for investigation, the tuberculin skin tests, which had been negative on a previous occasion, were now strongly positive. With rest in bed for almost four months the tolerance returned to its original state and the M.-S.R. fell to normal readings. A raised M.-S.R., therefore, in the presence of slight fever and newly positive tuberculin tests, will be confirmatory evidence of primary tuberculous infection.

In miliary tuberculosis and tuberculous meningitis the M.-S.R. was not consistent. In some cases it was very high, but in others, normal. Prior to death a fall in the rate was the more usual finding, but in one case there was a well-marked rise. These variable results rule out the possibility of the test being of value in differentiating tuberculous meningitis from other conditions, such as encephalitis, which occasionally resemble it.

Acute Infections. In the majority of the acute infections, such as bronchopneumonia, lobar pneumonia, acute pyuria and acute nephritis, the M.-S.R. behaved as if it reflected the activity of the disease process. In the acute stages the rate was usually very high and, as in rheumatism, the return to normal was delayed in comparison with the other symptoms and signs. Unlike rheumatism, however, it does not seem necessary to insist on a normal M.-S. reading before dismissing the patient, provided clinical recovery is present; and the value of the test is therefore very much less in these conditions than in rheumatism. A very high M.-S.R. in the initial stages has no prognostic significance, but a sudden fall in the rate in a seriously ill patient is to be regarded as a serious omen. Persistently high readings in a patient who is apparently recovering satisfactorily suggest careful examination for a possible hidden complication, such as otitis media. In general, however, the test does not give information which can not equally well be obtained by the ordinary careful clinical examination.

Other Conditions. In the more chronic infections the M.-S.R. again appeared to reflect, more or less accurately, the probable degree of activity present. Thus in the cases of chronic pneumonia and bronchiectasis the readings were raised, but rarely high, and fluctuated slightly from week to week. It did not appear, however, that the test could be considered of proved

value in estimating the result of treatment.

The sedimentation rate might be expected to be of some use in distinguishing functional from organic disease, as, in the absence of organic changes, the rate should not be affected. Unfortunately, as has been commented on earlier, the M.-S.R. was often found to be normal in non-infective diseases of the nervous system, and thus a normal reading can not be held to exclude the possibility of organic disease. Nevertheless, in certain cases, estimation of the M.-S.R., considered in conjunction with the other findings, may help to throw light on an obscure condition.

Fall in Rate before Death. A fall in the M.-S.R. preceding death was noticed in a number of different cases, besides those suffering from congestive cardiac failure, and has been commented upon by several writers. Various suggestions have been put forward to explain this finding, such as an excess of carbon dioxide in the blood, lowering of plasma fibrin, and dehydration of the blood. No hypothesis, however, satisfactorily explains why the sedimentation rate should fall in some cases and yet, in other apparently similar cases, rise, or remain stationary; and it would appear that one must conclude that the phenomenon responsible for the sedimentation reaction disappears in some cases shortly before death.

CONCLUSIONS.

I. Partly due to the fact that the cause of the phenomenon is not yet clearly understood, the sedimentation test must be regarded as non-specific and empirical.

II. In performing the test on children the use of a micro-method is desirable, and gives results of equal practical value to those given by a macromethod.

III. Landau's modification of the Linzenmeier-Raunert micro-method is simple to use and reasonably accurate, and possesses distinct advantages over the other micro-methods in use. The most notable of these advantages is the ability to make satisfactory delayed readings, which renders the method suitable for use in the private house.

IV. Severe degrees of anaemia cause a well-defined acceleration of the M.-S.R., but the latter is not apparently influenced when the erythrocyte count is four millions per cubic centimetre or over.

V. There is no apparent relationship between the blood chloresterol, or the blood sugar and the M.-S.R.

VI. Increase in the M.-S.R. is the rule in diseases of an infective nature, poliomyelitis and gastro-enteritis being exceptions. The M.-S.R. parallels the course of the disease more or less closely, but tends to reach normal values after clinical recovery has occurred.

VII. In all forms of juvenile rheumatism where there is evidence of clinical activity, with the exception of uncomplicated chorea, a raised M.-S.R. is found. It is suggested that the M.-S.R. will not show normal values until the rheumatic infection is absolutely quiescent.

In uncomplicated chorea there is no rise in the M.-S.R.

Routine weekly microsedimentation estimations are strongly recommended in rheumatic patients, who should be kept in bed until the M.-S.R. has become normal, and remained so for at least two weeks.

VIII. From this study, it has been impossible to form any conclusions as to the value of the M.-S.R. in chronic lung tuberculosis in children, for the reasons stated earlier; but there is good presumptive evidence that estimation of the M.-S.R. will be of assistance in judging the activity of the process, a raised value pointing to an active process, and repeated low values indicating inactivity.

IX. Routine performance of the M.-S.R. in other diseases of childhood is of limited value, but readings taken in conjunction with the ordinary methods of examination will sometimes prove useful in assessing the degree of disease activity, and in distinguishing functional from organic disease.

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4. EDRIDGE, G. E., and HAYCOCK, J. W. "The Erythrocyte Sedimentation Rate - A Comparison of the Methods." Lancet, London, 1935, II, 15.

5. BIERNACKI. Wien med. Wochenschr., Vienna, 1894, XLVI and XLVII.
Zeitschr. f. Physiol. Chem., Berlin, 1896, XXI, 1897, XXIII
Dent. med. Wochenschr., Leipzig, 1897, XVIII and XIII. Quoted by Fahraeus, R. (25) and Hunt, H. P. (59).

6. HOCHREIN, M., and WASSILEW, F. "The Blood Sedimentation Test (Fahraeus) in the Diagnosis and Prognosis of Disease." Jour. Lab. and Clin. Med., St. Louis, 1926, XI, 211.

7. BIERNACKI. "Aphorismi de cognoscendis et curandis aegris." Erlg. Quoted by Fahraeus, R. (25).

8. HOCHREIN, M., and PLIPPIN, H. F. "A Study of Some of the Factors Influencing the Sedimentation Rate." Jour. Lab. and Clin. Med., St. Louis, 1926, XI, 209.

BIBLIOGRAPHY.

1. ALDRED-BROWN, G. R. P., and MUNRO, J. M. H. "The Plasma Proteins and Non-Protein Nitrogen, and the Sedimentation Rate, in Chronic Rheumatic Disorders." Quart. Jour. Med., London, 1935, IV, 269.

2. ANDRAL and GAVARRET. "Recherches sur les modifications de proportion du quelques principes du sang." Paris, 1840. Quoted by Fahraeus, R. (23).

3. ASHHURST, J. "Principles and Practice of Surgery." Philadelphia, 1893. Quoted by Cutler, J.(18).

4. BEAUMONT, G. E., and MAYCOCK, J. W. "The Erythrocyte Sedimentation Rate - A Comparison of the Methods." Lancet, London, 1935, II, 19.

5. BIERNACKI. Wien med. Wochenschr., Vienna, 1894, XXXVI and XXXVII.
Zeitschr. f. Physiol. Chem., Berlin,1894,XIX. 1897,XXIII.
Deut. med. Wochenschr., Leipzig, 1897, XLVIII and LIII. Quoted by Fahraeus, R. (23) and Hunt, H. F. (59).

6. BOCHNER, M., and WASSING, H. "The Blood Sedimentation Test (Fahraeus) in the Diagnosis and Prognosis of Disease." Jour. Lab. and Clin. Med., St. Louis, 1925, XI, 214.

7. BOERHAAVE. "Aphorismi de cognoscendis et curandis morbis." 1709. Quoted by Fahraeus, R. (23).

8. BOERNER, F., and FLIPPIN, H. F. "A Study of Some of the Factors Influencing the Sedimentation Test." Jour. Lab. and Clin. Med., St. Louis, 1934, XX, 583.

9. BRIEGER, E. "Über den Wasserhaushalt des tuberkulösen Organismus und sein Verhalten bei spezifischer und unspezifischer Behandlung." Klin. Wchnschr., Berlin, 1923, II, 1162.

10. CARVALHO, L. and FERREIRA de MIRA fils. "L'epreuve de la vitesse de sédimentation des globules rouges chez le Cobaye normal." Compt. rend. de la Soc. de biol., Paris, 1926, XCIV, 908.

11. CHERRY, T. H. "Factors Influencing the Sedimentation Rate of Erythrocytes." Jour. Lab. and Clin. Med., St. Louis, 1934, XX, 257.

12. CHUNG, H. "A Simple and Accurate Method for Standardising the Cell Volume Percentage of Any Blood for the Sedimentation Test." Jour. Lab. and Clin. Med., St. Louis, 1935, XX, 633.

13. CLAUDE, H., LÉVY-VALENSI; LAMACHE, A. and DAUSSY. "Influence des toxiques sur la vitesse de sédimentation des globules rouges." Compt. rend. de la Soc. de biol., Paris, 1927, XCVI, 1294.

14. CLARK, E. B. "The Surface Tension of the Blood Plasma in Children." Amer. Jour. Dis. Child., Chicago, 1928, XXXV, 18.

15. COBURN, A. F. and KAPP, E. M. "Observations on the Development of the High Blood Sedimentation Rate in Rheumatic Carditis." Jour. Clin. Invest., New York, 1936, XV, 715.

16. COOPER, H. N. "The Sedimentation Rate of Red Blood Cells." Jour. Lab. and Clin. Med., St.Louis, 1925, XI, 615.

17. CROCKET, J. "The Sedimentation Rate in Tuberculosis." Glas. Med. Jour., Glasgow, 1930, CXIV, 106.

18. CUTLER, J. "The Graphic Presentation of the Blood Sedimentation Test." Amer. Jour. Med. Sci., Philadelphia, 1926, CLXXI, 882.

19. CUTLER, J. "A Finger Puncture Method for the Sedimentation Test." Amer. Jour. Med. Sci., Philadelphia, 1927, CLXXIII, 687.

20. DAWSON, M. H., SIA, R. H. P., and BOOTS, R. H. "The Differential Diagnosis of Rheumatoid and Ostearthritis: The Sedimentation Reaction and its Value." Jour. Lab. and Clin. Med., St. Louis, 1930, XV, 1065.

21. DE HAAN. "Über die Senkungsgeschwindigkeit der Blutkörperchen verschiedener Blutarten im Hinblick auf deren Verwendbarkeit für Phagocytoseuntersuchungen." Biochem.Zeitschr., Berlin, 1918, LXXXVI, 298.

22. ERNSTENE, A. C. "Erythrocyte Sedimentation, Plasma Fibrinogen, and Leukocytosis as Indices of Rheumatic Infection." Amer. Jour. Med. Sci., Philadelphia, 1930, CLXXX, 12.

23. FAHRAEUS, R. "The Suspension Stability of the Blood." Acta Med. Scand., Stockholm, 1921, LV, 3.

24. FLACK, R. E., and SCHEFF, L. D. "The Effect of Specific Substances of Tubercle Bacilli on the Differential White Blood Picture, Skin Sensitiveness, and Rate of Sedimentation of the Red Cells." Amer. Jour. Med. Sci., Philadelphia, 1927, CLXXIII, 59.

25. FORMAN, J. "The Sedimentation Rate of Erythrocytes, the Corpuscle Volume and the Icterus Index." Jour. Lab. and Clin. Med., St. Louis, 1927, XII, 373.

26. FOSTER, D. P. "A Clinical Study of Blood Fibrin." Arch. Int. Med., Chicago, 1924, XXXIV, 301.

27. FREEDMAN, S. "The Corrected Sedimentation Rate in Tuberculosis." Amer. Rev. Tuberc., New York, 1934, XXIX, 198.

28. FREEDMAN, S. "The Corrected Sedimentation Rate in Scarlet Fever." Amer. Jour. Med. Sci., Philadelphia, 1933, CLXXXVI, 683.

29. FREUCHEN, I. "Epreuve de Compatibilité se déduisant de la vitesse de Précipitation des Globules Sanguins." Acta Med. Scand., Stockholm, 1927, LXV, 355.

30. FRIEDLANDER, A. "Microsedimentation Rate in Pulmonary Tuberculosis in Children." Acta Paediatrica, Uppsala, 1933, XIV, 550.

31. FRISCH, A., and STARLINGER, W.

Med. Klin., Berlin, 1921, XVII, 1147. Quoted by Rubin, E. H. (116).

32. FROSCH, H. L. "The Sedimentation Test as an Aid to Diagnosis and Prognosis." Jour. Lab. and Clin. Med., St. Louis, 1925, XI, 43.

33. GALEN. "De clementis ex Hippocrate." Opera omnia: ed. Kühn, Lipsiae, 1821, I, 496. Quoted by Fahraeus, R. (23).

34. GARNIER, M., and OUMANSKY, V. "La sédimentation des globules rouges dans les liquides pleureaux et ascitiques." Compt. rend. de la Soc. de biol., Paris, 1926, XCV, 1306.

35. GALLAGHER, J. R. "The Value of the Blood Sedimentation Test in Routine Medical Examination of Adolescents." Amer. Jour. Med. Sci., Philadelphia, 1934, CLXXXVIII, 450.

36. GILBERT, A., and TZANCK, A. "Mesure de la sédimentation sanguine." Compt. rend. de la Soc. de biol., Paris, 1923, LXXXVIII, 873.

37. GILBERT, A., TZANCK, A., and CABANIS. "De l'accélération de la sédimentation sanguine au cours de la Lèpre." Compt. rend. de la Soc. de biol., Paris, 1926, XCIV, 837.

38. GILLIGAN, D. R., and ERNSTENE, A. C. "The Relationship between the Erythrocyte Sedimentation Rate and the Fibrinogen Content of Plasma." Amer. Jour. Med. Sci., Philadelphia, 1934, CLXXXVII, 552.

39. GOLDING, F. C. "Spondylitis Ankylopoietica." Brit. Jour. Surg., Bristol, 1936, XXIII, 484.

40. GRAM, H. C. "On the Causes of the Variations in the Sedimentation of the Corpuscles and the Formation of the Crusta Phlogistica on the Blood." Arch. Int. Med., Chicago, 1921, XXVIII, 312.

41. GRAM, H. C. "Composition and Physical Properties of Normal Human Blood: A Compilation of Values from the Literature." Amer. Jour. Med. Sci., Philadelphia, 1924, CLXVIII, 511.

42. GRAM, H. C. "The Sedimentation of the Blood Corpuscles in Various Internal Diseases and the Result of Correction of this Value for the Variations of the Haemoglobin Percentage." Acta Med. Scand., Stockholm, 1929, LXX, 242.

43. GRAY-HILL, N. "The Erythrocyte Sedimentation Rate in Juvenile Rheumatism." Brit. Jour. of Child. Dis., London, 1932, XXIX, 181.

44. GREISHEIMER, E. M. "The Blood Sedimentation Test in Normal Men and Women." Amer. Jour. Med. Sci., Philadelphia, 1927, CLXXIV, 338.

45. GREISHEIMER, E. M., JOHNSON, O. H., and RYAN, M. "The Relationship between Sedimentation Index and Fibrin Content in Relatively Normal Individuals." Amer. Jour. Med. Sci., Philadelphia, 1929, CLXXVII, 816.

46. GREISHEIMER, E. M., TRELOAR, A. E., and RYAN, M. "The Inter-relation of Cutler, Linzenmeier and Westergren Sedimentation Tests." Amer. Jour. Med. Sci., Philadelphia, 1934, CLXXXVII, 213.

47. GREISHEIMER, E. M., WARWICK, M., and WALTON, M. "The Relationship between Fibrin Content and Sedimentation Index in Orthopaedic Cases." Amer. Jour. Dis. Child., Chicago, 1929, XXXVII, 953.

48. HADEN, R. L., and ORR, T. G. "The Sedimentation Rate of the Erythrocytes in Experimental Obstruction of the Gastrointestinal Tract." Jour. Exper. Med., New York, 1926, XLIV, 429.

49. HARVEY, W. F., and HAMILTON, T. D. "Studies in Method and Standardisation of Blood Examination: II. Sedimentation Rate and Sedimentation Volume of Blood." Edin. Med. Jour., Edinburgh, 1936, XLIII, 29.

50. HASKINS, H. D., TROTMAN, F. E., OSGOOD, E., and MATHIEU, A. "A Rapid Method for the Sedimentation Rate." Jour. Lab. and Clin. Med., St. Louis, 1931, XVI, 487.

51. HENDERSON, J. M. "Studies on the Sedimentation of Erythrocytes." Indian Jour. Med. Research, Calcutta, 1929, XVII, 40.

52. HENKEL, M. "Zur Technik der Blutuntersuchungsprobe." Deutsch. med. Wchnschr., Leipzig, 1924, L, 1138. Quoted by Cutler, J. (18).

53. HERMAN, E. and HALBER, W. "Etude des Isoagglutinines et de la Sédimentation des globules rouges dans le liquide céphalorachidien." Compt. rend. de la Soc. de biol., Paris, 1924, XCI, 959.

54. HEWSON. "Experimental Inquiries in the Properties of Blood." London, 1771. Quoted by Gram, H. C. (40).

55. HIPPOCRATES. "De Natura Hominis." 4. Quoted by Fahraeus, R. (23).

56. HOBER, R., and MOND, R. "Physikalische Chemie der Blutkörperchen-Sedimentierung." Klin. Wchnschr., Berlin, 1922, I, 2412.

57. HOUGHTON, L. E. "Blood Examinations in the Prognosis and Treatment of Pulmonary Tuberculosis." Brit. Med. Jour., London, 1936, II, 1246.

58. HOVERSON, E. T., and PETERSEN, W. F. "Meteorologic Effects on the Sedimentation Rate of Erythrocytes." Amer. Jour. Med. Sci., Philadelphia, 1934, CLXXXVIII, 455.

59. HUNT, H. F. "Studies of the Sedimentation of Erythrocytes". Jour. Lab. and Clin. Med., St. Louis, 1929, XIV, 1061.

60. HUNT, T. "Carcinoma of the Stomach." Brit. Med. Jour., London, 1936, I, 650.

61. HUNTER, J. Works ed. Palmer, London, 1835. Quoted by Cutler, J. (18).

62. JUARROS, C., and GALARIETA, P. "Sedimentation Speed in Abnormal Children." Siglo Médico, Madrid, 1926, LXXVII, 577. Ref. in Jour. Amer. Med. Assoc., Chicago, 1926, LXXXVII, 797.

63. KAHLMETER, G. "Über die Bedeutung der Fähreusschen Senkungsreaktion bei akuten und chronischen Arthritiden." Klin. Wchnschr., Berlin, 1926, V, 889.

64. KATZ, G., and LEFFKOWITZ, M. "Die Blutkörperchensenkung." Ergebn. d. inn. Med. und Kinderh., Berlin, 1928, XXXIII, 266.

65. KESSLER, R. "Die Blutkörperchensenkungsreaktion in der Differentialdiagnose maligner Tumoren." Deut. med. Woch., Leipzig, 1936, LXII, 258. Ref. in Brit. Med. Jour., London, 1936, Feb. 21.

66. KILDUFFE, R. A. "Observations on the Estimation of Blood Sedimentation Time." Jour. Lab. and Clin. Med., St. Louis, 1930, XV, 54.

67. KURTEN, H. "Die Senkungsgeschwindigkeit der roten Blutkörperchen in ihrer Beziekung zu Cholesterin und Lecithin." Pflügers Arch. f. d. ges. Physiol., Berlin, 1920, CLXXV, 248.

68. LANDAU, A. "Microsedimentation." Amer. Jour. Dis. Child., Chicago, 1933, XLV, 698.

69. LANDORF, N. "Érythèmes Noueux avec Réaction Négative à la Tuberculine." Revue Franç. de Pédiat., Paris, 1935, XI, 157.

70. LANGER, H., and SCHMIDT, W. "Ein Mikromethode zur Bestimmung der Erythrocytensenkungsgeschwindigkeit." Ztschr. f. Kinderh., Berlin, 1926, XLI, 72.

71. LASCH, F. "Der Einflub des Chloresterins auf die Senkungsgeschwindigkeit der roten Blutkörperchen." Ztschr. f. d. ges. exper. Med., Berlin, 1925, XLII, 548.

72. LEE, T. "The Sedimometer - A. Photographic Apparatus for Automatic Recording of Blood Sedimentation Rate." Brit. Med. Jour., London, 1936, II, 809.

73. LÉVY-SOLAL. "Différence de sédimentation entre le sang maternel et le sang foetal." Compt rend. de la Soc. de biol., Paris, 1923, LXXXVIII, 875.

74. LINZENMEIER, G. "Die Senkungsgeschwindigkeit der roten Blutkörperchen und ihre praktische Bedeutung." München med. Wchnschr., Munich, 1923, LXX, 1243.

75. LINZENMEIER, G. and RAUNERT. "Eine Mikromethode zur Messung der Senkungsgeschwindigkeit der roten Blutkörperchen." Zentralbl. f. Gynäk. Leipzig, 1924, XLVIII, 786. Quoted by Landau, A. (68).

76. LUNDGREN, R. "A Study of the Physical Nature of the Sedimentation of Blood Corpuscles." Acta Med. Scand., Stockholm, 1927, LXII, 63.

77. MAIA, C. "Causes d'erreur dans la détermination de la vitesse de sédimentation sanguine; hauteur de la colonne, diamètre des tubes." Compt. rend. de la Soc. de biol., Paris, 1929, CII, 248.

78. MAIA, C. "Causes d'erreur dans la détermination de la vitesse de sédimentation du sang: verticalité des tubes, température." Compt. rend. de la Soc. de biol., Paris, 1930, CIII, 838.

79. MAYERS, L. H. "A Study of the Erythrocyte Curve at Various Ages and its Relationship to the Haemoglobin Curve." Arch. Int. Med., Chicago, 1922, XXX, 478.

80. MILLER, W. G. "Observations on the Haematocrite Method of Measuring the Volume of Erythrocytes." Quart. Jour. Exper. Physiol., London, 1925, XV, 187.

81. MORA, J. M., and GAULT, J. T. "The Sedimentation Velocity of Erythrocytes in Thyrotoxicosis." Jour. Lab. and Clin. Med., St. Louis, 1930, XV, 590.

82. MORRISS, W. H., and RUBIN, E. H. "The Sedimentation Reaction of Erythrocytes - Clinical Applications and a Micromethod." Jour. Lab. and Clin. Med., St. Louis, 1926, XI, 1045.

83. MURAKAMI, J., and YAMAGUCHI, T. "La teneur du sang en fibrinogène et fibrinferment dans les maladies internes. Sa corrélation avec la vitesse de sédimentation des globules rouges, la teneur du sang en calcium, et le temps de coagulation du sang." Ann. de Med., Paris, 1924, XV, 297.

84. NASSE, H. "Das Blut." Bonn, 1836. Quoted by Fahraeus, R. (23).

85. NEWHAM, H. B. "The Sedimentation Rate of Erythrocytes in Certain Tropical Diseases." Quart. Jour. Med., Oxford, 1926, XX, 371.

86. NEWHAM, H. B., and MARTIN, P. H. "Further Notes on the Sedimentation Rate of Erythrocytes." Quart. Jour. Med., Oxford, 1928, XXII, 145.

87. NITZESCU, I. I., and GAVRILA, J. "Vitesse de Sédimentation des globules rouges dans le Diabète humain." Compt. rend. de la Soc. de biol., Paris, 1928, XCVIII, 63.

88. NORTHROP, J., and FREUND, J. "The Agglutination of Red Blood Cells." Jour. Gen. Physiol., New York, 1924, VI, 603.

89. OLIVER, J., and BARNARD, L. "Electric Charges and Stability in Suspension of Red Blood Cells." Proc. of the Soc. for Exper. Biol. and Med., New York, 1924, XXI, 529.

90. OSMAN, A. A. "Treatment of Bacillus coli Pyelitis with Alkalies." Brit. Med. Jour., London, 1936, I, 575.

91. PARSONS, L. G., HAWKSLEY, J. C., and GITTINS, R. "Studies on the Anaemias of Infancy and Early Childhood." Arch. Dis. Child., London, 1933, VIII, 159.

92. PAYNE, W. "The Sedimentation Rate in Acute Rheumatism." Lancet, London, 1932, I, 74.

93. PAYNE, W., and SCHLESINGER, B. "A Study of the Sedimentation Rate in Juvenile Rheumatism." Arch. Dis. Child., London, 1935, X, 403.

94. PERRIN, M., MOSINGER, M., and GRIMAUD, R. "Action des eaux minérales sur la sédimentation globulaire." Compt. rend. de la Soc. de biol., Paris, 1926, XCV, 683.

95. PERRY, C. B. "The Sedimentation Rate in Rheumatic Carditis." Arch. Dis. Child., London, 1934, IX, 285.

96. PETERMAN, M. G., and SEEGAR, S. J. "The Sedimentation Reaction in Children." Amer. Jour. Dis. Child., Chicago, 1929, XXXVII, 693.

97. PEYRE, E. "Études sur la sédimentation globulaire: du rôle des différentes concentrations des liquides anticoagulants sur les phénomènes observés." Compt. rend. de la Soc. de biol., Paris, 1924, XC, 1152.

98. PEYRE, E. "Études sur la sédimentation globulaire: rapport entre le volume du tassement globulaire et le poids d'hémoglobine que renforment les globules." Compt. rend. de la Soc. de biol., Paris, 1924, XCI, 876.

99. PICO, C. E., FRANCESCHI, C., and NEGRETE, J. "Influence de l'insuline sur la rapidité de la sédimentation de globules, chez les chevaux." Compt. rend. de la Soc. de biol., Paris, 1925, XCII, 907.

100. PINNER, M., KNOWLTON, K., and KELLY, R. G. "The Sedimentation Rate of Erythrocytes." Arch. Path., Chicago, 1928, V, 810.

101. PLASS, E. D., and ROURKE, M. D. "The Effect of Venous Stasis on the Proteins of Blood Plasma and on the Rate of Sedimentation of the Red Blood Corpuscles." Jour. Lab. and Clin. Med., St. Louis, 1927, XII, 735.

102. POLAK, J. O., and TOLLEFSON, D. G. "The Clinical Significance of the Sedimentation Test." Jour. Amer. Med. Assoc., Chicago, 1928, XC, 168.

103. PONDER, E. "On Sedimentation and Rouleaux Formation - I." Quart. Jour. Exper. Physiol., London, 1925, XV, 235.

104. PONDER, E. "On Sedimentation and Rouleaux Formation - II." Quart. Jour. Exper. Physiol., London, 1926, XVI, 173.

105. POPPER, M., and KREINDLER, F. "La Vitesse de Sédimentation des Hematies." Ann. de Méd., Paris, 1925, XVII, 57.

106. RADOSSAVLIÉVITCH, A. "La réaction de sédimentation des globules dans les liquides organiques autres que le plasma sanguin. Vitesse de sédimentation dans les exsudats et transudats." Compt. rend. de la Soc. de biol., Paris, 1927, XCVI, 1001.

107. REICHEL, H. "Blutkörperchensenkung." Vienna, 1936.

108. REES-WALTON, A. C. "The Erythrocyte Sedimentation Test." Quart. Jour. Med., Oxford, 1933, II, 79.

109. REILLY, W. A. "Blood Sedimentation in Tuberculous Children." Amer. Rev. Tuberc., N. York, 1934, XXIX, 220.

110. REYNER, C. E. "The Sedimentation of Red Blood Cells." Jour. Lab. and Clin. Med., St. Louis, 1928, XIV, 630.

111. RHODIN, H. "La réaction de sédimentation du sang dans la fièvre scarlatine." Acta Med. Scand., Stockholm, 1927, LXV, 336.

112. ROCHE, H. "The Blood Sedimentation Rate in Pulmonary Tuberculosis - its Value in the Management of the Patient." Brit. Med. Jour., London, 1932, I, 466.

113. ROGER, H., and BINET, L. "Influence de la respiration sur la sédimentation des globules sanguins." Compt. rend. de la Soc. de biol., Paris, 1925, XCIII, 1002.

114. ROTHE, E. "Über den Wert der Blutkörperchensenkung in der Chirurgie." Zentralbl. f. Chir., Leipzig, 1923, I, 1327. Quoted by Cutler, J. (18).

115. RUBIN, E. H. "The Relation of the Erythrocyte S. R. to the Ability of Flocculation of the Plasma and Serum." Arch. Int. Med., Chicago, 1926, XXXVII, 848.

116. RUBIN, E. H. "The Sedimentation Reaction in Cancer." Amer. Jour. Med. Sci., Philadelphia, 1927, CLXXIV, 680.

117. RUBIN, E. H., and SMITH, N. N. "Relation of Hemoglobin, Cell Count and Cell Volume to the Erythrocyte Sedimentation Reaction." Arch. Int. Med., Chicago, 1927, XXXIX, 303.

118. SCHLOSS, E. M., and MILLER, P. R. "Blood Sedimentation Test combined with a Serum Reaction in the Diagnosis and Prognosis of Tuberculosis." Amer. Jour. Med. Sci., Philadelphia, 1929, CLXXVII, 523.

119. SCUDAMORE. "Ein Versuch über das Blut." German Translation. Würzburg, 1826. Quoted by Fahraeus, R. (23).

120. SMITH, C. T., HARPER, T., and WATSON, A. "Sedimentation Time as an Aid in Differentiating Acute Appendicitis and Acute Salpingitis." Amer. Jour. Med. Sci., Philadelphia, 1935, CLXXXIX, 383.

121. STRÖM, J. "Mikromethode für die Senkungsreaktion." Acta Paed., Uppsala, 1933, XIV, 567.

122. SULKOWITCH, H. W. "A Photographic Suspension Stability Apparatus." Amer. Jour. Med. Sci., Philadelphia, 1934, CLXXXVII, 65.

123. SYDENHAM, T. Works ed. Swan. London, 1753. Quoted by Fahraeus, R. (23).

124. TOWNSEND, D., and ROGERS, H. B. "A Contribution to the Study of the Erythrocyte Sedimentation Reaction." Jour. Lab. and Clin. Med., St. Louis, XIII, 818.

125. VAN ANTWERP, L. D. "Repeated Sedimentation Tests." Amer. Jour. Dis. Child., Chicago, 1934, XLVIII, 814.

126. WALLGREN, A. "Primary Pulmonary Tuberculosis in Childhood." Amer. Jour. Dis. Child., Chicago, 1935, XLIX, 1105.

127. WALLGREN, A. "Post-primary Erythema Nodosum Tuberculosum". Acta Tuberc. Scand., Copenhagen, 1935, IX.

128. WARNER, E. C. "The Sedimentation Rate in Juvenile Rheumatism." Proc. of the Royal Soc. of Med., London, 1934, XXVII, 963.

129. WESTERGREN, A. "Studies of the Suspension Stability of the Blood in Pulmonary Tuberculosis." Acta Med. Scand., Stockholm, 1921, LIV, 247.

130. WESTERGREN, A. "On the Clinical Import of the Red Cell Sedimentation Reaction in Diseases of the Joints." Acta Med. Scand., Stockholm, 1927, LXV, 343.

131. WINGFIELD, R. C., and GOODMAN, R. "The Rate of Sedimentation of Red Blood Corpuscles in Pulmonary Tuberculosis." Lancet, London, 1926, II, 805.

132. WINTROBE, M. M. "Microscopic Examination of the Blood." Amer. Jour. Med. Sci., Philadelphia, 1933, CLXXXV, 58.

133. WINTROBE, M. M., and LANDSBERG, J. W. "A Standardised Technique for the Blood Sedimentation Test." Amer. Jour. Med. Sci., Philadelphia, 1935, CLXXXIX, 102.

134. WITTS, L. J. "Gastric Carcinoma with Normal Erythrocyte Sedimentation Reaction." Lancet, London, 1935, I, 1329.

135. WOOD, P. "The Erythrocyte Sedimentation Rate in Diseases of the Heart." Quart. Jour. Med., Oxford, 1936, V, No. 17, I.

136. ZECKWER, I. T., and GOODELL, H. "The Sedimentation Rate of Erythrocytes." Amer. Jour. Med. Sci., Philadelphia, 1925, CLXIX, 209.

137. ZUNZ, E. "Relations entre la vitesse de sédimentation des hématies et le tension superficielle dans les états de choc." Compt. rend. de la Soc. de biol., Paris, 1925, XCII, 1119.

138. ZUNZ, E. "A propos de la vitesse de sédimentation des hématies de Chien." Compt. rend. de la Soc. de biol., Paris, 1926, XCIV, 1024.