STUDIES ON THE ERYTHROCYTE SEDIMENTATION RATE IN THE TREATMENT AND PROGNOSIS OF PULMONARY TUBERCULOSIS.

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INTRODUCTION.

More than fifty years have elapsed since Robert Koch's discovery of the tubercle bacillus, which gave such an impetus to research in tuberculosis.

In spite of the manifold investigations carried out since then, there still remain many problems to be solved in this disease.

In the case of pulmonary tuberculosis, the two great needs to-day are, first, a satisfactory method for the early diagnosis of the condition, and, second, a specific form of treatment.

Apart from these fundamental problems, there are several minor problems to be solved. Among these, one of everyday importance is the estimation of the progress of a patient suffering from pulmonary tuber-:culosis, and the evaluation of the results of any special therapy which may be employed.

We have, of course, at our disposal several clinical guides to the progress of a case, viz. the temperature, the pulse rate, the weight, and the physical signs, aided by radiological appearances. But frequently the temperature and pulse rate are within normal limits, and changes in the physical signs are difficult to evaluate. Also, the exudative type

of/

of lesion is frequently to a great extent "silent" on auscultation. It is in these cases that the diffi-:culty arises.

Fortunately, a laboratory test has been discovered, which has been shown to be of definite value in esti-:mating the progress of the condition. It is known that, if blood be citrated to prevent clotting, and be set up in a vertically placed tube, the red cells sink, leaving the clear plasma as a supernatant fluid. This "Sedimentation Rate" has been shown to be constant in normal individuals, but in persons suffering from, among other conditions, pulmonary tuberculosis, it is increased in proportion to the severity of the disease.

This test has now been used in the study of pul-:monary tuberculosis for a period of fifteen years, and numerous papers have been published on the subject.

While its value has been definitely established, several important problems in connection with it remain to be solved.

In these studies two main problems have been investigated. The first - a serological one - deals with the influence of red cell concentration on the sedimentation rate. It has been shown that the smaller the red cell concentration, the more rapid is the sedimentation rate. The majority of methods of estimating the sedimentation rate do not take this factor into account. In the method used by the author/

author, a correction is applied to the reading in order to allow for any change in the red cell concentration from normal. The object of this study is to determine whether such a corrected reading gives a more accurate estimation of the patient's progress.

The second study is a pharmacological one, and deals with the action of gold therapy on the erythro-:cyte sedimentation rate. This is a problem of some interest, in view of the present widespread use of the method, and the conflicting opinions which have been expressed regarding its value in the treatment of pulmonary tuberculosis.

We begin with a historical survey of the erythro-:cyte sedimentation rate, followed by a consideration of the technique and theory of the subject. There-:after, the practical application of the subject to the study of pulmonary tuberculosis is entered into in detail.

HISTORICAL.

The phenomenon of erythrocyte sedimentation is by no means a recent discovery, although the accurate measurement and scientific study of the sedimentation rate is a development of the last twenty years.

The phenomenon was noted in the days when the treatment of many diseases was vomiting, purging and bleeding.

If the blood of a healthy person is allowed to clot, after a little time the red blood clot contracts, and expresses a light yellow coloured liquid - the blood serum. It had been noticed for hundreds of years, however, that, in certain diseases, this blood clot was not coloured regularly red, but that the upper part consisted of a whitish mass - the "fibrin-clot". This was found to be of differing size, and was frequently, indeed, greater than the red part of the clot.

The old doctors called the fibrin clot by various names - "crusta sanguinis", "crusta inflammatoria", "phlogistica", "pleuritica", "inflammation skin", "inflammation blood" and similar descriptions. It seems to have been valued as one of the first signs of illness in the beginnings of medical science, and it was just the observation of this property of the blood in different illnesses, which led to the search for

all/

all causes of disease in changes in the body fluids. Thus arose "humoral pathology".

Hippocrates (460-380 ? B.C.) already mentions fibrin-clotting. He gave it a Greek name indicating "burning", "flame", metaphorically "inflammation", or "inflammatory phlegm". The increase of the "phlegm" in the blood was considered the expression and cause of various diseases. For the excessive appearance of "phlegm" in the blood played an important part in various diseases, especially angina, nephritis, pneu-:monia and epilepsy. By blood-letting they sought to remove this injurious substance from the body.

In the medicine of the Romans Galenus (131-201 A.D.), more than anyone else, took up the teaching of the Greeks, and handed it on to the medicine of the Middle Ages, with his own speculative additions.

Paracelsus (1493-1541) was the first to recognise that "phlegm" was not the cause of diseases, but was a symptom of the same. He maintained that if "humors" existed, they arose from the disease, and not the disease from them.

In the beginning of the new era, the cause of illnesses was sought for in the blood, and "humoral pathology" celebrated great speculative triumphs. Sydenham showed the fibrin-clotting as an expression of the inflammation of the blood, which was the cause of different diseases. Quesney (1694-1774) was the first to/

to maintain that fibrin-clotting was not the cause but the expression of many diseases.

In the eighteenth century and the first half of the nineteenth century, the diagnostic and pathogenetic significance of fibrin-clotting was the object of great attention, and numerous treatises were written about it.

It was then observed that in pregnancy the fibrin-clotting in the let-blood was strongly formed, and Piorry (1794-1879) went so far as to consider as ill every pregnant woman whose blood showed fibrin-clotting formation.

The physicians of the seventeenth, eighteenth and early nineteenth centuries knew full well the diagnostic significance of fibrin-clotting, first of all in inflam-:matory diseases - of serous membranes (pleurisy, peritonitis, pericarditis); of organs (pneumonia, hepatitis, nephritis); of mucous membranes (bronchitis, enteritis). It was also noted in inflammations of joints, and in acute inflammatory conditions of the skin, e.g. furunculosis and erysipelas.

It was known, further, to be a sign of acute infectious diseases, such as smallpox, measles, etc. It was then already known that fibrin-clotting in infectious diseases differs from that occurring in conditions of local inflammation. In the former fibrin-clotting is formed relatively less strongly, and relatively more serum is expressed. Also it/

it was noted that, in anaemias, fibrin-clotting is strongly formed and copious serum is expressed.

It was indeed observed that, in the course of different diseases, fibrin-clotting changed in inten-:sity, and was a measure of the extent of the disease (especially of pulmonary tuberculosis).

Finally, it was known that in very grave illnesses fibrin-clotting could again disappear (Boerhave, 1763).

In addition to making these remarkable observa-:tions, the old physicians also sought to study, with the limited means at their disposal, the more scientific aspects of this phenomenon.

Hewson (1739-1774) recognised that the "inflammatory crust" was not a new formation of the blood, but a clotting product of the "lymph", after it had separated from the blood corpuscles. The separation of the lymph from the blood corpuscles can occur in two circumstances - by delaying of the clotting, or by increased velocity of the sinking of the blood corpuscles.

Hermann Nasse made extensive studies on the causes of increased fibrin-clotting. Hewson had already determined that differences in the specific gravity of the erythrocytes, or of the plasma, are not the cause of altered fibrin-clotting. Nasse increased this knowledge by showing that, in artificial lessening of the specific gravity of the plasma, by thinning with isotonic salt solutions, fibrin-clotting was not hastened/

hastened but slowed.

After addition of specifically heavy substances, such as gum arabic, fibrin-clotting was hastened.

By lessening the erythrocyte concentration, by the addition of serum in vitro, the fibrin-clotting was also hastened.

The most important fact established, however, was that the fibrin-clotting is dependent on the degree of agglomeration of the erythrocytes.

While already by earlier investigators (especially Hewson), a role in sedimentation hastening was ascribed to fibrin, Nasse it was who recognised that sedimentation is far from being in all cases due to the fibrin increase.

It was already known in the first half of the nineteenth century that

(1) the fibrin-clotting is dependent on the height of the blood column, and on the time taken for the blood to clot;

(2) fibrin-clotting is dependent upon the erythrocyte content of the blood, and on the size of the erythrocyte agglomerates. It is hastened by the raising of the viscosity of the plasma (addition of gum arabic), and slowed by lessening of the same (thinning with sodium chloride solution). It is hastened with increased fibrin content, but in many cases also without fibrin increase;

(3)/

(3) fibrin-clotting is hastened in pregnancy, in infec-:tive illnesses, especially pulmonary tuberculosis, inflammatory diseases - pneumonia, hepatitis, nephritis, pleuritis, pericarditis, peritonitis, poly-:arthritis, furunculosis, and erysipelas - among others.

Sedimentation increases in the advancing spread of the inflammation, and may in very severe cases become normal again.

These paragraphs summarise the knowledge gained concerning the phenomenon, by the first half of the nineteenth century, and it is seen that it is of no mean extent.

In the second half of the nineteenth century, however, the phenomenon of fibrin-clotting had practi-:cally vanished into the "limbo of forgotten things" owing to

(1) the decline of blood-letting as a therapeutic measure;

(2) inexactitude of the sedimentation due to variations in the rate of fibrin-clotting, depending on the rate of taking off blood, quantity of blood, temperature, etc.

For these reasons, this important subject was neglected until almost the close of last century, when an impetus to further research was given by the inves-:tigations of Biernacki (1), (2), who may be looked upon as the father of the study of the sedimentation rate/

rate, as we know it. Indeed on the Continent the sedimentation rate is frequently spoken of as "Biernacki's Reaction". He recommended the estima-:tion of sedimentation in non-clotting oxalated blood. He also introduced the method of reading off the degree of sedimentation after half an hour, one hour, and twenty-four hours.

In spite of this important advance, the subject still remained in obscurity, until its diagnostic significance was brought forward by two authors simul-:taneously, and independently of one another. In 1917 Hirszfeld (3) described it as a symptom of malaria, while in 1918 appeared the first works of Fähraeus (4), (5), (6). Fähraeus first investigated the subject of sedimentation as a means of early diag-:nosis of pregnancy. Unfortunately, early hopes in this respect did not materialise, it being found that no help was obtainable from the sedimentation rate until the diagnosis was fairly obvious clinically. In spite of this failure, the method was seized upon by workers in all branches of Medicine, and a large series of researches resulting in the publication of a flood of papers then started, and have continued ever since. The sedimentation rate has now been studied in almost every pathological condition, but amongst the earliest investigations, those directed to the study of Tuberculosis were numerous and impor-:tant/

:tant. The pioneer in this department was Westergren (7), who carried out extensive researches into the method, theory, and application to internal medicine, especially tuberculosis.

From the above account, it is seen that this subject has a long, interesting and somewhat chequered history. In spite of the numerous and wonderfully accurate observations made more than a century ago, it is only within the past few years that the great value of this important subject has been recognised.

TECHNIQUE.

INTRODUCTION.

If an anti-coagulant be added to a specimen of blood, and the blood be allowed to stand in a tube, the corpuscles sediment to the bottom of the tube, while the plasma remains as a clear supernatant fluid. The amount which the corpuscles sediment depends partly on the time allowed, being greater the longer the time, partly on the red cell content of the blood, and partly on certain physiological and pathological conditions; in a given time it is relatively constant for normal human beings. The rate of settling or sedimentation is known as the Sedimentation Rate (S.R.).

The technique of measurement of the sedimentation rate is very simple, but the factors governing the S.R. are very complex, with the result that there are numerous fallacies to be avoided. Consequent upon this, several different methods of estimation have been evolved, differing one from another according to the fallacy to the correction of which particular attention has been paid.

METHODS.

The various methods of estimating the erythrocyte sedimentation rate may be broadly classified into two groups:

(1) The distance methods - those in which the time is arbitrarily/

arbitrarily fixed, and the distance through which the erythrocytes fall in this time is recorded;
(2) the time methods - in which the distance sedimen-:ted is fixed, and the time taken is recorded.

Distance Methods.

The original method of Fåhraeus belonged to this group, and was carried out as follows:-

The apparatus consists of a glass tube 17 cm. in length, with an internal diameter of 9 mm., and graduated at intervals of 0.1 cm. 2 c.cm. of sodium citrate solution (2 per cent) are placed in the tube, and blood from a vein is introduced up to the 10 c.c. mark. The tube is inverted to mix the blood with the citrate, and allowed to stand. The height of the clear plasma layer above the column of red cells is read at definite inter-:vals of time.

This method was modified by Westergren (8), (9) in his studies on the sedimentation rate in tuberculosis. His method is the one most commonly used on the Continent, and is performed thus:-

A tube of small bore is used, and a solution of 3.8 per cent sodium citrate is the anti-coagulant. 0.4 c.c. of this solution is drawn up into a Record syringe, the needle of which is then introduced into a vein, and the barrel drawn up to the 2 c.c. mark. The mixture is then emptied into a specimen tube, and should be manipulated without delay. The blood is drawn/

drawn up into a standard Westergren tube, which is 2.5 mm. in diameter, and closely resembles a 1 c.c. pipette. Instead of being graduated in c.cs., however, the tubes are calibrated in mms. of length, the figures reading from above downwards, and the calibration being carried to the extreme point. The zero mark is exactly 200 mm. from the point; the blood is drawn up to this mark. The tube is now set upright in a stand, in which a spring clip, pressing on the top, holds the point firmly against a piece of rubber at the lower end. The tube is now left to stand, and the red corpuscles begin to settle down, leaving a clear supernatant plasma. The upper level of the red cell column is usually sharp and distinct. The level of the red cell column should be read after one, and again after two hours. The result is reported as the distance sedi-:mented in mms. by the top of the red cell column.

The distances sedimented by a normal person are found to be fairly constant. In men these are usually 3-5 mm. at the end of one hour, and from 7-15 mm. after two hours. In women the normal values are from 4-7 mm. after the first hour, and from 12-17 mm. at the end of the second hour.

Figures of 30-35 mm. at the end of two hours are definitely pathological.

It is sometimes not possible to obtain the full 2 c.c. of blood, and in these cases a micro-method is permissible/

permissible, but is not as satisfactory. When no vein is available, blood may be taken from a puncture wound by the following technique. A test-tube is marked at a level of 1.25 c.c. Into this tube is placed 0.25 c.c. of citrate solution. The hand or foot is placed in a warm bath and then dried. A suitable site is punctured, and the blood is allowed to fall straight into the citrate, being mixed by gentle shaking. This is continued until the blood reaches the 1.25 c.c. mark. By this method it is usually possible to obtain a full 200 mm. column of blood. Proportionate dilu-:tions may be used for even less quantities of blood, and in these cases a Westergren tube cannot be filled, but a reasonable correction can be applied for a column not less than 50 mm. long.

A third method in this group is one introduced in America by Zeckwer and Goodell (10). A larger tube is used in this method, and the results are expressed differently, being taken as the corpuscle or plasma volume. 2 c.c. of 3.8 per cent solution of sodium citrate are drawn into a Record syringe, together with 8 c.c. of blood obtained from a vein. The citrated blood is placed in a 15 c.c. centrifuge tube graduated in tenths of a c.c. The tube is allowed to stand, and the volume of corpuscles read off at the end of an hour and two hours. Certain investigations express the result by the volume of the supernatant plasma.

All/

All difficulties are avoided if the volume of both plasma and corpuscles is stated when making the report. Zeckwer and Goodell give a figure of 7 c.c. as an average normal value (volume of red cells at the end of one hour), using 10 c.c. of citrated blood.

The main advantage of this method is, that the unit being a standard one of volume, does not necessi-:tate the use of a tube of special calibre, thus lessening the cost.

Although the findings in the methods of Westergren and of Zeckwer and Goodell are expressed in such differ-:ing terms, it is nevertheless possible to express them in similar fashion, and Beaumont and Maycock (11) have shown that when this is done, the two methods give results which are comparable. In the case of Wester-:gren's method, the reading in mms. is divided by two to bring it to a percentage, while the reading in c.c. obtained by Zeckwer and Goodell's method (volume of red corpuscles) is subtracted from 10, and the result multiplied by 10. This gives the result in mm. per cent. of supernatant fluid, which is comparable with the percentage reading on the Westergren tube.

Time Methods.

This type of method was introduced by Linzenmeier (12).

Special tubes are used necessitating only 1 c.c. of/

of blood. The time is noted at which the level of red cells reaches definite marks, noted as mm. height of the plasma column. The results are recorded in minutes. 2 hours is generally accepted as the lower level of normal readings.

The main disadvantage of this method is that repeated examinations of the tube are required to determine the time at which the red cells reach given points. This makes it a more time-consuming method than the "distance methods".

Several modifications of Linzenmeier's method have been described but none are of special importance.

Critical Study of Experimental Conditions.

Having described the more commonly used methods for the estimation of the erythrocyte sedimentation rate, we may now proceed to a study of the details of technique.

As pointed out above, the estimation of the sedi-:mentation rate is a simple process, but the reaction is so delicate that, unless certain fallacies are corrected, results which are grossly inaccurate will be obtained.

We might conveniently start this discussion by summarising, in tabular form, the main factors which influence the sedimentation rate, dividing those factors into two large groups - those which hasten and those which delay, sedimentation.

Hastening/

Hastening Factors.	Slowing Factors.
(1) Temperature over room temperature. (2) Oblique position of the sedimentation tubes. (3) "Wetting" of the tube above the sedimentation column.	(1) Temperature essentially under room temperature. (2) Temperature over 50°C which produces clotting. (3) Blood thinning with anti-coagulant salts and their solutions (sodium citrate, etc.). (4) Sinking of erythrocytes after a determined sedimentation period. (5) Too narrow lumen of the sedimentation tube (under 1 mm.). (6) Rather long keeping of the blood (over 2-4 hours) especially with raised temperature.

We shall now discuss each stage of the technique in detail.

(1) Taking off Blood.

Several points have to be attended to during this process.

(a) All instruments - syringe and needle - must be scrupulously clean from a chemical point of view, as any traces of alcohol left in the syringe after clean-:ing, will influence the S.R. It is not necessary that the syringe should be sterile.

(b) In carrying out the venipuncture it will usually be necessary to use a tourniquet, but this should be applied for as short a time as possible, otherwise a degree of in vivo sedimentation may occur.

(c) The blood should be taken off quickly, in order to prevent clotting, before adequate mixing with the anti-coagulant/

coagulant takes place. At the same time aspiration by the syringe should be avoided, as air bubbles are thereby produced. If possible, the blood should be allowed to press out the barrel of the syringe, though, in practice, with patients who have small veins, this may be impossible.

A final air bubble must be taken in for purposes of mixing the blood with the anti-coagulant.

(d) Anti-coagulants.

The idea of using unclottable blood in the study of blood sedimentation was introduced by Biernacki (loc. cit.). There are three main ways of preventing the blood from clotting.

(i) By rendering the walls of the tube smooth by means of oil, paraffin, etc. These processes have not proved successful, as the blood usually clots after a time.

(ii) By the addition of clot-preventing substances. This may be done in one of two ways -

(a) In solid form - hirudin, heparin, oxalate, citrate. By this means all thinning of the plasma is avoided, but, through changing of the osmotic pressure of the solution of substances in the blood, the form of the erythrocytes, and their agglutinability, are altered, which interferes with the sedimentation rate to no small degree.

Hirudin/

Hirudin and heparin are, besides, expensive, and the addition of small quantities to the blood technically not simple.

(b) In isotonic solution.

In this way a thinning of the plasma takes place, which essentially alters the sedimentation, but the form of the erythrocytes is almost un-:influenced.

While it has not yet been definitely decided whether the addition of anti-coagulant in solid form, or in isotonic solution, is the more suitable method, the following arguments are in favour of the latter method -

The solid substance necessary for a single blood sedimentation estimation cannot be measured off simply. The result is that at times a larger, at other times a smaller, quantity is added, thus rendering the experimental conditions inconstant. With isotonic solutions, however, it is easy to measure an always equal quantity of the solution. Small differences in concentration do not appear to influence the sedimentation (Westergren (13)).

Linzenmeier (14) recommends a 5 per cent sodium citrate solution, but Westergren has rightly empha-:sised the importance of using a solution which will interfere as little as possible with the osmotic pressure effect on the erythrocytes - i.e. an isotonic solution.

By/

By the addition of an isotonic solution, two effects are produced on sedimentation -

(1) a slowing of sedimentation by thinning of the plasma;

(2) a hastening of sedimentation by dilution of the erythrocytes.

The former outweighs the latter. If dilution takes place with citrated plasma, the hastening of the sedimentation outweighs the slowing.

Varying concentrations of citrate cause great differences in S.R. Hence the volume of citrate solution must be measured accurately.

Most methods use the proportions of blood to isotonic solution as 4:1. One tenth of citrate solu-:tion is sufficient to prevent clotting, but most methods prefer the larger quantity, to be on the safe side. In the method used by the author, which is described later, only one tenth of citrate solution is used, and it was found that clotting took place rarely, and then only when inadequate mixing of blood and citrate had occurred.

Keeping of Blood and of Citrate Solution.

Fresh sterile citrate solutions must be used, as older solutions tend to grow a fungus, which alters the citrate.

With regard to the keeping of blood, it is naturally best that sedimentation should be allowed to proceed/

proceed forthwith, after the blood has been drawn. If this is inconvenient, however, it may safely be left, mixed with citrate, for a period up to twelve hours (Leffkowitz (14)), preferably at room temperature. No evaporation must be allowed to occur during this time.

(2) Temperature.

Temperature exerts a marked influence on the S.R. Gordon and Cohen (15) were the first to publish results of experiments on this point.

A much greater speed of fall is obtained when a sedimentation tube is set up in an incubator at 37°C, than when it is placed at ordinary room temperature (19-23°C). 19-23°C is the optimum temperature - above or below this, marked deviations are found, which may lead to erroneous interpretation of results (Walton, (16)).

(3) Sedimentation Tubes.

The sedimentation rate has been found to vary according to the height and width of the sedimentation tubes used.

(a) Width of tube.

An extensive literature has grown up on the influence of the width of the tube on erythrocyte sedi-:mentation. Some authors find that sedimentation is slower in narrow tubes - Westergren, Wiemer (17), while/

while Ducceschi (18) and Feuerstein (19) find the opposite to be the case.

Walton (16) found that when the tube was of very fine diameter, the upper layer of red cells is ill-defined, due to their irregular fall, and a tube of less than 2 mm. internal bore should therefore not be used. Walton also emphasises that the sides of the tube must be parallel and the lower extremity flat.

(b) Height of the blood column.

Three stages of sedimentation have been described by Rothe (20) viz.

(i) Sedimentation of the single erythrocyte, which is relatively slow;

(ii) Sedimentation of the erythrocyte agglomerations, which show an increasing rate reaching a constant rate.

(iii) Sedimentation is slowly stopped by "braking" of erythrocyte aggregates, (stage of settlement). The setting-in of this stage is dependent on the height of the blood column, and the corpuscle volume - settlement begins the shorter the column and the greater the erythrocyte volume. Unfortunately, no formula is available for correcting this factor.

(4) Method of Filling the Sedimentation Tube.

Linzenmeier (loc. cit.) has shown that "wetting" of the tube above the column during filling, produces an/

an increased S.R., especially during the first five mm. sedimentation. This is due to agglomeration of erythrocytes in the wetted area. Hence care must be taken during filling to prevent wetting of the tube.

(5) Position of Sedimentation Tube.

The position of the tube during sedimentation exerts an influence on the rate, although in the opposite manner to what might be expected. One would expect sedimentation to be more rapid in vertical, than in sloping tubes, but the contrary is found to be the case. Boycott (21) was the first to observe that the S.R. is increased, within limits, with increasing slanting, especially in narrow tubes. This fact was also demonstrated experimentally by Lundgren (22), and shown theoretically by Eric Ponder (23).

This is important from a theoretical, as well as from a practical point of view, as, if sedimentation were merely a falling down of the erythrocytes in the plasma, the rate would be greatest in the vertical position.

(6) Times of reading off Sedimentation.

In the distance methods, the time of reading off sedimentation is important. It is essential that it be done to the minute, except in the case of a 24-hour reading, where a difference of an hour or two in either direction is of no importance.

Several/

Several authors, notably Westergren, suggest that sedimentation be read off at one hour, two hours and twenty-four hours. It has been shown (Zeckwer and Goodell (10)) that a 24-hours reading is of little value, except to indicate cell volume, this reading being directly proportional to the volume per cent of cells in the blood. With regard to the one hour reading, it is found that in normal persons at the end of this time, practically no sedimentation occurs, whereas in pathological cases showing an increased sedimentation rate, a considerable degree of sedimen-:tation always occurs during the first hour, and less occurs during the second hour. It is thus generally agreed that a one hour reading is the most valuable one, in differentiating the pathological from the normal, and it has the advantage of being less time-con-:suming.

(7) Influence of Red-Cell Count.

That the concentration of erythrocytes in the blood influences the S.R. has long been known. Fåhraeus himself (loc. cit.) mentioned that the S.R. is faster in anaemic blood. Westergren (loc. cit.) also noted this point, but he dismissed it as having no practical bearing. Since then, various authors have studied the influence of anaemia on the S.R., with varying results.

Bönniger/

Bönniger and Herrmann (24), and Hubbard and Geiger (25) have found that the S.R. is hastened in anaemic blood, while Cooper (26), and Rubin (27) state that the red cell factor plays no important part.

Gram (28), however, described a method for correc-:ting the S.R., by fixing a certain haemoglobin percen-:tage (100%) as normal. On reference to a chart, which he had constructed, he was able to correct the S.R. on the basis of the haemoglobin content of the blood. Rourke and Ernstene (29) give a method which aims at correcting the S.R. on the basis of cell volume.

The most recent investigation on the influence of the red cell count on the S.R. is by Rees Walton (16), (30). He carried out a comprehensive clinical and experimental study on animals, and on patients suffer-:ing from various diseases. He was soon struck by the fact that, using various dilutions of red cells in their own plasma, the erythrocyte content was a most important factor, and that, in order to compare the S.R. of different samples of blood, it was necessary to keep the concentration of red cells constant. To this end an arbitrary figure of 5,000,000 red cells per c.mm. was chosen. In his experiments, a series of tubes containing dilutions of from 5,000,000 down to 1,000,000 red cells per c.mm. was used. A simple method of calculating dilutions devised by Blacklock (31) was employed.

As/

As applied to the dilution of blood, the following example may be quoted - Initial red cell count 5,400,000 per c.mm.; the million figure is noted, and a similar quantity of blood in cubic centimetres (i.e.. 5 c.c.) is placed in a suitable tube; to this blood is added a quantity of plasma (obtained from a previously centrifugalised sample of the same blood), which is represented in fractions of a cubic centimetre, just as the red cell count figure below the million cipher is represented in fractions of a million. Thus to 5 c.c. of blood is added 0.4 c.c. of plasma, and this tube now contains 5.4 c.c. of blood at a concentration of 5,000,000 red cells per c.mm. This is now redis-:tributed into five sedimentation tubes, each contain-:ing 1 c.c. of blood in descending concentration. On the same principle, anaemic blood can be concentra-:ted, and by suitable removal of plasma at least 1 c.c. of blood at a concentration of 5,000,000 red cells per c.mm. can be obtained.

Using this method Walton was able to show the great differences in the S.R. produced by varying the erythrocyte concentration. He quotes the following case:-

Case 1. Normal. Red cell count 4,680,000 per c.mm.

Tube No.	Contents.	S.R.in 1 hour.
5	5,000,000 red cells per c.mm.	1 mm.
4	4,000,000 " " " "	6 mm.
3	3,000,000 " " " "	10.5 mm.
2	2,000,000 " " " "	20.0 mm.
1	1,000,000 " " " "	27.5 mm.

It was found that in the higher dilutions relatively little difference existed between normal and patholo-:gical cases, whilst in the 1,000,000 tube a S.R. of 27.5 mm. was nearly always recorded in the slowest, as in the fastest, sedimentation specimens. On the other hand, the most uniform sedimentation, and the greatest difference between normality and abnormality, was always observed in the 5,000,000 tube.

As a routine basis for comparison, the sedimenta-:tion height in a tube containing 1 c.c. of blood at a concentration of 5,000,000 cells per c.mm. was recorded.

Walton's technique is as follows:-

The sedimentation tubes are 6 cm. long, 6 mm. internal diameter, with flat bottoms. A mark is cut on the glass at a height of 32.5 mm. from the base, this height indicating the level reached by 1 c.c. of blood. The tubes may be graduated in half millimetres, or a flat metal millimetre scale may be employed. A special rack is used to maintain the tubes in a vertical position, containing a series of holes in its upper platform and corresponding slots in the base, so that the tubes should fit snugly when inserted. All apparatus - glass tubes, pipettes and syringes - must be kept scrupulously clean and dry.

Sterile, freshly prepared 3.8 per cent sodium citrate is used as the anti-coagulant.

4.5 c.c. of blood is withdrawn from an ante-cubital vein/

vein in the usual way, taking care not to produce unnecessary venous stasis. The blood withdrawn is quickly placed in a tube containing 0.5 c.c. of the citrate solution, with which it is thoroughly mixed. A red cell count is then made to determine roughly the division of the specimen for dilution or concen-:tration. Usually 2 c.c. are placed in a small tube, while the remaining 3 c.c. are centrifuged, to obtain the necessary plasma for dilution purposes. The object is to obtain at least 2 c.c. of blood which will have a content of an even million figure in red cells. From this suspension can be readily transferred to the sedimentation tube, after suitable dilution or concen-:tration, 1 c.c. of blood which shall contain 5,000,000 red cells per c.mm. When this is obtained the tube is inverted several times and rotated about its long axis to produce an even suspension; bubbles on the surface of the blood are removed by touching with a heated glass rod, and sedimentation is allowed to proceed, the height of sedimentation being read off after an hour.

The normal figure for a normal person whose blood has been concentrated or diluted to 5,000,000 red cells per c.mm. is given by Walton as

Men	0.0 - 5.5 mm.	Average 2 mm.
Women	0.0 - 5.5 mm.	Average 3.5 mm.

The blood of women thus sediments rather more quickly/

quickly normally than that of men.

More range of variation is found to occur between a normal and a pathological case in tubes containing 5,000,000 per c.mm. It seems that when the blood is so dilute that only 1,000,000 red cells per c.mm. are present, no difference can be found to exist in the S.R. of normal and abnormal specimens. At the end of one hour the erythrocytes in normal blood at such dilution fall through a distance of 27.5 mm. In equivalent concentration, erythrocytes from a patholo-:gical case traverse a similar distance.

After extensive observations, Walton came to the conclusion that it was possible to estimate the S.R. of any given concentration of blood, if the S.R. of a known concentration were obtained.

When S.R. values were plotted upon a graph, with the blood count values as abscissae and the S.R. as ordinates, a curve was obtained which almost described a straight line. In very slowly sedimenting blood the curve bends with the convexity downwards, and the more rapid the S.R. the more nearly straight is the line. From these curves, if we know the S.R. in a tube containing, say, 5,000,000 red corpuscles per c.mm., the S.R. at any given concentration of blood may be found by plotting a graph, and drawing a straight line between the known figure and the 27.5 mm. mark. By producing a line from the red cell count line to cut this/

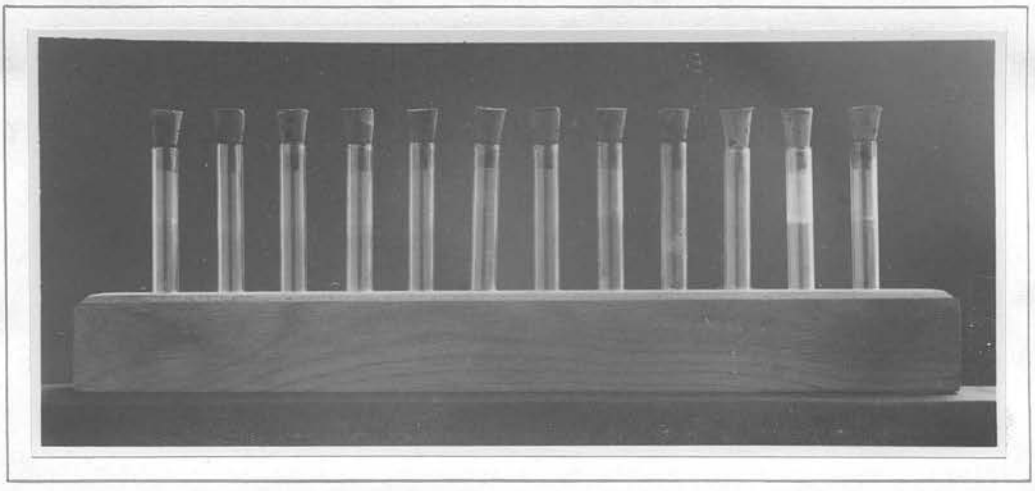
this straight line, the S.R. for the red blood count desired can be read off. Conversely, if we have a tube of blood at a concentration of, say, 4,500,000 cells per c.mm., a straight line is drawn upon the graph, joining the S.R. figure for this count and the 27.5 mm. mark. By producing this line, we can obtain the theoretical S.R. of a specimen of blood containing 5,000,000 red cells per c.mm.

Upon this graphic method, Walton based a simple procedure for estimating the S.R. by merely taking 1 c.c. of blood. The procedure is as follows:-

A small, dry 1 c.c. "Record" syringe is taken, and 0.1 c.c. of 3.8 per cent sodium citrate sucked up into it. A tourniquet is placed on the arm, and blood sucked up by the syringe exactly to the 1 c.c. mark, thus giving 1 c.c. of citrated blood. The contents of the syringe are evacuated into the sedimentation tubes previously described, making sure that blood and citrate are thoroughly mixed. A haemocyto-meter pipette is introduced into the suspension, and blood enough withdrawn for a red cell enumeration, after which sedimentation is allowed to proceed in the usual way. When the red blood cells have been counted, the S.R. at the end of one hour is plotted on the graph opposite the corpuscle number of that blood. From this it can readily be estimated what the S.R. would be if the red cell count were 5,000,000 per c.mm.

This/

This graphical method is the one which was used in making the author's observations on the sedimentation rate. Walton's original method was followed closely except for unimportant details. A flat metal scale graduated in millimetres, for reading off the sedimen-:tation heights, was used, and was found to be quite satisfactory. The stand which was used for holding the sedimentation tubes consisted of a block of wood with twelve holes drilled vertically in it, in series, the holes being of such a size as to hold the tubes firmly in the vertical position.



Apparatus for Estimation of
Sedimentation Rate.

Although so small a quantity of citrate is used as anti-coagulant in this method, trouble was rarely ex-:perienced with the blood clotting. On such few occasions as clotting did occur, it was due to inadequate mixing of blood and citrate having been performed.

It was found that considerable care had to be exercised/

exercised in introducing the haemocytometer pipette into the sedimentation tube, as the difference in diameter between the two is small enough to render very easy "wetting" of the tube above the blood cell column, which, as has been pointed out above, tends to hasten sedimentation.

In reading off the sedimentation height, we took the distance between the top of the red cell column and the lower level of the meniscus of the supernatant plasma.

Walton points out that when the erythrocyte count is below 3,000,000 per c.mm., the graphical method is not so accurate as his original method, especially in quickly-sedimenting specimens. Therefore, in these cases, he suggests that the blood should be concentrated, so that a tube of 1 c.c. may contain 5,000,000 red cells per c.mm.

In the application of this method to patients suffering from pulmonary tuberculosis, and who are of the sanatorium type of case, we have rarely found such a degree of anaemia as evidenced by a red cell count of below 3,000,000 per c.mm., and hence in this type of work such an objection is rarely of importance.

Thus, in a series of 24 cases examined on admission, it was found that

10 cases (41.6%) showed a red cell count of 5 million per c.mm. or over.

1 case (4.1%) showed a red cell count between 4½-5 million per c.mm.

9/

9 cases (37.5%) showed a red cell count between 4-4½ million per c.mm.
3 cases (12.5%) " " " " count between 3½-4 million per c.mm.
1 case (4.1%) " " " " count between 2-2½ million per c.mm.

The case showing a count of below 3 million was not really of the sanatorium type, and had later to be transferred to hospital.

From the above figures it is seen that 83.2 per cent of sanatorium cases have, on admission, a red cell count of over 4 million per c.mm.

This is an interesting observation in view of the pallor (often extreme) which these cases exhibit. It bears out the point, which has been frequently stressed by Sir Robert Philip, that the pallor of patients suffering from pulmonary tuberculosis is not necessarily due to anaemia, but is frequently the expression of vasomotor disturbance.

In this section, we have considered the technique of sedimentation, describing the important methods of carrying out the test, and considering in some detail the various experimental errors. Special emphasis has been laid on the work of Rees Walton, in connection with the influence of the erythrocyte concentration on the S.R., as his method has been employed in the author's observations. As stated in the Introduction, one of the main objects of this thesis is to study this re-:lationship, and to determine, if possible, the practical value of such a correction for erythrocyte concentration, as/

as Rees Walton suggests. Discussion of its value will be postponed until later, when it will be dealt with from the theoretical aspect in the section on Theory, and from the practical point of view in the Practical Application or the Reaction to the Prognosis of Pulmonary Tuberculosis.

THEORY.

The theory of erythrocyte sedimentation is one of the most complicated problems of biological chemistry. A considerable amount of knowledge has accumulated but many gaps still remain.

It was pointed out in the Historical section, that some very sound observations on the theoretical side had been made by the first half of the nineteenth century. Blood consists of plasma and corpuscles. The latter are of greater specific gravity, and hence tend to sink. It was known at this time, as a result of the investigations of Hewson, that differences in the specific gravity of the erythrocytes, or of the plasma, are not the cause of altered sedimentation rate. Then Nasse showed that with artificial lessen-:ing of the specific gravity, by thinning the plasma with isotonic salt solutions, sedimentation of the erythrocytes was not hastened but slowed. After addition of specifically heavy substances such as gum arabic, sedimentation was found to be hastened.

Lessening/

Lessening of the erythrocyte concentration, by the addition of serum, was also found to produce increased sedimentation.

The most important fact established by these early workers was, that sedimentation is dependent upon the degree of agglomeration of the erythrocytes. Single erythrocytes sediment but slowly, but when they become clustered together, the momentum is greatly increased, and hence a hastened sedimentation rate results.

As a result of the accurate and elaborate methods of modern physical chemistry, we are now in a position to partially explain the phenomenon of sedimentation. As far as recent researches take us, two factors appear to be of primary importance:-

(1) The electrical condition of the erythrocytes.

Höber (32) has shown that erythrocytes move to the anode, and hence carry a negative electrical charge. They are thus kept in suspension, owing to their electrically similar charge. Therefore, it is essential that this charge be neutralised if sedi-:mentation is to take place to any degree.

(2) The influence of protein on sedimentation.

Bloch and Oelsner (33) showed that if corpuscles be placed in a protein-free medium, e.g. physiological saline, agglutination of the corpuscles is prevented, and sedimentation is considerably slowed.

Höber and Mond (34) showed that, <u>in vitro</u>, the sedimentation hastening effect of the various plasma proteins/

proteins parallels their ability to electrically discharge the erythrocytes.

The order of the power of discharging erythrocytes is

Fibrinogen > Globulin > Albumin.

Experience has also shown that, in general, a certain parallelism exists between the fibrinogen and globulin content of the plasma and the sedimentation rate.

Further, Fähraeus (loc. cit.) demonstrated that, in blood showing hastened sedimentation, the negative charge on the erythrocytes was smaller.

From the above findings, the explanation of the phenomenon appears to be as follows:-

The erythrocytes are maintained in suspension in virtue of their being electrically negatively charged.

The plasma proteins, in varying degree as stated above, have the power of becoming adsorbed to the surface of the erythrocytes, and, in virtue of the electrical charges which their molecules possess, neutralise the negative charge of the erythrocytes, thus allowing agglomeration of the latter to occur.

The Influence of the Erythrocyte Concentration on Sedimentation Rate.

That the concentration of the red cells exerts an influence on the sedimentation rate, has been known almost as long as the subject has been scientifically studied/

studied. Fähraeus and Westergren, in their early studies, both noted that an anaemic condition of the blood produced an increased sedimentation rate, but they considered the fact had little practical impor-:tance. Later workers studied the subject, and many concluded that the subject had a practical significance, and accordingly endeavoured to correct the readings for the S.R. in respect of the degree of anaemia present. A brief review of these methods is given in the section on Technique. The most recent of these methods is that of Walton (16), (30), which was described in the foregoing section and is the method which was used by the author. As described in the said section, Walton carried out numerous experiments on the effect on the S.R. of varying the red cell concentration, using citrated plasma for this purpose. He was able to show, by these means, that a relatively slight lessening of the erythrocyte concentration resulted in an astonish-:ingly great increase in S.R.

This corresponds well with experience in certain severe anaemias, where one almost always finds a greatly increased S.R., and conversely in polycythaemia a slowing is observed.

Walton (loc. cit.) quotes a case in which the S.R. at concentration of 5,000,000 red cells per c.mm. was 1 mm. at the end of one hour, and 6 mm. when the concentration was 4,000,000. Can we thus assume that

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a concrete case with 4,000,000 red cells per c.mm. would have only one sixth of the S.R. if this mild degree of anaemia were absent? Can we, in other words, correct the S.R. of anaemic blood to normal blood status?

Walton and other advocates of these corrections hold that this is so, but other authorities, including Westergren, reject the argument as faulty for the following reasons -

(1) In many cases of severe anaemia the S.R. is normal, in spite of very low erythrocyte and haemoglobin values - a state of affairs which cannot be reproduced by thinning of a blood with its own plasma to the same degree of anaemia.

(2) If one concentrates, by pipetting off the citrated plasma of different anaemic bloods, so that the haemoglobin content is now 100%, one finds, especially with severe anaemias, slowing of the S.R. as a rule - indeed in many cases the S.R. after one hour is zero, (Reichel and van de Stadt (35)).

(3) With artificial alteration of the blood concentration, <u>in vivo</u>, the S.R. mostly does not alter parallel to the change in the erythrocyte and haemoglobin content.

So far, we have been considering the subject from the point of view of erythrocyte concentration only. But it has been shown that, in many cases, the change in/

in the erythrocyte concentration is compensated through change in the properties of the plasma.

There are also various other factors to be investigated, in addition to changes in concentration of the erythrocytes. Thus, it is well-recognised that, in anaemia, not only is there a diminution in the concentration of the red cells, but there are also changes in size and shape. Thus the cells may be larger or smaller than normal (megalocytosis and microcytosis), or they may vary in size (anisocytosis), or they may vary in shape (poikilocytosis).

These changes CANNOT be imitated by artificially thinning the blood. Nevertheless, they probably exercise an influence on the power of the erythrocytes to form agglomerations, which, as we have seen, is one of the principal factors in the production of sedimentation.

Further, changes in the plasma may be produced in an anaemia - alterations in specific gravity and in viscosity - which will affect the S.R.

Westergren has shown that, as in severe anaemias, sedimentation is relatively much slower than with blood which is artificially thinned, <u>in vitro</u>, by its own plasma, there must be present in anaemias, sedimentation checking factors, the analysis of which in the single case is difficult.

On these theoretical considerations, therefore, we/

we are inclined to agree with those observers who have had the greatest experience of the clinical value of the S.R. (Westergren, Katz and Leffkowitz), that corrections of the S.R. for any degree of anaemia present, whether according to erythrocyte count, haemoglobin content, or haematocrit reading, give an erroneous value. In the words of Leffkowitz, the S.R., for practical purposes, gives the best results through its complexity. Any corrections which may be made, can only attack one factor, and as such are valueless, if not actually misleading.

That these theoretical considerations with regard to corrections for the red cell count are borne out in practice, we shall endeavour to show in the section dealing with the practical application of the S.R. to the prognosis of pulmonary tuberculosis.

THE APPLICATION OF THE SEDIMENTATION RATE TO PULMONARY TUBERCULOSIS.

The Erythrocyte Sedimentation Rate has three main applications to the study of pulmonary tuberculosis - firstly in diagnosis, secondly in prognosis, and thirdly in treatment.

Scope of Present Investigation.

Much work has been done on the application of the erythrocyte sedimentation rate to the study of pul-
:monary tuberculosis, but several problems still require/

require investigation.

Two chief problems have been pursued in these studies.

The first concerns the influence of red cell concentration on the erythrocyte sedimentation rate. It has long been known that in certain forms of anaemia the S.R. is hastened, and recently corrections have been applied to the S.R. on the basis of anaemia present. We have pointed out, in the section on Theory, that such corrections are, on theoretical grounds, probably erroneous. It now remains to determine the precise practical value of such a correction. Does it give a more accurate indication of the condition and progress of a case than the uncorrected rate?

This problem will be considered in the section on Prognosis.

The second problem concerns the influence of Gold Therapy on the S.R. The literature on this subject is scanty, and the results obtained are variable.

We have, therefore, reviewed the literature, and set forth the results of observations on a series of cases of pulmonary tuberculosis undergoing this form of treatment.

II. Diagnosis.

An increased S.R. is not diagnostic of tuber-

:culosis. This must be borne in mind at the outset. It is merely an indication that there is going on in the patient a process involving tissue destruction. This stimulates fibrinogen formation, and the increased fibrinogen content of the blood neutralises the nega-:tive electrical charge of the erythrocytes. This enables the erythrocytes to form into agglomerates. Thus sedimentation is hastened.

Hence an increased S.R. is only diagnostic of tuberculosis if other possible causes of the increase can be excluded.

Nevertheless, all untreated active exudative cases of pulmonary tuberculosis show an increased S.R. (Westergren (38)).

Hence a normal S.R. is of great importance in excluding pulmonary tuberculosis in a suspect case.

Walton (16) and others claim that the S.R. has considerable diagnostic value when employed in con-:junction with a small provocative dose of tuberculin.

Most observers, however, are agreed that the sphere of usefulness in the diagnosis of pulmonary tuberculosis of an increased S.R. is an extremely limited one.

II. Prognosis.

The value of the Sedimentation Rate in assessing prognosis has now been generally accepted by most authorities/

authorities. Leon Bernard (36) recently stated that of all the reactions that have been advanced, the Sedimentation Test is probably the one which offers the best guarantee and security in prognosis.

Westergren (37) points out that low figures, and particularly normal values of the S.R., point to a good prognosis, while high figures indicate a greater intensity of the pathological processes. The same author, in another place (38), states that the height of the S.R. can be correlated to the activity and extent of the lesion.

Thus, in general, the acute exudative types of tuberculosis give rise to a higher S.R. than the more chronic fibrotic types.

He has correlated the S.R. to the Turban classi-:fication thus::

Stage I.

The most benign cases show normal values. Probably active cases up to about 30 mm. per hour (Westergren's Method).

Stage II.

Inactive cases show normal or very low figures. Active cases - 15-50 mm.

Stage III.

The most benign cases show figures below 10 mm. frequently, sometimes even a normal reaction. Active cases show figures from 30-100-120 mm. per hour/

hour.

Westergren states in the same paper that no single test of an active, or probably active case, has given a normal value, and no case which must be considered quite benign, and certainly shows no sign of activity, has given a high, or even medium high, figure.

Can a normal S.R. be taken as an index that active tuberculosis is not present?

Banyai and Anderson (39) state that among 2000 patients admitted to Muirdale Sanatorium with a tentative diagnosis of pulmonary tuberculosis, 128 (7.35%) were found who had active tuberculosis, diagnosed by physical examination and corroborated by radiological and laboratory observations, and whose S.R. on repeated examination was normal. Westergren, however, as quoted above, states that, in his experience, no active case ever gives a normal figure for the S.R.

In our experience, we have never found an active case of pulmonary tuberculosis with a normal S.R. when first diagnosed. We have noted time and time again, however, that cases undergoing treatment, while still showing signs of activity as evidenced by physical signs, show normal values for the S.R.

S.R. and Ultimate Prognosis:-

In an investigation on this question Traill (40), after/

after pointing out how the usual criteria of prognosis - physical signs, temperature, pulse, sputum tests and fitness for exercise - are frequently misleading, goes on to state that a patient entering a sanatorium with a high S.R., and leaving with a moderately raised S.R., means a bad prognosis. This statement, he maintains, applies to both "open" and "closed" cases. While the gravity increases with open cases, and particularly with those who remain so in spite of treatment, it appears that it is better to remain "positive", and secure a fall in S.R. to a low level, than to be a "closed" case with a discharge figure which persists in the medium-high levels.

The above observations demonstrate the value of the S.R. as a prognostic test. At the same time, in case of misunderstanding, it must be emphasised that the S.R., like all other clinical laboratory methods, must be correlated with the other findings - physical and radiological - before an interpretation is attempted. This has been pointed out by Melville Dunlop (41).

Also one estimation is of little value in estimating prognosis. By repeating the test at intervals of days, weeks or months, a conception of the progress of the disease is obtained, which is, as

a/

a rule, more valuable than that given by the body temperature (Westergren (9)).

In estimations obtained in this way, increasing figures point to a bad prognosis, while decreasing figures are usually of favourable significance.

In addition to its use as an index of prognosis, the S.R. is also of value in indicating spread of the disease, and the occurrence of complications.

Duffy (42) has shown that an increased S.R. is often an earlier indication of extension of the disease than X-ray examination.

Reichel (43) points out that by means of the clinical and radiological picture one can estimate nearly the S.R. Considerable variations from the expected value makes one alive to the possibility of complications.

As a rule, the onset of complications produces a rise in S.R. Such a rise occurs in pleurisy, dry or exudative, and haemoptysis (the rise depending upon the amount of blood, and on the consequent specific or non-specific broncho-pneumonia).

Sinus exudates arising during Artificial Pneumo-:thorax treatment usually produce no noteworthy change, but fresh large effusions produce a marked rise, which often goes down to low, or quite normal, values although the effusion persists.

Large cavities are usually accompanied by a high S.R./

S.R., which Westergren (44) explains as being due to mixed infection, the latter causing a worsening of the tuberculous process, hence the high S.R.

Intestinal tuberculosis is rather peculiar in that early cases show a high S.R., while late cases with marked diarrhoea and cachexia give a low S.R. (Rother (45)).

We can find in the literature no explanation of this terminal fall in S.R. in these cases. We put forward the suggestion that the fall is due to de-:hydration, consequent on the diarrhoea. The dehyd-:ration leads to a concentration of the blood giving rise to a condition of polycythaemia. Such a con-:dition, as pointed out above, brings about a lowering of the S.R.

Low values of S.R. are found in marasmus, and in persistently high pyrexial cases, also in certain cases just before death, when a rapid sinking is often noted.

Low and even subnormal values, after a previously high reading, were found by Westergren (loc. cit.) in miliary tuberculosis.

We have, in the foregoing pages, endeavoured to summarise the present state of knowledge with regard to the value of the S.R. in relation to the prognosis of pulmonary tuberculosis.

THE PRACTICAL VALUE OF APPLYING A CORRECTION TO THE S. R. FOR RED CELL CONCENTRATION.

In the foregoing paragraphs we have been dealing with problems on which there is now more or less general agreement among the leading authorities. It is now proposed to take up a subject which is still greatly debated.

In the section on technique, it was mentioned that, from time to time, methods have been evolved in which a correction is applied to the S.R. for any degree of anaemia present. Later we showed that, from theoretical considerations, such corrections are probably unsound. It is one of the main objects of this thesis to show the precise value of correcting the S.R. for any degree of anaemia which may be present, and to determine whether such a corrected figure gives a more accurate estimate of prognosis.

With this aim in view, we have observed some 36 cases of pulmonary tuberculosis in the Royal Victoria Hospital, Edinburgh, for a period of three to five months. Estimations were carried out at monthly intervals, using Rees Walton's method. This method involves the performance of a red cell count, and correcting the S.R. obtained by a specially constructed graph, as described in the section on Technique.

From these observations, we have come to the conclusion that such a correction is valueless, and, at times, may be misleading.

An/

An analysis of our cases enables us to divide them up into three groups for the purpose of discuss-:ing this subject.

Group I comprises a series of cases in which the corrected S.R. differed to such a slight extent from the uncorrected rate as to render such a correction of no practical moment.

Group II - those cases in which it was found that, when the point was plotted on the graph for the S.R., and the erythrocyte concentration, and the line from the 27.5 mm. mark to this point was produced to meet the five million mark, it did so at a point below the sedimentation zero. This suggests that, without anaemia being present, no sedimentation would have occurred in the time allowed (1 hour).

Group III. A group of cases in which the pro-:gress of the case, as shown by the corrected rates, was impossible of correlation with the other findings - clinical and radiological - in contradistinction to the uncorrected rate, which followed the antici-:pated course.

We shall now proceed to set forth our observations - classified according to the above groups - and discuss the significance of each group in turn.

Note:- Only those cases with a red cell count below 5,000,000 per c.mm. can, of course, be discussed in this section.

Group/

Group I.

Date	Red Cell Count	S.R.	
		Uncorrected	Corrected
Case 1. Mary C.			
29.4.36.	3,970,000	24.5 mm	23 mm.
27.5.36.	4,550,000	21.5	21
25.6.36.	3,850,000	21	19
29.7.36.	3,920,000	21	19
Case 2. Isobel S.			
15.4.36.	4,330,000	19.5	18
13.5.36.	4,100,000	19.5	17
18.6.36.	4,220,000	14	11
15.7.36.	4,940,000	5	4.5
Case 3. Elizabeth A.			
29.4.36.	4,440,000	16.5	15
27.5.36.	4,740,000	12	11
25.6.36.	4,410,000	9	6
Case 4. Annie L.			
29.4.36.	4,070,000	21	19
27.5.36.	4,980,000	18.5	18.5
25.6.36.	4,510,000	12.5	10.5
Case 5. Margaret C.			
29.4.36.	4,310,000	16	13.5
27.5.36.	4,830,000	5	4
25.6.36.	5,010,000	10	10
Case 6. Molly A.			
13.4.36.	4,210,000	18.5	16
18.5.36.	4,830,000	18.5	18
15.6.36.	3,810,000	18.5	15
15.7.36.	4,090,000	19	16.5

Discussion.

A consideration of the above figures shows that, in/

in this group, the corrected rate differs so little from the uncorrected, as to be of no practical impor-:tance. After all, in following the progress of a case by means of S.R. estimations, it is the general trend of the successive readings, whether rising or falling or stationary, on which we base prognosis. A difference of one or two millimetres in a single reading is of no importance from this point of view.

This aspect is of no little importance, as the S.R. has come to be reckoned as an everyday clinical laboratory procedure in estimating prognosis. One of the main criteria of a method which is employed in everyday work is, that it should be as simple in carrying out, and as little time-consuming, as possible.

The S.R. is simply and speedily carried out, but if a correction is to be applied on the basis of red cell concentration, the time required for doing a red cell count adds considerably to the time necessary for the estimation. Thus it is possible to withdraw blood and set up a sedimentation tube in less than 3 minutes from start to finish, but when a red cell count has to be done in addition, the time taken is appreciably greater. Furthermore, the technique of red cell counting requires considerable skill, if trustworthy results are to be obtained. We found, working single-handed, that the time of taking blood off/

off one patient, till the time of taking off blood from the next patient, averaged ten minutes. This included the time necessary for drawing off blood, setting up a sedimentation tube, washing out the syringe, doing a blood count, and, finally, washing out the red corpuscle pipette. It can, therefore, be readily seen that, in a busy laboratory, such additional expenditure of time is of great importance, as it would be also to any doctor in practice who might contemplate carrying out such estimations.

In view of the above findings, we consider that such a correction is, in a considerable number of cases, quite valueless.

Group II.

Date	Red Cell Count	S.R. Uncorrected	S.R. Corrected
Case 1. Margaret B.			
15.4.36.	3,550,000	9 mm.	)No sedimenta-
13.5.36.	3,350,000	3.5 mm.	):tion would
17.6.36.	3,200,000	3	)occur.
15.7.36.	4,470,000	4	1 mm.
12.8.36.	3,150,000	2	No sedimenta- :tion would occur.
Case 2. Mary B.			
15.4.36.	4,120,000	6.5 mm.	0.5 mm.
13.5.36.	4,450,000	10	7.5
17.6.36.	3,610,000	9	)No sedimenta-
15.7.36.	3,650,000	7	):tion would)occur.

Case/

Date	Red Cell Count	S.R.	
		Uncorrected	Corrected
Case 3.	John B.		
30.4.36.	4,060,000	14.5 mm.	10.5 mm.
28.5.36.	4,010,000	5.5	No sedimentation would occur.
29.6.36.	4,750,000	4	3 mm.
31.7.36.	3,970,000	3	No sedimentation would occur.
Case 4.	George A.		
30.4.36.	4,440,000	9.5 mm.	7 mm.
28.5.36.	4,660,000	2	No sedimentation would occur.
29.6.36.	4,250,000	1.5	
Case 5.	Janet W.		
8. 6.36.	5,010,000	7.5 mm.	7.5 mm.
6. 7.36.	4,380,000	3	No sedimentation would occur.
7. 8.36.	4,620,000	3.5	1 mm.

Discussion.

When a correction is applied in this group, apparently no sedimentation would have taken place, in the given time, had no anaemia been present. In other words, in these cases the S.R. is due entirely to the anaemia present.

Such a state of affairs is obviously absurd as some degree of sedimentation must occur. We therefore put forward this finding as an argument against such a correction being made.

Group/

Group III.

Case 1. Mabel M.

This patient was admitted with an exudative lesion at the right apex. She had 1/4 oz. of sputum, daily, which was T.B. positive.
On 17.4.36 her red cell count was 4,180,000 per c.mm., her S.R. being 10.5 (uncorrected), 6.5 (corrected).
She then developed signs of infection of the left apex, and her daily quantity of sputum rose to 1/2 oz.
On 18.5.36 her red cell count was 5,190,000 per c.mm., her S.R. being 7.5 mm.

On 15.6.36 Red cell count 3,940,000 per c.mm., S.R. 8 (uncorrected), 1 (corrected).

On 17.7.36 Red cell count 4,120,000 per c.mm., S.R. 6.5 (uncorrected), 0.5 (corrected).

We thus see that while, in accordance with the extension of the disease, the uncorrected rate remains high, the corrected rate falls to minimal levels, which are quite inconsistent with the clinical picture.

Case 2. Margaret W.

This patient had an exudative lesion at the left apex. Although under sanatorium treatment for almost a year, her temperature was very unstable, and frequently reached 99.4°F. in the evening.

Date	Red Cell Count	S.R.	
		Uncorrected	Corrected
23.4.36.	5,050,000	9 mm.	9 mm.
20.5.36.	4,250,000	9.5	6
25.6.36.	3,910,000	10.5	4

During/

During the month April 23rd to May 20th, she had an exacerbation, and was strictly in bed. During this period, we see that the uncorrected S.R. remained high, while the corrected S.R. shows improvement. Thus, while the temperature and general condition of the patient show activity of the lung process, (and this is also borne out by the uncorrected S.R.), the corrected S.R. gives an erroneous impression of the course of the disease.

Case 3. Catherine S.

This patient was admitted with a fibro-caseous lesion of both upper lobes. Her evening temperature was 99.4°F. on the average.

Date	Red Cell Count	S.R.	
		Uncorrected	Corrected
7.5.36.	3,960,000	16.5 mm.	13 mm.
8.6.36.	2,860,000	18.5	9
6.7.36.	3,770,000	8.5	0.5

While the patient's general condition improved, and there was less moisture present in the lungs, nevertheless there was considerable activity remaining in both lungs, which was not consistent with a S.R. of 0.5 mm. The uncorrected S.R. of 8.5 mm. was a more approximate index of activity.

Case 4. David G.

This patient was admitted with a fibro-caseous lesion of both upper lobes. He subsequently developed

a/

a right lower lobe lesion of pneumonic type, from which he was recovering when we first performed a S.R. on him (24.4.36).

Red cell count 3,920,000 per c.mm.
S.R. 9.5 (uncorrected), 3 (corrected).

During the ensuing 2 months, the right basal condition relapsed, and his temperature was persistently elevated to circa 100°F. His sputum increased from 1 oz. to 2-3 oz. daily, and was double positive.
On 25.5.36. his red cell count was 3,490,000 per c.mm., while his S.R. was 11.5 (uncorrected), and 2 (corrected).
On 24.6.36 the red cell count was 3,520,000 per c.mm., and the S.R. 14 (uncorrected) and 6 (corrected).

From this we see that, while his worsening clinical condition was reflected by a rising uncorrected S.R., the corrected S.R. was within normal limits.

Conclusions.

From the above observations, we suggest that the application of a correction for the red cell count to the S.R. is valueless and erroneous.

From a study of the cases in Group I, we see that frequently the difference between the uncorrected and corrected rates is so small as to be of no practical importance, especially as the correction requires the performance of a red cell count, which adds considerably to the time and labour required for the estimation.

The/

The cases in Groups II and III show that the corrected rate is often erroneous.

An analysis of the Group III cases demonstrates that the corrected rate cannot be correlated with the clinical findings, whereas the uncorrected rate can be so correlated.

Some may argue that, in spite of this, the corrected rate reveals the true state of affairs. We emphasised, however, at the beginning of this section, that the S.R. is only one factor in assessing progress. It is therefore reasonable to take the clinical findings into account, before accepting the S.R. without question. When we do this we find that the uncorrected rate corresponds more accurately with the clinical picture.

We therefore conclude that practical experience with the corrected values bears out the theoretical considerations which we discussed in the section on Theory. These were that there are other factors to be taken into account, when dealing with the blood of anaemic patients, than the red cell concentration. We agree with Leffkowitz (14), who rejects all corrections of the S.R., and maintains that for practical purposes sedimentation gives the best results through its complexity. Further, the great part of its practical significance lies in the simplicity of the technique and reading of results.

For/

For these reasons we have, in the subsequent section on the application of the S.R. in the Treat-:ment of Pulmonary Tuberculosis, recorded all estima-:tions in terms of uncorrected rates of sedimentation.

III. Treatment.

One of the great problems in the conduct of a case of pulmonary tuberculosis is the assessment of the value of any therapeutic method which may be employed.

While the usual clinical and radiological signs are of value on occasion, frequently there are lacking any objective signs on which to base an opinion as to the value of a particular method of treatment.

Thus temperature and pulse rate may be normal. Increase of weight is of certain value, but is not necessarily a sign of improvement. The amount of sputum and its content of tubercle bacilli are also an indication, but again are not to be relied on in many cases. Physical signs and radiological findings are often of little help, especially in cases undergoing treatment by Artificial Pneumothorax.

In the evaluation of methods of treatment, estimation of the S.R. at intervals is often of great value. Thus cases undergoing ordinary routine sanatorium treatment can be followed, and their response noted.

A/

A rising S.R. in such cases often demonstrates the necessity for introducing further methods of treatment.

In those cases undergoing treatment by Artificial Pneumothorax, estimations of the S.R. are of great value, as will be discussed later.

The influence of gold therapy on the S.R. is of considerable interest for two reasons. Firstly because very little has been written on the subject. Secondly, in view of the present greatly debated position of gold therapy, investigations into its effect on the S.R. may be of some value in deciding one way or the other.

The S.R. is also said to be influenced by Tuberculin therapy. We have had no personal exper-:ience of this matter, but will refer to the subject again later.

The S.R. in Artificial Pneumothorax Therapy.

Artificial Pneumothorax is now a well-recognised and successful method of treatment, in selected cases of pulmonary tuberculosis. Nevertheless, the diffi-:culties in the conduct of a case undergoing this form of therapy are great. The usual criteria are of little help in estimating the activity of a tuber-:culous lesion in a lung treated by artificial pneumo-:thorax. When the diseased lung is put at rest, constitutional/

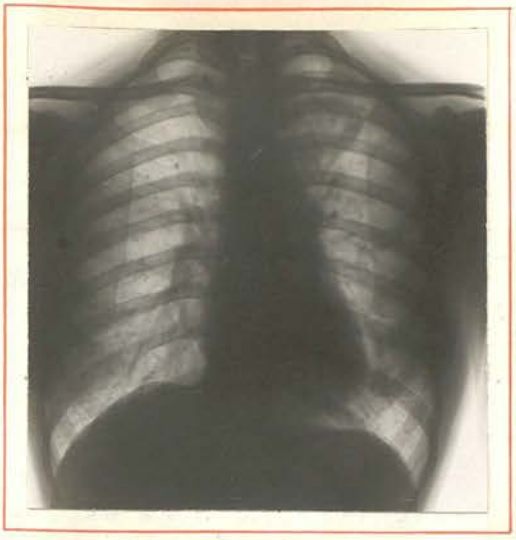
constitutional symptoms usually disappear, and the physical signs and radiological appearances reflect, not the pathological process, but the induced collapse. As Cutler, in a paper on the Sedimentation Test in the Management of an Artificial Pneumothorax case (46), asks how is one to advise such a patient, when and how far to limit exercise, and when to permit a return to active life? In the ordinary way, there is the greatest uncertainty on these points, and the case has to be conducted, as it were, by a system of trial and error. It is thus obvious that we are in great need of some objective sign, whereby we can assess the activity of the tuberculous process in a patient undergoing this treatment. We suggest from our observations, which are recorded below, that we have in the sedimentation test such an objective method. We have had the opportunity of estimating the S.R., over a period of several months, on eleven cases undergoing artificial pneumothorax therapy, the results of which we shall now proceed to record in tabular fashion.

(T = average maximum temperature;
P = average maximum pulse rate).

Case/

Case 1. Nora C.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
27.4.36	17.5 mm.	98.4°F.	88	7st.12½lb.	Exudative infiltration at left apex. Sputum ⅛oz. daily. T.B. present. A.P. induced 6.5.36.
27.5.36	7.5 mm.	98.2°F.	84	7st.13lb.	Silence on auscultation. Satisfactory collapse radiographically. Sputum ½oz. daily. T.B. present.
25.6.36	6.5 mm.	98.2°F.	84	7st.13¼lb.	As above. Sputum ¼-½ oz. No T.B.present.
29.7.36	3.5 mm.	98.2°F.	82	8st.2lb.	As above. Sputum ¼ oz. T.B. scanty.



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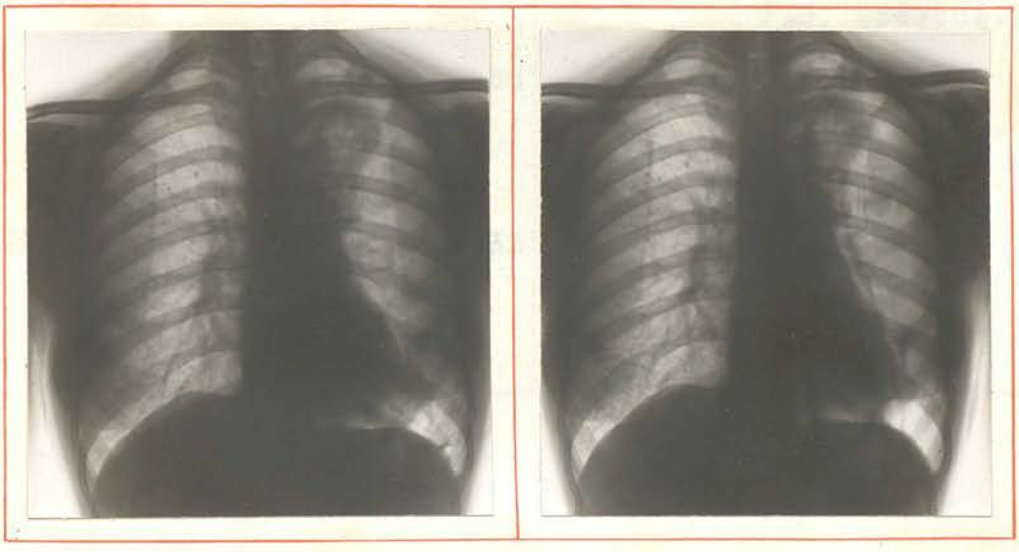


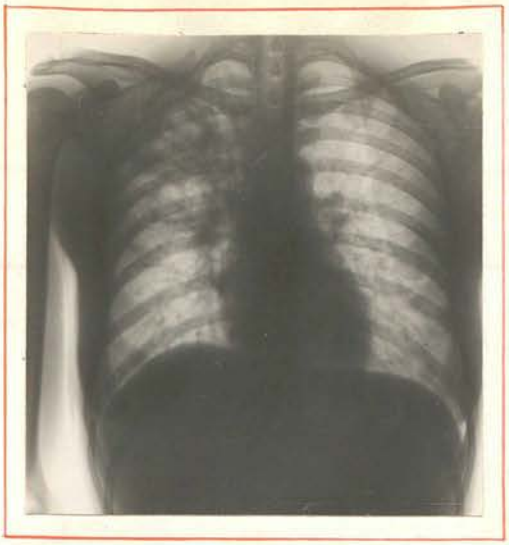
b. c.

Case 1. Nora C.

Fig.a. X-ray photograph of chest before induction of A.P. showing infiltration at left apex.
Fig.b. Immediately after induction of A.P. Note small pocket of air in pleural cavity.
Fig.c. Three days after induction. Good collapse. Note pathological signs now obscured.

Case 2. Jane G.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
29.4.36	17.5 mm.	98.4°F.	84	6st.10lb.	Cavitation in right apex. Sputum 1 oz. daily. T.B. present. A.P. induced 7.5.36.
27.5.36	13 mm.	98°F.	84	6st.9½lb.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. Sputum 1-1½ oz. daily. T.B. present.
25.6.36	8 mm.	98°F.	88	6st.7lb.	As above. Sputum ½ oz. daily. T.B. present.
29.7.36	7 mm.	98°F.	82	6st.8lb.	As above. Sputum ⅛-¼ oz. daily. T.B. present.



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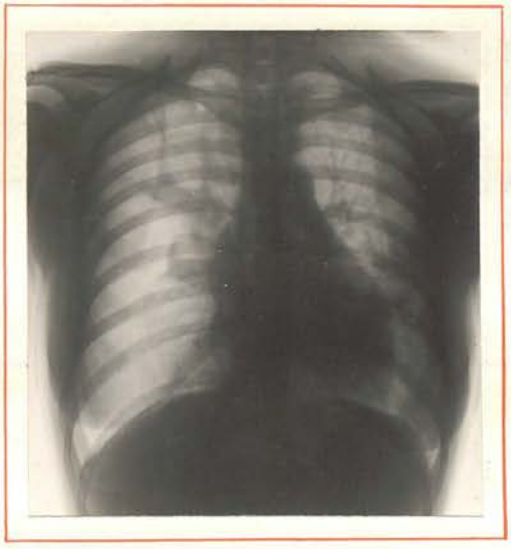


b.

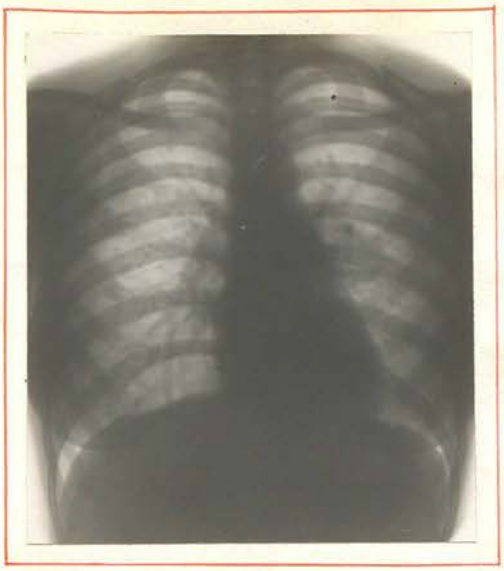
Case 2. Jane G.

Fig.a. X-ray photograph of chest before induction of A.P. showing cavitation in right upper lobe.

Fig.b. Ten weeks after induction of A.P.
Good collapse. Pathological signs obscured.

Case 3. Annie L.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
29.4.36	21 mm.	99°F.	88	8st.11 lb.	Cavity with fluid level in left midzone. Sputum ⅛ oz. daily. T.B. present. A.P. induced 2.5.36.
27.5.36	18.5 mm.	98.4°F.	84	8st.9lb.	Silence on auscultation. Satisfactory collapse radiographically. Sputum 1/8 oz. daily. No T.B.
25.6.36	12.5 mm.	98.4°F.	84	8st.8¼lb.	As above. No sputum.
29.7.36	4.5 mm.	98°F.	82	8st.9lb.	As above. No sputum.



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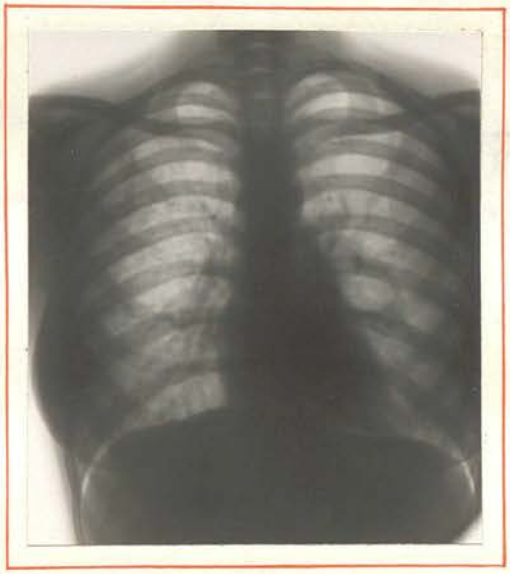


b.

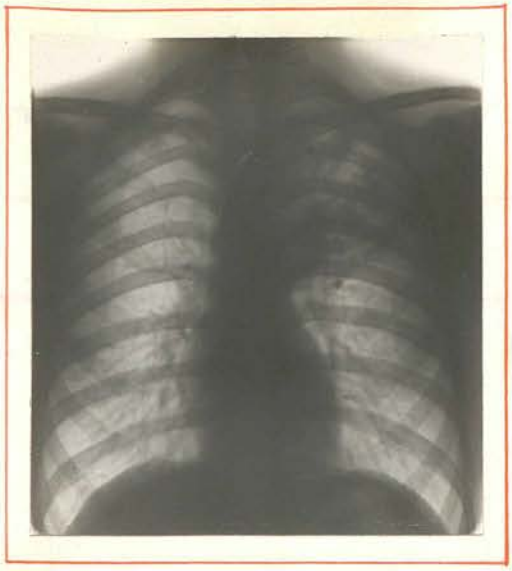
Case 3. Annie L.

Fig.a. X-ray photograph of chest before induction of A.P. showing cavity with fluid level near left hilar region.

Fig.b. Four days after induction of A.P. Satisfactory collapse.

Case 4. Lennan F.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
7.5.36	16 mm.	98.4°F.	88	8st.13½lb.	Exudative infil-:tration of left upper lobe. No cavitation. Sputum 1/8 oz. on two occasions. T.B. present. A.P. induced 8.5.36.
15.6.36	10 mm.	98°F.	90	9st.8lb.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. No sputum.
17.7.36	2.5 mm.	98.4°F.	90	9st.10¾lb.	As above. No sputum.



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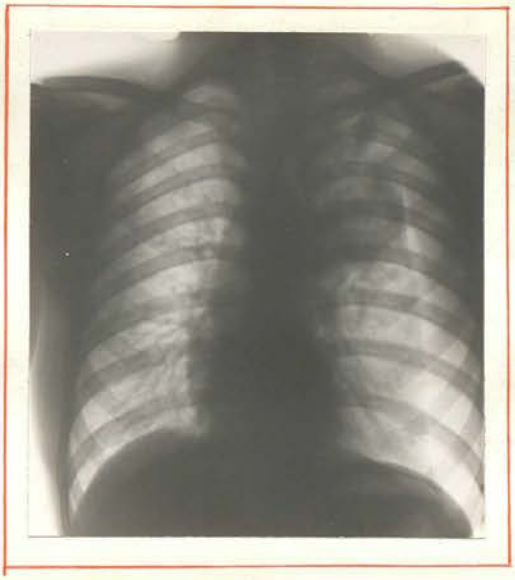


b.

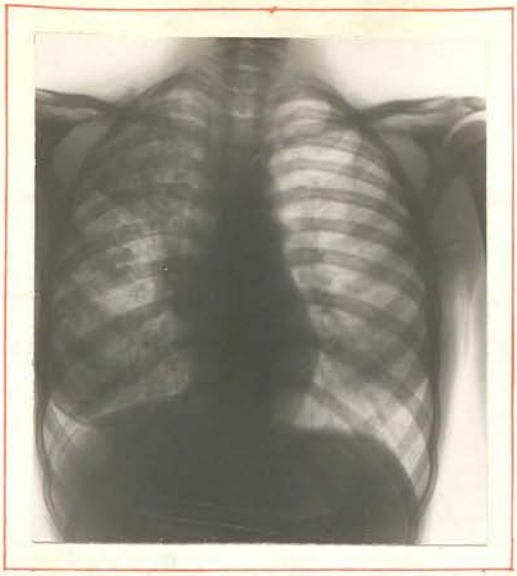
Case 4. Lennan F.

Fig.a. X-ray photograph of chest before induction of A.P. showing marked infiltration in left upper lobe.

Fig.b. Immediately after induction of A.P.
Satisfactory collapse.
Pathological signs already largely obscured.

Case 5. Mary Y.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
13.4.36	20 mm.	98°F.	84	6st.5lb.	Extensive exu-:dative process affecting all lobes of right lung. No cavitation. No sputum. A.P. induced 6.4.36.
13.5.36	17 mm.	98.4°F.	82	6st.8lb.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. No sputum.
17.6.36	16 mm.	98°F.	82	6st.10½lb.	As above. No sputum.
15.7.36	8 mm.	98°F.	82	6st.8½lb.	As above. No sputum.
12.8.36	4 mm.	97.8°F.	82	6st.7lb.	As above. No sputum.



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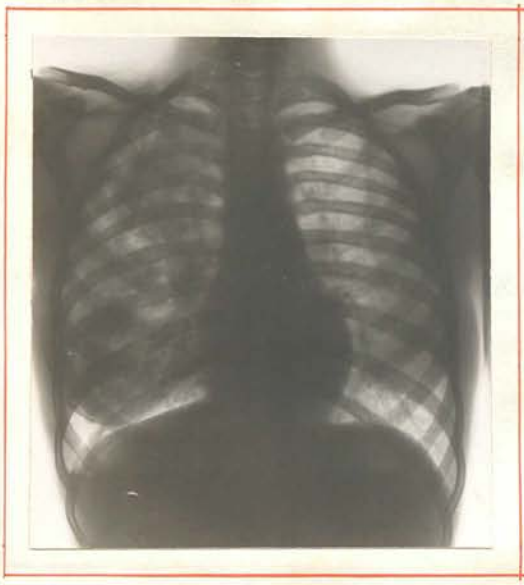

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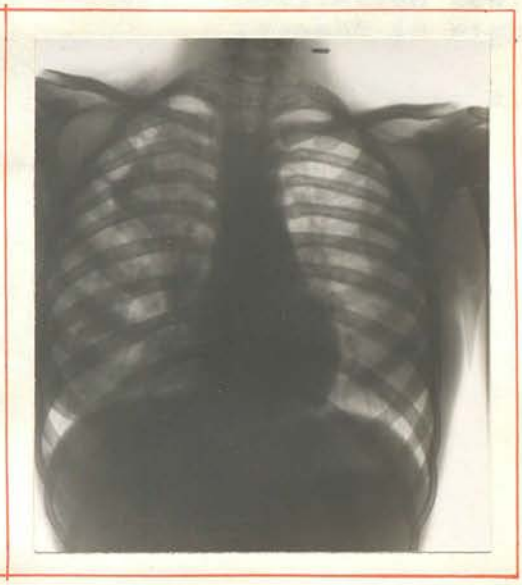


c.

Case 5. Mary Y.

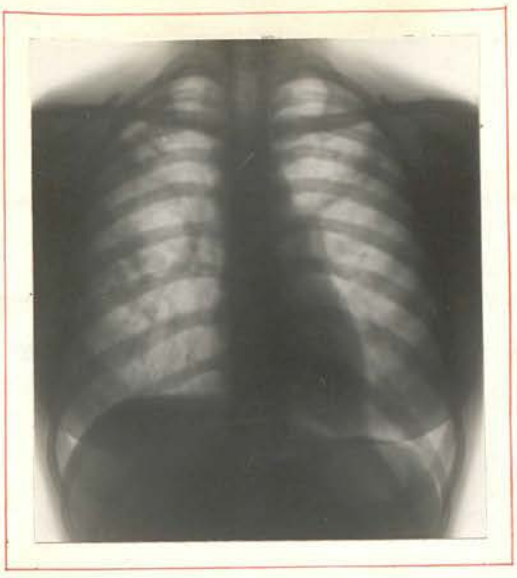
Fig.a. X-ray photograph of chest before induction of A.P. showing marked right-sided infiltration.

Fig.b. Immediately after induction of A.P.
Note small pocket of air in the pleural cavity.

Fig.c. Four days after induction.
Satisfactory collapse.
Pathological signs already obscured.

Case 6. Elizabeth A.

Date.	S.R.	T.	P.	Weight	Clinical Data.
29.4.36	16.5 mm.	98.6°F.	88	8st.5lb.	Exudative infil-:tration of right upper lobe. Sputum ½ oz. daily. T.B. present.
27.5.36	12 mm.	98.6°F.	84	8st.6lb.	As above. Sputum ½ oz. daily. T.B. present.
25.6.36	9 mm.	100°F.	88	8st.½lb.	Cavitation now present in right upper lobe. Sputum ¾-1½ oz. daily. T.B. present. A.P. induced 27.6.36.
31.7.36	5.5 mm.	98.6°F.	84	8st.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. Sputum ¼ oz. daily. T.B. present.



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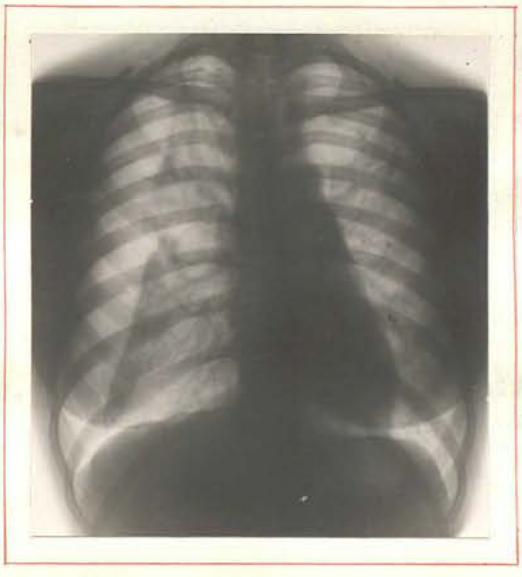


b.

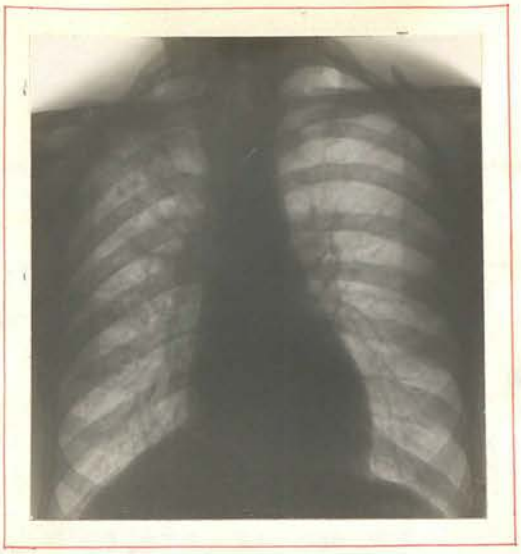
Case 6. Elizabeth A.

Fig.a. X-ray photograph of chest before induction of A.P. showing commencing cavitation on the right side.

Fig.b. Three weeks after induction of A.P.
Good collapse.
Pathological signs now largely obscured.

Case 7. James L.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
11.5.36	4.5 mm.	98.4°F.	84	10st.4½lb.	Exudative infil-:tration of right upper lobe. Sputum ½ oz. daily. T.B. present. A.P. induced 13.5.36.
15.6.36	6 mm.	97.6°F.	82	11st.	Silence on aus-:cultation. Un-:satisfactory collapse radio-:graphically. Sputum ⅛-½ oz. daily. No T.B.
17.7.36	4 mm.	97.6°F.	82	11st.9½lb.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. Sputum ½-¾ oz. daily. No T.B.
12.8.36	3 mm.	97.4°F.	84	11st.12¼lb.	As above. Sputum ½-1 oz. daily. No T.B.



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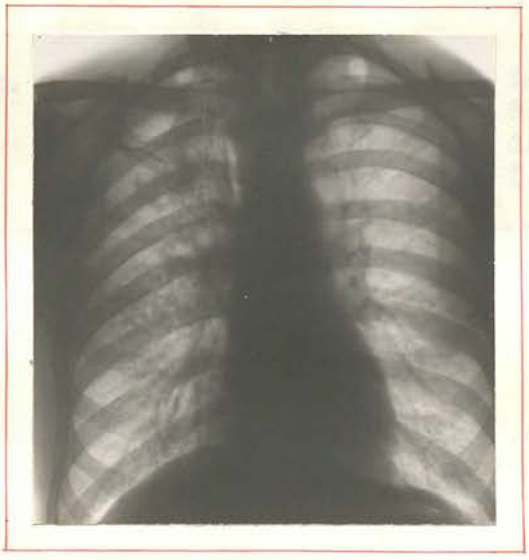


b.

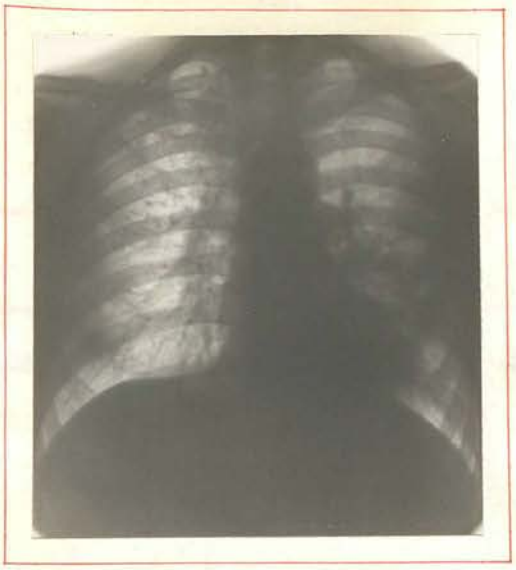
Case 7. James L.

Fig.a. X-ray photograph of chest before induction of A.P. showing infiltration at right upper lobe.

Fig.b. Immediately after induction of A.P. Note small pocket of air in pleural cavity.

Case 8. Alec M.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
4.5.36	18 mm.	97.8°F.	88	9st.10¾lb.	Large cavity in left lower lobe. Sputum 1 oz. daily. T.B. present. A.P. induced 9.5.36.
8.6.36	15 mm.	97.8°F.	88	9st.5¾lb.	Silence on aus-:cultation but X-ray shows no collapse of cavity. Sputum 1 oz. daily. T.B. present.
6.7.36	16 mm.	98°F.	100	9st.1 lb.	As above. Sputum 1½ oz. daily. T.B. present.



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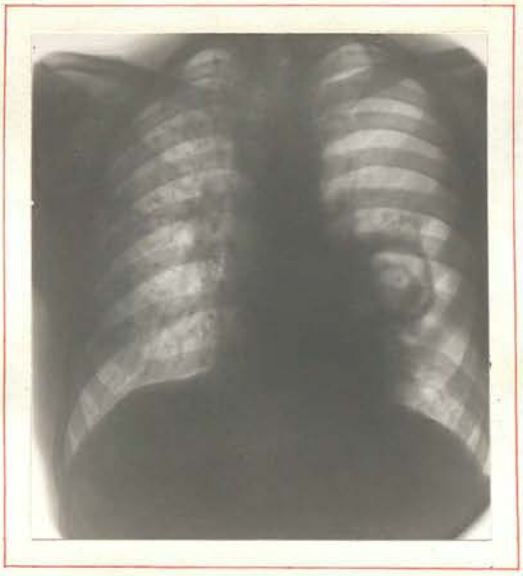


b.

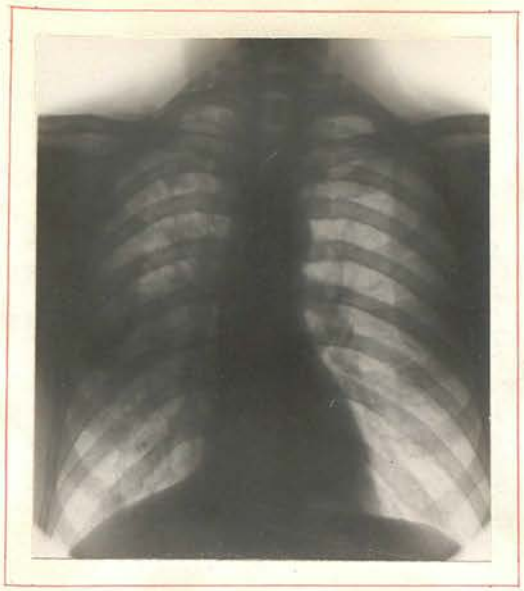
Case 8. Alec M.

Fig.a. X-ray photograph of chest before induction of A.P. showing marked infiltration with cavitation towards left base.

Fig.b. Four days after induction of A.P. Good collapse of lung generally, but thick-walled cavity unaffected.

Case 9. John H..

Date.	S.R.	T.	P.	Weight.	Clinical Data.
4.6.36	15.5 mm.	101°F.	96	10st.2½lb.	Exudative in-:filtration at right apex with pneumonic pro-:cess at right base. Sputum 1 oz. daily. T.B. present. A.P. induced 5.6.36.
6.7.36	19.5 mm.	100°F.	94	10st.5lb.	Silence on aus-:cultation. Poor degree of collapse radiographically. Sputum ½-1 oz. daily. T.B. present.
6.8.36	18 mm.	99°F.	88	10st.8½lb.	As above. Sputum ½ oz. daily. No T.B.



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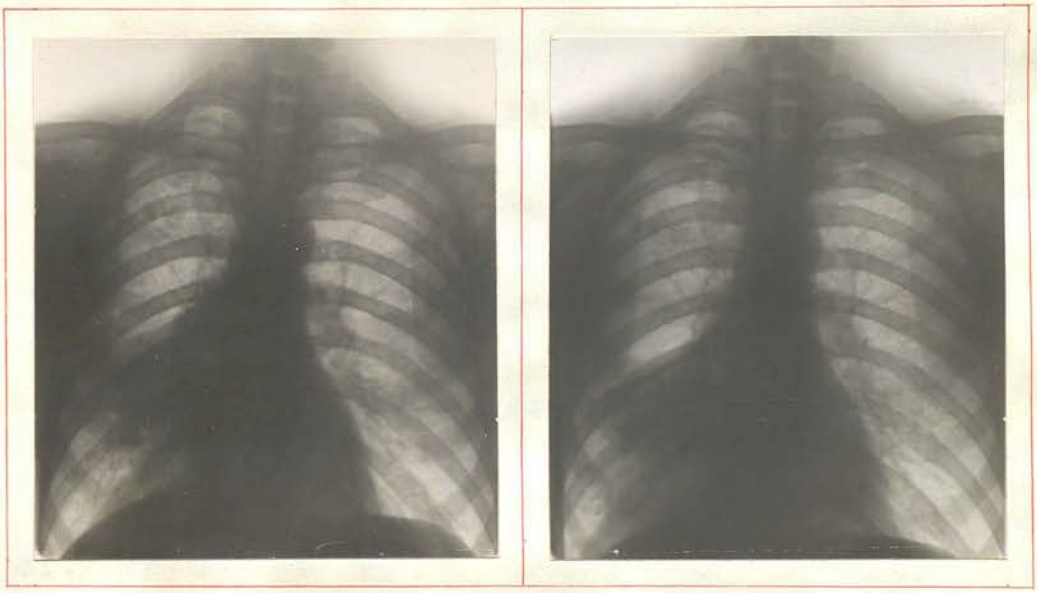


b. c.

Case 9. John H.

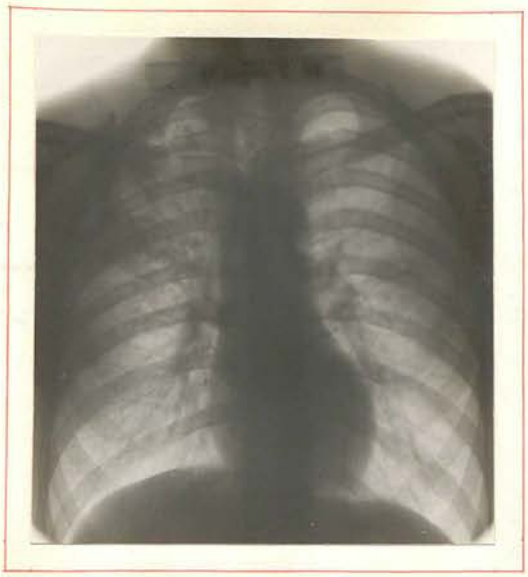
Fig.a. X-ray photograph of chest before induction of A.P. Note pneumonic condition of right base.

Fig.b. Six days after induction of A.P. Note pocket of air in pleural cavity.

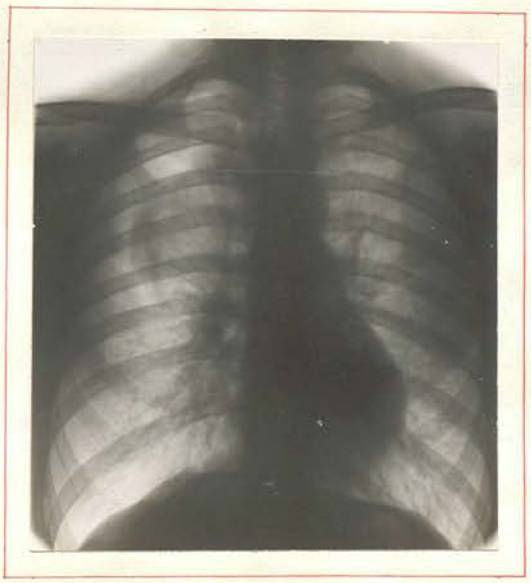
Fig.c. Three weeks after induction. Satisfactory collapse prevented by pneumonia at right base.

Case 10. Archie P.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
30.4.36	13 mm.	98°F.	88	9st.4¼lb.	Cavitation in right upper lobe, towards apex. Small area of active infiltra-:tion in left mid-zone. Sputum ⅛ oz. daily. T.B. present. A.P. induced 14.5.36.
28.5.36	7.5 mm.	98°F.	88	9st.7½lb.	Silence on aus-:cultation. Satisfactory collapse radio-:graphically. No clinical or radiographical evidence of ex-:tension of con-:tralateral focus. Sputum ⅛ oz. daily. T.B. present.
29.6.36	1.5 mm.	97.6°F.	84	9st.8¼lb.	As above. Sputum ⅛-¼ oz. very occasionally. T.B. absent.
31.7.36	0.5 mm.	97.4°F.	80	9st.9¼lb.	As above. No sputum.



a.



b.

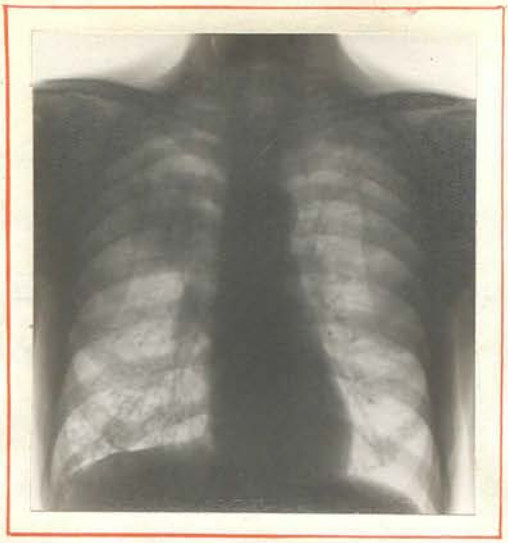
Case 10. Archie P.

Fig.a. X-ray photograph of chest before induction of A.P. showing cavitation in right upper lobe and infiltration in left mid-zone.

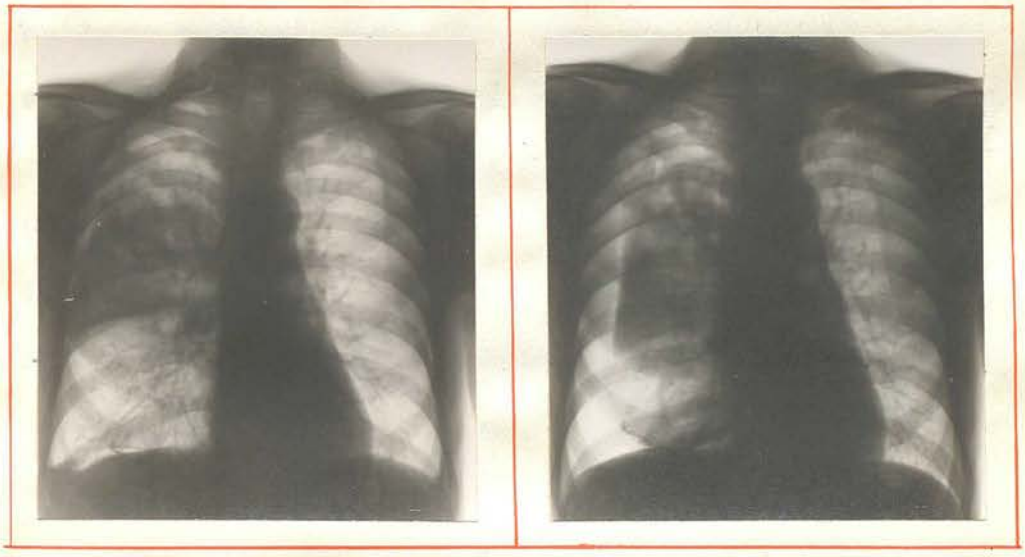
Fig.b. Eight weeks after induction of A.P.
Good collapse. Note pathological signs on right side now obscured.
No increase of activity on left side.

Case 11. Ernest K.

Date.	S.R.	T.	P.	Weight.	Clinical Data.
13.5.36	20 mm.	101°F.	96	7st.4½lb.	Pneumonic process right middle lobe also moderate degree of infiltration at left apex and base. Sputum 4 oz. daily. T.B. present. A.P. induced 15.5.36.
15.6.36	22.5 mm.	99.6°F.	96	6st.11½lb.	Silence on auscultation. Moderately good collapse radiographically. No clinical or radiographical evidence of extension of disease in contralateral lung. Sputum 3-5 oz. daily. T.B. present.
17.7.36	21.5 mm.	100°F.	110	6st.9¼lb.	Silence on auscultation. Moderately good collapse radiographically. Clinical evidence of extension at contralateral base also intense dyspnoea. A.P. discontinued 19.7.36. Sputum 2 oz. T.B. present.



a.



b. c.

Case 11. Ernest K.

Fig.a. X-ray photograph of chest before induction of A.P. showing bilateral disease - worse on right side.

Fig.b. Immediately after induction of A.P. on right side. Note small pocket of air in pleural cavity.

Fig.c. Three weeks after induction. Good collapse. Note pneumonic process in collapsed lung. No evidence as yet of increased activity on left side.

Discussion.

From a consideration of the above cases, it is seen that, provided a satisfactory degree of collapse has been obtained, the effect of artificial pneumo-:thorax therapy is, in general, to produce a fall in the S.R. This finding is in agreement with the results of investigations by other authors on this subject (Cutler (46), Traill and Stone (47)).

Traill and Stone (loc.cit.) and Fischel (48) have noted an initial rise in the S.R., following the induction of an artificial pneumothorax. The former authors suggest that this rise is due to worry or shock, or perhaps to auto-inoculation from the com-:pression of the diseased lung. Fischel suggests that "the augmented destruction of tissue, due to inflammatory demarcation in the compressed areas, leads to a temporary increase in sinking velocity".

This rise is seen in two of our cases (Cases 7 and 9).

When we examine the clinical and radiological data in the above cases, we see how little we have to go on to determine the progress of a case. The temperature and pulse rate, if they were elevated before the induction, usually fall to normal levels soon after. We have already seen above that a normal temperature and pulse rate give no indication of the activity of the lesion. Then the physical and radio-:logical/

:logical signs are obscured by the collapse. A study of the S.R., however, shows a progressive decrease in velocity, indicating a lessening degree of activity of the tuberculous lesion in the collapsed lung. Thus, it is readily seen that we have in the S.R. an invaluable objective sign of pathological activity in these cases.

We are thus able to control exercise, and the general life of the patient undergoing this treatment, in a scientific manner quite impossible except with the aid of this simple clinical laboratory procedure.

In those cases in which a satisfactory degree of collapse is not obtained, the S.R. fails to fall to any marked degree. This is seen in Cases 8 and 9.

In case 8, a large cavity remained almost unaffected by the artificial pneumothorax, with the result that the S.R. remained practically unchanged.

In case 9, a pneumonic condition was present, rendering collapse very difficult.

One type of case undergoing artificial pneumo-:thorax treatment gives the physician in charge end-:less worry, and that is the type in which both lungs are affected, and the worse side has been collapsed. The strain thereby thrown on the uncollapsed lung very often results in increased activity in that lung, with disastrous results. In these cases, frequent estimation of the S.R. is of immense value. A

falling/

falling S.R. indicates satisfactory inactivity in both lungs, whereas a persistently high or rising S.R. indicates a spread of the disease in the contralateral lung, and demands cessation of the artificial pneumo-:thorax.

While clinical and radiological investigations may be of help in such cases, an estimation of the S.R., at intervals, provides definite contributory evidence as to the state of the contralateral lung.

These points are illustrated in Cases 10 and 11.

Case 10 was admitted with a bilateral lesion - cavitation in the right upper lobe, and infiltration in the left midzone. The right side was in urgent need of an artificial pneumothorax, but the affection of the left lung held us back. It was decided, how-:ever, to collapse the right side, a careful watch being kept, clinically and radiologically, on the contralateral lung. No evidence of spread could be found. Periodical estimations of the S.R. showed a steady fall to normal levels. This was consistent with the satisfactory collapse obtained on the one side, and the lack of clinical or radiological evidence of spread of disease on the other side.

Thus in this case, the S.R. yielded valuable corroborative evidence of the satisfactory state of both lungs.

Case 11 shows the opposite state of affairs, and provides/

provides a contrast to case 10. He was admitted with marked bilateral disease, worse on the right side. He was obviously very ill, and the question was, were we to pursue conservative treatment, or were we to make a desperate, possibly life-saving, attempt at an artificial pneumothorax on the more involved side. We decided on the latter course, and were able to produce quite a satisfactory degree of collapse. Periodical estimations of the S.R., however, showed a persistently high rate, with a tendency to rise.

Clinical examination revealed a spread of the disease at the left base, and the patient started having severe attacks of dyspnoea. The artificial pneumothorax was therefore discontinued.

It is said (Traill and Stone (47), Reichel (43)) that with the onset of a pleural effusion, during artificial pneumothorax therapy, the S.R. rapidly increases. In our series we have been fortunate enough not to have had an effusion, and hence are not in a position to make a statement on this question.

The Influence of Tuberculin Injections on the S.R.

This is a subject of considerable theoretical and practical interest, and it was naturally investigated early on in the scientific study of the sedimentation rate. We have no personal experience in the matter, and must therefore be content with a summary of the literature on the subject.

Westergren/

Westergren (49), himself, studied the question, and found that, following a series of injections of tuberculin, a definite effect was produced on the S.R. He followed up the injections with an estimation of the S.R. every day, or every second day. He found that, without exception, an obviously increased S.R. appears. This rise may be noticed earlier, and always lasts for a longer time, than the reaction of the organism, which is manifested in the general state, and by careful measurements of the temperature.

This observation is confirmed by Zinn and Katz (50), who recommend that tuberculin therapy should be controlled by S.R. estimations. They state that the typical course of the S.R. curve, in this treatment, is an increase within twenty-four hours to four days. If this increase amounts to only a few millimetres the cure is continued, perhaps more quickly if at first the S.R. is not influenced.

A greater increase indicates more cautious dosing, or interruption of the treatment. A small rise indi-:cates that one is working with therapeutically effec-:tive doses. The most desirable type of therapeutic curve thus shows a wavy form, in general, with fairly rapid decreases.

When instead of this, the curve shows slow, or all too great sudden rises, the case is to be considered as less suited for this therapy.

The Influence of Gold Therapy on the S.R.

The influence of Gold therapy on the S.R. is a subject to which very little attention has been given. This is rather remarkable in view of the great interest which has been taken in gold therapy, since it was introduced by Mollgard in 1924. With the heated discussions which have taken place regarding its value, and mode of action, one would have thought that a study of its influence on the S.R. might have been considered of some value in shedding light on these problems. Nevertheless, a fairly comprehensive search of the literature has revealed only six papers which mention the subject, and there is no general agreement as to the influence exerted. Thus Herborg (51), in a series on "Sanocrysin Problems", states that injections of Sanocrysin, in fifteen cases of various types of tuberculosis, caused no increase in S.R., in comparison with the rise in rate usually experienced following Reiz therapy, or injections with sulfusin. In four cases of typical erythema-exanthema, there was no relation between the degree of severity of the skin reaction and the increase in the S.R. All other authors who have investigated this question, however, hold that gold therapy does influence the S.R. in a definite manner. Thus Heaf (52), in 1926, found that the S.R. was markedly decreased at the end of the course of treatment, but that in over 75% of cases the rate/

rate slowly increased after stoppage of administration of the drug. This he regarded as a very disappointing sign as to the permanency of the benefit obtained from the drug.

In the same year, Sayé (53) observed that the introduction into the blood stream of gold salts is followed by a fall in S.R., which lasts from 24 to 48 hours.

Houghton (54) in 1932 published observations which confirm those of Sayé. He found that the temporary drop in the S.R. in some cases, following the injection, was striking, although it did not by any means invariably occur, even in the same case. In one case blood taken at 12 noon (immediately before an injection of 0.5 gm. Sanocrysin) sedimented 10 mm.; a specimen taken at 12.30 p.m. sedimented 11 mm., and a specimen taken 24 hours later sedimented 4 mm. In another case an initial S.R. of 19 mm. was changed one hour after injection to 7 mm. In each of these cases the S.R. returned approximately to its original state four days later. Houghton regards this temporary fall, when it occurs, as a favourable reaction to Sanocrysin. He admits that the immediate reactions to Sanocrysin are irregular, and attempts to explain the occasional sudden drops in rate of sedimentation, as occurring only when the dose happened to coincide with a suitable "phase"/

"phase" in the state of the patient's blood.

Traill and Stone (55), and Gutiérrez, Alix, Paz and de Vega (56) find that while the ultimate influence of gold therapy is to produce a decrease in the S.R., the initial effect is the appearance of a rise in the S.R. The latter authors devote an entire paper to the subject, and conclude that the first phenomenon in the course of the S.R., under the influence of gold salts, is acceleration, which by itself does not indi-:cate clinical worsening. This increased rate is transitory, and soon a decrease in S.R. sets in.

Nevertheless, a closer inspection of these authors' figures shows that the course of the S.R. is not so clearcut as their conclusions would suggest. Their method was to estimate the S.R. at monthly intervals during the course of treatment. At the end of the first month, of 46 cases

23 (50%) showed increased S.R.
20 (43.5%) showed decreased S.R.
3 (6.5%) showed no change in S.R.

After 1 to 2 months of 36 cases

10 (27.8%) showed increased S.R.
24 (66.7%) showed decreased S.R.
2 (5.5%) showed no change in S.R.

It is readily seen from these figures that neither the initial rise, nor the subsequent fall, in S.R. are invariable findings or nearly so. A considerable percentage of cases shows the opposite change. These authors have attempted to correlate the changes in the S.R./

S.R., which they observed, with the clinical condition of the patient. They conclude that the rise in S.R. is not related to an improvement, or a worsening, of the patient's condition, and that the fall in S.R. is not related to clinical progress.

From the foregoing summary of the literature, the diversity of opinion on this subject is readily apprec-:iated. We have therefore thought it worth while to record our observations on a number of cases under our care. Then we propose to discuss these results, com-:paring them with those of other authors, and, if possible, evaluate the influence of gold therapy on the S.R.

Unfortunately, the number of cases which we have been able to observe is small, but this is counter-balanced to some extent by the fact that estimations of the S.R. were made thrice weekly on each patient, bringing the total number of estimations to round about 250, from which figure we think certain conclusions are justifiable.

The method adopted was as follows:- the S.R. was estimated 24 hours before each injection of gold, and then again 24, and 48 hours, after the injection. It was assumed that any immediate reaction on the S.R. was likely to occur within these limits. The gold prepara-:tion used was Mollgard's Sanocrysin.

The results obtained are recorded below.

Case 1. Molly A.

Date	S.R. Before Sanocrysin	S.R. 24 hours after	S.R. 48 hours after	Dose.
27.4.36.	22.5 mm.	21.5 mm.	20 mm.	0.05 gm.
4.5.36.	19	20.5	17	0.06 gm.
11.5.36.	18	20	21	0.08 gm.
18.5.36.	18.5	19	-	0.1 gm.
25.5.36.	20	22	20	0.2 gm.
1.6.36.	19	4	17	0.3 gm.
8.6.36.	20	20	17	0.4 gm.
15.6.36.	18.5	-	18	0.4 gm.
22.6.36.	-	-	-	Papular rash.
29.6.36.	17.5	19	18	No Sanocrysin given.
6.7.36.	19	19	18.5	" "
13.7.36.	17	19	17.5	0.2 gm.
20.7.36.	18	17	17.5	0.2 gm.
27.7.36.	16.5	16	16	0.3 gm.
3.8.36.	13.5	15.5	13.5	0.4 gm.
10.8.36.	9.5	9.5	12	0.5 gm.

Case 2. Margaret G.

Date	S.R. Before Sanocrysin	S.R. 24 hours after	S.R. 48 hours after	Dose.
4.5.36.	10 mm.	9.5 mm.	6 mm.	0.04 gm.
11.5.36.	4 mm.	8.5 mm.	-	0.1 gm.
18.5.36.	10	10	6	0.1 gm.
25.5.36.	10.5	-	-	Menstruating. No Sanocrysin.
1.6.36.	-	-	-	Dermatitis. No Sanocrysin.
8.6.36.	10	4	10	0.1 gm.
15.6.36.	9.5	10	8.5	Dermatitis. No Sanocrysin.
22.6.36.	10	10	10.5	0.1 gm.
29.6.36.	6	10	4	0.2 gm.
6.7.36.	1	8	5.5	Papular rash. No Sanocrysin.
13.7.36.	7.5	7.5	8.5	" "
20.7.36.	8	7	5.5	" "
27.7.36.	4	5	3	" "
3.8.36.	1.5	4	1	" "
10.8.36.	1.5	1.5	3.5	" "

Case 3. William M.

Date	S.R. Before Sanocrysin	S.R. 24 hours after	S.R. 48 hours after	Dose
27.4.36.	21.5 mm.	20 mm.	21 mm.	0.01 gm.
4.5.36.	19	19.5	19	0.02 gm.
11.5.36.	18	18	18	0.04 gm.
18.5.36.	17	15.5	15.5	0.06 gm.
25.5.36.	17	16.5	17.5	0.08 gm.
1.6.36.	16	16.5	16	0.1 gm.
8.6.36.	7	3	17.5	0.2 gm.
15.6.36.	17	17	16.5	0.3 gm.
22.6.36.	16	16	15.5	0.4 gm.
29.6.36.	16	17.5	15.5	Papular rash. No Sanocrysin.
6.7.36.	16	16.5	16	" "
13.7.36.	15	15	17	0.3 gm.
20.7.36.	16	16	16	0.4 gm.
27.7.36.	17	17	12	0.5 gm.
3.8.36.	15	14.5	3.5	0.6 gm.
10.8.36.	13.5	15	14	0.7 gm.

Case 4. James D.

Date	S.R.			Dose
	Before Sanocrysin.	24 hours after	48 hours after	
11.5.36.	12.5 mm.	11 mm.	13 mm.	0.1 gm.
18.5.36.	14	12	13	0.2 gm.
25.5.36.	12.5	12	10	0.3 gm.
1.6.36.	10	10	10.5	0.4 gm.
8.6.36.	2	10	6	0.5 gm.
15.6.36.	11.5	13	15	0.5 gm. (Developed cold at this point).
22.6.36.	13	14	13.5	0.5 gm.
29.6.36.	14	13.5	15	0.5 gm.
6.7.36.	12.5	14	14	0.5 gm.
13.7.36.	11.5	6	7.5	0.5 gm.
20.7.36.	11	10	8.5	0.5 gm.
27.7.36.	9.5	13	12.5	0.6 gm.
3.8.36.	13.5	11	2	No Sanocrysin.
10.8.36.	7	11.5	11.5	" "

Case 5. Mabel M.

Date	S.R.			Dose
	Before Sanocrysin	24 hours after	48 hours after	
4.5.36.	11 mm.	10.5 mm.	5 mm.	0.4 gm.
11.5.36.	5.5	9	4.5	0.6 gm.
18.5.36.	7.5	4	2	0.6 gm.
25.5.36.	9	7	7	0.7 gm.
1.6.36.	-	-	-	Seborrhoeic Dermatitis. No Sanocrysin.
8.6.36.	-	-	-	" "
15.6.36.	8	7.5	9	" "
22.6.36.	8	9	10	0.5 gm.
29.6.36.	6.5	7	6	0.6 gm.
6.7.36.	6.5	9	9	0.7 gm.

Case 6. William C.

Date	S.R. Before Sanocrysin.	S.R. 24 hours after	S.R. 48 hours after	Dose
22.6.36.	10 mm.	-	15 mm.	0.05 gm.
29.6.36.	13	15 mm.	13	0.075 gm.
6.7.36.	11.5	13	13	0.1 gm.
13.7.36.	13	-	13.5	0.2 gm.
20.7.36.	15	16	12.5	0.2 gm.
27.7.36.	10	14	6	0.3 gm.
3.8.36.	11.5	11.5	9	0.4 gm.
10.8.36.	10	11.5	-	No Sanocrysin.

Case 7. John L.

Date	S.R.			Dose
	Before Sanocrysin.	24 hours after	48 hours after	
27.4.36.	8.5 mm.	8.5 mm.	7 mm.	0.5 gm.
4.5.36.	7	5	-	0.5 gm.
11.5.36.	4.5	1	6	0.5 gm.
18.5.36.	6.5	4	-	0.5 gm.

Discussion.

(1) Tabulated above are the results of 78 injections of Sanocrysin. After 43 injections (55%) a rise in S.R. occurred. After 32 injections (41%) a fall in S.R. occurred. After 3 injections (3.8%) no change in S.R. occurred.

It is therefore seen that the behaviour of the S.R. after Sanocrysin injections is not uniform. A closer study of the figures shows that, with the exception of 8 cases (10%) which show a marked fall in S.R. following injection, and whose significance will be discussed later, the rise or fall in the S.R. after injection is of small magnitude - up to 3 mm. It will be seen that such a variation can also be observed when estimations were made at the same intervals of time when, for some reason, Sanocrysin was witheld. Such variations are therefore, we submit, within the limits of experimental error, and occur apart from Sanocrysin treatment.

(2) A study of the above figures reveals no initial marked rise in S.R., comparable to that found by Traill and Stone, and Gutiérrez, Alix, Paz and de Vega, quoted above.

(3) From time to time in the above series, a striking temporary fall in S.R. was seen following an injection, as noted in paragraph (1) of this discussion. This observation agrees with that of Houghton quoted above/

above. He attempted to explain it by assuming that only those doses which coincide with a suitable "phase" in the state of the patient's blood, produce such an effect, which he considers to be beneficial. We are unable to accept Houghton's view for four reasons:
(a) the very low frequency of the occurrence (10% of injections);
(b) the fact that on several occasions a very low S.R. was present before the injection, which had risen to the usual level for the patient 24 hours after the injection, with no further fall subsequently;
(c) we have noted that an unexpectedly low S.R. has occurred at times when we have suspected the cleanliness of the sedimentation tube in which the estimation was performed;
(d) on one occasion such a fall occurred although no Sanocrysin had been given (case 4).

On the above grounds we find it difficult to accept the view that such occasional dramatic drops in the S.R. are a sign of a favourable effect of the drug, and suggest that they are more probably the result of faulty technique.

(4) An examination of these cases shows a tendency to lowering of the S.R. as Sanocrysin treatment proceeds.

This can, we think, be justifiably regarded as a sign of improvement, but is not, without further ado, to be put down to the influence of Sanocrysin therapy.

Such/

Such a conclusion can, we hold, only be drawn as the result of the study of a large series of cases undergoing this treatment, together with an equally large number of controls. If it can be shown that, under these conditions, the S.R. decreases more rapidly under Sanocrysin therapy than under ordinary sanatorium treatment, the point is proved. We are, however, not aware that any such investigation has been carried out. In any case, this is unimportant for the present purpose, as such a fall in S.R. cannot be regarded as an immediate direct reaction to Sanocrysin therapy, comparable to the rise obtained after an injection of tuberculin.

From the above observations we therefore conclude that injections of Sanocrysin produce no direct immediate specific effect on the S.R. This is interesting from the standpoint of the theory of the pharmacological action of Sanocrysin which we shall now discuss.

Relation of the Pharmacological Action of Sanocrysin to the results of S.R. Investigations.

The pharmacological action of Sanocrysin is still a much discussed problem. Møllgard's original view was that gold exerted a direct bactericidal effect on the tubercle bacillus, and that a general reaction resulted from the absorption of its toxic products, which was beneficial to the patient. This view has now been abandoned. The modern view (Beaumont and Dodds (57)) is that gold possesses a twofold action: (1)/

(1) a tuberculin-like action, as a result of increased capillary permeability around the tuberculous focus, permitting of the absorption of toxins. This action gives rise to pyrexia, malaise, headache and loss of weight;

(2) a metallic action similar to that produced by any heavy metal. This action is evidenced by such signs and symptoms as nausea, vomiting, diarrhoea, stomatitis, albuminuria, various skin eruptions, jaundice, etc.

It has been suggested by Lyle Cummins (58) that the success of treatment by gold "Seems to depend on the degree to which the patient is able to neutralise, or tolerate, the toxic substances set free in the circulation, as the result of the focal hyperaemia."

Now we have seen above that Westergren has shown that injections of tuberculin are followed by a rise in the S.R., and this result has been confirmed by other workers. Also we noted that a rise in the S.R. was sometimes the initial change following the induc-:tion of an artificial pneumothorax, which is probably due to the absorption of toxins (i.e. tuberculin) from the collapsing lung. In view of these findings, one would naturally expect, on the above theory, that the result of injections of Sanocrysin would be to raise the S.R. temporarily.

In none of our cases did such a rise occur. There are two possible explanations of this: either the/

the above theory is erroneous, or the amount of tuber-:culin absorbed from the focus, after each injection, is so small as to be without influence on the S.R. We do not think it is possible at this stage to say which explanation is the correct one, but, in any case, should the latter prove correct, it is very doubtful if the absorption of such small quantities of tuber-:culin, insufficient to influence the S.R., can produce any appreciable effect on the tuberculous patient. This is an interesting point in view of the changing attitude towards gold therapy. It has been practically abandoned in Canada and the U.S.A., and many authorities in this country are now doubtful as to its therapeutic value. The great difficulty in assessing the value of any form of treatment in pulmonary tuberculosis is the inability to arrive at a comprehensive understanding of the actual status of a case, and thus to have a standard for the comparison of one case with another; for it is commonly recognised that clinical improvement is apt to be more apparent than real. This is espec-:ially true of gold therapy, and, in the past, criteria have been used which are of no real value in assessing the efficacy of the treatment. In this connection, we believe that the S.R. provides a method of definite value for judging the results of this therapy. As was pointed out above, there is a tendency to lowering of the S.R. during sanocrysin therapy. If an investigator, having/

having access to a large number of cases undergoing Sanocrysin treatment, and an equally large number of control cases, could determine whether this tendency to fall in the S.R. occurs more rapidly under the influence of sanocrysin therapy or not, we are convinced that the position of gold therapy in pulmonary tuberculosis would be thereby greatly clarified.

SUMMARY AND DISCUSSION.

A review is given of the History, Technique and Theory of the Erythrocyte Sedimentation Rate, special attention being paid to the influence thereon of the red cell concentration.

It is pointed out that it has long been known that in certain forms of anaemia the S.R. is increased. Various methods have been advanced which employ corrections for the degree of anaemia present, the most recent of these being that of Rees Walton, who corrects the S.R. on the basis of red cell concentration. This is the method which we have used.

It has been one of the chief objects of these studies to determine whether such a corrected S.R. gives a more accurate indication of prognosis. It is concluded, both from theoretical considerations and from practical experience, that such a correction applied to the S.R. is both valueless and erroneous. From the theoretical aspect it is pointed out that, while in specimens/

specimens of blood diluted with plasma *in vitro*, decrease in red cell concentration is accompanied by increased S.R., in practice in many cases of severe anaemia the S.R. is normal. In addition to the red cell concentration, which is the only factor in anaemia taken account of in this correction, there are other factors such as changes in the size and shape of the erythrocytes, which influence the agglomeration of these cells, and thus probably markedly affect the S.R. There are, therefore, present in anaemias sedimentation checking factors, the analysis of which in the single case is difficult.

The above theoretical considerations are borne out by the results of practical experience.

From this point of view it has been possible to divide cases into three groups.

Group I comprises those cases in which the corrected S.R. differs to such a small degree from the uncorrected rate as to be of no practical importance. The correction can, therefore, be criticised on the ground that it is time-consuming, and that the differ-:ence obtained is not great enough to justify the extra labour involved. Furthermore, the technique of red cell counting requires considerable skill, if trust-:worthy results are to be obtained. In Group II it was found that certain cases would apparently have shown no sedimentation, in the given time, had no anaemia been present. Such a state of affairs is obviously/

obviously absurd as some degree of sedimentation must occur. While in Group III cases, the uncorrected S.R. followed closely the clinical progress, the corrected S.R. could not be so correlated. It is therefore concluded that the corrected S.R. is both valueless and erroneous, and that for practical purposes the sedimentation rate gives the best results through its complexity. Further, the great part of its practical significance lies in the simplicity of the technique and of the reading of results.

The application of the S.R. to the assessment of methods of treatment in pulmonary tuberculosis is considered in some detail in relation to three forms of therapy - artificial pneumothorax, injections of tuberculin, and treatment with gold salts.

It is pointed out that, in Artificial Pneumothorax therapy, frequent estimations of the S.R. are of great value in determining the state of activity in the collapsed lung. The temperature and pulse rate are often normal in these cases, and the physical and radiological signs are those of the induced collapse. In such circumstances the S.R. affords a definite indication of activity, a slight initial rise followed by a gradual decrease of S.R. to normal limits showing satisfactory progress. In those bilateral A.P. cases, the S.R. is of value in detecting any tendency to increased activity in the contralateral lung, indicating the necessity/

necessity to discontinue the collapse.

We have had no personal experience of tuberculin therapy in relation to the S.R., but authorities are agreed that injections of tuberculin are immediately followed by a rise in the S.R. It has been suggested that this rise can be utilised in controlling the treat-:ment.

It is pointed out that the literature on the influence of gold therapy on the S.R. is scanty, and what there is shows no agreement.

Our own observations suggest that injections of gold salts produce no immediate direct specific effect, comparable to that produced by tuberculin. With the exception of a few instances, any change produced was within the limits of experimental error. In a few instances a marked lowering of S.R. occurred after an injection - a phenomenon also observed by Houghton, who looks on it as a favourable response to treatment. For reasons stated in the text, we are inclined to attribute this fall to errors of technique.

That the S.R. decreases during the course of gold treatment is probable from these results, but it still requires further observation before it can be stated that this fall occurs more quickly under the influence of gold therapy, than it would under ordinary sanatorium treatment.

The relation of these findings to the pharmacolo-:gical/

:gical action of Sanocrysin is discussed, and it is concluded that the modern theory of the action of Sanocrysin cannot be correlated thereto.

It is suggested that the S.R. affords a definite criterion whereby the value of Sanocrysin therapy may be assessed, in contradistinction to the criteria which have been used in the past.

CONCLUSIONS.

(1) In a series of 24 cases of pulmonary tuber-:culosis, examined on admission to the sanatorium, 83.2% were found to have a red cell count of over 4 million per c.mm.

This finding supports the view that the pallor of these patients is due, in the majority of cases, to a vasomotor disturbance, and not to severe anaemia.

(2) Correction of the S.R. on the basis of red cell concentration is theoretically unsound, and from practical experience valueless and erroneous.

(3) The volume of 3.8% sodium citrate used as anti-coagulant was one-tenth that of the blood. Rarely was difficulty encountered with clotting. Most methods use the proportions of blood to isotonic solution as 4 : 1.

(4) No untreated active exudative case of pulmonary tuberculosis/

tuberculosis was found to have a normal S.R. On the other hand, cases undergoing sanatorium treat-:ment showing a normal S.R., and yet with physical signs of activity, were frequently encountered.

(5) During the course of Artificial Pneumothorax treatment, the S.R. shows an initial rise, followed by a gradual fall to normal levels in favourable cases.

This fall is frequently the only indication of satisfactory progress which we have at our disposal. In bilateral cases undergoing this treatment, the S.R. affords a valuable clue to the state of activity of the contralateral lung.

(6) Gold therapy was found to exert no immediate direct specific effect on the S.R.

A gradual fall in S.R. occurred during the course of the treatment, but could not be attributed to the influence of gold without further investiga-:tion. Occasional sudden falls in S.R. were noted during gold treatment. We ascribe these to errors in technique.

The modern theory of the pharmacological action of gold is difficult to uphold in the light of the above observations.

It is suggested that estimations of the S.R. afford a reliable criterion in the study of the therapeutic value of gold in pulmonary tuberculosis.

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