The figure shows the character of the jugular pulse associated with the bigeminal rhythm in the radial pulse. The appended diagram explains the nature of the events. *As* signifies auricular systoles; *Vs*, ventricular systoles; and *A-V*, the conduction between auricle and ventricle.

for me. He confirmed the existence of this peculiarity, and kindly indicated the diagram appended to the tracing, which shows very clearly the nature of the events. Mackenzie divides extra-systoles into three types—auricular, ventricular, and nodal—the ventricular including the rare form of interpolated extra-systole. He has suggested that the probable origin of the extra-stimulus lies somewhere in the remains of the primitive cardiac tube, in auricle, ventricular bundle, or auriculo-ventricular node. In the nodal extra-systole the auricles and ventricles contract together, or nearly so, and usually prematurely. It may, however, happen that the combined wave appears at the normal period of auricular contraction, and it may then be difficult to determine whether the extra-systole is of nodal or ventricular origin. In the present instance, from the regularity and persistence of the bigeminal character, and the fact that the auricular wave is always synchronous with the ventricular, it is probable that the extra-systoles are of nodal origin. Although there is no time record in the tracing, it may be taken as certain that the *a-c* interval is increased. In an earlier tracing, in which the combined wave was nearer the middle point, the *a-c* interval was less. The increase of the *a-c* interval is no doubt due to the incomplete restoration of conductivity as a result of the short period between the extra-systole and the following normal auricular beat.

I am unable to explain this peculiar rhythm. It is evident that alternate auricular contractions failed to appear at the normal period, but whether the sinus rhythm remained regular or not it is impossible to say. On the day of death the pulse became very feeble and quick, and the patient was too ill to allow of a tracing being taken. It is consequently uncertain whether the heart in the final stage became continuously irregular (nodal rhythm).

THE INEFFECTIVENESS OF CALCIUM SALTS AND OF CITRIC ACID AS USED TO MODIFY THE COAGULATION TIME OF THE BLOOD FOR THERAPEUTIC PURPOSES.

WITH A DESCRIPTION OF A MODIFICATION OF MCGOWAN'S METHOD OF ESTIMATING THE COAGULATION TIME OF THE BLOOD.

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By means of a more accurate method than Sir A. E. Wright's, I have shown that he was mistaken in his statement that soluble calcium salts and citric acid are capable of altering the coagulation time of the blood of people in health. The fact that this initial experimental result of his cannot be confirmed is sufficient in itself to throw great doubt on his later work in this connexion. Since 1893 he has published a number of papers on the use of calcium in the treatment of haemophilia, and of haemorrhage in many other conditions, and also in what he terms "serous haemorrhages"—a group of conditions said to be characterized by an abnormally long coagulation time, which could be cured when the coagulation time was reduced by the administration of soluble calcium salts. Further, citric acid was recommended as a prophylactic against thrombosis in typhoid fever. Although clinical

reports as to the value of this method of treatment have been conflicting, the general idea that the coagulation time in disease can be shortened or lengthened at will, by giving the proper dose of calcium lactate or citric acid, has never been effectively disputed, and has been very widely accepted and acted upon.

It was not possible to test the accuracy of this belief 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. Another method was therefore necessary, and the modification of McGowan's method, which is described below, is one which is applicable clinically, and which yields results which can be relied upon within certain limits.

In reviewing the different methods I found that the means adopted by Sabrazès and McGowan of determining the presence of a certain definite amount of coagulation is more accurate than those employed in the other methods, although it is not possible to obtain constant or comparable results with either of their methods, because in the case of the former the means of maintaining a constant temperature is not sufficient, and in the latter is wanting altogether.

McGowan believed that for clinical purposes it was superfluous to have an apparatus to maintain his glass tubes at a constant temperature, since variations of temperature between 15° C. and 20° C. did not appreciably affect the coagulation time.

This, however, as I have already shown, is very far from being the case. With my method the following coagulation times were found to correspond with the temperatures between 15.5° C. and 20.5° C.:

15.5° C., 11 min. 46 sec.;	18.5° C., 7 min. 34 sec.;
16.5° C., 10 min. 10 sec.;	19.5° C., 6 min. 2 sec.;
17.5° C., 8 min. 7 sec.;	20.5° C., 5 min. 22 sec.

The necessity of the maintenance of a constant temperature is, therefore, fully apparent. The variable results which are obtained by these and other coagulometers are said by those who use them to indicate true variations in the coagulation time of the blood, but the coagulation time is found to be constant when a more accurate method is used, and those apparent variations are really due to experimental errors, of which the most important is a deficiency in, or a total neglect of, the maintenance of a constant temperature for all observations.

Description of the Method.

McGowan's method consists in partially filling a capillary glass tube, 6 in. long and 1.5 mm. in diameter, with blood under certain precautions, sealing up one end, and at intervals of a minute breaking off a small part until a fine fibrin thread is seen on slowly drawing the fractured ends apart. The coagulation time is the time elapsing between the filling of the tube and the first appearance of fibrin.

Undoubtedly the simplest and most accurate way to keep the tubes always at the same temperature would be to use a gas regulator. But in the wards of most hospitals there is no gas, and it is absolutely necessary that the whole procedure should be carried out by the bedside of the patient. An electrical thermostat would be sufficient, but is expensive, so it was better to dispense with any mechanical regulator, and to make use of the following device.*

When a closed cylindrical vessel is placed in the centre of a similar but considerably larger vessel, and both are filled with

* The apparatus can be obtained from Paul Altman, scientific instrument maker, 56, Louisen Strasse, Berlin, for 36 marks.

water at a temperature of 20° C., a fall in the temperature of the water in the outer cylinder shows itself before any change in the temperature of the inner cylinder can be seen. If, whenever this is observed, a little hot water be added to the outer cylinder until the water is again at 20° C., the temperature of the water in the inner cylinder may, with a little care, be kept practically constant for any time that may be desired.

When the McGowan's tubes are introduced into the inner vessel their environment has thus a constant temperature of 20° C. This was chosen as the temperature at which all observations were conducted because it is a little above the ordinary ward temperature, which generally varies from 15° C. to 20° C. Usually the ward temperature is only slightly below the temperature of the water in the apparatus, so that it is only necessary to add a little hot water every half hour or so.

The outer cylinder is made of metal and is covered with asbestos. It is 9 in. high and has a diameter of 6½ in. Piercing the lid there is on one side a tube leading down almost to the floor, so that where hot water is introduced it may enter below and gradually rise upwards. On the other side there is a thermometer, enclosed for protection in a brass tube, which is open below. The mercurial bulb lies in the water, about half-way between the floor and the lid, while the scale, which reads in half degrees Centigrade, is outside the apparatus. In the centre of the lid there is a circular opening into which the part designed for the reception of the McGowan's tubes is fitted.

The inner cylinder is of glass, 5 in. long and 1½ in. in diameter, and is so placed that it is nearly equally distant from the lid, floor, and sides of the outer cylinder. It is open at the end next the hole in the lid of the outer cylinder. Through these openings both cylinders can be filled with water at 20° C., the inner to the brim, the outer not quite to so high a level, so that when water has to be added it may not overflow into the place where McGowan's tubes are placed. These cannot be put directly into the water of the inner cylinder, because when a part of a tube is broken off to test for the presence or absence of fibrin the water would come into direct contact with the blood when it was replaced. This is avoided by having fine brass tubes in the inner cylinder into which they can be put.

These open round the circumference of a brass plate which closes the inner cylinder. Another plate closes the opening in the lid of the larger cylinder, and through the centre of both plates runs a thermometer protected by a closed brass tube, the bulb lying in the centre of the inner cylinder, so that the reading indicates the temperature of the air in the tubes in which the McGowan's tubes lie.

Six small holes, 2 mm. in diameter, in the outer plate correspond in position to the openings of the six tubes in the plate which closes the inner cylinder. Small funnels are placed over these openings to facilitate the introduction of the glass tubes.

In obtaining the blood, a fairly large drop should follow the puncture immediately. This does not occur if the patient's hands are cold, and so it is often necessary to warm them first with a hot-water bottle. Then, if a slip-knot is tightened round the base of the thumb, an entirely painless puncture on the extensor surface near the nail will immediately produce a sufficient quantity of blood.

The best thing to use for pricking the finger is, I think, Jenner's vaccinostyles. One of McGowan's tubes, 8 in. instead of 6 in. long, is then taken and introduced into the drop of blood until about 4 in. have been filled. The other end is then closed with sealing-wax and it is put into the apparatus. The time at which the blood appears is noted. This is repeated with two more tubes, using each time a new pricker and making a fresh puncture.

It is essential that there should be no contact with the blood from previous punctures. The apparatus contains receptacles for six tubes, so it is possible to fill and introduce three others from another patient before it is time to examine the first tubes for fibrin.

After eight minutes the first tube is taken out. It is held by the left hand in forceps covered with rubber in order to avoid contact with the fingers which would considerably raise the temperature of the blood. A slight scratch is made with a glass file about ½ in. from the end. This part is then carefully broken off by the finger and thumb of the right hand, and the two fractured ends drawn slowly apart holding them up against the light. If a fine filament of fibrin is seen, it is not to be taken as indicating coagulation, but only as showing that the end-point is near.

The reason for this is that the blood at the end of the tube is the part of the blood which last left the wound. This coagulates sooner than the blood which first appears, and as the amount of this acceleration is inconstant, it is better to disregard it, and to take as the end-point the appearance of a thread of fibrin only in the last inch of the blood. The tube is, therefore, broken a little higher up, and if, as often happens, no fibrin is seen, it is returned to the apparatus and the second tube is taken. The differences between the times when the three drops of blood appeared and the time when a fibrin thread was seen in the last part of the tubes, gives three coagulation times, and the average of these is taken as representing the approximate coagulation time of the blood in the case in question. This tends to reduce the error arising from the deficiency in delicacy of the end-point.

Of course a certain amount of error arises from the fact that the tube must be removed from the apparatus into a medium of inconstant temperature in order to test for the presence of coagulation, but as this time is short, and as there is not a great difference between the ward temperature and 20° C., it is not of great importance.

Altogether, I am convinced that, so far, this is the only method, clinically applicable, which yields results upon which reliance may safely be placed.

The limits of experimental error for this modification of McGowan's method were determined in the following way. I had already found, in observations with my method extending over several months, that my own coagulation time was constant from day to day. It was, therefore, fair to assume that any irregular

variations found in making daily determinations with this method were due to experimental error.

The average of three readings at 20° C. was taken as representing the coagulation time of my blood, and this was repeated daily for fifty days. The average of these fifty observations was 9 min. 50 sec., and the average

A. The complete apparatus with the McGowan's tubes in position.

B. The separate parts. I, The lid of the outer cylinder. 1, The thermometer enclosed in a tube open at its lower end. 2, The funnel and tube for the introduction of warm water into the outer cylinder. 3, The opening through which the part designed for the reception of the McGowan's tubes fits. II, The two cylinders—I, the outer; 2, the inner. III, 4 McGowan's tube charged with blood. The blood should not reach quite to the other end of the tube. IV, The part in which the McGowan's tubes are placed. 1, The thermometer in a tube closed at its lower end. 2, One of the fine brass tubes into which the McGowan's tube (3) runs. 4, The plate which closes the opening in the lid of the outer cylinder. 5, The plate which closes the inner cylinder.

variation from this mean was 34 sec.; while the possible variation is given by the longest and shortest times—that is, 11 min. 41 sec. and 8 min. 45 sec.; that is, 1 min. 51 sec. above and 1 min. 5 sec. below the average.

In a large number and variety of pathological conditions only a very small percentage of cases were met with in which the coagulation time overstepped these limits, and these were patients who were very seriously ill. In one or two of these daily observations disclosed variations so progressive and considerable that there appeared to be good reason to suspect a real change in the coagulation time of the blood, but further observations will be necessary to confirm this. In all the other cases daily readings gave slight irregular variations within the limits of experimental error, indicating that in all probability the coagulation time would have been found to be constant if a perfectly accurate method had been used.

The approximate accuracy of the method having been thus determined, the following plan was adopted in order to test the value of calcium lactate and citric acid. A period of about eighteen days was divided into three periods of six days, and during the whole time the coagulation time was taken every other day. During the first period neither calcium nor citric acid was taken, while in the second period calcium was given, and in the third citric acid, or vice versa. This was carried out in 8 cases, namely:

Two of thrombosis.

Advanced arterio-sclerosis with a failing heart and general oedema.

Marked jaundice probably due to cancer of the liver.

Tuberculous peritonitis.

Lobar pneumonia.

Lead poisoning with chronic interstitial nephritis.

Dysentery.

Each coagulation time given represents the average of three observations. The calcium was given as calcium lactate dissolved in water. The total average of the coagulation times taken under these three conditions shows that neither the calcium nor the citric acid had any effect:

	Total Average Coagulation Time.
Period without calcium or citric acid ...	9 min. 39 sec.
Period in which calcium was taken ...	9 min. 31 sec.
Period in which citric acid was taken ...	9 min. 34 sec.

The following are the details by which it can be seen that in none of these cases was there at any time any indication of a change in the coagulation time during the administration of calcium or citric acid:

C. G., aged 59. Thrombosis of left internal saphenous vein.

1. Period without calcium lactate or citric acid:
First day, 9 min. 55 sec. Third day, 11 min. 20 sec. Fifth day, 10 min. 50 sec.
2. Period during which citric acid 30 grains was given 4-hourly:
Sixth day, 10 min. 0 sec. Eighth day, 10 min. 20 sec. Tenth day, 9 min. 35 sec.
3. Period during which calcium lactate 60 grains was given 4-hourly:
Twelfth day, 9 min. 40 sec. Fourteenth day, 10 min. 10 sec. Sixteenth day, 9 min. 10 sec.

J. C., aged 61. Thrombosis in veins of right lower extremity. Cause unknown.

1. Period without calcium lactate or citric acid:
First day, 10 min. 50 sec. Second day, 9 min. 40 sec.
2. Period during which citric acid 30 grains was given 4-hourly:
Third day, 9 min. 20 sec. Fifth day, 9 min. 40 sec. Seventh day, 9 min. 0 sec.
3. Period during which calcium lactate 30 grains was given 4-hourly:
Ninth day, 9 min. 20 sec. Eleventh day, 9 min. 55 sec. Thirteenth day, 10 min. 0 sec.

J. L., aged 48. General arterio-sclerosis, aortic and mitral incompetence, general anasarca.

1. Period without calcium lactate or citric acid:
First day, 8 min. 30 sec. Second day, 8 min. 15 sec.
2. Period during which citric acid 30 grains was given 4-hourly:
Third day, 9 min. 30 sec. Fifth day, 9 min. 40 sec. Seventh day, 9 min. 15 sec.
3. Period during which calcium lactate 30 grains was given 4-hourly:
Ninth day, 10 min. 15 sec. Eleventh day, 8 min. 50 sec. Thirteenth day, 8 min. 20 sec.

J. H., aged 65. Deeply jaundiced. Symptoms suggested cancer of the liver.

1. Period without calcium lactate or citric acid:
First day, 8 min. 50 sec. Third day, 9 min. 40 sec. Fifth day, 10 min. 10 sec. Seventh day, 9 min. 35 sec.
2. Period during which calcium lactate 15 grains was given 4-hourly:
Eighth day, 9 min. 40 sec. Tenth day, 9 min. 30 sec. Twelfth day, 8 min. 50 sec.
3. Period during which citric acid 30 grains was given 4-hourly:
Fourteenth day, 9 min. 10 sec. Sixteenth day, 10 min. 50 sec. Eighteenth day, 9 min. 30 sec.

N. I. T., aged 25. Tuberculous peritonitis.

1. Period without calcium or citric acid:
First day, 10 min. 10 sec. Third day, 10 min. 35 sec. Fifth day, 10 min. 0 sec.
2. Period during which calcium lactate 30 grains was given 4-hourly:
Seventh day, 9 min. 15 sec. Ninth day, 9 min. 55 sec. Eleventh day, 10 min. 10 sec.
3. Period during which citric acid 30 grains was given 4-hourly:
Thirteenth day, 10 min. 45 sec. Fifteenth day, 10 min. 10 sec. Seventeenth day, 10 min. 30 sec.

F. W., aged 17. Lobar pneumonia. Crisis on second day.

1. Period without calcium lactate or citric acid:
First day, 9 min. 30 sec. Second day, 9 min. 50 sec. Third day, 9 min. 10 sec.
2. Period during which citric acid 30 grains was given 4-hourly:
Fifth day, 9 min. 10 sec. Seventh day, 9 min. 40 sec. Ninth day, 9 min. 15 sec.
3. Period during which calcium lactate 30 grains was given 4-hourly:
Eleventh day, 9 min. 30 sec. Thirteenth day, 9 min. 25 sec. Fifteenth day, 10 min. 30 sec.

G. O., aged 37. General arterio-sclerosis and chronic interstitial nephritis, the result of lead poisoning. Severe headaches, vomiting, and colic for the first seven days.

1. Period without calcium or citric acid:
First day, 10 min. 10 sec. Third day, 9 min. 25 sec. Fifth day, 11 min. 10 sec.
2. Period during which calcium lactate 30 grains was given 4-hourly:
Seventh day, 10 min. 20 sec. Ninth day, 11 min. 35 sec. Eleventh day, 10 min. 45 sec.
3. Period during which citric acid 60 grains was given 4-hourly:
Thirteenth day, 9 min. 55 sec. Fifteenth day, 10 min. 25 sec. Seventeenth day, 10 min. 0 sec.

W. W., aged 35. Dysentery.

1. Period without calcium or citric acid:
First day, 7 min. 45 sec. Third day, 8 min. 15 sec. Fifth day, 8 min. 20 sec.
2. Period during which calcium lactate 15 grains was given 4-hourly:
Seventh day, 8 min. 35 sec. Ninth day, 7 min. 35 sec. Eleventh day, 7 min. 20 sec. Thirteenth day, 8 min. 15 sec.
3. Period during which citric acid 30 grains was given 4-hourly:
Fifteenth day, 8 min. 15 sec. Seventeenth day, 8 min. 45 sec. Nineteenth day, 8 min. 45 sec.

Some observations were made on patients with typhoid fever, but the results are not comparable with those given above, because a less accurate and constant technique and one which tended to give shorter times was then used. So far as they go, however, they fail to show that any change was produced on the coagulation time, for in seven patients who were taking citric acid, the average of 27 estimations was 7 min. 57 sec., while the average of 30 estimations in two patients who were taking calcium was 8 min. 43 sec.

A well-marked case of haemophilia with a characteristic family and personal history was admitted for haemorrhage of four days' duration following on the extraction of a tooth. On the second day after admission, the bleeding still continuing, the coagulation time was 12 min. 35 sec. at 7.30 p.m. At 7.45 p.m. 60 grains of calcium lactate in solution were taken, but two and a quarter hours later the coagulation time was 14 min. 30 sec., and no effect had been produced on the bleeding, which continued for four days more, and ultimately appeared to be stopped by the application of a pledget of cotton-wool soaked in the blood of another person.

A case of urticaria was found to have a coagulation time of 10 min. 15 sec. Calcium lactate was given 4-hourly, and on the two following days the times were 10 min. and 10 min. 15 sec. During these two days the urticaria gradually disappeared, but this was not because the coagulation time had been shortened by the calcium.

These results are, no doubt, few in number, and since no cases of chilblains or of physiological albuminuria are included, do not cover all the territory which Sir A. E. Wright claims for calcium and citric acid, but as in no single instance was any effect whatsoever found to follow their use I think that the general conclusion that they are unable to effect any change in the coagulation time of the blood is fully justified.

As I have shown elsewhere, the reason for this is that the increase or decrease in the content of the blood in ionisable calcium which follows their administration is far smaller than that amount of change which is necessary to produce an appreciable effect on the coagulation time.

I have to thank Dr. A. K. Gordon, of Monsall Fever Hospital, and Dr. Oscar Clark and Dr. Grosvenor, of Gloucester General Infirmary, for having kindly allowed me to make these observations on patients under their charge.

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THE late Mr. James Fletcher, of Nottingham, whose will has now been proved, made a bequest of £500 to the General Hospital in that city.