THE COAGULATION - TIME OF THE BLOOD IN DISEASE:

Some clinical records and considerations.

Being a thesis submitted for the

degree of M.D.,

in the
University of Edinburgh.

by

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March 1913.

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Some Clinical Records and Considerations.

INTRODUCTION.

It is now almost twenty years since Wright first drew attention to the value of measuring the rate of coagulation of the blood in disease. Since then much has been written upon the subject and many new methods of observation have been devised.

Much of the work done in the earlier days was rather of the nature of physiological experiment: but indeed the results obtained by the various methods differed so widely and were so inconsistent even in themselves that there was little encouragement given for an advance to clinical observations. Later, with improved technique (most especially with a due regard to the knowledge of the effect of temperature as a factor in variation) much more reliable and consistent results were obtained and the advance to clinical problems was made with more assurance. Yet even now there are but few records in the literature of research into the coagulation time of the blood in disease. Haemophilia and purpura, it is true, have been studied in some detail, as also the assertions of Wright respecting the value of calcium salt administration (though/

(though in this last the examination has been chiefly, as by Addis,[1] along pharmacological lines) but in other diseases the records are few and imperfect. This comparative scantiness of clinical records has encouraged me to embark upon the series of observations here recorded. They have been arrived at by the use of yet another method - a method borrowed from Drs. Dale and Laidlaw, as set forth by them in the Journal of Pathology and Bacteriology.[2] (This for brevity's sake I have termed the "Ball method")

In their article, following a description of the method, were recorded a few of their experiments. In my opinion these compared very favourably, as regards self consistency, with the recorded results of other methods, while the method itself seemed eminently suitable for clinical work. I therefore tested their observations by experiments extending over some weeks, and, finally, after making some slight modifications tending towards greater accuracy, was so well satisfied with the reliability of the instrument that I adopted it for the purposes of my investigation.

The initial experiments were made, first to test the/

1. T. Addis: "The coagulation time of the blood in man: a physiological study" Thesis (M.D.Edin) 1908, also in Quarterly Journal of Medicine, 1908-9.

2. "A Simple Coagulometer", Vol.XVI, 1912.

the observations of the inventors, and thereafter, slight modifications being introduced, to amplify them and to set up a standard for the normal before attacking the problem of the abnormal.

As this paper has for its object the discussion of the coagulation time of the blood in disease I have not thought it advisable to give in extenso the result of my findings in the normal. These, though of great primary importance, and, indeed, quite indispensable to a proper appreciation of pathological variation, can yet very well be condensed and summarised without prejudice to the discussion. Nor have I thought it advisable to give any historical survey of the subject or any detailed criticisms or comparisons of the various methods which up to the present time have been employed in measuring the coagulation time of the blood. Such discussion is away from the main purpose of the work and would swell it to unnecessary dimensions. Moreover, it has been well done already, notably by T. Addis who in his "Physiological Study", has given a collective and very clear account of all the different instruments and methods.

Any critical observations or comparisons which here and there appear have been included only because I thought them indispensable to the argument in favour of the method here employed.

Thus limited the discussion divides itself naturally/

ally into three parts:-

(1) The method, its use, etc.

(2) Its time-findings in health.

(3) Its " " disease.

Of these the first two are but the necessary preludes to the third and will be treated a such.

My connection with the Edinburgh Royal Infirmary and its Convalescent House, and with the Royal Hospital for Sick Children has afforded me ample access to material for purposes of this research and I should like here to conclude these prefactory remarks by thanking the various chiefs under whom I have worked for the many kindnesses and priveleges extended towards me.

PART 1.

DESCRIPTION OF BALL METHOD

SOURCES OF FALLACY, ETC.,

THE METHOD:-

Such modifications as I have introduced in the method of Dale and Laidlaw tend merely towards an easier and more accurate working of the instrument and in no way affects its essentials. For a description, therefore, I cannot do better than quote their own words. "The essential part of our apparatus is a short length of capillary glass tubing. We found 2 Cms. a convenient length but this is purely a matter of convenience. The internal diameter is of more importance. We have been accustomed to draw out a supply of capillary tubing at a blow-pipe, cut into lengths of about 2 Cms., and pick out those with internal diameters of 1·3 to 1·4 Mm. For this sorting we used a gently tapering gauge made from a steel crochet-hook, on which the two limiting diameters were found with a screw-gauge and marked with annular scratches. Great accuracy is not essential or practicable, but we do not doubt that the uniformity of results improves up to a point with the rigour of this selection.

In each capillary is a clean leaden shot (see Fig.1)

Fig. I

Before this is introduced the capillary is narrowed in the/

the flame at one end, just enough to prevent the passage of the shot. The shot being introduced at the other end, this is similarly narrowed, so that the shot can roll the whole length of the tube. The size of the shot should be uniform, again within certain limits, and must be so chosen that it will move quite freely up and down the tube, and yet be clearly visible when the latter is filled with blood. We find a shot weighing 9 m grms. is of suitable size for a tube of the diameter quoted above. Sufficient accuracy can be obtained by choosing from a packet of mixed small shot one of this weight and picking out others which are not visibly larger or smaller than this standard. If the apparatus were to be used for a determination in which all the factors were strictly constant it would doubtless be desirable to calibrate the tubes accurately and to choose shot of exactly uniform weight. In determining the coagulation-time of a drop of blood obtained by a finger prick we believe that greater accuracy than that indicated would entail wasted labour. The shot should be clean, and misshapen ones should not be used. If necessary they can be cleaned by washing with dilute nitric acid, water, alcohol, and ether, and then drying. They should be kept in a clean dust-tight box till required.

This capillary tube with its contained shot is the essential part of the apparatus, and a new one is taken/

taken for each determination. A basin of water with a thermometer is required, and, provided that the temperature chosen is between 35° and 40° C., within which range the temperature coefficient is small, the temperature can be kept quite sufficiently uniform by adding small quantities of hot water from a bottle as required and stirring thoroughly. A good light is essential and a white basin should be chosen. If this be placed near a bright window light the reading can be made without difficulty. We have obtained excellent illumination by allowing an electric glow lamp to hang partly immersed in the water, and recommend this arrangement where it is available. This is the only essential apparatus; the tubes can be held in the fingers and the ends closed by the clean thumb and finger of the observer for immersion in the constant temperature bath. It is convenient, however, to have a small pair of tongs of some kind for holding the tube while filling, and a spring clip with the jaws furnished with little cups for holding clean plasticine, the filled tube being placed longitudinally between the opened jaws, so that when these approximate the tube is held with its ends sealed with plasticine (Fig.2).

The clip with the tube is then plunged into the bath and the handle of the clip serves for further manipulation/

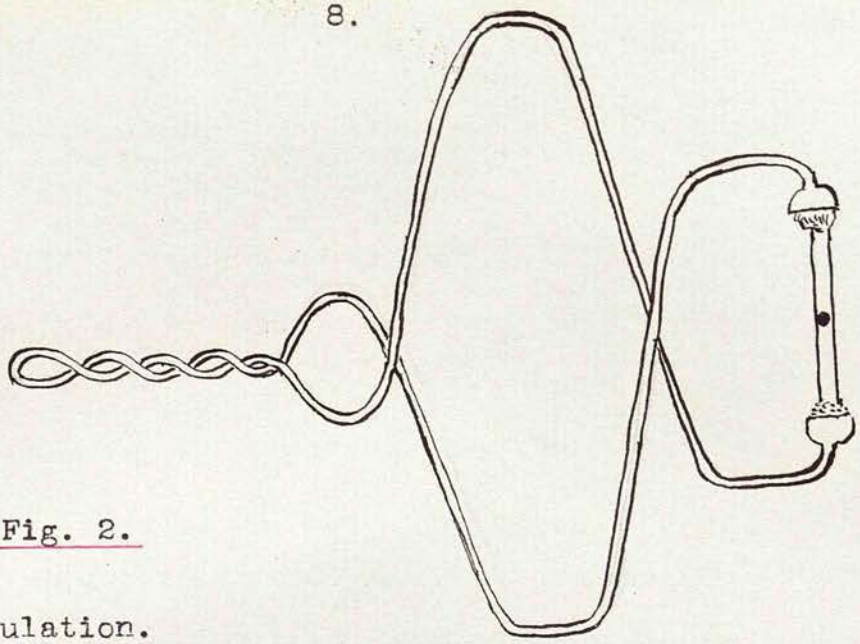


Fig. 2.

manipulation.

The blood is obtained in the usual way by pricking a carefully cleaned finger in which passive congestion has been produced by swinging the arm and binding. The prick should be made with a perfectly sharp, clean needle."

As soon as the drop of blood follows the prick a stop watch is started, one of the tubes with its enclosed ball is filled with the drop by capillary action, is then fixed in its holder, and immersed in the constant temperature bath. "Not more than 10 seconds should elapse between appearance of the blood and immersion of the tube in the bath".

By suitable movement of the holder the ball is made to travel slowly to and fro in the blood until the end-point is reached, when the watch is stopped and the reading taken. The end-point is the cessation of movement of the ball. This appears quite suddenly and gives a very definite end point; warning of its approach is given by a slowing down for a second or two/

two in the movement of the ball.

Of this end-point the authors say: "doubtless other end-points could be devised with the same apparatus, but we have found this moment , when the shot stops dead with the tube held vertical, the most convenient. We have repeatedly verified the fact that, when the tube is cut open at this moment of stoppage the shot is found entangled in delicate clot. What we measure is the time after which, in the given apparatus, the clot attains just sufficient consistency to support against gravity a spherical leaden shot of the given mass in a tube of the given diameter".

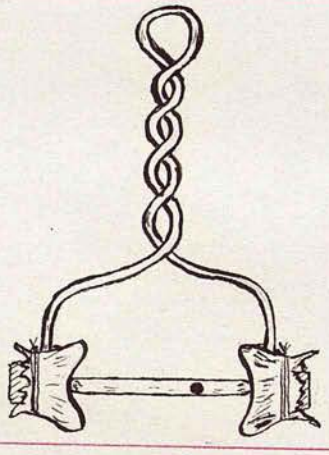
So much for the authors description of their instrument and method:- After some little experience I found it much better to use tubes drawn and calibrated by a glass-blower. The cost was trifling (about 300 for 1/-) and the results much more satisfactory.

I would lay stress on the necessity of rejecting any shot which is misshapen. The requisite size is of the smallest on the market and such contains a large percentage of imperfect spheres. Any local flattening or tiny adherent globule may cause the shot to jam in the tube and give a false end point. With a little care, shot perfect for the purpose can be selected from Eley Brothers' Dust shot, No 12.

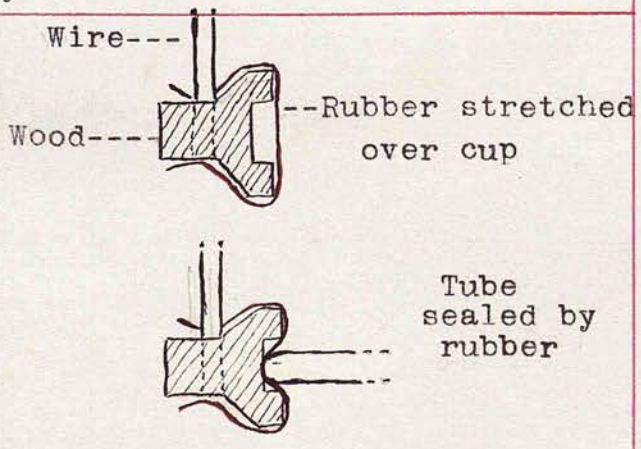
It is naturally very important that, on immersion in the water-bath, no water be allowed to mix with the/

the blood. To prevent this the authors suggest that the ends be held (and sealed) by finger and thumb or by means of a clip with plasticine. Both methods are troublesome and the latter in addition is very objectionable on the score of contamination. A simple and efficient clip may be made with small pieces of wood or cork, cupped, and with rubber (as from a strong finger cot) stretched over the cup. The ends of the tubes being rounded by the flame in the act of enclosing the ball, they do not cut the rubber and are very efficiently sealed by it, provided always that there is sufficient spring in the clip and that the openings in the tubes are terminal (this latter is assured if the glass be clean-cut transversely).

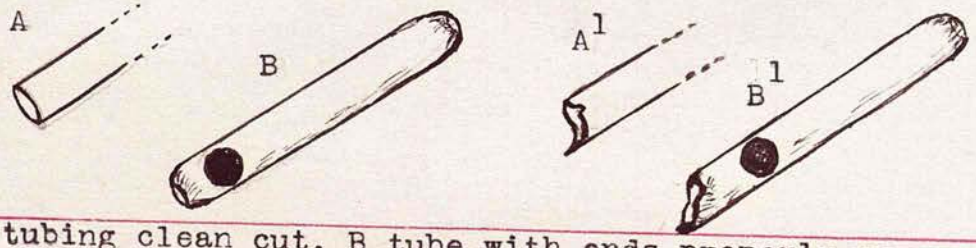
The diagrams sufficiently illustrate these points and are self explanatory.



Tube & Holder
(actual size)



Sectional view of cups
(enlarged)



A tubing clean cut. B tube with ends properly narrowed.
A^1 " " badly " B^1 result of action of flame on badly cut tubing, A^1. Such a tube will not seal well

In all of my cases readings were taken in the first drop of blood drawn from the finger. Four, or at least three, observations were taken in each case (each from a separate finger), and the result expressed as an average of the readings.

The fingers were cleaned with ether (soap and water first, if necessary), blood flow arrested by a couple of turns of a thin elastic bandage, and the finger pricked above the nail-root by a clean sharp vaccinostyle.

A fresh tube was used for each reading. A temperature of 104° F (= 40° C) was used throughout. Here let me say that I have found the immersion of an electric glow lamp in the water to be a most excellent idea, for its light enables one to follow the movements of the ball accurately, and, with careful adjustment of the degree of immersion, its heat can maintain the temperature at a constant level.

A discussion as to my reason for selecting this temperature and as to the degree of accuracy in its maintenance required for accuracy of results will be found on page 17 et seq.

The use of an elastic bandage to assist blood flow might be criticised on the ground that one might get thereby a variable amount of expressed serum from the tissues with the blood. But Addis with the instrument he employed in his "Physiological Study"[1] - admittedly/

1. See p.1.

admittedly the best and most reliable of all instruments for the purpose - was unable to find any difference between the coagulation-time of blood obtained by such means and that obtained without pressure.

Moreover, I have been careful to use as far as possible the same degree of pressure in all the observations. Only a slight pressure is required and it has the additional advantage - by no means inconsiderable when four fingers have to be bled and especially where one is dealing with children - of making the prick practically painless.

The resultant coagulation time is, of course, in part the expression of the instrument, and must of necessity have a certain artificial value. Yet from its readings valuable deductions can be made, providing the instrument be proved reliable.

From the experiments of others it has been shewn that in a healthy individual one would expect the separate readings taken at any one time to approximate closely to their average.

In other words the coagulation-time of the blood at any one time has a certain value for that time and it is the test of a good instrument to record it so.

Yet in such a delicate process experimental error must creep in and it is highly important to know within what limits it can, with reasonable care, be kept:/

kept:

I found the average reading for a normal individual to be 1 min. 38 secs. Typically this would be made up of readings such as these:

1 - 41)	
)	
1 - 37)	average 1 min. 38 secs.
)	
1 - 39)	
)	
1 - 35)	

where the highest and lowest readings give a difference of 6 secs., and where the variation from the mean is ±3 secs. Numerous examples will be given later and I need not here specify further.

From my experience in the normal individual I judge any reading to be faulty which gives a difference of more than 10 secs. between the maximal and minimal components of the mean. This is true also of the vast majority of diseased conditions.

Such faulty readings can usually be traced to one or more of the following:

(a) lack of cleanliness.

(b) faulty tubes.

(c) variations of temperature.

(a) Lack of Cleanliness:-

Neither tubes nor shot as a rule require cleaning before use. (Prior to drawing, the interior of/

of tubes should be freed from dust). Fresh tubes must be used. It is practically impossible to cleanse them after use.

If the tubes should require cleansing they must be taken through water to alcohol and ether. They must not be allowed to dry in methylated spirit.

I found that tubes so dried gave shorter readings than tubes dried from distilled water, thus:

I Subject: J.F. (female, aet.10)

(a) Tubes filled with distilled water and allowed to dry slowly without draining.

Coagulation Time =

1 min. 37 secs.)
1 min. 32 secs.) average 1 min. 34 secs.
1 min. 32 secs.)

(b) Tubes filled with methylated spirits and allowed to dry slowly without draining.

Coagulation Time =

1 min. 27 secs.)
1 min. 25 secs.) average 1 min. 28 secs.
1 min. 32 secs.)

II Subject: W.A.S. (male, aet.26)

(a) Tubes from distilled water as above

Coagulation Time = 1 min. 49 secs.

(b) Tubes from methylated spirit as above

Coagulation Time = 1 min. 33 secs.

The/

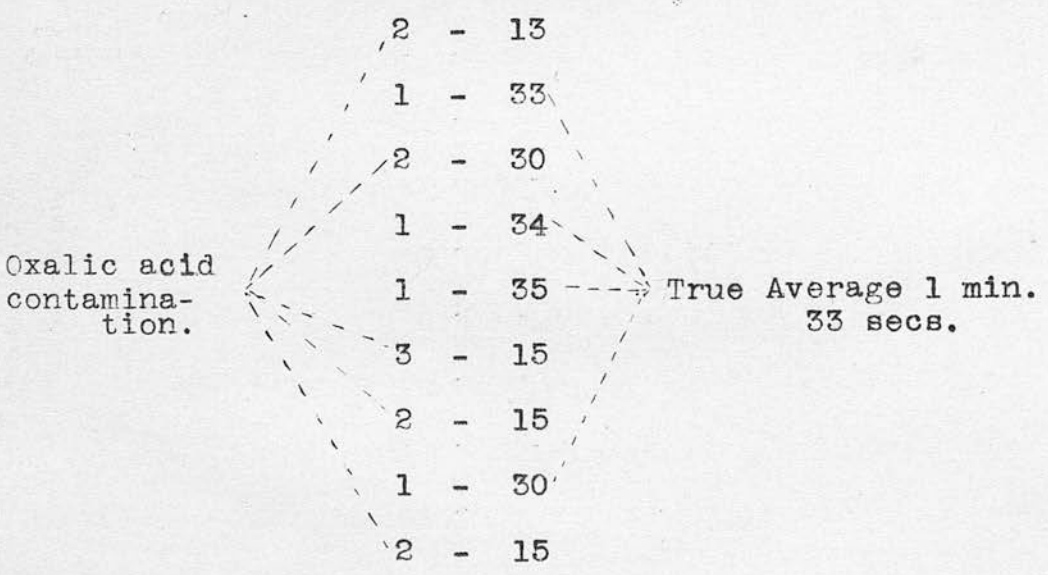
The naphtha present in the spirit probably accounts for this shortening.

The necessity of freedom from contamination with oils and chemicals is obvious, but perhaps the following example is instructive.

May 29 J. Y. (aet.11) Renal colic $\bar{c}$ haematuria

Min.	secs.	
1	37	average 1 min. 34 secs.
1	33	
1	38	
1	29	

June 10.



The enormous variations in the readings of June 10 puzzled me very much until I discovered that I was using a mixture of two sets of prepared tubes, one lot of which had been accidentally contaminated by a very dilute solution of oxalic acid used in some experiments/

periments on the previous day.

Blood itself is a very well recognised contamination source of error. It tends to make the readings very short. Addis has shewn that this holds true of fresh blood only, dry blood being without effect. Fingers, needle, and tube holder must therefore be scrupulously clean and free from blood.

Water as a source of contamination must be especially remembered in this method. It may come from imperfectly dried fingers, or a wet needle, but most especially from the water bath by way of imperfectly sealed tube ends. The means of preventing this latter accident have already been discussed. It is an accident to which this method perhaps more than any other which uses water as a means for preserving an equable temperature is liable. For the constant movement required to keep the ball in motion encourages an intermingling of blood and water if the two fluids are not efficiently separated. This admixture of water with the blood gives an unduly accelerated coagulation. As a source of fallacy I learned early in the course of my investigation to guard against it, and the means of doing so are very simple.

Sir A.E. Wright[1] says: "An admixture of water with the blood accelerates coagulation.- This fallacy may/

1. "Handbook of Technique" (Constable, London, 1912)

may come in if the finger from which the blood is drawn off is not perfectly dry; and of course it may also come in if water should find access to the coagulation tubes".

This action of water in hastening coagulation has also been noted by W.H. Howell.[1]

(b) Faulty Tubes (1) Calibre:-

Variation in the size of tubes,or of shot relative to the tubes undoubtedly gives some slight diversity of results, thin tubes giving short readings. Practically, only differences in calibre which are striking to the eye give definite time differences. (2) Openings not terminal:- see above. (3) Shot:- The danger of using irregularly shaped balls has been already mentioned.

(c) Temperature Variations:-

The chart of temperature experiments on page shews very clearly the necessity for the maintenance of an even temperature throughout one experiment, and, if the various experiments are to be compared, for the setting up of a standard temperature at which all experiments shall be conducted.

As already mentioned the standard for all my cases has been 40 C., and this for two reasons. First, because at this temperature the end-point is more sharp/

1. Cleveland Medical Journal Vol. IX 1910.

sharp and sudden, and second, because around this temperature the curve of the coagulation time is least variable. By selecting such a temperature the instrument loses somewhat in sensitiveness, but the gain in stability (a very important matter when one wishes to avoid cumbersome heat-regulating apparatus) and the above mentioned sharper definition of the end point largely compensates this loss.

I have not found the difference of $\frac{1}{2}^{\circ}$ C either way to make any appreciable difference in the readings. This would not be so at a lower temperature.

Another source of error in temperature appears with any variation in the length of time between the appearance of the drop of blood and the immersion in the bath. As is pointed out by the authors 10 secs., is ample for the operations between these points. This I have made a standard time.

PART II.

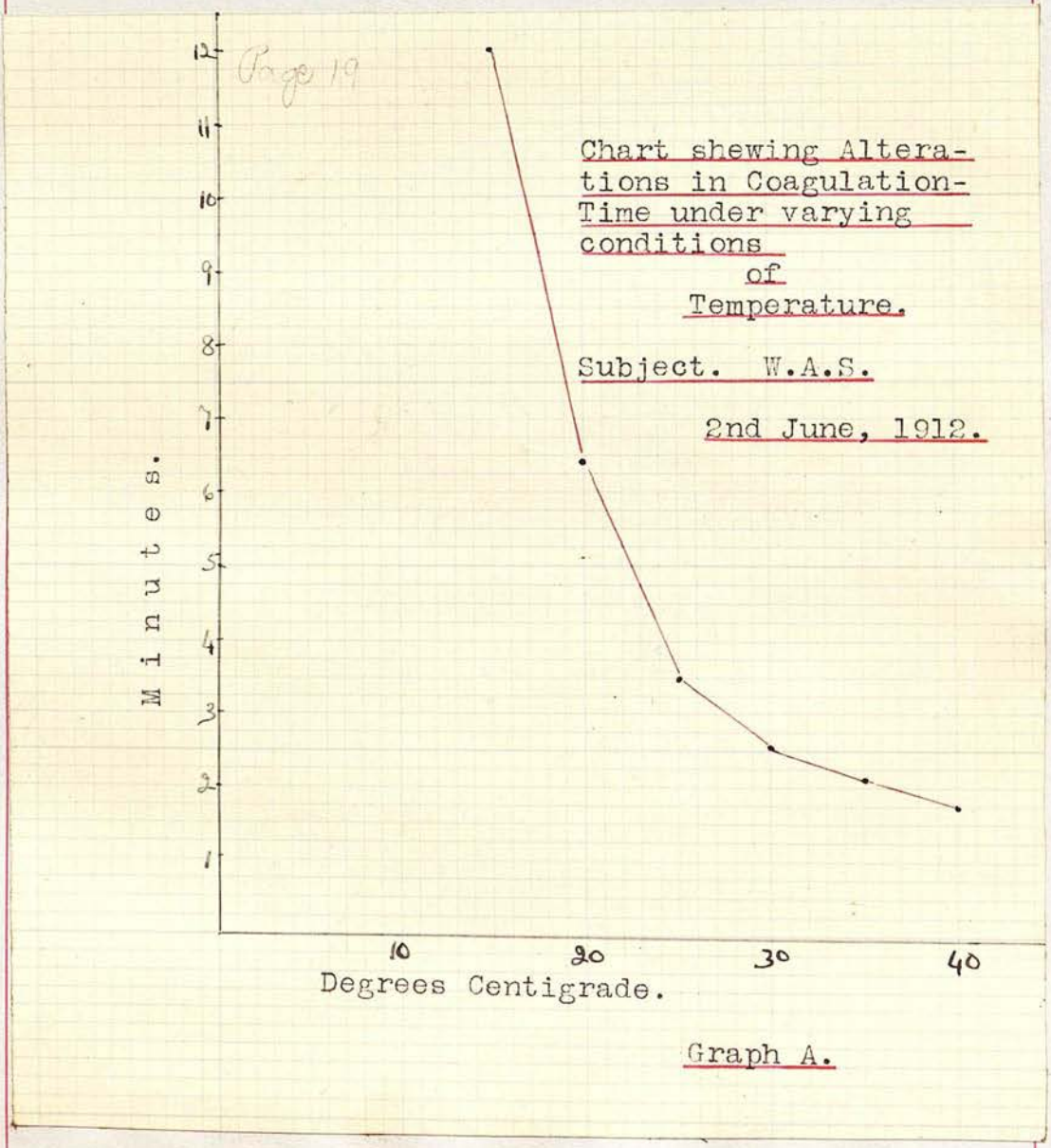
TEMPERATURE EXPERIMENTS.

NORMAL VARIATIONS AND NORMAL LIMITS.

COMPARISONS, ETC.

TEMPERATURE EXPERIMENTS.

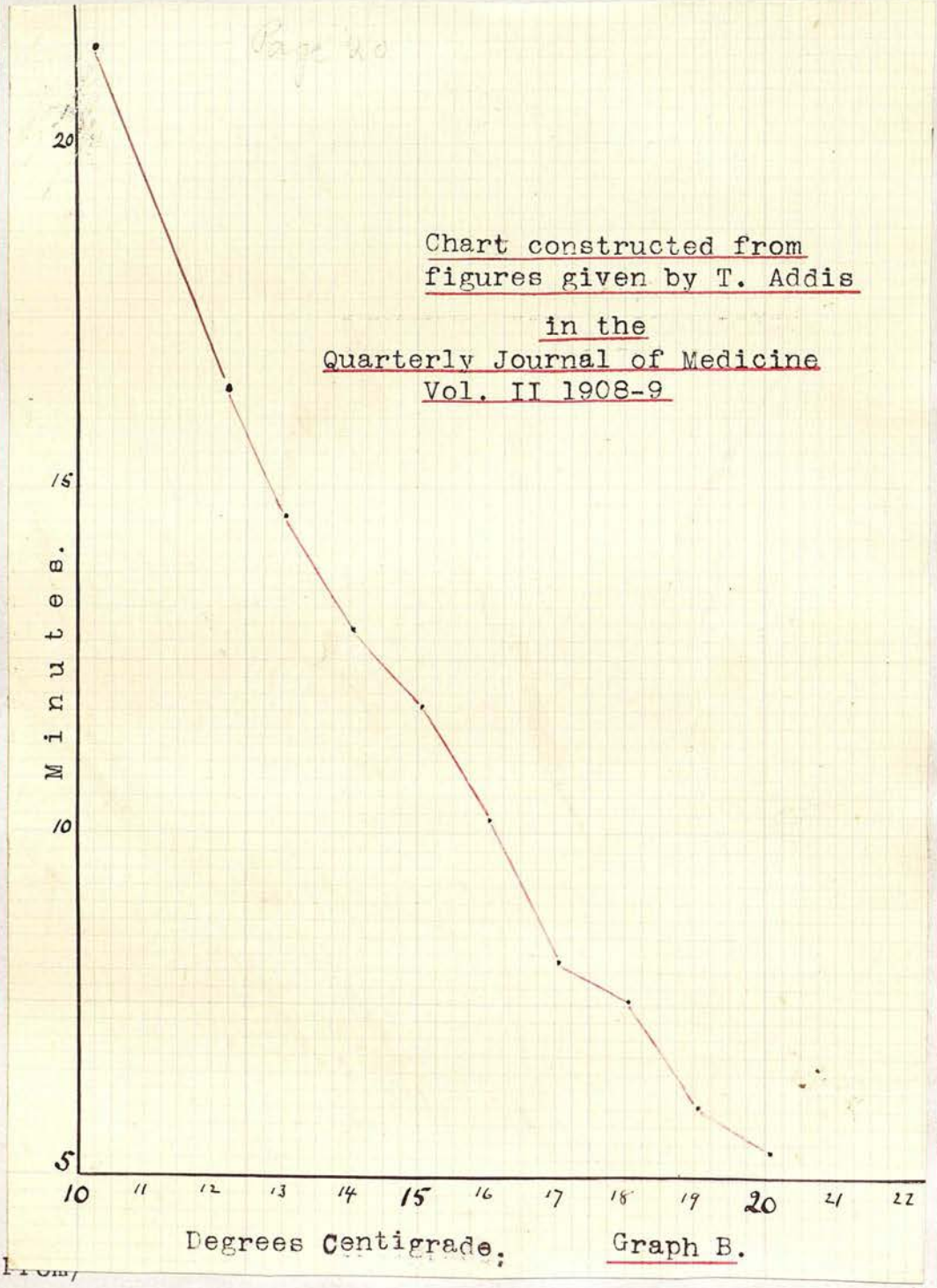
Among the earliest of my experiments were some made in series on the same individual but at varying temperatures. Such an experiment had already been made by Dale & Laidlaw with this instrument and my own were made merely to test this, and in order that I might observe for myself the degree of sensitiveness of the instrument to variation in temperature.
The result of one such experiment is set out in the following graph.



Graph A.

The graph obtained and shewn by Dale & Laidlaw in their article/

article is practically the same as the above and I have not, therefore, troubled to reproduce it. Of more interest is a graph which I have constructed from figures given by Addis.



Graph B.

From

From a study of these two graphs two important deductions may be drawn. First, that there appears to be a very definite relationship between temperature and rate of coagulation and that this relationship can be expressed by a graph which shows a remarkably steady curve. Second, it would appear where different time values are got by the use of different instruments, that such are little, if at all, the expression of any differences in the instruments on their adopted end-points, but rather of the employment of different temperatures during the experiments. This point is brought out by a comparison of the two foregoing graphs between the temperatures of 15° & 20° C (the only temperatures common to both). The readings are seen to be very much alike for like points between these temperatures. Keeping in mind the fact that they are graphs from different subjects, some slight differences are to be expected.

This point is further illustrated by the following table which I have constructed by aid of the foregoing graph (A) and of some figures from observations by other methods. A fuller description of these latter is to be found on page 27.

Table on next page.

Coagulation - Time of individual, W.A.S. by Graph A.

(page 19)

	C.	Min.	Sec.	Min.	Sec.	Observer.
equals at	37	1	56	2	0	A.E. Wright.
				2	40	Turner (same method)
	20	6	15	7	40	R. D. Rudolf.
	15-20	6	15 to 12	7	0 to 11	J.P. McGowan
	18·5	7	30	7	34	T. Addis
	20·5	5	45	5	22	T. Addis.

Frequently in the course of these investigations I have had occasion both to observe the use of, and to use, McGowan's tubes in conjunction with the ball method, and have found, on noting the room temperature and translating accordingly, that the readings were much alike.

On page 13 I have discussed what degrees of variation may be expected between the various components of any one reading. What differences must one allow for the same individual at different times? In health (and in disease where the disease is stationary) I have found that the time value for each individual remains wonderfully constant and that but a few seconds/

seconds either way have to be allowed for possible normal variation from time to time. In the following pages ample opportunities for the observation of this constancy are given. For the present I may quote some readings which have been made from time to time on my own blood.

Subject W.A.S.

Date.	Coagulation Times		Average	
	Min.	Sec.	Min.	Sec.
May 17	1	48)		
	1	45)		
	1	43)	1	47
	1	52)		
May 30	1	45)		
	1	39)		
	1	41)	1	42
	1	43)		
July 10	1	37)		
	1	34)	1	35
	1	35)		
Aug. 16	1	45)		
	1	52)	1	46
	1	41)		
Aug. 20	1	40)		
	1	45)	1	44
	1	47)		
Aug. 21	1	45)		
	1	38)	1	43
	1	47)		
Jan. 6	———		1	45
Jan. 30	———		1	41

The above gives an idea of the range of variations which one may expect to find from time to time in a normal individual. Very frequently I have had occasion/

occasion, perhaps when in doubt about the result of some experiment, to examine my own blood as a sort of check and have always found its coagulation time to be within the above limits - practically always in the forties.

The question of diurnal variation in the coagulation time of the blood has been the subject of much discussion and experimentation in the past. Many have upheld the view that the coagulation rate varies with time of day, with exercise, with ingestion of food, etc. Such variation, if it existed, would have to be taken into account in the consideration of any experiments. But Addis sums up a very careful investigation of the subject by saying "There is no such thing as a daily variation in the coagulation time". Moreover, even if there were - and what note I have made of the question by the way inclines me to the view point of Addis - this work could be little affected by it, for where patients have been examined more than once the examinations in practically every case have been made throughout at the same time of day.

So far we have seen what degree of variation may be expected in individuals

(a) at any one time
(b) at various intervals of time.

Next comes the very important consideration in what degree may the findings differ in different individuals? Utmost limits. To know them a very much wider series of/

of observations would have to be made and as long as such diseases as haemophilia are wanting from the list it is useless to discuss the utmost limits. For the many and various diseases were recorded the utmost range has been found to be from 1 minute to 2 minutes 35 seconds.

Limits in Health. In healthy subjects as already stated, the average for this method is about 1 min. 38 sec. This I arrived at from between two and three hundred observations. I have never found the read - ings to be shorter than 1 min. 20 sec. or longer than 2 min. 0 sec. Very few lie between 1 min. 20 sec. and 1 min. 30 sec. or between 1 min. 50 sec. and 2 min. 0 sec. The vast majority lie between 1 min. 30 sec. and 1 min. 50 sec. so much so that I reckon all readings less than 1 min. 30 sec. as short and all above 1 min. 50 sec. as long, recognising that a few seconds outside these limits may be in a few cases an expression of the normal.

In the following table I have instituted a comparison between some of the best known methods of estimating the coagulation time of the blood. It will be noticed that in all save No. iv., an attempt is made to maintain a constant temperature. It is very difficult to say in how far failure to maintain the temperature absolutely constant is responsible for the wide variations got in observations on the same individual./

idual. My present purpose is to compare among the different methods, the degree of variation which occur between the readings from any one individual subject in its relationship to the average time for the instrument. This comparison may at first sight appear unjust for one is thereby comparing at the same time the amount of divergence of the findings in any one subject against the average of the findings in many instead of against the average of the findings in the same subject. But from observation of the figures as given by the various authors I have satisfied myself that such variation could well have occurred in individuals where average coagulation time was practically the average for the series. Therefore by taking the two columns to represent coagulation times of the same individual the figures, though passing from the real to the supposition, yet lose little or nothing in accuracy.

Table on next page.

Table for Comparison of some of the Methods.

Investigator.	Short Indication of Method.	I. Average coagulation-time	II Limits of normal variation	III. Limits of individual variation
A.E. Wright	Blowing from capillary tubes at 37 C.	2 min.	?	
Turner	same method	2 min. 40 sec.	?	as much as 2 min. between longest and shortest.
J.P.McGowan	Tubes 1·5 m m bore, 6" long. Broken at intervals to observe formation of fibrim thread. Room temperature (15-20C)	7 - 11 min.		about 2 min.
R.D.Rudolf	as in McGowan's method, but temperature constant at 20 C.(in Thermos flask)	7·7 min.	?	$6\frac{1}{2}$-$10\frac{1}{2}$ min.
T. Addis	Immersion in oil, circulation of drop by tangential stream of oil at constant temperature			as much as 2 min. where times are long.
	(1) at 18·5 C.	$7\frac{1}{2}$-8 min.	6 min.	
	(2) at 20·5 C.	5 min.22 sec.		
"	Modified McGowan's method.(Temperature constant at 20 C.)	9 min.50 sec.	Taken as Column III.	8 min.45 sec. to 11 min.41 sec
Dale & Laidlaw	Ball Method as described. Temperature 38 C.	1 min.42 sec.		
W.A.S.	as here used, temperature 40 C.	1 min.38 sec.	1 min.25sec. 1 " 55 "	20 sec.

It will be seen that the method of Addis (immersion in oil, etc) gives the best result and next to it, as shewing proportionally only a little more variation, which will demand consideration as possible individual variation, comes the ball method. This is yet another respect in which the method of Addis has shewn its superiority to all others. But for clinical work his method has grave disadvantages. It is exceedingly cumbersome and for this reason alone is in most cases unsuitable. Its chief condemnation, however, is pronounced by Addis himself[1]. "It was not possible to test the accuracy of this belief (referring to the alleged effect of calcium salts and citric acid on the blood coagulation time) by the method of estimating the coagulation time of the blood which I have described since it is not applicable clinically because of the presence of a greater or less degree of auto-agglutination of the red blood corpuscles in very many pathological conditions".

As I shall have occasion throughout the remainder of this work to refer here and there to the work of Rudolf and Cole and of Addis, observers who have published the results of extended investigations into the coagulation time of the blood in disease, it may be advisable here to tabulate some of their findings and so avoid unnecessary repetition.

Addis, for the reason quoted above, found his "oil immersion" method unsuitable for clinical work and accordingly modified McGowan's method, adopting a devise to regulate the temperature. A full description of this apparatus is given in the British Medical Journal, 24th April, 1909. The results of his investigations (which did not comprise a large series of cases) are set forth in the Edinburgh Medical/

1. B.M.J. April 1909.

Medical Journal Vol. V 1910. He reckons as normal all readings found between 8 mins. 45 secs. and 11 mins. 41 secs.

Rudolf and Cole published a much larger series of cases. A first paper by R.D. Rudolf appeared in the "Transactions of the Association of American Physicians" 1910 Vol. XXV. This deals with the method (McGowan's, but at a constant temperature of 20° C), and with problems of the normal.

The second paper appeared in Vol. XXVI 1911 of the same, this time in conjunction with C.E.C. Cole, and entitled "The coagulation time of the Blood in various diseases". In this latter 148 cases were investigated. Some of these results I have set forth below for purpose of comparison.

Table next page.

R.D. Rudolf (T.A.A.P. Vol XV 1910)

Average normal coagulation time = 7.72 min.

Rudolf & Cole (T.A.A.P. Vol. XXVI, 1911)

Table of Coagulation Time in Diseases.

Disease	No.of cases	No of observations.	Average clotting time	Longest	Shortest
Chlorosis	2	4	6.9	8.0	6.2
Secondary Anaemia (1) not due to haemorrhage	6	12	7.8	10.5	6.4
(2) due to haemorrhage	8	14	6.6	10.0	5.2
Pernicious Anaemia	4	8	9.4	10.7	7.0
Myelogenous Leukaemia	1	5	8.1	9.5	6.2
Purpura	3	8	6.2	7.6	4.9
Jaundice	6	10	9.6	12.0	6.5
Diabetes Mellitus	3	6	7.0	8.0	5.6
Pneumonia	17	48	8.1	12.7	5.5
Acute Rheumatism	15	38	10.2	14.3	7.0

As the majority of the pages now to follow are to be devoted to the quotation of observations in disease it may be convenient here to recapitulate what I have found by the ball method to exist in the normal.

I

(a) Normal readings may lie anywhere between 1 min. 30 secs. and 1 min. 50 secs., the average reading being 1 min. 38 secs.

(b) Readings are most commonly found between 1 min. 35 secs., and 1 min. 45 secs.

II

(a) In about 5% of the normal the readings may lie between 1 min. 20 secs. and 1 min. 30 secs. or between 1 min. 50 secs. and 1 min. 60 secs.

(b) Of these by far the greater number give readings within 5 secs. on either side of the normal (i.e. between 1 min. 25 secs. and 1 min. 30 secs. and between 1 min. 50 secs and 1 min. 55 secs.

III

(a) Readings in any individual tend to remain as characteristics of that individual.

(b) They may vary slightly from time to time but in no discoverable relationship to time of day, ingestion of food, etc.

Inasmuch, then, as the great majority of readings in the normal occur between 1 min. 30 secs. and 1 min. 50 secs., I hold it legitimate to argue, where in any disease (provided always a sufficient number of cases have been investigated) the coagulation time is found to/

to be persistently outside these limits, that such variance is due in some manner or other, direct or indirect, to the disease.

From the following pages it will be seen that not many diseases shew any persistent effect upon the coagulation time. Among those which do shew some such effect are certain of the diseases of the blood itself, and with these I shall open upon the main interest of this work, which is the study of the coagulation time of the blood in disease.

The various cases have been tabulated according to their disease but beyond this no process of selection has been attempted, the cases being entered up, as they were examined, irrespective of their severity or of the resultant findings.

To complete the study of these conditions it would be desirable - and this applies to all diseases - in order to fulfill the conditions of a properly constituted scientific experiment, that the condition of the blood in respect of its coagulability be examined before, during, and after the existence of the disease. Of these, the first is, of necessity, practically never done. To the second and third, the examination at intervals during the progress of the disease and the period of convalescence, I have paid what attention was possible.

In the study of blood diseases this is peculiarly/

ly difficult, for the patient so often leaves hospital or even the convalescent home, feeling, it may be, restored to health, but with the blood still away from the normal standard.

I have not thought it advisable to split off such subsequent examinations from the rest of the cases, but have placed them, with their date of examination below the initial finding.

In cases where only one examination has been made, dates are not given. In such, they are of little use and by their omission the tables gain much in clearness.

PART III

COAGULATION TIMES IN DISEASE.

DISEASES OF THE BLOOD.

	Disease	Cases
I	Chlorosis	11
II	Simple Anaemias	2
III	Simple Secondary Anaemias	
	(a) not due to haemorrhage	12
	(b) due to haemorrhage	14
IV	Pernicious Anaemia	19
V	Lymphatic Leukaemia	4
VI	Myelogenous Leukaemia	4
VII	Splenic Anaemia (Infantum)	2
		68

TABLE I - CHLOROSIS.

No.	Patient	Sex Age	Date	Coagulation Time* in Minutes & Seconds Min.	Sec.	Additional Information
1	J,C.	F 17		1 -	23	R. 4,950,000 H 65% W. 6,000
2	M.A.	F 28		1 -	19	R. 4,050,000 H 40% W. 5,400
3	J.M.	F 19	Aug.7	1 -	28	
			" 21	1 -	29	after 14 days, much improved
4	M.S.	F 19	" 21	1 -	27	R.3,650,000 H. 34%
			Sept.2	1 -	22	very slight improvement
5	L.H.	F 17		1 -	26	slight case
6	K.T.	F 14		1 -	19	R. 4,100,000 H. 21%
7	K.G.	F -		1 -	20	R. 2,700,000 H. 25%
8	M.G.	F 20		1 -	23	H. 60%
9	W.G.	F -		1 -	26	
10	W.D.	F 18		1 -	28	
11	M.G.	F 19		1 -	40	4 weeks in hospital almost normal.

* It is to be noted that the time given here and in the succeeding tables is an average of at least three readings. As already explained the coagulation time in this method is always expressed as an average, but for the majority of the cases nothing is to be gained by giving the components of the mean, and much space would be lost.

Dates have been entered only where the case demands it.

Table 11.

Simple Anaemias.

No.	Patient.	Sex. Age.	Date	Min.	Sec.	Additional Information.
1	M.H.	F 45		1	18	R.3,110,000 H.40% W.4200 Blood platelets Numerous
2	T.F.	M 1½	July 31	1	27	R.3,200,000 H. 51%
			Oct. 3	1	35	Cured. Normal.

Table 111.(A)

Simple Secondary Anaemias.
not due to haemorrhage.

No.	Patient	Sex. Age.	Date	Coagulation-Time. min.	sec.	Additional Information
1	L.B.	F 20		1	17	Secondary to Hyperthyroidism. R 3,850,000.H 70% W.65
2	T.K.	M. 21		1	40	Mitral Stenosis. No haemoptysis.H 88%
3	Mrs M.	F 20	June 22	1	22	Hodgkin's Disease. Large masses in neck. A.4,490,000 H 65% W.8,600.
			July 9	1	36	Glands & Blood condition much improved.
4	Mrs M.A.W.	F.		1	21	Addison's Disease
5	E.G.	F. 17		1	29	Heart Disease R 4,000,000 H 64% W 67
6	P.G.	M 48		1	25	Anaemia from rheumatoi arthritis.
7	P.S.	M 56		1	38	? Gastric Carcinoma R 4,000,000 H 60%
8	E.H.	F 67		1	27	Abdominal Tumour R 2,750,000 H 30%

Table 111 (A) (Contd.)

No.	Patient.	Sex. Age.	Date	Coagulation-Time. Min.	Sec.	Additional Information.
9	R.H.	M 53		1	24	?Cancer of Liver R.2,500,000 H.28%
10	G.McL.	F 4		1	26	Chronic Suppuration R 2,800,000 H 38%
11	M.K.	F 15	Jan.28	1	15	Acute Rheumatism R.2,880,000 H 44%
			Feb. 7	1	14	Ulcerative Endocarditis developed. Died a few days later.
12	P.W.	M 71		1	27	R 2,250,000 H 30% Secondary to parasite

Table III (B)

Simple Secondary Anaemias, due to Haemorrhage.

No	Name	Sex / Age	Date	Coagulation Time of Blood Min.	Sec.	Additional Information.
1	J.Y.	M / 9		1	34	Haematuria:very slight.
				1	33	
2	A.M.	M / 24	May 29	1	30	Mitral Stenosis: slight haemoptysis.
3	Mrs A.McL.	F / 53		1	35	Gastric Ulcer:haematemesi R. 2,400,000 H.44% W 6200
4	W.D.	M / 43		1	20	Haemoptysis
5	M.D.	F / 19		1	17	Gastric Ulcer Haematemesi R 2,790,000 H 60% W 4,200
6	R.S.	M / 31		1	27	Gastric Ulcer Haematemesi R 4,700,000 H 55% W 5000
7	T.C.	M / -		1	27	Duodenal Ulcer Melaena R 3,850,000 H 60% W 8800
8	J.B.	M / 36	Aug 12	1	25	Haemoptysis. H 6 100%
			" 14	1	21	calcium chloride admin-
			" 19	1	24	istration.
			Sept 2	1	31	(See p 75)
9	Mrs J.W.	F / 39		1	8	Gastric Ulcer, severe haemorrhage four days ago
10	M.H.	F / 20	Nov 30	1	18	Haemorrhoids: severe bleeding during last thre days.
			Dec 10	1	32	No bleeding since Nov.30.
11	M.M.	F / 26		1	22	R.3,900,000 H 60%
12	-S	M / 27		1	27	Post-operative anaemia H 6 60%
13	T.A.	M / 27		1	14	Severe haematuria. R 2,900,000 H 6 32% W 4200
14	E.H.	F / 26	Jan 16	1	19	Haematemesis Gastric Ulc Anaemia.
			" 28	1	27	Blood much improved.

Table iv. Pernicious (Idiopathic) Anaemia.

No.	Patient.	Sex / Age	Date	Coagulation-Time Min.	Sec.	Additional Information.
1	Mrs M.	F / 35		1	37	R 3,700,000 H 68 W 6250
2	M.E.	F / 29		2	20	Moribund R.560,000 H 15% Viscosity of Blood, almost that of blood serum (see page 48)
3	R.N.	M / 37		1	38	R 2,460,000 H 50%
4	Mrs G.	F / 24		1	31	Labour induced three weeks ago because of anaemia. R 2,600,000 H. 40%
5	Mrs M.A.	F / 53		1	40	R 670,000 H. 40% W.2900
6	R.T.	M / 26		1	40	R.2,600,000 H. 28% W 2900
7	J.A.	F / 61		1	46	R 2,320,000 H 80% W 3,800
8	J.G.	M / 56	Aug.12	1	35	R.2,250,000 H 54%
			" 20	1	33	" 2,800,000 H 64%
			" 31	1	31	" 3,600,000 H 70%
			Oct.24	1	24	" 3,500,000 H 90%
			Dec.18	1	33	
9	J.C.	M		1	41	R 830,000 H 20% W4,400
10	Mrs G.	F		1	36	R 2,400,000 H 55% W3,000
11	Mrs J.	F / 43		1	42	R 1,830,000 H 30% W 3600
12	A.G.	F / 38	Aug.24	1	40	R.2,150,000 H. 45%
			Nov.20	1	38	R.620,000 H 15% W.1,900
13	Mrs J.	F		1	52	R.500,000 H. 25%
14	J.G.	M / 56	Nov.4	1	53	R.1,600,000 H 34% W.8400
			Dec.18	1	57	3,210,000 " 68% 3800

Table IV. (contd.)

No.	Patient.	sex / age.	Date.	Coagulation-Time Min.	Sec.	Additional Information.
15	Mrs B.	F.	Nov.4	1	32	R.3,680,000 H 51% W 5200
			Dec.18	1	35	———
			Jan.12	1	36	———
16	Mrs P.	F / 60		1	31	———
17	J.C.	M / 64		1	37	———
18	A.D.	M / 59		1	37	R.950,000 H 11% W.6,800
19	Mrs B.	F / 49		1	50	R.720,000 H 19%

Table V. Lymphatic Leukaemia.

No.	Patient.	Sex / Age	Date.	Coagulation-Time Min.	Sec.	Additional Information.
1	D.M.	M / 30	July 2.	1	38	R.5,100,000 H. 70% W 36,600
			Aug. 2	1	37	Glands smaller and softer. W. 33,000
2	M.C.	M / 3		1	51	R.1,100,000 H 30% W. 61,200 Liver and spleen much enlarged.
3	J.B.	M / 17		1	30	R.4,300,000 H 65% W.26,000 Glands of neck, axilla, and groin much enlarged, also liver and spleen.
4	Mrs M.	F / 61		1	35	R.8,000,000 H. 40% W.5,000

Table vi.

Myelogenous Leukaemia.

No.	Patient	Sex. Age.	Date	Coagulation-Time Min.	Sec.	Additional information.
1	M.G.	F. -		1	39	R.3,200,000 H 58% W. 22,000
2	M.M.	F. 41	Aug.1	1	52	R.3,640,000 H.70% W. 1,500
			Sep.3	2	3	R.3,300,000 H.42% W.30,000 Much worse; developed irregular pyrexia
3	Mrs B.	F 51		1	17	R.3,000,000 H.50% W.270,000
4	R.S.	F 13		1	30	R.2,500,000 H.50% W.640,000

Table vii.

Splenic Anaemia (Infantum)

No.	Patient	Sex. Age.	Date.	Coagulation-Time Min.	Sec.	Additional information.
1	D.B.	M 1¾		I	50	R.2,200,000 H.30% W.9100 very big spleen.
2	J.G.	F 1½		I	42	R.3,700,000 H.40% W.17,000

Below is set forth a summary of the foregoing diseases, which, though much less illuminating than the actual tables, yet throws some additional light upon the subject.

	Disease	No of cases	Average	Coagulation - Times	
				Longest	Shortest
I	Chlorosis	11	1-25	1-29	1-19
II	Simple Anaemia	2	1-22	1-27	1-18
III	Simple Secondary Anaemia				
	(a) not due to haemorrhage	12	1-27	1-40	1-14
	(b) due to haemorrhage	14	1-23	1-35	1-8
IV	Pernicious anaemia	19	1-41	2-20	1-31
V	Lymphatic Leukaemia	4	1-38	1-51	1-30
VI	Myelogenous Leukaemia	4	1-34	1-52	1-17
VII	Splenic Anaemia Infantum	2	1-46	1-50	1-42
	Total	68			

This last table shews that striking differences are to be found in the coagulation times of the blood in the various blood diseases.

They shew at a glance that the average coagulation time for chlorosis and the simple anaemias is shorter than normal, and that the average for pernicious anaemia, the leukaemias, and splenic anaemia, is unaltered. From the last two columns (longest and shortest coagulation times) interesting information can be obtained as to possible deviation from the normal in each disease. But it is much more instructive to study the extended tables, comparing the individual members of each group with the group as a whole, and then the groups with each other.

Thus, Table I - Chlorosis - shews an average of 1 min. 25 secs. for the first ten cases, and the value of this average is enhanced by noting how close the individual readings keep to it. Not one of the ten cases gives a reading within normal limits; all shew a greater or less degree of acceleration of coagulation.

This is a very marked contrast to the cases of Pernicious Anaemia (Table IV) where not one of the eighteen cases gives a reading under 1 min. 30 secs. Such presistent differences in the rates of coagulation must surely be attributable, directly or indirectly to the diseases in which they occur.

The coagulation time in Chlorosis, then, tends to be/

be shortened. Is this shortening in any way proportionate to the degree of anaemia? Is there any relationship, for example, between the rate of coagulation and the colour index? This question is a general one, and it is therefore convenient to discuss it in respect not of chlorosis only, but of all the simple anaemias (i.e. of the results found in Tables I - III B).

It will be found on reference to these tables (where in addition to the coagulation time many records of the blood count are given) that no definite relationship can be said to exist between the rate of coagulation and the degree of anaemia. There is a tendency for the severest simple anaemias to have the shortest coagulation times, but this is by no means regular, and examples can readily be picked out where severe anaemias have coagulation times longer than those of a less grave type, or where slight anaemias may have very marked acceleration of coagulation.

This, indeed, is what one would expect to find where such wide limits must be allowed for possible personal variation. For this great width of the normal limits precludes the possibility of saying by how much the rapidity in any individual case has been increased. It does not follow, of course, that where wide differences exist in the readings for normal individuals that such must of necessity persist where, as the result for example, of equal degrees of anaemia/

anaemia, the readings have passed beyond the normal. But it is a possibility, and, until further observations are obtained shewing the state of the blood before the onset of the disease or at such time afterwards as may fairly allow of a complete return to normal, the knowledge of this possibility prevents one from saying in how much the degree of gravity of an anaemia is responsible for the degree of acceleration of the coagulation-time.

Records of coagulation-times in chlorosis are difficult to find. In books the statement is usually met with that in this disease the rate of coagulation is accelerated, but this opinion would appear to be based chiefly on the clinical fact of thrombosis Beattie and Dickson in their text book of Pathology state that "the coagulability is distinctly greater than in other anaemias of equal degree, an important point in connection with the occurrence of thrombosis which has frequently been described in chlorosis.

This is the most usually accepted opinion, but against it though the authority is not stated may be quoted the following from Clifford Albutt in his "System of Medicine": discussing thrombosis in chlorosis he says "coagulation is slower in chlorotic blood outside the body, notwithstanding the tendency to thrombosis within it, facts which are not easy to reconcile with that accident".

Rudolf/

Rudolf and Cole[1] in a table of recorded experiments quote two cases of chlorosis whose average was 6·9 min. This in their scale (of which the normal was 7·7 min) shews a distinct acceleration of coagulation.

Addis[2] in his series quotes two cases in which the time was normal, Neither, unfortunately, gives the degree of anaemia present, though the latter states that his cases were "severe".

Of the anaemias included under Table II and Table III (a) nothing more need be said beyond that they also shew a very distinct average acceleration of coagulation.

It is when we come to study the table of observations in cases of anaemia secondary to haemorrhage (Table III B) that there appears the most pronounced departure from the normal in the direction of acceleration of clotting. Here the average of fourteen cases is 1 min. 23 secs., and this in spite of the fact that the degree of anaemia produced by the haemorrhage has seldom been so severe as in the other simple anaemias. In two of the cases indeed (cases 4 and 8) short/

1. Trans. Assoc. Amer. Phys. XXVI p. 460.

2. The coagulation-time of the Blood in disease, B.M.J. April 24 1909.

short readings are found where the blood examination revealed no anaemia. In the course of my experiments in this series I have received the impression - perhaps scarcely justified by the number of observations - that the shortest readings are got where the haemorrhage has been sudden, sudden and moderately severe. This point is brought out by a study of the cases of haematemesis, especially cases No. 5, 9, 10 and 13, giving readings of 1 min. 17 secs, 1 min. 8 secs., 1 min. 18 secs., and 1 min. 14 secs., respectively. Such readings are among the shortest to be observed in any morbid process.

An exception to the above will be noted in case No. 3, where there is a severe anaemia of rapid onset. Patient was examined on admission to hospital within twenty-four hours of the haemorrhage.

In support of my findings in this, as in the other anaemias, I may refer to the figures of Rudolf Cole. They are to be found tabulated for convenience on page 30.

Pernicious Anaemia.

I have already alluded to the striking contrast to be found between the coagulation times of the simple and pernicious anaemias. It has been my privilege to examine nineteen cases of the latter, cases in all degrees/

degrees of severity, and in none of them have I found a coagulation rate shorter than normal. The average time for the series is 1 min. 41 secs. and it will be seen that the great majority of the cases lie in or around this figure. While none shew acceleration of coagulation, only one, (No.2) shews definite retardation, and this was a case exceedingly far advanced in the disease. At the time of examination the patient was moribund and her death occurred about three days after. Such a marked retardation of coagulation is of especial interest and I therefore give here full figures of the experiment:

Min.	Sec.	
2	22	Average 2 min. 20 secs.
2	24	
2	21	
2	14	

The clot when formed was not found to be peculiarly delicate or indeed in any way to be distinguished - expect for its pallor - from the clot got in far different conditions. An interesting contrast to this is afforded by the study of case No. 12. Here, on Aug. 24, the rate was 1 min. 40 secs., and yet on Nov. 20, by which time in spite of treatment the blood had sunk to one third of its former value, and to a value practically identical with the above, the coagulation/

coagulation time shewed no appreciable change. It is to be noted, however, that though the blood counts of the two patients were at this point identical, their general conditions were in striking contrast. In case No. 12 considerable improvement set in at a later date.

Cases 13 and 14 shewing readings of 1 min. 52 secs. and 1 min. 53 secs., though practically within normal limits may be considered to point to some tendency to lengthening. The fact that both are cases of some severity might strengthen this view were it not that case 14, in an observation at a later date, when considerable improvement had taken place, shewed the reverse of any tendency to correction of the retardation.

Here, then, is an observation of great interest: that, while in very severe cases there may be considerable delay, the majority of cases of pernicious anaemia shew no tendency to any alteration in the rate of coagulation; that the haemoglobin may sink to as low as 30% (Case 11), 20% (Case 9) or even to 15% (Case 12), without the appearance of any change.

In view of the well known tendency to oozing and persistent bleeding which at times is observed in this disease it would appear, as, indeed, has been emphasized by Addis, that the factor responsible for this condition is to be looked for in some default of quality rather than of speed in clot formation.

As/

It is perhaps argument from their clinical observations more than from any experimental data which makes some writers observe that in pernicious anaemia the rate of coagulation is retarded. Most writers, if indeed they touch upon the question at all, content themselves with generalities. Thus Herbert French,[1] discussing pernicious anaemia, says "it (the blood) clots less readily than usual"; others, that "its coagulability is much diminished", and so on.

Such statements must not be construed as having any necessary bearing on the rate of coagulation of the blood. They may refer merely to the effectiveness or firmness of the clot.

Sabrazes[2] mentions a case of pernicious anaemia where the blood count was as follows:

R. 734,600 H. 20% W. 1,240

and where there was a reduction in the blood platelets. He says "le debut de la coagulation se faisait dans un laps de temps normal, mais le caillot se rétractait très incomplètement". This bears out my own findings, that there may be a very grave degree of anaemia present/

1. Allbutt's System of Medicine.
2. Folia Haematologica 1905 III p. 330.

sent without any change in the rate of coagulation.

On reference to page 30, it will be seen that Rudolf and Cole quote four cases of the disease which, in the average, shew a definite tendency to retardation, though this does not appear to any marked degree in any of the eight individual readings. Unfortunately the degree of severity of the anaemias is not mentioned. On the other hand, Addis has two cases in his list, both severe. One was normal while the other was persistently short.

Summed up, the state of the coagulation time of the blood in this disease may be expressed as follows:-

(1) In the great majority of cases of pernicious anaemia, even where the condition is very pronounced, there is no change in the coagulation time of the blood.

(2) In very advanced cases there may be a slight or a very considerable delay, the actual blood count being no safe guide as to the degree of retardation which may be expected.

(3) The rate of coagulation is never accelerated.

It appears to me that we have here a point of some diagnostic value. Every now and then a case appears for diagnosis in which it is extremely difficult to pronounce between a pernicious and a severe secondary anaemia. A satisfactory history may not be obtainable

and/

and it may happen that at the time of examination neither blood count nor film examination reveals anything of diagnostic value. At such a juncture a knowledge of the coagulation time of the blood is of value. If the rate be accelerated the probability is strongly in favour of an anaemia of a secondary type; if normal or retarded the probability (though in this case not so strong) favours the pernicious type. For it is to be remembered that while pernicious anaemias do not give short coagulation times, the simple anaemias though in the great majority of cases giving short, may give normal times.

A case in point is to be found in Table IV, No. 18. there the patient, a plumber of fifty-nine, gave a very low count with low colour index, and no myelocytes, megaloblasts, etc., to be found in the blood films.. There was a history of prolonged work in lead but no history of previous lead poisoning. Diagnosis lay between an anaemia due to ~~xxxxx~~ lead poisoning and pernicious anaemia. The coagulation time was taken and favoured pernicious anaemia (i.e. was normal). About a week afterwards this was confirmed by a rise in the haemoglobin coincident with a fall in the number of erythrocytes and the appearance of characteristic cells in the film. It is to be noted that the case might have been one of the (exceptional) secondary anaemias with normal coagulation time. Had it shewn

a/

a short coagulation time opinion would have been very strong against pernicious, for in differentiating the two conditions it is of more positive diagnostic value to find an accelerated than a normal coagulation time.

Tables V, VI, and VII - the records respectively of cases of Lymphatic Leukaemia, Myelogenous Leukaemia, and of Splenic Anaemia - may be conveniently classed together. They shew practically the same findings as in pernicious anaemia; i.e., the majority, despite the grave changes in the blood, shew no alteration in the rate of coagulation.

One of the Myelocythaemias (Case 2) shews a slight retardation, accentuated at a later date in association with an increased depravity of the blood.

Only one case (Table V, No. 3) gives a reading such as one would expect to find in chlorosis or secondary anaemia and here it is of interest to note in connection with certain theories which have been advanced (see Page 64), the high leucocyte count (270,000).

PURPURA.

Since completion of Thesis another case of Purpura has come under my observation. It was one of some severity, probably rheumatic in origin.

As follows:-

N. C.	$\frac{F}{10}$	-	1 min. 35 Sec.	Associated with Urticaria.

Table VIII

Purpura.

No	Patient	Sex / Age	Date	Average Coagulation Time	Additional Information.
1	C.G.	M / 11		1 43	Herpes. Subcutaneous Haemorrhage
2	M.E.McG.	F / 8	Aug 10	1 33	Large purpuric spots. ? Rheumatic origin.
			" 12	1 35	
			" 21	1 27	Fresh spots developed at this date.
3	J.M.	M / 20	Nov 11	1 41	Henoch's Purpura see following notes.
			" 20	1 26	
			" 28	1 25	
			Jan 14	1 30	Died, acute nephritis, Feb 11.
			Feb 7	1 26	
4	J.McG.	M / 43	Aug 13	1 17	Aortic Incompetence. Purpura
			" 19	1 28	Spots on legs. H = 60%

Although the opinion is more and more gaining ground that purpuric conditions are not in the majority of cases associated with any alteration in the rate of coagulability of the blood the question is yet sufficiently unsettled to warrant my bringing forward some observations made in these conditions.

They are conveniently placed here after the discussion of the blood diseases.

Only four cases are adduced and of these, the last is rendered of little value by reason of the anaemia present at the outbreak of the rash. Nevertheless cases 2 and 3 are in themselves well worthy of comment.

Case/

Case 3 (J.M.) was an exceedingly severe case of Heriock's Purpura. At the time of the first record (Nov. 11) there was a freshly developed and very severe purpura affecting trunk and limbs, with haemorrhages into the mucous membranes, severe colic, and vomiting with traces of blood in the vomit. By Nov. 13th, fresh crops still appearing, there was more pronounced vomiting of blood, and, by Nov. 20th at which time the second examination was made - there had developed in addition severe malaena and haematuria. By this time the patient must have lost between three and four pints of blood and this progressing anaemia accounts, I think, for the shortening of the coagulation time observed at this date.

The condition was a very obstinate one, and resisted all treatment. Acute Nephritis supervened and the patient died on February 11th of anaemia and exhaustion. The interesting point to observe is that at the date of the first examination when the purpuric symptoms were in full evidence and when the case was uncomplicated by anaemia the coagulation time of the blood was normal. Later, by reason of the succeeding anaemia, it changed to quicker than normal, so that at no time in the course of the disease could the coagulability be said to be delayed.

Case/

Case No. 2 (M.E. McG.) was a purpura simplex of moderate severity, and had two successive crops of purpuric spots on legs and arms, with no other symptoms. At the time of the first test (Aug. 10) I found the blood count normal. The shortening on the day of the appearance of the second crop (Aug. 21) is so slight as to be negligible.

Case No. 3 (C.G.), a purpura haemorrhagica, was of more severity. There were very extensive subcutaneous haemorrhages together with symptoms (localised convulsions, squint, etc.) suggestive of haemorrhage into the meninges.

Case No. 4 (J. McG.) I have already stated to be of little value on account of the co-existing anaemia, with its evident effect upon the coagulability. In any case the purpuric symptoms were slight, and, occurring as they did in the lower limbs and in association with oedema some authorities would regard them as of purely mechanical origin.

The above investigations agree in their findings with the present general trend of opinion in that they shew no disturbance of the rate of coagulation in association with purpuric conditions. Many years ago Wright claimed that the blood in certain types of purpura shewed very definite delay in clotting, sometimes to as much as two or three times beyond the normal. This claim has been much criticised and certainly/

certainly the tendency now is to seek for some explanation of the condition apart altogether from the question of the rate of coagulability, or even to look for causes outside the blood altogether..

W.K.Hunter (1) states that in the majority of the cases of purpura the coagulation time is about normal, and that the most noted abnormality is a diminution in the number of blood platelets, while J.H.Pratt, working in conjunction with Krehl, could not discover in the course of his investigations any relationship between the number of blood platelets and the coagulation time . According to Hayem the clot which forms in drawn purpuric blood is peculiar in that it does not contract to the exclusion of serum.

In connection with these statements it is interesting to note that in case No. 3 the blood platelets (I quote the investigations of another observer using Pratt's Sodium Metaphosphate method) numbered only 52,000. With Pratt's method the normal varies in round numbers from 200,000 to 500,000; there is thus in this case a very considerable reduction. In this case also the clot which formed in the tubes had very much the character of an open meshwork, and was not firm and stringy as it usually is. This was best observed on leaving the tubes sealed for a short period/

(1) "Recent Advances in Haematology". 1911.

period after reaching time end-point. None of the others showed this phenomenon.

Table IX.

Jaundice.

No.	Patient.	Sex Age.	Date.	Average Coagulation-Time. Min.	Sec.	Additional Information.
1.	W.B.	M 47		1	48	Carcinoma. Very deep recent jaundice.
2.	Mrs I.D.	F 53	June 18	1	49	Marked jaundice ? carcinoma.
			Aug. 14		9	Large masses now
3.	Mrs M.	F -		1	47	palpable in liver.
4.	I.S.	F 49		1	41	Long standing and very marked.icterus
5.	L.R.	F 15		1	53	Hanot's Cirrhosis. Jaundice.very pronounced.
6.	J.G.	M 41		1	33	Deep; three years duration.
7.	Mrs M.	F 49		1	29	Marked jaundice; some anaemia.
8.	R.H.	M 53		1	24	Carcinoma; icterus slight. W.2,500,000 H 28% W 5600

The above cases of jaundice do not shew any striking departure from the normal. Case 5 alone is outside the normal limits, shewing slight retardation. Cases 1 and 2, both with very pronounced icterus are within normal limits, but on the long side of normal. Cases 7 and 8 are complicated by anaemia. In the latter the anaemia

was/

was very pronounced while the jaundice was slight. Its coagulation time is therefore that of a secondary anaemia. I have cut it off by a line from the others of the table in order to emphasise this point. Cases 1, 2, 4 and 5 were such as one would expect to shew retardation, for in all of them the serum in the tubes after separation of the corpuscles was of a very decided icteric tinge. Yet all that one could say of them is that they tend to shew retardation of coagulation. Nos. 1 and 2, it is to be noted also, are causes of malignant jaundice - the condition in which of all diseases in their series Hinman and Sladen have recorded the longest coagulation time. On the other hand Addis[1] quotes a case of malignant disease with an associated very profound jaundice where the coagulation time was normal, and where, indeed towards the end, it became accelerated.

1. Edinburgh Medical Journal. Vol. V. 1910.

Table X

Diabetes Mellitus.

No	Patient	Sex / Age	Date	Average Coagulation Time Min.	Sec.	Additional Information.
1	P.R.	M / 21	May 29	1	17	Acute onset: illness dates from 2 months ago. Sugar 30 grains per oz. H. = 80%
			June 1	1	21	
			" 4	1	20	
			" 10	1	18	
			" 14	1	18	(R) Experiment with Bier's congestion
			" "	1	15	(L) Right hand normal, Left ½ hour's congestion.
2	M.C.	M / 63		1	18	+ Rheumatoid Arthritis.
3	J.S.	F / 74		1	46	Gangrene of foot: sugar 2 oz. per diem.
4	J.M.	M / 46		1	18	Acetone and diacetic acid in urine. Blood count normal.
5	Mrs M.B.	F / -		1	22	Sugar: 30 grs. per oz.
6	P.R.	M / -		1	30	Sugar: 30 grs. per oz. coma. Reading taken within 10 min. of transfusion with Sod. Bicarb.
7	A.B.	M / 27		1	19	History of about 5 weeks illness. Blood count normal
8	R.B.	M / 37		1	20	5 months duration.
9	- A.	M / 30		1	17	
10	R.R.	M / 19		1	15	Disease of 2 years standing Sugar: 30 grs. per oz.
11	-	M / 26		1	25	
12	W.S.	M / 23		1	22	Sugar: 36 grains per oz.
Average for 12 cases				1	22	

Table X wherein are recorded observations in cases of diabetes gives somewhat surprising results. At a glance is seen the almost uniform rapidity of coagulation. The average for the series works out at 1 min. 22 secs. and only two of the cases are within normal limits.

Case No. 3 came to hospital for surgical treatment only; in her the disease was of more than twenty years standing. Case No. 6 was examined, as is stated in the table, immediately after an intravenous injection of sodium bi-carbonate. He had been in coma for two days. Case No. 2 was complicated by the presence of a severe rheumatoid arthritis, but there was no anaemia. Polycythaemia was not noted in any of the cases. Although the series is small, a comparison of the individual members with each other does not encourage the idea that differences in the degree of alteration in the coagulation-time will be found to depend on such factors as the age of the patient, acuteness of onset, or severity of the disease. With the blood elements apparently normal it is as difficult to see how such changes in the coagulation rate should occur as it is to know why. Rudolf and Cole[1] give three cases in their list, the average shewing slight acceleration of clotting. Addis[1] quotes two cases which were normal.

1. See page 29 et seq.

Table XI.

Pneumonia, Acute Lobar.

No.	Patient.	Sex Age.	Date.	Coagulation Time. Min.	Sec.	Additional Information.
1.	J.S.	F 9	June 19.	1	26	Temp.102° Leucos. 22,000.
			"22	1	31	Pseudo-crisis.
			July 6	1	42	5 days after discharge from hospital.
2.	J.K.	M 13		1	35	Temp.102°
3.	W.W.	M - F		1	33	Temp.104° L. 10,500.
4.	Mrs R.	39		1	27	Temp.102° L. 18,000.
5.	W.S.	M 47	July 31	1	51	Temp.103° L. 19,000. 4th day of disease.
			Aug. 1	1	40	Temp.102°
			" 5	1	23	Crisis. Temp. normal.
			" 9	1	26	" "
			" 12	1	31	" "
6.	E.H.	M 20	Aug. 7	2	6	Temp.103°. L.17,000.
			" 12	1	48	Third day after crisis.
7.	J.W.	M 9		1	30	

The above table of pneumonias, though short, is worthy of a detailed study as it raises some interesting points in connection with the state of the blood in this disease.

Dealing/

Dealing with first observations only it will be seen that there is not, as was the case in most of the foregoing tables, any settled uniformity in the rate of coagulation. (The average works out at 1 min.38 secs. but when such wide differences exist there is obviously little to be gained by striking an average). Of the seven readings it will be seen that three are normal, two accelerated and two retarded. None of the cases shew any pronounced departure from the normal, but the fact that readings are obtained towards both extremes suggests something erratic in the behaviour of pneumonic blood. Periodic examination of the blood of individuals during the progress of the disease reveals the same thing. Thus, taking Case No. 5, it is seen that the coagulation swings from long to short and then back again to normal, a difference of 28 secs. separating the extremes. Case No. 1 shows only the return from a short period to the normal, Case No. 6 a return from long to normal, but the finding in case No. 5 suggests that these might have shewn long and short readings respectively had they been examined at other stages of the disease. Rudolf and Cole (1) brought together a much larger series of cases in this disease. They adduced 17 cases (in all 47 observations) and found that the average coagulation time was 8.1 min. (which is identical with their average for the whole series/

1. See page 30.

series of 142 cases published). Their longest and shortest readings were respectively 12.7 mins. and 5.5 mins. shewing that there may be very definite retardation or acceleration of the coagulation time. T. Addis, using his modified McGowan's method obtained similar results. He quotes two cases of pneumonical empyema in which "the time was normal". "Of three cases of lobar pneumonia one was normal, in the other the coagulation time was slightly irregular, and in the third, a case in which observations were commenced on the second day of the disease before there was any recognizable pulmonary consolidation, the coagulation time was at first above normal and afterwards fell below it."

It would appear, then, that in pneumonia the coagulation time may be short or normal or long, and that these various states may be found to exist in the individual at different stages of the disease. Some explanation of this varying condition of the blood in pneumonia may be sought from the evidence brought forward by J.A.Welsh (1) in a paper on the "Positive and Negative Phase of coagulation of blood in man". Therein he shows that the degree of coagulability of the blood depends probably upon the amount of kinase in the blood and upon the rate of its entrance into the blood. He gives a summary of 450 post mortem examinations/

(1)Journ. Path. & Bact. Cambridge. 1910-11. XV.p.467 et seq.

examinations (80% of the cases pneumonias) and studies them in relation to the occurrence of intracardiac (pale) thrombosis and to the occurrence of fluid non-coagulable blood on the right side of the heart. The following is quoted from Mellanby. "Whether intravascular coagulation or fluid blood results or the injection of Kinase in animals the effect of the Kinase is the same in the two cases - the generation of fibrin ferment and the formation of fibrin from fibrinogen. The diverse final effects depend only on the rate of formation of fibrin. If the rate be too great for the tissue cells to deal with, intravenous coagulation results; if the rate be sufficiently small to allow the tissue cells to work the fluid blood ultimately results". In pneumonia the excess of Kinase comes, of course, from excessive cell destruction associated with the disease.

In addition to a consideration of the amount and rate of production of Kinase there is the question of the degree of aëration of the blood. It has for long been held that carbon dioxide tension in the blood directly influences the coagulation time, the higher the tension the greater the acceleration of coagulation.

Welsh in the above article says: "in pneumonia, moreover, owing to embarrassment of the respiratory exchange/

exchange there is presumably also a higher tension of carbon dioxide in the pulmonary circulation and consequently a greater acidity of the blood determining again a more marked positive phase than in other inflammations". The systemic blood in most cases of pneumonia is markedly venous, and it is also, therefore, to be presumed, other things being equal, that pneumonic blood would tend to have a more ready coagulability than normal blood.

In respect of the tension of carbon dioxide in the blood see also page 77 et seq.

Table XII — Acute Rheumatism.

No	Patient	Sex / Age	Date	Coagulation Time	Additional Remarks.
1	G.M.	F / 20	June 5	1 48	Temp. 102 No treatment.
			" 7	1 35	240 grains Sod. Salicyl. since June 5th.
2	M.S.	F / 16	" 29	1 52	
			July 9	1 41	
3	M.P.	F / 9	" 2	1 50	Before treatment.
			" 8	1 50	after heavy doses of salicylates. (see notes)
4	J.D.	M / 25	" 26	1 31	
			" 4	1 31	
5	Mrs W.	F / -		1 54	Temp. 103.

The cases of acute rheumatism above detailed are also too few in number to justify in themselves the drawing of any conclusions as to the disturbing effect of this disease upon the coagulation time. If anything they shew a tendency to retardation. Here, as in Pneumonia, Rudolf and Cole are at an advantage in having a much larger series of cases to quote. Their records shew that in 15 cases (of which there are 38 observations) the average is 10.2 mins, the longest 14.3 mins, the shortest 7 mins. This gives for the disease a pronounced average retardation of coagulation.[1]

Three cases are instanced by Addis, all examined in the acute stage, and all shewing slight delay. The times were 11 min. 15 secs; 11 min. 10 secs; 11 min. 45 secs., (i.e. all at the extreme of the possible normal/

1. See page 30.

normal delay).[1]

Case No. 3 in my own series of observations is worthy of note in that for the six days between the two observations the patient a girl of nine, received the following:

Sod Salicyl gr XXX
Sod Bicarb gr LX
every four hours.

The child weighed 2 st. 10 lbs: the dosage must therefore be reckoned very heavy,and yet, on the sixth day of such treatment,the coagulation time was unchanged. Case 1 shews in lesser degree the same state of affairs.

In respect of acute rheumatism it is to be noted that for an accurate study of the coagulability as influenced by the disease care must be taken to avoid any masking of the effects of the disease proper by the changes which are produced by a secondary anaemia. As anaemia may develop very rapidly in this disease it is well to make observations early in its course. In the above table all the initial experiments were made at an early stage. A good example of this source of fallacy is seen in Case No. 11, Table III, where with fever and joint pain still present, the blood had fallen to R. 2,880,000 H. 44%. The coagulation/

1. See Page 30.

coagulation time was much accelerated. This acceleration I attribute directly to the anaemia, and only indirectly therefore to the acute rheumatism.

The following cases of rheumatoid arthritis may be conveniently entered here.

Table XIII Rheumatoid Arthritis.

No	Name	Sex Age	Date	Coagulation Time Min.	Sec.	Additional Information.
1	P.G.	M 48		1	25	pronounced anaemia
2	J.D.	M 41		1	34	
3	Mrs S.	F 31		1	52	Blood normal
4	T.McD.	F 42		1	34	
5	McA.	M 38		1	22	very severe case but not anaemic.

Table XIV

Acute Nephritis.

No	Patient	Sex / Age	Date	Coagulation Time		Additional Information.
1	B.L.	M / 7		2	0	oedema: albumin, no blood.
2	L.C.	M / 10	June 22	2	9	
			July 6	2	23	Salt free diet: see below.
			Feb 9	1	34	
3	D.McI.	M / 35		1	32	Albumin and blood H = 95%
4	H.B.	F / 11		1	43	Acute exacerbation of subacute interstitial nephritis. Albumin = ·45 grains per oz.
5	E.T.	F / 7	Aug. 5	1	45	
			" 11	1	36	After 3 days haematuria. Blood not much affected.
6	I.R.	F / -		1	54	Uraemia, almost comatose. Blood count normal.
7	W.H.	M / 31		2	1	
	T.A.	M / 27		1	14	Albumin and much blood. Blood reduced to 32% haemoglobin.

The above observations in nephritis do not call for much remark. They are all of them cases either of acute, or acute exacerbation of sub-acute nephritis. The last (Case No. 7) should not properly be considered here. It has already appeared under the anaemias due to haemorrhage (Table III) but has been reproduced because at the time of examination the acute mischief was still at work. The marked disturbance of the coagulation/

tion time I take to be due to the anaemic condition.

For the rest, four out of the six cases shew a retardation of coagulation, but in how far this is characteristic of the disease it would require a bigger series of observations to discover.

Case No. 2 I am at a loss to understand. The patient, a boy of ten, was a case of advanced parenchymatous nephritis who had been on many occasions an inmate of the Royal Infirmary and of the Sick Childrens Hospital. There was persistent and pronounced albuminuria and, usually, at each admission a severe anasarca which responded well to salt free diet.

At the time of the first observation (June 22) there was pronounced oedema of face and legs, but none was evident in the arms and hands (from which last the observations were taken). The oedema not responding to ordinary measures, the patient was put on a salt free diet as on past occasions. On the eighth day of this diet (July 6th, by which time the oedema had almost entirely disappeared) the blood was again examined and the above very pronounced retardation discovered.

Suitable occasion for examination after recovery from this attack did not present itself, but in the following year the boy turned up again in hospital, again with pronounced oedema. This time he was not treated with salt free diet and during convalescence-

every/

every trace of oedema gone - the coagulation time was normal.

The case of uraemia (No. 6), it will be noticed, only shews slight retardation. Addis quotes a case in which there was very pronounced lengthening up to 16 min. 50 secs. (normal limit, see page 29, 11 min. 41 secs.)

Drugs and Coagulation Time, etc.

A Administration of Salicylates.

B " " Potassium Citrate

C (1) " " Calcium Salts

(2) Case of Gastric Tetany.

(3) Cases of Rickets.

A.

Administration of Salicylates: examples are given in Table XII and discussed in the notes appended thereto.

B.

Administration of Potassium Citrate.

I have made numerous blood examinations in patients who were receiving potassium citrate, but in none of them could I trace any effect which might be put down to the action of the salt.

Two of the cases, by reason of the big doses given, are worthy of note.

Case I Subject E.F. (female, aet.9) Pyelonephritis.

Date	Coagulation-Time min.	sec.	Remarks
July 8	1	53	Before treatment. Urine acid.
" 11	1	46	Pot.Citrate(gr X t.i.d.) since 8th.
" 14	1	48	Pot.Citrate(grs.XXX t.i.d. since 12th
Aug. 1	1	53	" " " " " (urine now strongly alkaline).

Case 2. Subject Mrs N. (aet. 25) B. Coli Cystitis.

Here only one examination was made but, although on that date and for ten days previous to it, the patient had received

Pot. Citratis gr. XXX
every 4 hours.

the coagulation time was to the short side of normal, being 1 min. 31 secs.

In case 1 it is seen that when the salt had attained its full effect (as evidenced by the change in the urine) it had yet produced no change whatsoever in the coagulation time.

Administration of Calcium Salts.

Case 1. Subject J.B. (male, aet. 36) Haemoptysis.

Date	Coagulation Time Min.	Secs.	Remarks.
Aug 12	1	25	Two pints of blood coughed up on Aug. 9th
" 14	1	21	Calcium Lactate gr X t.i.d. since 12th
" 19	1	24	Dose doubled. after gr LX to-day.
Sept 2	1	31	Calc. Lactate gr XX t.i.d. since 19th. No haemorrhage since Aug. 14th.

Case 2. Subject J. McG. (male aet. 43) Purpura.

Date	Coagulation Time Min.	Secs.	Remarks.
Aug 13	1	17	Calcium Lactate gr. X t.i.d. since 3rd.
" 19	1	28	Calcium Lactate gr. X t.i.d. since 13th.

The effects of calcium salts and of citrates and citric acid on the coagulation time of the blood have been much disputed. Addis shewed, conclusively I think, that in the normal individual at any rate the exhibition of these drugs is without effect. He and others have attempted to shew that this holds good also in pathological conditions but here the study is more complex. My investigations in the subject have been/

been too few to warrant any discussion of the question here and I accordingly give the above cases without comment.

It is convenient however to quote here a case of gastric tetany, a disease held by some[1] to be due to a disturbance of calcium metabolism, (which is said in turn to be due to some disturbance, functional or otherwise, of the parathyroids).

The patient (a boy aet. $2\frac{1}{4}$) was under my care at the Royal Infirmary and again, six months later, at the Sick Childrens Hospital. The tetany on both occasions was severe but responded gradually to the regulated diet of hospital and no drugs were used. On the second admission the blood was examined and the coagulation time found to be normal, being

1 min. 40 secs.

Rickets too is a disease supposed to be associated with deficiency of calcium salts in the blood. Several cases of severe rickets were examined by me at the Sick Childrens Hospital, but unfortunately the records are lost. As far as my recollection goes none of the cases gave abnormal readings, certainly none were lengthened.

1. See, among others, McCallum & Voegtlèr in the "Journal of Experimental Medicine" 1909 Vol. XI.

Cerebral Haemorrhage and Venesection: 3 Cases.

The following cases of cerebral haemorrhage treated by venesection illustrate very clearly some important points, already touched upon in the preceding pages, in connection with the clotting of blood. They are best treated individually and in extenso.

Case I Subject W.N. Male (aet. 63)

Admitted unconscious, stertorous breathing, marked cyanosis. Temperature 100°.

The coagulation time was taken from the fingers in the usual manner, and the blood was noted to be markedly venous.

Coagulation Time (11 P.M.)

1 min. 30 secs)
1 " 25 ")
1 " 20 ") average = 1 min 25 secs.
1 " 24 ")

One half four after, venesection was performed and eight ounces of blood withdrawn. Tubes (held in forceps) were filled from the column of blood as it spouted from the vein, care being taken that no tube should touch the wound. These gave:-

Coagulation Time (11.30 P.M.)

1 min. 3 secs)
0 " 57 ")
0 " 50 ") average 0 min. 55 secs.
0 " 52 ")
0 " 51 ")

One hour after venesection the blood was again examined from the fingers in the usual manner; it was noted to be much less venous than on the first occasion.

Coagulation Time (12·30 a.m.)

1 min. 35 secs)
1 " 37 ")
1 " 38 ") average = 1 min. 36 secs.
1 " 34 ")

About an hour after this the patient died.

Case 2. Subject Mrs B.L. (aet. 60)

Admitted unconscious. Temperature 101°.

The coagulation time was taken from the fingers in the usual manner, the blood being noted as "not venous".

Coagulation Time

1 min. 32 secs.)
1 " 35 ") average 1 min. 33 secs.
1 " 33 ")

Venesection was proceeded with immediately after and the blood taken as in Case 1.

Coagulation Time.

1 min. 23 secs)
1 " 22 ")
1 " 23 ") average 1 min. 22 secs.
1 " 21 ")
1 " 22 ")

No/

No further examinations were made and the patient died a few hours after.

Case 3. Subject Mrs A.D. (aet. 58)

Unconscious, cyanosed, B.P. 220 M.M. Hg. (Riva Rocci)

As in the other cases the fingers were first used, the blood being noted as very venous.

Coagulation Time

1 min. 23 secs.)
1 " 19 ") average 1 min. 22 secs.
1 " 22 ")

The patient was then bled (twelve ounces) and tubes filled from the stream as in the other cases.

Coagulation Time.

1 min. 0 secs.)
1 " 5 ") average = 1 min. 3 secs.
1 " 3 ")

The patient died shortly afterwards.

It is noteworthy that in cases 1 and 3 where the blood was markedly venous, the coagulation time was shorter than normal. Case 1 shews the lengthening to normal coincident with a reduction of this venosity. This effect of an abnormally high tension of carbon dioxide in the blood has already been mentioned in the discussion on pneumonic blood. Wright[1] lays so much stress/

1. Handbook of Technique (Constable, London. 1912)

stress upon this point that he mentions "the fallacy of diminished ventilation" as one of the things to be guarded against or to be noted in observing the coagulation time of the blood.

Case 1 Table X may be suitably mentioned here. Another point to be noticed in these cases is the pronounced uniform acceleration of coagulation when the blood is taken from the vein direct. In all three cases the blood flowed direct from the vein and the only wounded surface with which it could have been in contact was the divided vessel wall. This phenomenon of accelerated coagulation in blood from wounds is usually ascribed to the collection of Kinase in the injured tissues. The uniformity of the coagulation time as got in this way suggests that the variation in the coagulation time as obtained from separate wounds depends to some extent at least in variations in the needle prick as regards depth, laceration of tissue, etc. Hence the insistence on use of sharp needles only, and of uniformity, as far as can be, in the stabs.

Had not all three cases proved fatal it would have been of interest to note if, on examination subsequent to, and more remote from, the bleeding the coagulation time became accelerated as a result of the loss of blood.

Addis[1] quotes three cases in which twenty ounces were/

1. Edin. Med. Journ. Vol V 1910.

were removed for therapeutic purposes without any effect on the rate of clotting.

Table XV

Miscellaneous.

No	Name	Sex / Age	Coagulation Time Min.	Sec.	Disease.
1	T.K.	M / 21	1	40	Mitral Stenosis.
2	K.M.	F / 11	1	50	Abdominal Tuberculosis.
3	- D	M / 3	1	44	Constipation (Febrile)
4	J.W.	M / 9	1	30	? Pneumonia Crisis.
5	A.G.	F / 48	1	42	Hemiplegia.
6	J.F.	F / 11	1	42	Chorea (convalescent)
7	C.M.	F / 42	1	28	Leucoderma.
8	M.D.	M / 34	1	50	Aortic Incompetence
9	C.C.	F / 1	1	37	Cystitis.
10	M.J.	F / 55	1	33	Hysterical Aphonia.
11	Mrs B.	F / -	1	34	Myxoedema
12	W.C.	M / 1½	1	39	Urticaria Papulosa
13	D.C.	M / 31	1	42	Gastritis.
14	S.R.	F / 20	1	39	"
15	P.S.	M / 56	1	38	Gastric Cancer
16	Mrs M.	F / -	1	32	"
17	Mrs F.	F / 30	1	32	Pregnancy.
18	Mrs N.	F / 25	1	31	"
19	Mrs D.	F / 26	1	24	(Recently Delivered)
20	C.H.	F / -	1	38	Pyelo-nephritis.
21	L.B.	F / 20	1	17	Exophthalmic Goitre
22	E.L.	F / 19	1	24	all more or less
23	Mrs C.M.	F / 42	1	42	anaemic.
24	A.C.	F / 32	1	28	
25	W.B.	M / 27	1	26	

Table XV Continued.

No	Name	Sex / Age	Coagulation Time Min.	Sec.	Disease.
26	Mrs M.	F / 30	1	44	Parametritis (convalescent)
27	R.S.	M / 13	1	33	Banting's Disease.
28	H.L.	M / -	1	43	Lymphadenoma.
29	D.S.	M / 4	1	25	" (Moribund)
30	M.M.	F / 20	1	22	Hodgkin's Disease (Anaemia)
31	T.B.G.	M / 14	1	24	Pneumococcal Menengitis (Temperature 106°)
32	L.H.	M / 15	1	26	Pneumococcal Menengitis (Temperature 104°)
33	K.A.	F / 33	1	16	Phlegmatia alba Doleus.

CONCLUSIONS.

The more important conclusions arrived at by the investigations set forth in the preceding pages may be briefly summarised as follows:-

I The method herein used to estimate the coagulation time of the blood is a good one, and for these reasons.

(1) The instrument is eminently suitable for bedside work and temperature regulation is easy.

(2) The technique is very simple.

(3) The end-point is sharp and definite.

(4) The normal limits are not so wide as in some of the other methods and the readings, being subject to few variable influences in the technique, are very stable.

(5) Estimation of the strength and character of clot can be proceeded with after the time end point is obtained.

II The normal limits of the coagulation time of the blood are somewhat wide but individuals appear to have definite specific times which vary but little. (This latter applies also to most diseased conditions which are stationary).

III The majority of diseased conditions shew no alteration in the coagulation time.

IV Diseases of the Blood are divided in their action/

action on the coagulation time.

Chlorosis and the simple secondary anaemias as a rule give accelerated coagulation times, the acceleration being most pronounced in anaemias due to haemorrhage. Occasionally in the secondary anaemias (especially in those not due to haemorrhage) the time is normal, but such normal readings are exceptional. The coagulation time is never retarded.

In Pernicious Anaemia even where the disease is grave the time is usually normal. A few of the advanced cases shew retardation, none shew acceleration.

This absence of acceleration from cases of pernicious anaemia is so constant that a knowledge of the coagulation time becomes of value in the diagnosis of certain obscure anaemias. Thus in certain cases neither blood count nor film examination makes it possible to diagnose between pernicious (idiopathic) anaemia and an anaemia secondary to some known possible cause. Here, if the coagulation time is accelerated the probability is against, if retarded, it is in favour of pernicious anaemia; if normal it is more in favour of pernicious than of secondary anaemia.

Myelogemous and Lymphatic Leukaemias and Splenic Anaemia Infantum resemble Pernicious Anaemia in that the/

the blood may be gravely altered without any alteration in the time of clotting.

Two severe cases of purpura are quoted which shew no alteration in the coagulation time which could be ascribed to the disease.

Jaundice, Acute Rheumatism and Acute Nephritis shew a tendency to retardation.

Diabetes Mellitus shews a pronounced tendency to acceleration.

Pneumonia (Acute Lobar) may cause either lengthening or shortening of the coagulation time, and either condition may appear at different times in the course of the disease in the same individual.

Excessive venosity of the blood hastens clotting.

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