THE COAGULATION TIME OF THE BLOOD IN DISEASE.

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This subject is one to which, until recently, not much attention has been directed. It is true that in the days when bleeding was in general use, inferences as to the clinical condition were drawn from the time of formation, size, and form of the clot, but in the absence of an appreciation of how largely these factors vary under even slight differences in external conditions, the conclusions were not well founded, and do not appear to have been of much practical worth.

In 1875 Vierordt produced his method, and gave the first list of coagulation times in disease, but the results were variable and inconstant. Some years later Hayem, using another method, was led to the conclusion that, as a general rule, coagulability was diminished in acute febrile conditions. In 1893 Wright and others published the first of a series of papers on the subject, in which the time was shown to be shortened during convalescence from typhoid fever, and lengthened in cases of urticaria, chilblains, physiological albuminuria, and a certain type of headache. Milian, on the other hand, thought that no clinical method could give any reliable measure of the coagulability of the blood, since such large variations were introduced in the passage of the blood through the tissues. He was supported in this view by an elaborate and painstaking study made with his method by Jacquot, who also demonstrated the importance of several other factors which were apt to lead to error. Some of these sources of error were excluded in the method of Sabrazès used by Geneuil, but the results still showed considerable variability. Pratt, with Brodie and Russell's instrument, was unable to obtain any definite results, and concluded that the experimental errors were far larger than any pathological differences. With the same method, Murphey and Gould found no change from the normal in the coagulation time in catarrhal jaundice, and Hinman and Sladen, who besides this method also employed a modification of Milian's method, confirmed this, but found the time slightly longer in cholelithiasis and sometimes much longer in malignant jaundice. Morawitz and Bierich with another method arrived at the same result.
Turner, who examined a very large number of cases of epilepsy, found, on taking an average, that there was an increase in coagulability, and was thus unable to confirm the work of Besta and Perugia, who say that it is diminished. Douglass found the time normal in eclampsia. Solis-Cohen, in a general study of the effect of disease with Wright's method, found that his results were very inconstant, and with a modification of Milian's method was also unable to attain any certainty as to changes in coagulability in cases of tuberculosis. Robertson, Illman, and Duncan obtained coagulation times rather longer than normal in the febrile stage of the infectious diseases, including typhoid. Ciuffini states that the time is lengthened in purpura and in malignant disease of the liver, and shortened in typhoid. Denk and Hellmann, in some cases which gave a history of easily produced bruising and recurring epistaxis, found the coagulation time longer than normal.

There is thus no very general agreement among different observers, either as to actual conclusions, or even as to the value of the results as indications of the real coagulability of the blood. This must, I think, be attributed to the fact that the pathological variations are small, and the variations due to experimental error large. There is only one disease as to which all recent observers are agreed, i.e. haemophilia. Here the prolongation of coagulation is so great that it cannot be obscured by error, no matter what method is used.

It is obvious that, before entering into the study of the effect of disease, the coagulation time under normal conditions must first be observed, in order that any physiological variations due to age, food, sex, &c., may not be confounded with pathological changes.

This has already been done by means of another method, and I have been able to show that none of the factors mentioned above have any perceptible effect, so that the coagulation time is remarkably constant, and that there is no such thing as a normal daily variation, or that, at any rate, if it does exist, it is so slight as to escape detection even in a chart of the coagulation times at different periods of the day, based on over three hundred observations on different people. These points have recently been confirmed by Hartmann. The way is thus clear for an investigation of the present subject.

The method used was the modification of M'Gowan's method, which I have already described in detail; but there are two
points in connection with it which further experience has shown to be of importance. The first is, that the results cannot be relied on if the room temperature is above 20° C. (68° F.). On hot summer days the temperature in a ward often rises above 20° C. Coagulation times taken under such conditions were found to be shorter than normal, although the temperature within the apparatus was kept at 20° C. The higher temperature outside must therefore have accelerated the coagulation, although it only had an opportunity to act during the relatively short time during which the tubes were removed from the apparatus for examination. It follows that some degree of error must arise from variations of temperature between 15° C. and 20° C. A large part of the differences in the coagulation times of people in health was doubt due to this cause. At the same time it is a cause of error which, so far as I can see, it is impossible to avoid with this method, and it must be remembered that ward temperatures, except on exceptionally warm days, seldom fall or rise beyond the limits of 14° C. (57° F.) and 17° C. (63° F.).

Secondly, it is impossible to lay too much stress on the importance of adopting a method of obtaining the blood which in all cases will give an equally rapid flow of blood. The necessity for this is due to the fact that the amount of thrombokinase in the blood flowing from a wound is mainly determined by the length of time during which it has been in contact with the exposed tissues in the wound. The amount of thrombokinase is, of course, one of the most important factors which determine the coagulation time; so that if constancy is not attained in regard to this point, the results will be very variable and unreliable. This is only possible if in all cases the conditions are such that there is no perceptible interval between the making of the puncture and the appearance of the blood. The one must follow the other instantaneously. These conditions are often not naturally present. No matter how deep a puncture is made into fingers which are cold, the blood will not flow immediately. A constant circulatory condition must first be established by the immersion of the patient's hands in hot water, or by means of hot water bottles, &c. A slip-knot on a bandage is then placed loosely round the base of the fingers. Just before the puncture is made the knot is tightened, and the bandage is wound rapidly and fairly firmly round the finger as far as the distal end of the second phalanx. The blood is thus driven to the end of the finger, which becomes for the moment engorged with blood. The puncture is now made
on the extensor surface near the nail. Under these conditions a slight and quite painless prick with a Jenner's vaccinostyle is sufficient in all people except very small children to produce a large drop of blood. A tube which has been held ready is applied and the blood allowed to run in as quickly as possible, the other end is closed with sealing-wax and it is placed in the apparatus. Practice soon enables one to carry out this process in a constant and uniform manner. The employment of such means of obtaining a constant circulatory condition has been avoided by workers on this subject, because it has been several times authoritatively stated, although without any satisfactory proof, that it tends to squeeze out a greater quantity of thrombokinase from the tissues, and so leads to acceleration of the coagulation. But on examining the point experimentally, I found that the use of much greater pressure than is here described did not have such an effect, and that the only important factor in determining the amount of thrombokinase was the rate of outflow of blood from the wound.19

In the paper in which the method was described I gave the limits of error as lying between 8 min. 45 sec. and 11 min. 41 sec. These were the longest and shortest times found in fifty-one consecutive daily observations on one person.

It is obvious, however, that this is a very narrow basis on which to determine such a question, as it neglects errors possibly arising owing to difficulties in obtaining blood in exactly the same manner from different people. It was also necessary to find whether there were differences in the coagulation times of normal people, for if this were the case, it would not be possible to conclude that variations found in disease were due to disease alone. It is true that when working with a more accurate method I had not found any indication of the existence of such differences in normal coagulation times, but the number examined was not so large as to allow of a definite conclusion on this point.

For these reasons sixty-six normal people were examined. This number included some surgical patients with conditions such as varicose veins, hernia, &c., which did not interfere with their general health. With three exceptions, the times were within the provisional limits of error which I have given, and with nine exceptions they were between 9 min. and 10 min. 45 sec. These observations were, as a rule, not made in wards, but in rooms where the temperature was less constant, and the majority were carried out during the height of summer, when fluctuations of room temperature are most marked. I did not at the time fully
realise the importance of changes of temperature external to the apparatus, and probably, if attention had been paid to this point, the variations would have been less pronounced. I think that the possibility of these differences indicating true variations in the coagulation times of normal people may be laid aside, since they are entirely similar in extent to the differences found in consecutive observations on one person.

It was only possible to make further observations on four out of the nine cases which were less than 9 min. or more than 10 min. 45 sec., but in each of these the time was later found to be within the normal limits.

Therefore, although in view of the small number examined, one cannot definitely say that appreciable differences as regards the rate of coagulation in healthy people do not exist, it is justifiable to conclude that they must in any case be rare.

The average of these coagulation times was 9 min. 51 sec., so in judging the coagulation time in disease the rule is followed of calling it normal if it lies between 9 min. and 11 min. On the other hand, if a time shorter or longer than these is found, it is not described as abnormal and due to the pathological condition present, unless it has been confirmed in subsequent examinations.

**Cases in which the Coagulation Time was Normal.**

Out of one hundred and twelve cases, seventy-six, or about 70 per cent., were normal. This does not mean that only 70 per cent. of all hospital patients have a normal coagulation time, but rather that in 70 per cent. of those whose general condition was most profoundly altered by disease, there was nevertheless no abnormality in coagulation, for, as a general rule, cases of severe and advanced disease were selected for examination.

The following is a list of the conditions in which such normal times were found:—Diabetes (2 cases); myxoedema; exophthalmic goitre; parenchymatous degeneration of the thyroid; extensive burn; lead poisoning; carcinoma (6 cases); sarcoma; catarrhal jaundice (2 cases); cirrhosis of the liver; abscess of the liver; colitis (2 cases); cardiac disease with anasarca (2 cases); thrombosis (6 cases); chlorosis (3 cases); severe secondary anaemia; pernicious anaemia; tuberculous infections (12 cases); pneumococcal infections (3 cases); mixed pyogenic infections (12 cases); rheumatic cases (7); syphilis; malaria; pemphigus; urticaria (2 cases); locomotor ataxia; alcoholic neuritis.

In some of these normal cases there were very marked and
obvious chemical, physical, and morphological changes in the blood.

For instance, in one of the cases of diabetes, lipaemia was so pronounced as to cause a change in the colour of the skin, and to lead to a remarkable alteration in the appearance of the retina. The serum looked exactly like milk. In this patient repeated observations always showed a normal coagulation time, even during the course of diabetic coma. Again, no relation appeared to exist between the viscosity of the blood and its coagulation time. A rough indication of the viscosity was given by the rate of flow of the blood into the capillary tubes. Minor variations were of course lost sight of, but in cases where great differences existed, such as were found, for instance, in pernicious anaemia, the alteration in the rate of flow was very striking. Nevertheless, delayed, normal, and accelerated coagulation times were all observed in different cases where there was undoubtedly an increase or decrease of viscosity.¹

No evidence was obtained of any connection between leucocytosis and coagulability. Here, also, all varieties of coagulability were seen, both in cases with and without leucocytosis.

A few cases were met with who gave a history of frequent epistaxis, very easily produced bruising, &c., but the coagulation time was always normal. On the other hand, a slightly decreased coagulability was found in the case of a girl who had had previously two attacks of purpura, and had also suffered from haematuria, for which no cause could be found. Seven cases of thrombosis were examined. With one exception, the coagulation time was normal.

Finally, it may be noted here that none of the various drugs which were given appeared to have any effect on the coagulability of the blood. Determinations made for a considerable time before and after subcutaneous injections of normal saline solutions of antistreptococcal and of antipneumococcal sera (age not known) made it clear that these also were without effect.

**Cases in which Abnormal Coagulation Times were Found.**

The diseases from which these patients suffered were as follows:—Typhoid fever (10 cases); mixed pyogenic infections

¹ The belief that there is a connection between viscosity and coagulation is due, I think, to the fact that, unless the special precautions I have mentioned are taken, when the blood has an increased viscosity, it takes a longer time than usual to flow from a wound, and takes up more thrombokinase, and so gives a shorter time than normal blood, or blood in which the viscosity is low.
(9 cases); diseases of the liver (2 cases); diseases of the blood (3 cases); pneumococcal infections (3 cases); acute rheumatism (3 cases); diseases of the kidneys (4 cases); haemorrhages (4 cases).

Hereditary haemophilia is not included in this list, as I hope soon to publish the results of an investigation into the cause of the extraordinary delay in coagulation which occurs in this disease, and the coagulation times will there be given in full.

**Typhoid Fever.**

In all of the ten cases the coagulation time was shorter than normal during the acute stage.

The above chart shows the course of the coagulation curve in one of them.

In the other cases which were followed out the time became normal as convalescence set in, and there was no thrombosis, but in this case the time remained short, and there was thrombosis of the left internal saphena vein. It is, of course, impossible to say, unless a large number of cases were examined, whether there is any connection between this continuance of an increased coagulability of the blood and the occurrence of thrombosis, but the conjunction is suggestive, and would seem to be worthy of investigation.

In every case the coagulation time was below the normal during the acute stage. If this should be found to be constant in typhoid, it might turn out to be a point of some diagnostic importance, for it seems to be present before a positive Widal sign has developed. In several cases which were sent in as early typhoids, the coagulation time was found to be normal, and in all
of these cases the subsequent course of the illness, and the non-appearance of the Widal sign, showed the diagnosis to be mistaken.

The coagulation times in the other cases, taken as a rule every second or third day, were as follows:

Case 2.—8 min. 5 sec. 8 min. 0 sec. 8 min. 15 sec. 8 min. 52 sec. 10 min. 30 sec. 11 min. 25 sec.
Case 3.—7 min. 30 sec. 9 min. 10 sec. (Death.)
Case 4.—6 min. 35 sec. 8 min. 0 sec. 8 min. 50 sec. 8 min. 45 sec. 9 min. 15 sec. 9 min. 0 sec.
Case 5.—7 min. 20 sec. 7 min. 30 sec. 7 min. 50 sec. 8 min. 30 sec.
Case 6.—7 min. 50 sec. 8 min. 25 sec. 8 min. 30 sec. 8 min. 40 sec. (Death from haemorrhage.)
Case 7.—8 min. 10 sec. 7 min. 25 sec. 9 min. 15 sec. 8 min. 55 sec. 9 min. 45 sec. 8 min. 52 sec. 10 min. 30 sec. 10 min. 20 sec. 9 min. 52 sec.
Case 8.—7 min. 30 sec.
Case 9.—6 min. 10 sec. (Death from perforation.)
Case 10.—8 min. 25 sec.

Pneumococcal Infections.

The coagulation curve of the first case is given below, and it will be noted that the coagulation time remained steadily below the normal.

The patient was a middle-aged man who was admitted on the sixth day of an attack of double lobar pneumonia. The right knee-joint was full of pneumococcal pus. During the course of his illness several subcutaneous abscesses and a right-sided empyema developed, but in spite of all this his condition gradually began to improve, and he ultimately completely recovered, with the exception of some stiffness in his knee.

There are some grounds for supposing that the pneumococcus in some way induces or accelerates coagulation. Thus it is especially in pneumococcal pleurisy and peritonitis that large masses of fibrin are found in the exudate, and it is typically in pneumococcal pneumonia that the coagulation of the exudate in the alveoli leads to the firm consolidation of the lung. The above case of pneumococcal pyæmia supports this view. But when the disease is localised, no constant general effect on the coagulability of the blood is recognisable. In two cases of
pneumococcal empyema, the time was normal. Of three cases of lobar pneumonia, one was normal, in the other the coagulation curve 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 recognisable pulmonary consolidation, the coagulation time was at first above normal, and afterwards fell below it.

**STREPTOCOCCAL AND STAPHYLOCOCCAL INFECTIONS.**

In twelve cases of severe localised septic infection the time was normal, whereas in the three cases of septicaemia which came under observation, coagulation was delayed.

The first case, whose chart is given above, was one of pyæmia, following on puerperal infection. Staphylococci and streptococci were found in the pus removed from freshly-opened abscesses.

The second case was found post-mortem to be one of ulcerative endocarditis. Streptococci in large numbers were present in the
urine. Daily observations during the six days he lived after admission showed a coagulation which remained steadily at, or slightly above, 13 minutes. The third case was admitted in a moribund condition. There was a pulmonary abscess, and pus was present also in one of the wrist joints. Times of 14 min. 20 sec. and 13 min. 35 sec. were found. It was in connection with the first two of these cases that a striking phenomenon was observed, which was due, I think, to an agglutination of the red blood corpuscles. After having been in the glass capillary tubes for only a few minutes, the blood had already begun to separate into two layers, the upper of plasma and the lower of red blood corpuscles. After eight minutes or so the length of the column of plasma was often half that of the total length of the original column of blood. With the naked eye the corpuscles could sometimes be seen to be collected into clumps, and the separation of the plasma appeared to be due to this aggregation of the corpuscles into bodies which quickly sank under the influence of gravity. It was only in these two cases that it was so marked, but the separation of \( \frac{1}{16} \) to \( \frac{1}{4} \) of an inch of plasma occurred in all cases of septic infection in which the symptoms of disturbance of the general condition were at all prominent. In such cases it gradually disappeared as the general health improved. It was present in moderate degree in acute rheumatism, very slightly in pneumococcal infections. The only bacterial disease in which it was quite absent was typhoid. Of non-bacterial diseases, it was well marked in a case of uremia, and slightly present in three cases of acute nephritis, and in one case of cirrhosis of the liver. This agglutination of the red blood corpuscles is of interest in connection with some recent experimental results. Pearce and Winne\(^2\) found that they could produce agglutination of the corpuscles of animals by the injection into the blood-stream of the filtered autolysed products of several varieties of organisms. Boxmeyer\(^3\) produced small areas of necrosis in the liver after injecting the hog-cholera bacillus. He showed that this necrosis was associated with "hyaline thrombi" composed of agglutinated corpuscles. Finally, Flexner\(^4\) has come to the conclusion that many poisons which have a destructive effect on the red blood corpuscles are productive also of their agglutination, and that a specific variety of thrombosis by means of masses of agglutinated corpuscles may result. He believes that this may be a cause of thrombosis in disease.
RHEUMATIC CASES.

In severe cases of rheumatic fever the coagulation time is slightly delayed. Times of 11 min. 15 sec., 11 min. 10 sec., and 11 min. 45 sec. were found in three cases during the acute stage. One case which passed in turn through endocarditis, pericarditis, and chorea, showed a curve which kept fairly constantly just above the normal limits. A similar chart was given by a case of chorea.

DISEASES OF THE LIVER.

It is especially in advanced disease of the liver that abnormal coagulation times might be expected to occur. In 1904 Doyen and Kareff found that the blood became incoagulable when the liver was removed, and this result was shortly afterwards confirmed by Nolf. Since then Doyen and others have shown that the loss of coagulability can be produced by the injection into the portal system of substances such as chloroform and phosphorus, which have a specially deleterious action on the liver.

I have examined five cases of very pronounced liver disease, one in which a large abscess was found, two of cancer, and two of cirrhosis. All these cases, except one, died while observations were being made, or shortly afterwards, and post-mortem examination revealed very far advanced disorganisation of the liver. Nevertheless, repeated examinations in three of these cases gave normal times. Of the other two, in one there was perhaps a very slight prolongation of coagulation, as the times were always over 10 minutes, but they only twice went slightly above the normal limits. The other case in which the coagulation was not always normal was one of cancer. The primary disease was in the pancreas, but the liver was studded with large secondary deposits. There was very profound jaundice, and towards the end subcutaneous haemorrhages appeared, and there was haematemesis. It was therefore all the more surprising to find that the coagulation time, which before this had been normal, sank below the normal limits. The haemorrhages, therefore, obviously occurred in spite of, and not because of, changes in the coagulability of the blood.

At the same time, if a larger number of cases had been examined, some would no doubt have been found to show delayed coagulation. It is very probable that such a condition exists in cases of acute yellow atrophy of the liver, and in chloroform and phosphorus poisoning. At this point the effect of acidosis may be
referred to. Mellonby has demonstrated how great a retarding influence on coagulation very minute traces of acid may exert, and one might therefore look for an abnormally long coagulation time in conditions where acidosis is present. The patient with diabetes who died with diabetic coma had throughout a normal time, but large quantities of sodium bicarbonate were given by mouth and subcutaneously, and this may possibly have prevented the development of an irregularity in this respect. A case of cyclical vomiting had a well-marked prolongation of coagulation, but this observation is not of much value, as it was not definitely shown that a condition of acidosis was really present in this particular case. No other examples of the condition came under observation.

Nephritis.

Only five cases of nephritis were examined. Three of them were acute, and all had abnormal times. One subacute case was normal, and one case of fibroid degeneration, the result of lead poisoning, had a normal time until uraemia set in.

Two of the acute cases were interesting clinically because of the unusual severity of the nephritis. The first was a man over middle age, who was admitted in a semi-conscious condition, with a history of not having passed urine for twenty-four hours. Next day his son came with the same complaint, except that in his case it had lasted for forty-eight hours. They were not living together, and had not been together recently—in fact they neither knew that the other was ill until they met in the ward, so that there were difficulties in the way of the otherwise very natural assumption that the same cause had produced both illnesses. Another interesting point was that they belonged to a haemophilic stock. A first cousin of the father, a haemophilic, was a patient in the ward at the time, suffering from prolonged and serious haemorrhage following a tooth extraction.

The father had complete anuria for twenty-four hours after admission, and the son for forty-eight hours. Both were in the same stuporose and semi-conscious condition. The father recovered first, and the only notable thing was the long persistence of a trace of blood in the urine. He never had any oedema, and recovered apparently completely.

The secretion of urine in the son set in very gradually, and he developed moderate oedema, which was very persistent. He was discharged after three months with a trace of albumen in the urine.
Both were bled on admission. The specific gravity of the serum of the father was 1017, and that of the son, 1022. It was surprising to find in cases which, at the commencement at least, were so similar that the coagulation curves were entirely different.

Both are shown on the chart below. The father had an abnormally short coagulation time, which became normal as improvement set in. The son had on the whole a prolonged time. The observations in his case were interrupted before recovery had advanced very far.

The third case of acute nephritis had a slightly delayed coagulation, and gave a curve very similar to this one.

One of the greatest prolongations of the coagulation time was found in the only case of uremia which was observed. The patient had been admitted before for lead poisoning, and numerous determinations then had shown the time to be normal. A few weeks later he was again admitted, with the history that he had recently had a “fit.” During the short time he lived after admission he was unconscious, and had several convulsions. There was epistaxis, and bleeding from the gums. The coagulation time was 16 min. 50 sec. Post-mortem, the kidneys were found to be very small, and in an advanced condition of fibroid degeneration.

**Diseases of the Blood.**

In one case of severe chlorosis the time was at first slightly above the normal limit, but as improvement set in the times became normal. In the other cases normal times were found.

A case of myelogenous leukaemia had a coagulation time of 5 min. 25 sec., but only one observation was possible, as the patient died on the day after admission.

Two cases of pernicious anaemia were examined, both of which on admission had less than 1,000,000 red blood corpuscles.
In one the time was normal, and in the other it was persistently short, in spite of a very great improvement in the blood condition (see Chart 5).

Hæmorrhages.

The fact that after large hæmorrhages the blood coagulates more quickly than before, has been known since the time of Hewson, and in recent times has been confirmed by Arloing, Arthus, and Milian. The cause is unknown. Von den Velden has indeed attempted to explain it, on the assumption that the fluids from the tissues which enter the vessels to replace the lost blood contain thrombokinase, but apart altogether from the difficulty of accepting this, in view of the well-established facts on which the present theories of coagulation are based, his argument is anything but convincing. In animals it has been shown that very large quantities must be lost before there is any appreciable effect, and the one or two observations which I had an opportunity of making, fully bear this out.

The removal of a pint of blood from a vein for therapeutic purposes was in three cases entirely without influence on the coagulation time. But there were two cases in which large and dangerous hæmorrhages occurred, and in these an acceleration of coagulation was seen. The first case was one of hæmorrhage from a gastric ulcer, which very nearly proved fatal. The blood coagulated in 5 min. 30 sec., five days later the time was 8 min., and eleven days afterwards it was 8 min. 30 sec. Nearly a month after the hæmorrhage the time was still below the normal limit.

The other case was one of very severe hæmorrhage following an operation for the removal of tonsils and adenoids. The coagulation time was 7 min. 7 sec.

Two other cases appear to show that long continued and
constant loss of blood may produce the same effect. A case of cancer of the bladder, who had had haematuria for three months, and who was very anaemic, gave coagulation times of about 8 min., and in the case of a man who had suffered from dysentery for years, and who had very frequent blood-stained motions, a coagulation curve was found which remained constantly well below the normal.

Conclusions.

The number of cases which have been examined is too small to permit of any wide conclusions being drawn as to the effect of disease on coagulation, but one striking fact is at any rate clear, namely, that in spite of extreme morphological, physical, and chemical alterations in the blood, the coagulation time may nevertheless remain normal. As regards the cause of those abnormalities of coagulation which were observed in non-bacterial diseases, nothing can be said. The first step towards such knowledge would have to be the establishment of the constancy of these changes, or if they were inconstant, the search for the conditions under which they appeared.

But in bacterial diseases it may be concluded that no marked effect is produced unless the organisms are actually present in the blood. When this occurs, the typhoid bacillus and the pneumococcus hasten coagulation, while streptococci and staphylococci delay it.

Auto-agglutination of the red blood corpuscles was seen in varying degree in all acute bacterial infections, except typhoid. It was most marked in cases of staphylococcal and streptococcal septicaemia and pyaemia.

Moderate loss of blood has no effect on coagulability, but very large haemorrhages are followed by an acceleration of coagulation.

I am indebted to the staffs of the Royal Infirmaries of Gloucester and Bristol for the opportunity of making these observations.

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