

Researches in clinical physiology / by Sir Almroth E. Wright.

Contributors

Wright, Almroth, 1861-1947.

Publication/Creation

London : William Heinemann, 1943.

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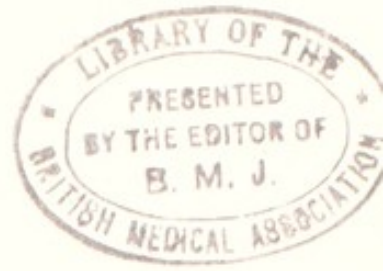
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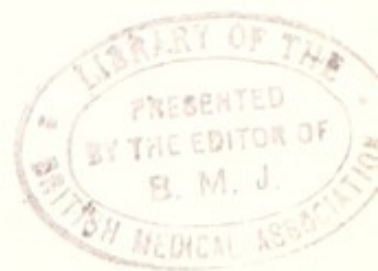




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RESEARCHES IN CLINICAL PHYSIOLOGY

LIST OF THE AUTHOR'S WORKS

- A SHORT TREATISE ON ANTI-TYPHOID INOCULATION. 1904. Constable, London.
- PRINCIPLES OF MICROSCOPY. 1906. Constable, London.
- STUDIES ON IMMUNISATION. 1909. Constable, London.
- TECHNIQUE OF THE TEAT AND CAPILLARY GLASS TUBE.
First Edition. 1912. Constable, London.
Second Edition. (With Leonard Colebrook, M.B.) 1921. Constable, London.
- ON PROPHYLACTIC INOCULATION AND PHARMACO-THERAPY APPLIED TO PNEUMONIA IN THE SOUTH AFRICAN NATIVE. 1914. Constable, London.
- // THE UNEXPURGATED CASE AGAINST WOMAN'S SUFFRAGE. 1913. Constable, London.
- PROLEGOMENA TO THE LOGIC WHICH SEARCHES FOR TRUTH. 1941. William Heinemann, London.

List of this Series of Collected Researches from The Inoculation Department, St. Mary's Hospital, London, W. 2

VOL. I. PATHOLOGY AND TREATMENT OF WAR WOUNDS.

VOL. II. RESEARCHES IN CLINICAL PHYSIOLOGY.

VOL. III. STUDIES ON IMMUNISATION. First Series. (*In the press.*) (Reprint of Papers published in collected form by Constable, London, 1909.)

VOL. IV. STUDIES ON IMMUNISATION. Second Series. (*In the Press.*) (With an Appendix on the Chemotherapy of Optochin and Sanocrysin.)

VOL. V. TECHNIQUE OF THE TEAT AND CAPILLARY GLASS TUBE. Third Edition. (*In preparation.*)

RESEARCHES IN CLINICAL PHYSIOLOGY



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ACKNOWLEDGMENTS

The Author's grateful acknowledgments for permission to reprint the papers which are collected in this volume are made here to the following :

The Editor of the *Lancet*.

The Editor, *British Medical Journal*.

The Controller of H.M. Stationery Office and the Director General Army Medical Services.

The Editorial Board, *Journal of Physiology*.

The Publishers, Clifford Albutt's *System of Medicine*.

The Royal Academy of Medicine in Ireland.

The Editor, *British Journal of Dermatology*.

The President and Council of the Royal Society.



ON THE METHOD OF MAKING A SUGARLESS MILK FOR DIABETICS

(Excerpt from a Paper entitled 'Some points connected with the Pathology and Treatment of Diabetes', 'British Medical Journal', 1891)

When we come to consider the very severe restrictions that have to be imposed on the diabetic in the matter of diet, we cannot help feeling some amount of regret in having to proscribe the valuable proteid and fat of milk because of the presence of the milk sugar. By putting together a few facts that have long been known about milk, I have been able to arrive at a solution of the problem. Instead of getting rid of the sugar from the proteid and fat of the milk, which I failed in doing, it was evidently possible to perform the reverse process, and to separate the proteid and fat of the milk from the sugar; in a word, to precipitate the casein and fat of the milk, to filter them off, allowing all the sugar to run away from them, and then to redissolve the washed precipitate in a solution of the normal salts of milk, to which a little alkali had been added. The process is a very simple one. Take a quantity of milk, dilute it with three or four volumes of water, to which 1 to 2¹ parts per 1,000 of acetic acid have been added. This produces a precipitation of all the casein and fat of the milk. The precipitate is allowed to settle for a few minutes, and then strained through a piece of calico. The precipitate is then washed, and redissolved in a 1 per cent. solution of the following mixture of salts: ²

Sodium chloride - - - 11·5 parts	Magnesium citrate - - - 4·4 parts
Potassium chloride - - - 9·9 „	Dicalcium phosphate - - - 8·0 „
Monopotassium phosphate - 13·8 „	Tricalcium phosphate - - - 9·6 „
Diopotassium phosphate - 10·0 „	Calcium citrate - - - 25·5 „
Citrate of potassium - - - 5·9 „	Calcium oxide - - - 5·5 „
Dimagnesium phosphate - 4·0 „	Sodium carbonate - - - 40·0 „

A trace of saccharin may be used to sweeten the milk, and the salt solution is best used at about blood temperature, and the casein and fat precipitate is to be mixed up with it, as in making cocoa, to the desired thickness. We obtain by this easy method a very fairly palatable and entirely sugarless milk. The precipitated casein and fat can also be dried without undergoing alteration, and then used for the preparation of the milk.

¹ 3jss to 3iij of acid acet, fort of the B.P. to Oj of water.

² This mixture of salts, which is based upon Söldner's analyses, is, no doubt, not the best that could be obtained, but it will do tolerably well. Some amount of insoluble salts sinks to the bottom of the vessel. The salt solution may simply be poured off from this.

ON THE CONDITIONS WHICH DETERMINE THE DISTRIBUTION OF THE COAGULATION FOLLOWING THE INTRAVASCULAR INJECTION OF A SOLUTION OF WOOLDRIDGE'S TISSUE-FIBRINOGEN¹

(Reprinted from the 'Journal of Physiology', vol. xii, No. 2, 1891)

Preliminary Communication.

The injection of a solution of *Wooldridge's tissue-fibrinogens* into the veins of a living dog results in thrombosis of the portal vein and its affluents, the blood in the systemic veins and arteries remaining liquid. These important facts were elicited by Wooldridge,² and only his premature death prevented his following up this fruitful discovery.

The observations which are to be communicated here will perhaps contribute towards carrying his work a step further.

Wooldridge while describing the usual result of an injection of tissue-fibrinogen to be the coagulation of the blood in the portal district alone, had not failed to observe that if the injection were made into an animal during active digestion coagula were also found in the right heart and in the pulmonary artery. The hypothesis which he put forward tentatively to explain these facts was, that the coagulation that occurred in the portal tract was due to the injected tissue-fibrinogen there meeting some substance which had been absorbed from the intestinal canal and which favoured coagulation. This body he supposed to be under ordinary conditions completely eliminated from the blood during its passage through the liver. In active digestion, however, he suggested it would be incompletely held back there, and the coagula found in the right heart would then be due to its overflow into the cardiac blood.

This hypothesis, however, becomes untenable in the light of the following facts :

1. The coagulation occurs in the portal district, even when the injection is made in an animal that has been kept for six or eight days without food.

¹ The substance which is here called Wooldridge's Tissue-Fibrinogen was obtained by Wooldridge from Thymus and from Testicles, by mincing them up and extracting them with normal salt solution ; and was found to induce when intravascularly injected into dogs thrombosis of the portal vein.

Further, Wooldridge showed that this substance which produced intravascular clotting was not an enzyme, like fibrin ferment, but an actual fibrin factor.

The Author, who followed up this work after Wooldridge's death, then showed (*British Medical Journal*, 19th September, 1891) that this substance, which was up to then called Wooldridge's Tissue-Fibrinogen, gave the chemical reactions of a nucleo-albumen.

Nine years later Morawitz gave to the nucleo-albuminous fibrin factor of Wooldridge's the name *Thrombo-kinase*, and nearly every text-book of physiology has followed him—flying in doing so directly up against the facts. (Added 1942.)

² *Proceedings*, Royal Society, 1886.

2. The coagulation occurs not in the portal vascular system alone but all over the body, when the injection of tissue-fibrinogens is made in an animal that has become dyspnoeic by compression of the trachea.

In evidence of this last fact the following protocol may be quoted :

Sept. 22, 1890. Fox-terrier—cannula inserted into the jugular vein, trachea compressed with a ligature ; as soon as dyspnoea has become marked 25 c.c. of a solution of tissue-fibrinogen were allowed to run into the jugular vein. Respiration came to an immediate stand-still. Ligature on the trachea was relaxed and the post-mortem was begun immediately. After the post-mortem had commenced the animal gave two or three of the deep 'ante-mortem' gasps constantly seen in asphyxia through acute deprivation of oxygen.

P.M. Thorax—Jugulars and Innominate veins empty, slight clot in S.V.C., Azygos Vein clotted ; right auricle and ventricle one solid blood-clot ; I.V.C. one solid clot ; left ventricle showed a slight brightly arterialised clot ; left auricle is distended with a brightly arterialised clot forming casts of the pulmonary veins. These last were clotted right through to the lungs. On cross-section the vessels in the lungs were seen to be filled with bright arterial blood-clots. The aorta is clotted solid right down to the level of the renal arteries. The aortic clot is a dark venous clot.

Heart begins to beat again when tension is relieved, and continues beating for more than a minute after all its cavities have been laid open.

Abdomen—Hepatic vein clotted, I.V.C., clotted firm down to the renal veins. Here a nick was made in the vein and the iliac veins were laid open. Blood poured out, solidifying immediately into a clot.

NOTE.—The bright arterial clot in the left ventricle, left auricle and lungs was evidently blood that was oxidised in the lungs during the 'ante-mortem' gasps, though, of course, there is nothing to show that it was arterial in the sense of its having freed itself from its excess of CO_2 .¹ The dark-coloured clot in the aorta on the other hand must have passed through the lungs while the trachea was being compressed.

It having thus been established that *asphyxia* will bring about a condition of general coagulability of the blood, experiments were now made with a view of determining whether an increase of the metabolism of an organ or tissue such as would probably induce a more venous condition of the blood in a particular vascular district would result in the blood in that district becoming coagulable by the injected tissue-fibrinogens. The following experiments were therefore made.

1. The sciatic nerve was exposed as high as possible in the back of the right thigh. It was divided and the peripheral end was stimulated by a strong interrupted current. After the stimulation had been continued for a couple of minutes, the usual quantity 20 to 30 c.c. of Wooldridge's coagulating fluid was allowed to flow into the jugular vein, the stimulation being continued while the injection was proceeding. The animal succumbed some few seconds after the injection was completed. The post-mortem which was undertaken immediately disclosed in addition

¹ *Vide infra*, p. 15, penultimate paragraph.

to the usual thrombosis of the portal tract a complete thrombosis of the femoral and iliac veins on the right side. The distribution of the clotting downwards accurately followed that of the branches of the sciatic nerve, the blood in the tributaries from the anterior part of the thigh remaining quite liquid, while the veins from the muscles that had been thrown into tetanus were clotted solid. Upwards towards the heart the thrombus began to thin out just above the junction of the iliac veins, and it ceased half way between that point and the lower margin of the liver. From the junction of the iliac veins the clot was continued downwards for about an inch or less into the left iliac vein, thinning out as it was followed downwards. Below that point there was not a trace of clot in the iliac or femoral vein of the left side or in any of their tributaries.

2. A dog was chloroformed and both his eyes were atropinised. For that purpose an equal amount of 1 p.c. solution was used upon each eye. The left eye was blindfolded, and the light of a polarimeter oil lamp fitted with a plano-convex lens was directed into the right eye from a distance of about a foot, the eye being fixed by means of a pair of fixation forceps. After an interval of some ten minutes, the usual amount of coagulating fluid was allowed to run into the femoral vein.

The post-mortem revealed the fact that all the vessels of the right eye stood out as dark prominent lines,¹ while the vessels of the left retina were only just perceptible to the naked eye. On examining the ophthalmic veins at the back of either eyeball, that on the right side was with certainty ascertained to be clotted, it being possible to push little cylinders of clot out of the vessel when it was cut across. On the left side the blood in the ophthalmic vein was as clearly made out to be liquid, the blood flowing away from the point of pressure when the back of a scalpel was pressed against the vein.

3. The chorda tympani was exposed on one side, and the sympathetic was separated from the vagus at the root, at the neck on the other side. Both nerves were then cut across and their peripheral ends were stimulated. The coagulating fluid was injected into the femoral vein, but no trace of coagulation was observed on either side in the veins emerging from the submaxillary gland.

On reviewing these facts it is evident that it is difficult to assume the formation of some new chemical body which favours coagulation under three such different conditions as those of asphyxia, muscle-tetanus and retinal stimulation. A more likely hypothesis would seem to be that an alteration in the gaseous composition of the blood is sufficient to determine its coagulation in the presence of tissue-fibrinogens. It was evident that such a change would have to be sought for in either one of two directions, either in an increase of CO_2 or in a diminution of the O_2 in the blood.

The following protocol is conclusive as to an excess of CO_2 , sufficing of itself to determine the coagulability of the blood all over the body.

Oct. 1, 1890. Small fox-terrier put under chloroform tracheotomised. Trachea-tube placed in connexion with a glass jar of some 3,000 c.c. capacity standing over

¹ I succeeded in getting a photograph of the retina of this eye, the vessels appearing very clearly in it. The light, however, failed before I could secure a photograph of the left retina for comparison.

water containing a mixture consisting of 80 p.c. CO_2 and 20 p.c. O_2 . As the oxygen was absorbed more was added to make up the deficiency, the water thus being kept at the same level in the jar. Breathing slightly quickened but quiet. After an interval of some three minutes the coagulating fluid was run into the left femoral vein, the animal dying almost immediately.

P.M. Abdomen. Both iliac veins and I.V.C. clotted solid right up to heart. Hepatic vein and all its tributaries clotted. Portal vein contains only a slight clot, but mesenteric veins are well clotted. Splenic vein not clotted. Renal veins firmly clotted.

Thorax. S.V.C., innominate veins and azygos, right heart and pulmonary artery one solid clot. Clot in the left heart, pulmonary veins and aorta.

Rest of body. No clotting in fore or hind limbs, all veins of head and neck clotted, including all the veins and sinuses of the brain.

Quite in harmony with this experiment is Wooldridge's observation that coagula occur in extra-portal tracts as well as in the portal area when the injection of tissue-fibrinogen is made in animals during active digestion, especially if their food has contained a large quantity of fat. The increased production of CO_2 during digestion, and especially after fatty food, is of course a commonplace of physiology.

Further, the influence of CO_2 gas upon blood-coagulation after injections of tissue-fibrinogens is borne out in the following case. The injection of coagulating fluid had been made and the post-mortem as usual disclosed coagulation in the portal tract only. The blood from the systemic veins was collected and was still liquid after several hours, and all the blood corpuscles had sunk to the bottom as in peptone plasma. The clear supernatant plasma which was decanted off, clotted immediately on passing CO_2 ¹ gas through it. A portion which was kept as a control was still liquid next morning.

Of some bearing also on the causation of the coagulation is the fact that the only instance I have seen where coagulation failed to occur after the injection of a tissue-fibrinogen solution was that of a dog, which had been used for a class demonstration of the accelerator nerves, and which had become dead cold under the influence of the anaesthetic and of prolonged artificial respiration. In this case not a trace of coagulation was revealed by the post-mortem, although the full quantity of coagulating fluid had been injected into the jugular. The coagulating fluid was immediately afterwards tested upon another dog and found to be perfectly active. In this case the lowering of the metabolism by cold and by the anaesthetic, the complete emptiness of the stomach as disclosed by the post-mortem and the efficient ventilation which was kept up, probably all contributed to the result by keeping down the amount of CO_2 to a minimum.

¹ Wooldridge states that the blood from the extra-portal tracts, after any injection of coagulating fluid, remains not only liquid but also uncoagulable by CO_2 . Such is undoubtedly the rule, the observation reported above being an exception to it.

P.S. (April 1). I have since writing the above seen cause to believe that what I have characterised as the exception is really the rule. The blood collected from the extra-portal tracts after thrombosis of the portal vein very seldom fails to coagulate, if it is heated to 37°C . in a water-bath, and a stream of CO_2 is then passed through it; the comparative frequency of clotting in the veins of the body cavities (interior of skull, thorax, abdomen) as contrasted with the veins returning in the limbs is possibly determined by this factor of temperature.

In view of these facts I think one may conclude with at least a certain amount of probability that the determination of the coagulation to the portal tract after an injection of tissue-fibrinogens is due to an excess of CO_2 in the blood of that region, and that the amount of CO_2 in the systemic veins through which the injection is made, is in ordinary circumstances insufficient to bring about the coagulation of the blood there.

Having thus far studied the effects of an increase of CO_2 in the blood upon its coagulability, it remained still to be determined whether a deprivation of oxygen unaccompanied by a rise of CO_2 tension would favour coagulation in a similar manner. An animal was therefore tracheotomised and the trachea-tube was fitted with **T**-piece, inspiration being made through one limb which was brought into connexion with a large vessel full of pure H_2 gas which was standing over water, while expiration took place freely into the outer air through the other limb, which was armed with a Speck's intestinal valve. Injection of the coagulating fluid was made through the femoral vein as soon as the respiration had become distressed. The usual prolonged respiratory stand-still then took place, and was followed by the few deep 'ante-mortem' gasps.

P.M. (Begun during the long pause.)

Thorax.—A slight clot in the S.V.C. filling about one-fourth of its calibre. Azygos and intercostal veins clotted. I.V.C. not clotted. Right auricle clotted, slight clot in right ventricle. In left heart a few traces of clot. Aorta clotted right down to the origin of the iliacs. All these clots very dark in colour.

Abdomen.—Only one or two mere shreds of clot in I.V.C. portal vein not clotted, rest of body blood in limbs everywhere liquid.

On this case it may be remarked that it can hardly be expected that the long respiratory stand-still which is an invariable occurrence in asphyxia through acute deprivation of oxygen should run its course without a considerable rise in the CO_2 tension in the blood. It seems probable that the blood, which was in this case found coagulated in the descending aorta, was blood that had passed through the lungs during the respiratory pause, whereas the blood which was found liquid in the I.V.C. is more likely to have passed through the lungs before that pause took place, and therefore to have had an opportunity of freeing itself from its excess of CO_2 . The same holds of the blood of the S.V.C., which was liquid with the exception of that portion of it which came from the azygos vein.

The absence of a coagulum in the portal vein is with all probability due to the blocking of the aorta by clot. The liquidity of the blood in the I.V.C. could, of course, not be explained in the same way, the injection having been made through the femoral vein.

Two methods of turning the difficulty introduced into the matter by the long respiratory pause suggested themselves.

(1) To ventilate with H_2 .

With the appliances at command I was only able to carry out this imperfectly. The coagulation was not limited to the portal district, but I was not able to satisfy myself that the ventilation had been adequate.

(2) To make the animal breathe out of a reservoir of CO gas. This was done,

but when connexion was made the respiration gradually became feebler and feebler. Ventilation was thus plainly inadequate, and the clots found on post-mortem examination were not limited to the portal area. The blood in the azygos and the intercostal veins, however, remained perfectly liquid. In this respect this case is the exact converse of the case quoted above, where after the violent respiratory struggles the azygos and its tributary intercostals were clotted solid. In fact it is easy to predict in an ordinary case from the character of the respirations whether the azygos will be found clotted or not.

After having pursued up to this point methods of direct enquiry into the conditions governing the distribution of the coagulation following upon the injection of Wooldridge's tissue-fibrinogen, I proceeded to investigate the changes introduced into the phenomena by the action of certain poisons. These experiments I hope to report upon more completely in a future communication.

It will suffice for the present to put upon record that when a dose of *atropin* is administered, such as is sufficient to dilate the pupil *ad maximam* and to paralyse the cardiac nerve-endings of the vagus, and presumably also the nerve-endings in the intestinal canal, an injection of Wooldridge's coagulating fluid was followed, in one case, by the usual coagulation of the portal area alone, the blood clot in the portal vein being, however, of the brightest arterial red. In two other cases the whole blood in the body was clotted solid, and here also everywhere, both in the arteries and also in the portal and systemic veins, the clots were of a brilliant arterial colour. I have also once seen the same bright arterial coloured clot in the portal vein after the administration of curare.

All the animals employed in these experiments were dogs. The coagulating fluid used was in all cases made from boars' testicles. The experiments were performed in the Physiological Laboratory of the University of Sydney.

P.S.—Since writing the above I have studied the effects of Wooldridge's coagulating fluid on cats. I find that when respiration is going on normally, a moderate injection of Wooldridge's fluid is not followed by any coagulation either in the portal or in the systemic veins. When, however, asphyxia is produced in the animal and an injection of the same quantity of coagulating fluid is made at its height the blood coagulates throughout the whole vascular system.

EXCERPT FROM A PAPER ENTITLED "A STUDY OF THE
INTRAVASCULAR COAGULATION PRODUCED BY THE IN-
JECTION OF WOOLDRIDGE'S TISSUE-FIBRINOGEN"

(Reprinted from the 'Proceedings Royal Irish Academy', 3rd Series, vol. 2, 1893)

The following experiment shows the sequence of events.

T Dog 119.—The acetic acid precipitate from a fresh extract of testicles was carefully washed, and a thin solution was then made in 1 per cent. Na_2CO_3 , and was filtered through calico, but not through paper. Cannulae were inserted into the external jugular vein and into the carotid.

Samples of a few c.c. each time were withdrawn from the carotid to test the condition of coagulability of the blood, and an assistant took down in writing from my dictation (a) the times at which the samples were withdrawn; (b) the times at which injections of tissue-fibrinogen were made into the jugular vein; and (c) the reports I made at intervals of about a minute upon the condition of coagulability in the various samples.

Sample No. 1.—Withdrawn 5.43 p.m.; begins to clot, 5.46; almost solid, 5.47; can invert, 5.51. *Coagulation time, 8 minutes.*

Ran in 10 c.c. of tissue-fibrinogen solution, 5.43 p.m.

Sample No. 2.—Withdrawn 5.44; liquid, 60 minutes afterwards. *Coagulation time, longer than 60 minutes.*

Ran in 10 c.c. more of tissue-fibrinogen solution, 5.44½.

Sample No. 3.—Withdrawn 5.45; liquid, 1 hour afterwards. *Coagulation time, longer than 60 minutes.*

Sample No. 4.—Withdrawn 5.46½; liquid, 1 hour afterwards. *Coagulation time, longer than 60 minutes.*

Sample No. 5.—Withdrawn 5.48; liquid, 1 hour afterwards. *Coagulation time, longer than 60 minutes.*

Ran in 10 c.c. more solution, 5.48.

Sample No. 6.—Withdrawn 5.50; still liquid, 5.53; can invert, 5.58 p.m. *Coagulation time, 8 minutes.*

Sample No. 7.—Withdrawn 5.51; liquid, 5.53; clot begins, 5.55; half solid, 5.57; solid, can invert, 6.4 p.m. *Coagulation time, 13 minutes.*

Ran in 10 c.c. more, 5.54.

Sample No. 8.—Withdrawn 5.53; half solid, 5.59; solid, 6 p.m. *Coagulation time, 7 minutes.*

Ran in 10 c.c. more, 5.54.

Sample No. 9.—5.55; solid at 6 p.m. *Coagulation time, 5 minutes.*

Ran in 10 c.c. more solution at 5.56.

Sample No. 10.—Withdrawn 5.56; solid at 6 p.m. *Coagulation time, 4 minutes.*

Ran in 10 c.c. more.

Sample No. 11.—Withdrawn 5.58½; solid at 6.2 p.m. *Coagulation time, 3½ minutes.*

Sample No. 12.—Withdrawn 6 p.m.; solid, 6.4 p.m. *Coagulation time, 4 minutes.*

Sample No. 13.—Withdrawn 6.2½; liquid at 6.6; solid at 6.9 p.m. *Coagulation time, 6½ minutes.*

Sample No. 14.—Withdrawn 6.7 p.m.; liquid at 6.10; clot begins, 6.12; solid at 6.14½. *Coagulation time, 7½ minutes.*

Ran in 20 c.c., 6.13 p.m.

Sample No. 15.—Withdrawn 6.14; half solid, 6.15; record of complete coagulation wanting.

Sample No. 16.—Withdrawn 6.14½; half solid, 6.15; quite solid, 6.16½. *Coagulation time, 2 minutes.*

Sample No. 17.—Withdrawn 6.16; solid, 6.20. *Coagulation time, 4 minutes.*

Sample No. 18.—Withdrawn 6.19; half solid, 6.20; solid, 6.22. *Coagulation time, 3 minutes.*

Sample No. 19.—Withdrawn 6.22; half solid, 6.23; solid, 6.26. *Coagulation time, 4 minutes.*

Ran in 15 c.c. more, 6.23 p.m.

Sample No. 20.—Clots almost instantaneously.

Clamped trachea, 6.26 p.m.

At 6.27 p.m. proceeded to inject 20 c.c. more of the coagulative fluid, but the injection came to a standstill of itself after a very few c.c. had been run in, the respiratory movements having suddenly ceased.

P.M. disclosed complete thrombosis of both sides of the heart, and of the first portion of the aorta. There was naturally, therefore, no clot in the portal vein.

The bladder contains some 20 c.c. of acid urine, in which an extremely well-marked biuret reaction can be developed by the addition of NaOH and CuSO₄.

We have thus in this experiment, if for the moment we leave samples 2 to 5 inclusive out of consideration, a gradual increase of coagulability in the blood as a consequence of successive small injections of tissue-fibrinogen, the gradual curve of ascent being, however, marked by partial remissions in the direction of a negative phase, wherever time enough was allowed between the injections for a reaction to make itself felt. These remissions are, for instance, well seen on comparing samples 6 and 7 together, or again on comparing samples 11, 12, 13, 14. There is also, I think, a perfectly similar remission in the case of samples 16, 17, 18, 19, the more rapid coagulation recorded upon the protocol for sample 18 being probably referable to either an inaccuracy of observation, or to a rise of CO₂ tension due to an unrecorded temporary cessation of respiration, such as would be brought about by the administration of a fresh supply of the anaesthetic. With regard to the apparent primary character of the negative phase of coagulability which samples 2 to 5 appear to establish the existence of, I can only state my belief that an unobserved positive phase of coagulability might have been placed upon record if the samples had been collected immediately after the injection of the tissue-fibrinogen. I omitted to collect these samples early enough, because I was at the moment occupied with supervising the injection.

ON THE POSSIBLE ADVANTAGES OF EMPLOYING DECALCIFIED MILK IN THE FEEDING OF INFANTS AND INVALIDS

(Reprinted from 'The Lancet', July 27, 1893)

Before Arthus and Pagès discovered that blood could be deprived of its coagulability by receiving it into solutions of oxalates and fluorides they had already discovered that milk in which the lime salts had been precipitated by these same additions would no longer clot with rennet. I shall endeavour to indicate a possible practical application of this fact. Milk curdles under two entirely distinct sets of conditions: (1) it curdles on addition of an acid, and (2) it curdles under the influence of rennet (when the reaction of the milk is either neutral or slightly acid). The two varieties of curd which are obtained under these circumstances may be denominated *acid curds* and *rennet curds* respectively. Acid curds must inevitably be formed in the stomach after milk has been drunk if the gastric contents are allowed to become acid. Such curds (we are familiar with them in ordinary life in the form, for instance, of cream cheese or sour milk) are probably not sufficiently firm to set up digestive disturbances. On the other hand, rennet curds (such as we are familiar with in the form of renneted milk and of ordinary cheese) may be extremely firm. It is therefore in all probability these rennet curds which set up the familiar infantile dyspepsia of bottle-fed children. If this is so, the facts elicited by Arthus and Pagès would appear to be of dominating importance in the treatment of these dyspeptic conditions.

In order to appreciate this correctly the following facts must be attended to: (1) rennet coagulation is delayed and curdling becomes less and less firm as an increasing proportion of the lime salts of the milk becomes precipitated as insoluble salts (Arthus and Pagès); (2) addition of soluble lime salts (up to a certain maximum) causes increased rapidity of rennet-coagulation accompanied by increased firmness of clot (Arthus and Pagès); (3) human milk contains 0·03 per cent. of lime (Bunge); (4) cow's milk contains 0·17 per cent. of lime (Bunge). It is evident from these facts that the rennet coagulation in the human stomach could be delayed by precipitating a portion of the lime salts contained in cow's milk. It is further evident that a great proportion of the lime salts in cow's milk could be dispensed with without injury to the nutrition of the human infant, inasmuch as the infant, who does not need to walk for more than a year after birth, is fed with milk which is provided with a view to the calf walking almost as soon as it is born. Lastly, the question of a suitable precipitant for the lime in the milk comes up for consideration. As I have already shown, the salts employed by Arthus and Pagès were the fluorides and the oxalates—that is, salts which have poisonous properties and which cannot be employed in dietetics. In lieu of these citrate of soda may be employed as an efficient precipitant. I find in the samples of milk with which I have experimented

that an addition of 1 in 200 of citrate of soda—one-fiftieth volume of 25 per cent. citrate of soda—suffices to prevent any rennet coagulation, whilst it can hardly be detected by the palate. Cow's milk with a somewhat less addition of citrate of soda (say 1 part in *three or four hundred*) would, with regard at any rate to its lime salts, constitute a true 'humanised' milk. If it should turn out that the acid curds are also contributory to the dyspeptic troubles of infants, super-addition of the customary bicarbonate of soda or lime-water would apparently be indicated.

POSTSCRIPT TO THE ABOVE PAPER ADDED 1942

Certain points in the above paper, some of them points which I took for understood, may perhaps be usefully emphasised in a postscript.

Regarded as food-stuffs for infants, human milk and cow's milk differ, as said, in their mineral composition in the fact that they contain different amounts of calcium salts.

Human milk, according to Bunge's analyses, contains 1 part in 3,000 of calcium salts, whereas cow's milk contains nearly 1 part in 500. All the other differences—small differences in the percentages of sugar and protein—which have been stressed by clinicians, are absolutely without interest.¹

The calcium salts of milk derive, as we have seen, theirs from the fact that the amount of these in milk determines the firmness with which it clots in the stomach.

And when one reflects upon it one sees that the condition of an infant after the ingestion of a large volume of undiluted cow's milk would be comparable to that of the unfortunates we read of, who were compelled—this was not an uncommon mode of execution—to swallow down draughts of bovine blood taken directly from the animal. This method of execution was effective because the blood clotted in the stomach and could then (because the anti-tryptic power of the serum abolishes protein digestion) be got neither up nor down.

While the prescription given above—that is, the instruction to add to each ounce of milk something under 2 grains of citrate of soda (about 1 part in 3 or 4 hundred)—satisfies all the requirements of practice, it is unlikely that this represents the best addition for all samples of milk. On the contrary, we may take it that the amount of calcium and magnesium in cow's milk must vary with the amount of those salts ingested by the cow in its food.

With a view to determining the optimum addition of citrate of soda to a particular sample of milk, and also with a view to showing medical students, and possibly also fairly intelligent female parents, the rationale of such an addition, the following tests should be carried out.

The milk whose content in calcium is to be ascertained (it is really that which

¹ There is, however, though this had escaped my notice, another material difference between human milk and cow's milk—to wit, the fact that human milk is incoagulable by ordinary rennet; and is incoagulable also (I owe my knowledge of this to my fellow-worker, L. Holt) when calcium salts are added. This difference between the two milks is, of course, one which does not affect the problem as to how cow's milk, when it has to be resorted to for infant feeding, can be rendered less coagulable by the rennet of the infantile stomach.

is put to proof in the test now to be described) should be heated to about 50° C., that is until it feels warm, but not hot, to the hand. This warm (and perfectly fresh) milk should be filled into test tubes (an equal volume going into each), and there should be added to all the tubes, except those which are to serve as controls, different quanta of citrate of soda—1 grain to the ounce of milk in the first tube, and 2, 3, 4 and 5 grains respectively to the others: in other terms, something like 1 in 500, 1 in 250, 1 in 170 and 1 in 100 of citrate in the successive tubes.

This done there should be added to each tube, including of course the controls, a measured volume of rennet, a volume such as has been found to give a rapid and firm coagulation in the control milk.

When all this has been carried out and the tubes are kept warm, the results which come under observation are as follows.

The control milk sets into a firm curd; that in the next tube into a less firm one; while that to which 2 grains of citrate to the ounce has been added gives a definitely loose clot; and the milk will probably remain unclotted in all the tubes to which a larger percentage of citrate has been added.

A thoughtful consideration of the results obtained in these last tubes brings home an important lesson. It teaches that milk to which excessive doses of citrate have been added is perilous food for infants.

I, in point of fact, know of two cases in which (by mistakes of the dispenser or nurse) an excessive quantity of citrate of soda was added to the milk. In one of these cases slight, and in the other (this was in the child of a doctor who had brought up all his previous children on citrated milk) quite formidable convulsions supervened. And in both cases the convulsions ceased as soon as the cause of the trouble was discovered and removed.

What happened in these cases is of particular interest in view of the fact that Sabbatani¹ had shown that convulsions are induced when decalcifying solutions are directly applied to the surface of the brain, and that these convulsions are arrested by a counteracting local application of calcium.

Coming back to the question of ascertaining by tests whether the optimum addition of citrate is being used, it requires to be kept in view that boiled milk, and perhaps also Pasteurised milk, differs from unboiled milk in its reaction to rennet. Boiled clots more slowly and much less firmly than unboiled milk.

Let us ask ourselves why.

It is familiar matter that a precipitate of calcium and magnesium salts comes down when a urine, which is neutral or very feebly acid, is brought to the boil. That must inevitably happen also when milk (which is, when fresh, either neutral or very feebly acid) is boiled, the precipitate of lime salts afterwards sinking to the bottom of the containing vessel.

It might, by hasty reasoning from the fact that boiled milk gives only a loose clot with rennet, be inferred that boiled, undiluted cow's milk would constitute an ideal food-stuff for infants.

But this would be a fallacious inference, for the precipitated lime salts would be brought into solution again by the hydrochloric acid in the stomach.

¹ *Riv. sper. di freniat.*, 1901, 27, pp. 946-956.

I have verified this by post-mortem examinations of a litter of puppies, half of which had been fed with unboiled, and the other half with boiled milk. The curd was as firm in the one case as in the other.

The same experiment can be carried out *in vitro* by adding to the boiled milk a trace of acid. And this experiment gives particularly striking results when carried out with a sample of boiled milk taken from the top, and another taken from the bottom of the vessel after the milk has been centrifuged or has been allowed to stand for a long time.

One last point. It might perhaps be useful to emphasise that citrate of milk should always be tried in cases of intractable vomiting and in which ordinary milk is rejected. In this I am speaking from personal experience. For when I had Malta Fever and suffered from intractable vomiting I found I could retain citrated milk when everything else was rejected.

ON THE INFLUENCE OF CARBONIC ACID AND OXYGEN UPON THE COAGULABILITY OF THE BLOOD *IN VIVO*

(From the 'Proceedings of the Royal Society', vol. 55, 1894)

I have, in the course of previous researches on blood coagulation,¹ had occasion to suggest that the phenomena with which I was dealing might be explained in a very simple manner by assuming that carbonic acid gas exercised a favourable influence on the occurrence of blood coagulation. The present research consists of an examination of the hypothesis in question.

The method of experimentation employed consisted in determining the alterations of blood coagulability which occurred in animals when alterations were effected in the respiratory gases with which they were supplied.

Details of the Method of Experimentation employed.

The animals experimented upon were dogs and rabbits. The animals were in all cases tracheotomised under the influence of ether (rabbits) or of a mixture of ether and chloroform (dogs). In the case of the dogs, the animals were kept under the influence of the chloroform and ether during the whole course of the experiment. In the case of the rabbits, the repeated inhalations of carbonic acid and other gaseous mixtures served to keep up the anaesthesia. The tracheotomy tubes were connected up with a T-tube; one limb of the T-tube was fitted with a Speck's intestinal valve (made of rabbit-gut), and allowed of free expiration into the outer air. The other limb of the T-tube was connected up at pleasure with reservoirs (4,000 c.c. capacity) of pure gases or gaseous mixtures standing over water. The water was carefully kept at the same level inside and outside of the reservoirs during the whole course of an experiment. A convenient check upon this was afforded by the regular opening and closing of the intestinal valve.

The blood for the coagulability estimations was obtained from the ear. In the case of the rabbits, the blood was invariably drawn off from the central artery of the ear. Only rabbits with full ear arteries were employed in the experiments.

The blood coagulability determinations were made by the method of capillary coagulation tubes recently² described by me. The method differs from the method previously described by Vierordt³ in the following particulars: 1. A series of capillary tubes, of equal calibre, is employed instead of the single capillary tube employed by Vierordt. 2. Coagulation time is determined by blowing down the capillary tubes, one after another, at regularly increasing intervals until a tube is found to

¹ *Vide supra*, pp. 2-7; also *Roy. Irish Acad. Proc.*, 3rd Series, vol. 2, No. 2; *Roy. Soc. Proc.*, February, 1893.

² *Brit. Med. Journ.*, 29th July, 1893, and 3rd February, 1894.

³ *Archiv für Heilkunde*, 1878.

have become blocked by clot. In Vierordt's method the occurrence and duration of coagulation is judged of by passing a chemically cleansed white horse-hair down the capillary tube, and observing the deposition of coagulum upon its surface.

In all cases I employed a column of blood of 5 cm. in length, and received it into tubes which had a diameter of approximately 0·25 mm.

The following precautions were observed in order to ensure accuracy of results : 1. The coagulation tubes were washed out before use successively with distilled water, absolute alcohol, and ether. 2. They were then warmed in an incubator to a temperature of 37° C. 3. A fresh drop of blood was employed for filling each tube. 4. The column of blood was aspirated some little distance up the tubes to prevent desiccation occurring at the orifice. 5. In testing for coagulation the blood was blown out on to a piece of white filter paper in order to ensure the detection of the first traces of clot.

The gases which were experimented with were the following : Atmospheric air, oxygen, hydrogen, carbonic acid, and a mixture of (approximately) 20 per cent. of oxygen with 80 per cent. of carbonic acid. I also examined the effect of clamping the trachea.

Effect of an Increase of Carbonic Acid.

In order to elicit the effect of an increase of carbonic acid upon coagulability, I caused the animals to inspire out of a reservoir containing a mixture of 1 part (approximately) of oxygen with 4 parts of carbonic acid. This mixture of gases presents the obvious advantage of supplying carbonic acid in association with the normal quantum of oxygen. Determinations of blood coagulability were made when the animals were breathing this mixture of gases, and the results were compared with the 'coagulation times' which were elicited immediately before when the animals were breathing atmospheric air. Thirty experiments were made. Out of these twenty-seven showed a marked increase¹ of coagulability while the animal was breathing the mixture of carbonic acid and oxygen. In two experiments coagulation time was unaltered, and only in one experiment was a slight diminution of coagulability observed.

In the three experiments last mentioned the coagulability of the blood was already at a maximum when the animal was breathing atmospheric air.

It is to be noted that the blood which was drawn off while the animal was breathing the carbonic acid and oxygen was arterial in colour in all the experiments which have been summarised above. The increase of coagulability must therefore be ascribed to the increase of carbonic acid in the blood, and not to any defect of oxygenation.

It has thus been demonstrated that the increase of carbonic acid in the blood does exert a favourable influence on coagulation.² Carbonic acid is therefore in all

¹ This increase of coagulability is well shown in the first ten of the protocols appended to this paper.

² I have found this statement to hold true also in the case of human blood. The inhalation of an atmosphere which is rich in CO₂ causes an increased coagulability in my own blood. I have obtained a similar increase of coagulability (associated with an arrest of hæmorrhage) in a case of severe bleeding in hæmophilia. I have also obtained an increased coagulability by inhalation of CO₂ in the case of three members of another hæmophilic family.—*Vide infra*, pp. 142-146.

probability what I assumed ¹ it to be, i.e. a *vera causa* in the determination of intravascular coagulation to particular vascular areas.

Effect of a Diminution of Carbonic Acid.

This question was studied by examining the condition of coagulability in animals when an atmosphere rich in carbonic acid was replaced by (a) ordinary air, or (b) by oxygen.

(a) *Results of experiments in which an atmosphere of carbonic acid was replaced by ordinary air.*—The result ² of such a replacement of carbonic acid and oxygen by atmospheric air is a decrease of coagulability to the original norm.

(b) *Results of experiments in which an atmosphere of carbonic acid and oxygen is replaced by an atmosphere of unmixed oxygen.*—The substitution of unmixed oxygen for the mixture of carbonic acid and oxygen is invariably followed by a decrease of coagulability. The diminution may be due to a specific effect of an atmosphere of unmixed oxygen. On the other hand it may with much greater probability be referred to the diminution of carbonic acid in the blood, for the rate of respiration is always extraordinarily accelerated (to 160 respirations per minute and upwards) by the inspiration of oxygen. This view is also suggested by the analogy of the experiments in which air is substituted for the carbonic acid mixture. It is further supported by the fact that the diminution of coagulability is apparently proportionate to the amount of carbonic acid which is present in the blood. The diminution is, for instance, well marked when the blood is rich in carbonic acid (e.g. in protocols of rabbits 165, 163 and 135), while there is practically no diminution of coagulability when the blood has been adequately ventilated by respiration in ordinary air (*vide* second oxygen inhalation in protocol of rabbit 155).

It evidently results from both these series of experiments that the diminution of carbonic acid in the blood which was assumed by me to afford a clue to the diminished coagulability of peptone blood³ is in reality capable of exercising a well-marked retarding influence upon coagulation.

Effect of a Diminution of Oxygen.

It is extremely difficult to determine with precision what effect the withdrawal of oxygen exercises upon the coagulability of the blood. The difficulty consists in the complication of the phenomena which are due to the withdrawal of oxygen by other phenomena which are due to an increase of carbonic acid in the blood. To elucidate the matter, we evidently require methods which allow of at least a partial dissociation of the effects of the two gases. Such methods should aim at (a) a limitation of the amount of carbonic acid produced in the system after the oxygen is withdrawn; (b) the elimination of the carbonic acid which is produced; (c) a minimising of the effect of the carbonic acid increase. These objects can be partially realised by the two following methods:

¹ *Vide supra*, p. 4 *et seq.*

² This result is well shown on the protocols of rabbit 161 and dog 2.

³ *Roy. Irish Acad. Proc.*, 3rd Series, vol. 2, No. 2, 1891; *Roy. Soc. Proc.*, February, 1893.

1. Inhalation of an atmosphere of indifferent gas (e.g. hydrogen) while provision is made for free expiration into the external air.

This method provides to some extent for the elimination of the carbonic acid which is produced after the withdrawal of the oxygen. On the other hand, the method does not provide against the accumulation of carbonic acid which must occur during the dyspnoeic standstill of respiration.

2. Substitution of an atmosphere of unmixed carbonic acid for an atmosphere of carbonic acid and oxygen.

This method presents two advantages: (*a*) it limits the production of carbonic acid in the system, inasmuch as the withdrawal of oxygen, when made under these particular circumstances, no longer evokes any dyspnoeic spasms; (*b*) it minimises the effect of any increased carbonic acid tension inasmuch as such increase takes place in a blood which is already almost saturated with carbonic acid.

1. Results of Experiments in which Oxygen was withdrawn by the Substitution of Hydrogen for Atmospheric Air.

I have employed this method in 29 experiments. In 15 of these experiments a diminution of coagulability was observed to result from the inhalation of hydrogen. In 14 other experiments an increase of coagulability was noted. With respect to the latter results, the following points are to be noted: (*a*) The increase of coagulability was invariably confined within very moderate limits;¹ (*b*) in 2² out of the 14 experiments expiration was found to have been obstructed by an accidental compression of the tracheal tube.

The results of these experiments are patently ambiguous. On the one hand we have a bare majority of experiments or (if we subtract the experiments in which expiration was accidentally obstructed) a majority of only 15 to 12 experiments in favour of the result that the inspiration of hydrogen conditions a diminution, and not an increase, of blood coagulability. On the other hand, it is evident that there is nothing in these experiments when taken by themselves to justify a conclusion as to whether it is the decrease or the increase of coagulability which is to be regarded as the effect of the withdrawal of the oxygen. In such a case the only available method of interpretation consists in subducting from the aggregate of the observed phenomena such phenomena as we know by previous inductions to be the result of disturbing factors which cannot be eliminated from the experiments. The accumulation of carbonic acid in the blood, which occurs when the inevitable dyspnoeic standstill of respiration takes place, or when (as in rabbit 176 and dog 4) expiration is accidentally obstructed, is just such a disturbing factor, and the effects of this disturbing factor must, in accordance with our previous inductions, manifest themselves in an increased blood coagulability. We may, therefore, legitimately assign to this cause all the phenomena of increased blood coagulability which came under observation in the hydrogen experiments. The residue of the observed phenomena,

¹ Coagulation-time was never found reduced below 1 minute 30 seconds (*vide* protocol of rabbit 176). Coagulation-times of less than 1 minute are frequent (*vide* protocols *passim*) during inspiration of carbonic acid and oxygen.

² *Vide* protocols of rabbit 176 and of dog 4.

in other words the diminution of blood coagulability, then emerges as the effect of the absence of oxygen from the inspired air.

If the above train of argument is valid, we must conclude that the diminution of the oxygen of the blood conditions a diminution of coagulability.

2. Results of Experiments in which Oxygen was withdrawn by a Substitution of Unmixed Carbonic Acid for a Mixture of Carbonic Acid and Oxygen.

This substitution of carbonic acid for the mixture of carbonic acid and oxygen tends to effectuate itself spontaneously by the slowing down and ultimate standstill of respiratory movements which supervene when an animal is continuously supplied with an atmosphere surcharged with carbonic acid. A defect of oxygenation was allowed to supervene in this manner in five¹ experiments. In all these cases a diminution of coagulability was observed.

Similar experiments were performed by the actual substitution of unmixed carbonic acid for an atmosphere of carbonic acid and oxygen. In the four² experiments which were performed a diminution of coagulability was invariably observed.

The diminution of coagulability which is observed by either variant of this method may be interpreted either (*a*) as an effect of an excess of carbonic acid in the blood, or (*b*) as an effect of the withdrawal of oxygen. Against the former interpretation of the facts the following considerations may be urged: (1) the tension of carbonic acid in the blood must already have been very high when the substitution of gases was effected; (2) with the then obtaining very slow respiratory movements the respiratory interchange in the lungs must have been at a minimum. It is, therefore, unlikely that any appreciable increase of carbonic acid tension can have effectuated itself in the blood in the interval during which the lungs were filled with unmixed carbonic acid.

If this reasoning is valid, we must evidently interpret the diminution of coagulability which came under observation in all these experiments as a direct result of the withdrawal of the oxygen.

It need hardly be pointed out that this interpretation would harmonise with the interpretation which has just been placed upon the hydrogen experiments.

Effect of a Restoration of Oxygen to Blood rendered Anoxyhæmic by the Inspiration of Hydrogen.

It may be premised that we have here, as in the case of the hydrogen experiments, to disentangle the effects of a duplicated series of phenomena, (*a*) the giving off of any excess of carbonic acid which has accumulated in the blood, and (*b*) the restoration of oxygen to the blood. The effect of (*a*) would, in accordance with our previous³ experiments, be a diminution of coagulability. On the other hand, if the interpretation which we have placed upon the results of our experiments on the effect of a diminution of oxygen is correct, we should expect an increase of coagulability to accompany the restoration of oxygen to the blood.

¹ Three of these experiments will be found on the protocols of rabbit 175, dog 3, and rabbit 171.

² Two of these experiments will be found on the protocols of rabbit 175 and rabbit 171.

³ *Vide supra*, Experiments on Effect of Diminution of CO₂.

The following is a summary of the results of the experiments which were directed to the determination of this point.

In a total of fourteen experiments, restoration of atmospheric air was in ten instances¹ found to result in an increase of coagulability. In the four remaining instances a decrease of coagulability was noted. It is, however, significant that in two of these instances the diminution of coagulability which was observed lay well within the limits of error of the method of determination, while in the remaining two instances² the diminution of coagulability was only a rebound from a condition of increased blood coagulability which was brought about by an accidental obstruction to the expiration of carbonic acid.

We may, therefore, conclude that the restoration of oxygen to *anoxyaemic blood* conditions an increase of coagulability.

Comparison of the Results obtained above with the Results obtained by other Observers.

In recent times the question of the influence exerted by the blood gases on coagulation has been investigated among others by Vierordt,³ Hasebroek,⁴ and Bonne,⁵ and also by Mathieu and Urbain.⁶ The two first of these observers employed Vierordt's method of coagulability determinations, and both observers performed their experiments chiefly upon themselves. In none of their experiments does any attempt appear to have been made to dissociate the effect of changes in the quantity of carbonic acid in the blood from the effect of simultaneous changes in the quantity of oxygen in the blood. On the contrary, the phenomena which came under observation appear to have been referred to either one or other of these causes according to the particular bias of either observer. Thus Vierordt ascribes the increased coagulability which he detected in the stagnating blood of his ligatured finger to an increase in the CO₂ tension. On the other hand, Hasebroek, who re-investigated this point, interprets the increased coagulability which is observed after a brief application of a ligature to the finger as an effect of a diminution of oxygen in the blood, while he ascribed the diminished coagulability which is observed after a lengthened application of the ligature to an excess of the carbonic acid. In like manner this observer ascribes (*a*) the increased coagulability which he obtained after holding his breath for twenty seconds to an increase of CO₂ in his blood, (*b*) the diminished coagulability he obtained after holding his breath for forty-five seconds to an excess of carbonic acid, (*c*) the diminished coagulability of venous, as compared with arterial, blood to the same cause, and (*d*) the diminished coagulability of his blood after rapid respiration to an excess of oxygen. There is nothing in the experiments to justify any of these inferences.

Exactly the same objections can be urged against Bonne's experiments. It will

¹ Examples of such increase of coagulability are given on protocols of rabbit 175, dog 4, rabbit 176, and rabbit 178.

² *Vide* third coagulation-determination on protocol of dog 4 and penultimate coagulation-determination on protocol of rabbit 176.

³ *Loc. cit.*

⁴ *Zeit. f. Biol.*, 1882.

⁵ *Ueber das Fibrin-Ferment*, Würzburg, 1889.

⁶ *Comptes Rendus*, 1874, vol. 2, pp. 665 *et seq.*, and 698 *et seq.*

suffice to point out that Bonne obtained a diminution of coagulability in a bare majority of experiments in pigeons in which asphyxia was produced by the inspiration of carbonic acid, and that he interprets this diminution of coagulability as an effect of the excess of carbonic acid tension, while the anoxyhaemia to which the animals succumbed is entirely left out of sight as a possible factor in the causation.

Lastly, the work of Mathieu and Urbain comes up for notice. These observers conjointly investigated the effect of carbonic acid upon blood coagulability, and came to the conclusion that carbonic acid was a very important, if not indeed the all-important, agent in the production of blood coagulation. This conclusion was based upon the following observations: (*a*) Blood coagulation is accompanied by a giving off of something like 50 per cent. of the carbonic acid originally present in the blood; (*b*) an artificial increase of the body temperature goes hand in hand with a diminution of the carbonic acid and with an increase in the oxygen in the blood, and this artificial increase of the body temperature results in a diminished coagulability; (*c*) the blood from the renal vein, which resembles in its gaseous composition the blood of the superheated organism, is characterised by a similar diminished coagulability; (*d*) an artificial reduction of the body temperature goes hand in hand with an increase of carbonic acid, which is quantitatively comparable to the increase which is produced by asphyxiating an animal by CO_2 . This increase of carbonic acid in the blood under the influence of cold goes hand in hand with an increased blood coagulability; (*e*) when blood is prevented from clotting by the addition of a few drops of ammonia (the ammonia is assumed to retard coagulation by binding the free carbonic acid), and when a new formation of carbonic acid is prevented by eliminating the oxygen from the blood by a stream of CO , the blood is found to have lost its spontaneous coagulability. Such blood becomes coagulable when a stream of CO_2 is passed through it; (*f*) strong solutions of neutral salts have a large absorbing power for free carbonic acid. The power which these solutions have of inhibiting blood coagulation is inferred to be associated with this property; (*g*) thrombosis of the pulmonary vessels occurs in dogs when they are caused to breathe atmospheric air in which the whole nitrogen has been replaced by CO_2 ; (*h*) after burns, the venous blood is found to contain a great excess of carbonic acid. The coagulability of such blood is abnormally high.

It will be observed that the experiments which have been the subject-matter of the present communication entirely confirm the conclusions which had already been arrived at by entirely different methods by Mathieu and Urbain. I have not in any systematic manner controlled the observations upon which the conclusions of these observers were based. I have, however, had many incidental opportunities of confirming their observations with respect to the alterations of blood coagulability which are conditioned by raising or cooling the general body temperature. On the other hand, I have not, in the very few cases I have examined for it, observed the occurrence of pulmonary thrombosis as an effect of a simple rise of carbonic acid tension in the blood, but I have, in one striking experiment, seen a rabbit whose blood coagulability had been increased by the administration of calcium chloride die instantaneously from universal intravascular coagulation, when it was supplied with an atmosphere which was surcharged with carbonic acid.

Appendix. Selected Protocols.

The appended protocols are to be read from left to right, and then back in a zig-zag manner, following the dotted lines from right to left. In accordance with the fact that the method of coagulability determinations which was employed is an approximal and not an absolute one, two data are given for each coagulability determination. These data (longest interval during which the blood was observed to remain in a tube unclotted, and shortest interval which the blood was found to require for complete occlusion of a tube) are entered in separate columns. Where only a single entry appears on the protocols this is indicative of a lacuna in the observations. Thus, when an entry appears in the first column only (as, for instance, in the case of the second coagulability determination on the last protocol on the list), it is to be understood that the last of the coagulation tubes which were appropriated to the particular coagulability determination was found liquid when tested after the interval noted in the protocol. Similarly, when an entry appears in the second column only, as, for instance, in the second determination on the first protocol on the list, it is to be understood that all the tubes were found completely clotted, although the testing of the tubes was not deferred beyond the fifty seconds noted on the protocol.

Rab. bit 163	2' 30"	2' 35"	45"	1' 45"	1' 55"	2'	2' 40"	2' 45"	1' 5'	2' 15"	1' 15"							
	interval of 2 min.		45"	1' 45"	1' 55"													
	interval of 5 min.								2'	1' 10"	1' 15"							
	interval of 1 min.		45"	2'	2' 15"				1' 5'	1' 45"	2' 1' 15"							
Rab. bit 149	2' 45"	2' 45"							—	—	—							
Rab. bit 135	2'	2' 15"					4' 15"	5'	—	1' 25"	1' 40"							
	interval of 25 min.						4'	4'										
Dog 1	10' 40"	10' 45"							2'	6' 25"	6' 30"							
	7'	6' 30"							4'	2' 50"	2' 50"							
Dog 2	6' 30"	6' 35"							4'	4' 53"	4' 56"							
	interval of 6 min.								6'	3' 25"	3' 30"							
	12'	6' 30"		1' 30"	5' 45"													
Dog 3	8' 30"	9' 15"	1' 30"	4'	5' 55"				4'	1' 40"	1' 45"							
	8'	4' 30"							6'	2'	2' 15"							
	10'	—																
	22'	5' 20"																
Dog 4	7'	7' 20"	1' 30"	2' 30"	2' 50"													
	7'	6' 30"	1'	7' 15"	8' 5"													
	10'	4' 30"																
	16'	4' 10"																

In this and in the next two experiments the animal was supplied with a mixture of CO₂ and air.

See remark to last experiment.

Vide remark to experiment with Dog 1.

Tracheal tube accidentally compressed during first hydrogen inhalation.

REMARKS ON METHODS OF INCREASING AND DIMINISHING THE COAGULABILITY OF THE BLOOD

(Reprinted from the 'British Medical Journal', 14th July, 1894)

We may begin by the consideration of the methods by which blood coagulability can be increased, since these methods form the basis of the rational therapeutics of haemophilia and of the treatment of all cases of haemorrhage and aneurysm which are not accessible to surgical treatment. I have already in the *British Medical Journal*¹ indicated one of these methods, which consists in the addition of lime salts to the blood, and I now propose to call attention to a further method of increasing coagulability which consists in increasing—by inhalation of the gas or otherwise—the amount of carbonic acid in the blood. It will be convenient to summarise in the form of a series of propositions the results which have been obtained by the experimental application of these methods.

The Addition of Calcium Chloride to Extravascular Blood causes it to coagulate more rapidly.

I have already established this in previous communications,² and I have suggested³ that this fact may be turned to practical account by employing weak (that is 0.25–0.5 per cent.) solutions of calcium chloride as 'physiological styptics'. I have further pointed out⁴ that the efficacy of these styptics may be increased by combining the calcium chloride with solutions of cell nucleo-albumens, that is, with albuminous substances which can be obtained from the aqueous extracts of any cellular tissues—for example, thymus, thyroid, testicle, gastric and other mucous membranes. The practical utility of such physiological styptics remains a matter for clinical experiment by others; but I desire to point out that the efficacy of any particular sample of styptic can now be readily put to the test before it is employed clinically by taking advantage of the coagulation tubes with mixing chambers which I have recently described and figured in this Journal.⁵ The following examples will suffice to indicate the amount of acceleration that may be expected:

*Blood drawn from finger of G. C. (a haemophilic boy).—*Coagulation time of unmixed blood 45 minutes. Coagulation time of blood which had received an addition of $\frac{1}{2}$ vol. of a 1 per cent. calcium chloride solution 9 $\frac{1}{2}$ minutes. (Experiment conducted at temperature of air, *circ.* 57° F.)

*Blood drawn from finger of the same boy one fortnight later.—*Coagulation time of unmixed blood exceeds 45 minutes. Coagulation time of the same blood after receiving an addition of $\frac{1}{8}$ th of a 1 per cent. calcium chloride solution less than 19 minutes. (Experiment conducted at temperature of air, *circ.* 42° F.)

*Blood drawn from the finger of a woman (Mrs. H.) who had handed down the haemorrhagic diathesis to two sons.—*Coagulation time of unmixed blood 5 minutes 25 seconds. Coagulation time of blood after receiving an addition of $\frac{1}{6}$ vol. of a 1 per cent. calcium chloride solution 2 minutes 45 seconds. (Experiment conducted at 18.5° C.)

*My own blood, 3rd June, 1894.—*Coagulation time of unmixed blood 5 minutes.

¹ *British Medical Journal*, 19th December, 1891.

² *British Medical Journal*, *loc. cit.*

³ *British Medical Journal*, *loc. cit.*

⁴ *The Lancet*, 25th February, 1893.

⁵ *British Medical Journal*, 3rd February, 1894.

Coagulation time after addition of $\frac{1}{6}$ vol. of a solution of nucleo-albumen combined with 1 per cent. calcium chloride 2 minutes 30 seconds. (Experiment conducted at temperature of 18.5° C.)

My own blood, 22nd June, 1894.—Coagulation time of unmixed blood 5 minutes 45 seconds. Coagulation time after addition of $\frac{1}{6}$ vol. of the same styptic 2 minutes. (Experiment conducted at 18.5° C.)

It will be observed from the above examples that the addition of a 'physiological styptic' may give us a very rapid coagulation. By its very nature, however, it cannot give us the instantaneous cessation of bleeding which we can obtain, if we care to pay the price for it, with an ordinary escharotic styptic.

The Internal Administration of Calcium Chloride increases the Coagulability of the Blood.

I have already in a previous paper shown this to be the case (*a*) in the blood of animals (dogs and rabbits), (*b*) in the blood of my friend Dr. Leonard Rogers and in my own blood; and (*c*) in the case of a haemophilic boy who was under my care in July, 1893. I need not do more than supplement this by the following observations on certain families of haemophiliacs:

CASE I. *Haemophilia inherited from Mother and Grandmother*.—This reported derivation of the disease was confirmed by the fact (*a*) that the mother's blood had a coagulation time of 7 minutes, as compared with a coagulation time of 3 minutes in the father's blood (both under identical conditions of temperature and diet), and (*b*) by the fact that the grandmother's blood had a coagulation time of 11 minutes as compared with a coagulation time of $5\frac{1}{4}$ minutes in the grandfather's blood (both under identical conditions of diet and temperature).

The effect of an administration of calcium chloride to a selected number of the members of this family was as follows:

Relationship to the haemophiliac boy	Age	Coagulation time before commencement of treatment		Temperature at which the determination was made	Date or dates on which calcium chloride was administered	Dose of calcium chloride cryst. and number of daily doses	Coagulation time after treatment		Temperature at which the determination was made
		Min.	Sec.	F.		Grammes.	Min.	Sec.	F.
Maternal grandmother - -	68	11		55°	2-11-93	0.6 b.i.d.	5		57°
		5		57°	3-11-93	0.6 „	6	30	52°
Mother - -	28	6	45	55°	2-11-93	0.6 „	4	35	57°
		4	35	57°	3-11-93	0.6 „	3	25	52°
Eldest sister -	$9\frac{1}{2}$	11	45	55°	2-11-93	0.3 „	9		57°
		9		57°	3-11-93	0.3 „	10		52°
Fifth sister -	$1\frac{1}{2}$	12	20	55°	2-11-93	0.3 „	10	15	57°
		10	15	57°	3-11-93	0.3 „	7	20	52°
		23	(?)	55°	2-11-93	0.3 „	35	(?)	57°
Haemophilic boy himself - -	3	35	(?)	57°	3-11-93	0.6 „	21	(?)	52°
		21	(?)	52°	4-7-11-93	0.3 „	29	(?)	41°
		29	(?)	41°	13-15-11-93	0.7 „	45	(?)	42.5°
		8	20	55°	2-11-93	0.6 „	4	30	57°

It will be noticed that evidence was obtained of increased coagulability of all the members of the family except the haemophilic boy himself. It is impossible to be certain whether in his case there was any increase of coagulability or not for the determinations of coagulability were made at such unfavourable temperatures that it was a matter of difficulty to obtain a correct measure of his coagulability.

I am indebted to Sir William Jenner, Bart., for the opportunity of studying, and for much help in the study, of these cases.

CASE II.—*Haemophilia said to be inherited through the Mother.* No confirmation of this history obtained on comparing the mother's coagulation time (3½ minutes at 18.5° C.) with the father's coagulation time (3 minutes 40 seconds at 18.5° C.).

Patient	Age	Coagulation time before treatment	Date on which CaCl ₂ cryst. was administered	Dose and number of daily doses	Coagulation time after treatment	Temperature at which determinations were made
Haemophilic boy -	9	Over 60 min.	14-4-94	2 grammes b.i.d.	27 min.	18.5° C.
		27 min.	15-4-94	2 grammes b.i.d.	13 min.	18.5° C.
Haemophilic boy - (younger brother)	7	6 min. 40 sec.	14-4-94	2 grammes b.i.d.	4 min.	18.5° C.

It will be seen that the administration of comparatively large doses of lime was successful in reducing coagulation time in both these cases.

CASE III.—*Haemophilia of very moderate degree.*

Patient	Age	Coagulation time before treatment	Date on which CaCl ₂ was administered	Dose and number of daily doses	Coagulation time after treatment	Temperature at which determinations were made
Male - - -	30 circ.	7 min. 30 sec.	22-3-94	2 grammes b.i.d.	5 min. 50 sec.	18.5° C.

I am indebted to my friend Mr. N. Ridley for the opportunity of studying these cases.

It has thus been shown in the case of four quite unrelated haemophilic families (that is, in the cases just reported and in the case reported in my previous paper ¹) that the administration of calcium chloride caused an increase of blood coagulability. I have collected some, but as yet insufficient, evidence of the same favourable effect in the case of three other haemophilic families which have come under my observation. I have also notes of a case in which the administration of calcium chloride enabled an operation for nasal polypi to be successfully carried out. An operation had been attempted on a previous occasion upon the patient in question (a girl who

¹ *British Medical Journal*, 29th July, 1893.

is a member of one of the families of haemophilics last referred to), but it was apparently found necessary to abandon it owing to the onset of serious haemorrhage. A brother of this girl died from haemorrhage after extraction of a tooth, and his case has been reported in the *Army Medical Reports* for 1893 by Surgeon-Captain Grenville E. Moffett. I am indebted to this officer for an opportunity of studying this haemophilic family.

Internal Administration of Calcium Chloride often causes an Arrest of Hæmorrhage.

The proof that internal administration of calcium chloride frequently brings about an arrest of haemorrhage is a much easier matter than the proof of the occurrence of increased blood coagulability after the administration of lime. This is evident when we consider that an arrest of haemorrhage obtrudes itself upon observation, whereas an increase of blood coagulability may occur and may pass unperceived, unless we are fortunate enough to hit off the proper time for making our examination of the blood. In actual experience I have on several occasions failed to obtain a record of increased coagulability in cases where there could hardly be any doubt that the arrest of haemorrhage which had taken place was attributable to the administration of the calcium chloride.

Instances of arrest of haemorrhage (haemoptysis, frequently recurring epistaxis) after the administration of lime salts have been put on record by me in my previous paper.¹ Since the date of that paper I have seen other and equally successful results from this treatment, especially in haemophilic menorrhagia. Mr. Mayo Robson has also put similar cases on record—arrest of bleeding in surgical operations on the liver and in menorrhagia. A much greater evidential value, however, attaches to cases of arrest of actual haemophilic haemorrhage, for in these we have an opportunity of contrasting hæmorrhages which were left untreated with hæmorrhages in the same patients which have been treated with calcium chloride. It will suffice to say that I have learned from four different sources—in three instances from the medical men in charge—of the successful arrest of haemophilic hæmorrhage under the influence of calcium chloride. The details of a fifth case, which was successfully treated by the inhalation of carbonic acid combined with the internal administration of lime salts, will be given in another part of this paper.

The Continued Administration of Large Doses of Calcium Chloride is not Effectual in keeping up a Permanent Condition of increased Blood Coagulability.

I have already pointed out this fact in connexion with the case of hæmophilia recorded in my previous ² paper. In the case in point, the administration of calcium chloride (1 gramme t.i.d.) reduced the coagulation time of the blood from 10 minutes to 5 minutes, but on the third day of the treatment, which was also the last day of the experiment, coagulation time was diminished beyond all previous record. The same phenomenon manifested itself in the case of my own blood, and precisely similar results are, as I have pointed out, obtained when calcium chloride is added in excessive quantities to extravascular blood. Since the date of the paper just

¹ *British Medical Journal*, 29th July, 1893.

² *Loc. cit.*

referred to I have repeatedly come across the same phenomenon. I may instance the case of a patient with abdominal aneurysm,¹ for it is especially in cases of aneurysm that a condition of long-continued high blood coagulability is desiderated. I do not propose to go into detail upon this matter here, for the problem of the treatment of aneurysm involves the subordinate problems of the influence of diet and of abstinence from foods and drink and from exercise upon the condition of blood coagulability. I need hardly point out that the study of these problems has not even been seriously commenced, and that there is therefore as yet no scientific justification for the processes of semi-starvation and drugging with iodide of potassium which have been adopted as the routine treatment for aortic aneurysm. If I might judge of the effects of a very spare diet from observations on myself and on the patient in question, I should conclude that such a diet considerably diminishes the coagulability of the blood. For instance, in the case of my own blood, I find that coagulation takes place more slowly than normally when a comparatively long period of inanition (for example, 10 hours) is allowed to intervene between breakfast and dinner. Under such conditions, I have observed my blood to remain fluid for 6 minutes.² Three hours after dinner on the occasion in point my coagulation time stood at 2 minutes. I have made several experiments with very similar results. On the other hand Vierordt³ found that his coagulability was decreased after meals, but I gather that he took beer⁴ at dinner, and surmise that he took beer also at his evening meal.

Reverting, however, to the question of the effect of a continued administration of large doses of lime salts to the aneurysm patient in question, I found that under the influence of doses of 4 grammes of calcium chloride administered twice daily the patient's coagulation time decreased from his normal of 6 minutes to a minimum of 4 minutes on the third day of the treatment. On the fourth day coagulability became subnormal, and it reverted to its original level when the administration of calcium chloride was stopped. Similar results were obtained with a morning and evening dose of 3 grammes of calcium chloride. Under the influence of these doses coagulability was increased till a coagulation time of $3\frac{1}{2}$ minutes came under observation on the fourth day of the treatment. On the next day coagulability again began to decline, and coagulation time stood at $6\frac{3}{4}$ minutes on the seventh day of the treatment.

The administration of the calcium chloride was then again suspended and coagu-

¹ This case was very kindly placed at my disposal for these observations by Surgeon-Colonel E. Fairland and Professor Cayley.

² Here and elsewhere in this paper where the temperature at which the determination was made is not directly stated it is to be understood that the determination was made at 18.5°C . or *circ.* 65°F . I find that this temperature has several advantages over the temperature 37°C . or 98.4°F ., which was originally proposed by me as a suitable standard temperature for coagulability determinations. A temperature of 18.5°C . presents the following advantages: (a) coagulation takes place more slowly than at 37°C ., and therefore the determinations can be made more accurately; (b) the temperature approximates to the temperature at which ordinary hospital wards are kept; (c) the tubes therefore require very little cooling or heating to bring them to the correct temperature; (d) the proposed standard temperature is a mean between freezing-point and blood heat, and therefore is easily remembered as 'half blood heat'.

³ *Archiv f. Heilkunde*, 1878.

⁴ *Vide infra*, p. 37.

lability increased (this was probably attributable to the elimination of an excess of lime) until the previous maximum coagulability ($3\frac{1}{2}$ minutes) was reached 24 hours after the administration of the lime had been suspended. After this coagulability reverted to its original level, and coagulation times ranging between $6\frac{1}{4}$ minutes and 8 minutes were recorded in the morning and evening determinations of the next two days. The administration of calcium chloride was now begun again (this time 2 grammes of the salt were administered thrice daily), and eight hours after the administration of the first dose coagulation time stood at $3\frac{1}{2}$ minutes, and under the influence of this treatment, combined with a more generous diet, coagulability increased gradually but irregularly (for there was a temporary fall caused by changes in diet), till on the 12th, 13th, 14th, 15th, and 16th days of this treatment coagulation times of $4\frac{1}{4}$, $4\frac{1}{4}$, $3\frac{1}{4}$, $2\frac{1}{4}$, and $1\frac{1}{2}$ minutes were registered. On the next day after this, though the treatment remained unaltered, coagulability again began to decline, and a few days afterwards the patient passed from under my observation.

Inhalation of Carbonic Acid Gas increases the Coagulability of the Blood.

After establishing ¹ the fact of the increase of blood-coagulability under the influence of carbonic acid by direct observations on the condition of blood-coagulability in animals (dogs and rabbits) which were supplied in an alternating manner with ordinary atmospheric air and with atmosphere in which the total nitrogen had been replaced by carbonic acid, and after having verified that the inhalation of carbonic acid had a similar effect on my own blood and also upon the blood of some children belonging to a haemophilic family under my care, I determined to employ the inhalation of the gas as a therapeutic measure in a case of almost desperate haemorrhage which occurred in the haemophilic boy who was referred to me for study by Sir William Jenner.

The history of the case is as follows: The haemophilic heredity can be traced back through three generations of maternal ancestors. The child is at present nearly 4 years old, and has suffered from an almost continuous succession of subcutaneous haematomata. In September, 1893, haemorrhage set in as a result of a fall upon the forehead, which left a scar which was visible for months after. The haemorrhage was treated by ordinary palliative measures, and finally ceased after lasting some six weeks. The blood is said to have shown no tendency whatever to clot, unless when the wound had been tightly bandaged up for several days at a time. The coagulation time of this child (taken at temperatures ranging between 42° and 57° F.) oscillated between 45 minutes and 1 hour. On 2nd February, 1894, the child had another fall against a chair, and hurt the fraenum of his upper lip, and bled a little at the time. Haemorrhage came on profusely at night, and his pillow was soaked with blood and a great deal of blood was swallowed. When this was discovered the parents, according to directions previously left with them, administered 0.6 gramme of calcium chloride, and they state ² that the blood,

¹ *Proceedings Royal Society*, vol. lv.

² These statements may, I believe, be accepted as accurate, for they were confirmed by the grandfather, who has an extraordinarily wide experience of haemophilic haemorrhage, as he has stood by the death-beds of his six sons who all succumbed to haemophilic bleeding or to its sequelae.

which had previously shown no sign whatever of clotting, began to clot firmly in two or three hours after the administration of the lime. Bleeding recurred the next day, and in the evening, after the child had fallen asleep, his mouth was found quite filled with blood clot. On 4th, 5th, and 6th February, bleeding recurred at intervals (probably owing to the frequent dislodgment of the clot). Calcium chloride had been administered all this time in 0.6 gramme doses twice daily. The child was seen by me on 6th February, and I found a scratch about one-eighth of an inch long, covered over by coagulated blood on the fraenum of the upper lip. There was no oozing from the wound. A drop of blood was drawn off from the child's finger, and coagulation time (determined at 37° C.) was found to be 2 minutes 25 seconds,¹ and the addition of lime to the extravascular blood was found not to effect any acceleration of coagulation time.² The calcium chloride appears, therefore, to have done all that could have been expected of it, and yet there had been frequent recurrences of the haemorrhage when the clot became dislodged. In view of these facts I determined to administer carbonic acid gas with a view to still further increasing blood-coagulability. I hoped in this way to cause the blood to clot, not only on the surface of the wound, but also some distance up the lumina of the ruptured vessels. Guided by these considerations I inserted a soft india-rubber tube into the child's mouth, and connected it up with a Kipp's gas apparatus, which I had brought with me. I determined the coagulation time of the child's blood while the carbonic acid was being administered to him, and found that it was accelerated to 1 minute 40 seconds (determined at 37° C.).

The child was not seen by me again till 12th February, when I received another urgent summons saying that the haemorrhage, which had ceased for 24 hours after the inhalation of the carbonic acid, had broken out afresh, and had continued ever since. Calcium chloride had been administered twice daily in 0.6 gramme doses from the 7th to the 11th, when the child vomited and refused to take it. On arrival I found the child absolutely blanched and tetchy to a painful degree. Determinations of coagulability were therefore out of the question. Blood was found to be oozing from the fraenum of the upper lip, and there was a trace, but only a trace, of clot around the wound. Carbonic acid was immediately administered in the same manner as before, and under its influence bleeding broke out copiously. When, however, the child came more under the influence of the gas, and his struggles ceased, the blood clotted instantaneously, so that even the film of blood which was drawn out between the upper and the lower lip when the mouth was opened instantly congealed into a clot. I proceeded to remove the large clot of blood which had formed round the gum, and found it to be of extraordinary firm texture. A small clot instantly reformed round the cut, and the haemorrhage ceased and the child fell asleep. The administration of the gas was continued for half an hour. The gasogene was then recharged and was left under the parents' charge. Haemorrhage

¹ The more favourable temperature conditions and the haemorrhagic increase of coagulability brought about by haemorrhage that had occurred are no doubt responsible for a good deal of the observed acceleration of coagulation time. It is, however, only legitimate to infer that the administration of calcium chloride was largely contributory to it.

² Compare the results already recorded of previous additions of lime to the extravascular blood of this child.

broke out afresh twice or three times in the course of the night, when the clots became dislodged, but clotting is reported to have taken place as soon as the inhalation of the gas was renewed. After this there was no further return of hæmorrhage, and convalescence took place.

In view of the apparently favourable results which have just been recorded, I resorted to inhalations of carbonic acid as a therapeutic measure in the case of abdominal aneurysm which I have already referred to. The method of administration which was finally selected as the most suitable consisted in filling an india-rubber bag (a water bed was pressed into this service) with carbonic acid gas, and in connecting up this bag with the mouthpiece of a Clover's inhaler. This arrangement allowed of the admixture of any desired amount of air with the gas as it escaped from the india-rubber bag. The administration of the gas was superadded to the medicinal treatment which was adopted. The results of these inhalations on blood-coagulability are recorded in the following table :

Date				Coagulation time of patient while breathing ordinary air	Coagulation time of patient a few minutes later when breathing a mixture of CO ₂ and air
				Min. Sec.	Min. Sec.
May	1,	1894	- - -	6 0	5 0
"	3,	"	- - -	6 45	5 0
"	4,	"	- - -	5 35	4 25
"	5,	"	- - -	4 7	3 18
"	6,	"	- - -	5 0	3 45
"	8,	"	- - -	7 45	6 15
"	13,	"	- - -	4 5	2 30
"	15,	"	- - -	3 30	3 15
"	16,	"	- - -	5 10	3 15
"	17,	"	- - -	9 40	5 47
"	18,	"	- - -	7 0	5 40
"	19,	"	- - -	4 25	3 15
"	20,	"	- - -	5 0	3 45
"	21,	"	- - -	4 52	2 42
"	22,	"	- - -	5 0	2 50
"	23,	"	- - -	4 20	3 0
"	24,	"	- - -	4 30	2 23
"	25,	"	- - -	3 22	1 55
"	28,	"	- - -	2 37	2 15
"	30,	"	- - -	3 52	3 20
"	31,	"	- - -	4 15	3 30
June	2,	"	- - -	10 0	4 30

It is thus evident that a very appreciable increase of coagulability can be obtained by the inhalation of carbonic acid. The following facts are to be noted with respect to the manner of administration : (a) It is essential to give a sufficiency of oxygen or of ordinary air with the carbonic acid, not only because a neglect of this precaution causes extreme dyspnoea, but also because an anoxyhæmic condi-

tion of the blood appears to induce a condition of diminished blood-coagulability. (b) Intravascular thrombosis may occur when carbonic acid is administered to an animal whose blood-coagulability is abnormally high. I have, for instance, seen it supervene under these circumstances in animals whose blood-coagulability had already been increased by the administration of calcium chloride. Naturally, therefore, the administration of carbonic acid was omitted in the case of the aneurysm patient in question on the days in which a coagulation time of less than $2\frac{1}{2}$ minutes was registered. In this connexion I may advert to the fact that Sir Joseph Fayrer has pointed out ¹ that in persons whose blood is abnormally coagulable intravascular thrombosis tends to occur (a) after any violent muscular exertion, (b) as a sequela of surgical operations. It is possible that an accumulation of carbonic acid in the blood is a determining factor in both these cases.

Having thus discussed at some length the methods by which blood-coagulability can be increased, we may now take a brief survey of the *methods by which blood-coagulability can be diminished*. The physiologist is familiar with some half-dozen methods by which the coagulation of the blood may be indefinitely postponed. Some of these methods—for instance, the addition of neutral salts to the blood or the cooling of the blood to a temperature approaching the freezing-point—are not applicable to the intravascular blood. Again, other methods—for example, the addition of peptone or leech extract ² to the blood—are therapeutically impracticable, because these substances fail of their effect when they are administered by the stomach, and because their injection into the veins is either dangerous or undesirable. In short, of the methods that are familiar to the physiologist, one method alone promises to be of service to the therapist. This method consists in operating upon the lime salts of the blood in such a manner as to render a certain portion of these salts unavailable for purposes of coagulation. Either oxalic, citric, tartaric, or malic acids, or the soluble salts of these acids, are at our disposal for this purpose. Oxalic acid and oxalates are, however, contra-indicated owing to their poisonous properties. I therefore experimented upon animals and upon myself with tartrates and citrates, taking them by the stomach. I was, however, unsuccessful in obtaining a diminution of coagulability by this method, either in animals or in myself, though I both administered and took large doses of the salts (half an ounce and upwards).

Citric Acid diminishes Blood-coagulability.

I then experimented with tartaric and with citric acids, and have by this method obtained a diminished coagulability in all my experiments. The protocols of some of these experiments are subjoined :

Dog 1 (*circ.* 6 kilos. weight) : 12.35 p.m., coagulation time 1 min. 50 sec. ; 12.55 p.m., 15 grammes of tartaric acid administered by mouth ; 1.5 p.m., dog vomits ; 3 p.m., 15 grammes of citric acid administered by mouth ; 3.45 p.m., coagulation time 3 min. 45 sec.

¹ *British Medical Journal*, 22nd July, 1893.

² Peptone is known to be inefficacious when administered by the stomach. Leech extract has in my experience also proved inefficacious.

Next day at 12.45 p.m., coagulation time 2 min. 55 sec. ; 1.30 p.m., 1 gramme citric acid administered hypodermically in 20 c.c. of distilled water ; 2.30 p.m., coagulation time 3 min. 50 sec. ; 4 p.m., coagulation time 4 min. 55 sec. ; bleeds very freely from puncture in the ear.

Dog 2 (*circ.* 6 kilos. weight) : 1.30 p.m., coagulation time 1 min. 30 sec. ; 1.35 p.m., 1 gramme of citric acid hypodermically in 20 c.c. of water ; 2.45 p.m., coagulation time 3 min. ; 8 p.m., coagulation time 3 min. 30 sec.

Next day at 11.35 a.m., coagulation time 1 min. 35 sec. ; 11.40 a.m., 2 grammes of citric acid hypodermically in 40 c.c. of water ; 1.20 p.m., coagulation time 2 min. 10 sec. ; 4.30 p.m., coagulation time 3 min. 30 sec.

Dog 3 (*circ.* 7 kilos. weight) : 12 noon, coagulation time 1 min. 50 sec. ; 12.5 p.m., 2 grammes of citric acid hypodermically in 40 c.c. of water ; 1.50 p.m., coagulation time 2 min. 30 sec. ; 4 p.m., coagulation time 1 min. 50 sec.

The injections were apparently painless, and no alteration of respiration was observed.

Experiments on myself : 1.45 p.m., $4\frac{1}{2}$ hours after a light breakfast, coagulation time 5 min. ; 4.15 p.m., $2\frac{1}{4}$ hours after a light luncheon, coagulation time 3 min. 10 sec. ; 4.30 p.m., 5 grammes of citric acid swallowed in 50 c.c. of water ; 6.40 p.m., coagulation time 7 min. 15 sec. ; 9.45 p.m., 2 hours after dinner, coagulation time 7 min. ; 11.45 p.m., coagulation time less than 3 min. 40 sec.

One week later : 2.30 p.m., one hour after a very light lunch, coagulation time 5 min. 40 sec. ; 2.50 p.m., swallowed 5 grammes of citric acid in 100 c.c. of water ; 4.50 p.m., coagulation time 6 min. 50 sec. ; 5.30 p.m., coagulation time 7 min. 50 sec. ; 7 p.m., coagulation time 7 min. 40 sec. ; 9.15 p.m., $1\frac{3}{4}$ hour after dinner, coagulation time 7 min. 30 sec.

The results which are shown upon these last two protocols appear to be conclusive with regard to the only question really at issue, that is, the question whether citric acid can be absorbed from the stomach in sufficient quantities and sufficiently rapidly to exert its influence on coagulation. The evidential value of coagulability determinations which have been recorded is brought out by the fact that, in the very numerous determinations of my own blood-coagulability which I have made in the course of the last year, 6 minutes and 15 seconds has been the longest coagulation-time which I have registered, and this was at the end of a long fast between breakfast and dinner. I would therefore suggest that we have here a method which may be clinically exploited whenever we find that the coagulability of the blood has become dangerously increased. I need not further particularise the conditions to which the treatment is applicable. I would, however, point out that the effects of the administration ought to be carefully watched, for it is a very easy matter indeed, at any rate when citrates are being injected intravenously, to bind up all the lime salts of the blood in the form of citrates, and thus to render the blood completely uncoagulable and to destroy the irritability of the heart muscle. Before dismissing the subject of the effects of citric acid on the blood, I may be allowed to direct attention to two matters which appear to have a certain clinical importance.

1. The administration of vegetable juices, such as lime juice, which contains citric and other organic acids (*circ.* 8 per cent.), with a certain small admixture (*circ.*

0·3 per cent.) of the soluble salts of these acids, constitutes the routine treatment for scurvy. It is impossible, however, to doubt that this administration of citric acid must be prejudicial in any disorder in which there is a tendency to hæmorrhage, and when there is actual hæmorrhage occurring from the gums even solutions of citrates are contra-indicated because of their local action in inhibiting the coagulation of the blood as it issues from the bleeding points. I have, through the kindness of Surgeon-Captain Whitehead, had a recent opportunity of actually observing the unfavourable influence that is exerted on incessant oozing hæmorrhage¹ from the gums by the daily exhibition of the juice of three lemons in the form of cooling drinks. The disadvantages of lemon juice in these cases will be apparent to anyone who will test the effect of addition of a minimal quantity of lemon juice to a little blood in a capillary tube provided with a mixing chamber. Further, if, as seems assured, scurvy is a condition in which the normal alkalinity of the system has been dangerously diminished, the administration of free citric acid, quite apart from its influence in diminishing blood-coagulability, is quite useless for all purposes of treatment, and it is evident that its place ought to be taken by the neutral citrates and tartrates, or preferably acetates, which would supply the alkaline bases which are required by the blood. If solutions of citrates and tartrates are administered in cases where there is hæmorrhage from the gums, the mouth ought evidently to be washed out afterwards with a dilute solution of calcium chloride.

2. The eating of unripe fruits which contain free vegetable acids is known to be a frequent cause of certain urticarious oedemas. These oedemas, and the frequent epistaxis also, if I may judge from my own case and from a few others which I have seen incidentally, are most prone to occur during the period of most active growth—in short, at the period when ossification is proceeding most rapidly, and when lime salts in large quantities are being withdrawn from the blood. It would evidently be interesting, in view of these considerations, to have the condition of blood-coagulability tested in these cases.

Having thrown out these suggestions, we may pass on to discuss a further method by which the coagulability of the blood may be intentionally or inadvertently diminished. This method consists in operating upon the gases of the blood with the view of diminishing coagulability by reducing the amount of carbonic acid in the blood. The following methods of diminishing coagulability may probably be subsumed under this heading.

Rapid Respiratory Movements diminish the Coagulability of the Blood.

This fact was established by Hasebroek² upon himself. I have not repeated the observation, but have elsewhere shown that the inhalation of oxygen gas will produce a very appreciable diminution of coagulability in the case of animals. This result is probably due to the very rapid respiratory movements which are induced.

¹ This hæmorrhage, which had continued for more than a month on the regimen of lemon juice, was brought to a complete standstill by the exhibition of 4 grammes of calcium chloride daily diluted in 3 pints of barley water, and taken in sips in order to produce a local as well as a general effect. Coagulation time, which stood at 6½ minutes before the exhibition of lime, came down by gradual steps to 3¾ minutes a few days after the commencement of the treatment.

² *Zeitschrift f. Biologie*, 1882.

Alcohol diminishes the Coagulability of the Blood.

Observations upon this subject have been made by Vierordt,¹ and he points out that the probable inference from them is that alcohol diminishes blood-coagulability.

The following experiments which I have made seem to establish this fact on a more certain foundation.

My Own Blood (3 to 4 hours after rising, 9 hours after last meal).—4.50 a.m., coagulation time, 6 min. ; 5 a.m., $\frac{1}{2}$ pint of champagne ; 5.10 a.m., coagulation time, 8 min. ; 5.20 a.m., coagulation time, 8 min. 5 sec. ; 5.30 a.m., coagulation time, 9 min. 30 sec.

Corporal S.'s Blood ($4\frac{1}{2}$ hours after last meal).—0 hour 5 min. p.m., coagulation time, 3 min. 15 sec. ; 0 hour 10 min., $\frac{1}{2}$ pint of champagne ; 0 hour 30 min., coagulation time, 4 min. 27 sec. ; 0 hour 55 min., coagulation time, 4 min. 40 sec.

My Own Blood (4 hours after last meal).—1.20 p.m., coagulation time, 4 min. 15 sec. ; 1.30 p.m., 10 c.c. absolute alcohol ; 2 p.m., coagulation time, 5 min. 30 sec. ; 2.10 p.m., 10 c.c. of absolute alcohol ; 2.25 p.m., coagulation time, 6 min. 30 sec. ; 2.50 p.m., coagulation time, 5 min. 30 sec.

The effect of alcohol on blood coagulability has evidently a considerable importance in connexion with the therapeutics of actual or threatened haemorrhage.

In conclusion, I have only to emphasise that the methods which have been under discussion are not put forward as adequately tested therapeutic measures. They may, however, chance to be, if I may so 'express them unblamed', contributions to the building up of the newer and better system of therapeutics.

Postscript on Alcohol.

Alcohol also regularly aggravates 'serous haemorrhage'. It became a practical joke in the Army Medical School, Netley, to offer a Surgeon on Probation, who had just been inoculated with anti-typhoid vaccine, a whisky and soda. If he accepted, the seat of inoculation immediately gave him increased pain.

¹ *Arch. f. Heilkunde*, 1878.

PREFACE TO THE TWO PAPERS ON SCURVY WHICH ARE HERE REPRINTED

Of the two papers which are here reprinted the first, which was published in 1895 (i.e. long before Vitamins had been discovered), was of necessity confined to a review of the literature of scurvy. It will be seen that that review (here reprinted with a few omissions) brings out the point that the dietary which produced 'Sea Scurvy'—a dietary consisting almost entirely of salt pork and ship's biscuits—was an exclusively acid dietary. And this is shown to hold true also of the practically similar dietary which produced 'Land Scurvy'—Land Scurvy being the term applied to the scurvy of explorers who had, because of the desert or frozen countries they set themselves to explore, to support life on such victuals as they could arrange to carry.

The second of the papers here reprinted, published in 1900—a date which is also antecedent to the discovery of vitamins—sets forth the results of the alkali titrations carried out on the blood of a group of soldiers who were invalided to Netley Hospital with scurvy, after being shut up in Ladysmith during the siege of that town from the beginning of November 1889 to the end of February 1900.

The results furnished by these blood examinations were, as the reader will see, in perfect accord with my anticipation that scurvy would turn out to be an acidaemia; and that the proper treatment of the condition would be to restore by an administration of easily oxydisable organic salts—the bases which had been removed from the body.

The problem as to whether scurvy is an acidaemia was again soon after taken in hand by two of my pupils—Lamb,¹ who examined sporadic cases of scurvy occurring in Indian prisons, and Dodgson,² who examined cases of sporadic scurvy in natives in the Transvaal Mines.

Neither of these observers—I leave out of account a single definite positive finding reported by Dodgson—could find any evidence of acidaemia in scurvy. It must, however, be noted with regard to the cases of scurvy examined that very little was reported about the symptoms upon which the diagnosis of scurvy had been based, and practically no information was given as to the dietaries which had produced the disease. But there was—this at any rate comes out plainly—in no case any such history of an exclusively acidaemic dietary as would be compulsorily imposed upon the inhabitants of a beleaguered town, or upon sailors of the past during long sailing voyages, or upon explorers when they had to subsist entirely upon such food as it was practicable to carry with them.

Ten or more years after the publication of the papers which are here reprinted quite new ideas on dietic diseases were launched upon the world.

Pekelharing in 1905 and Hopkins in 1906 (whose ideas had in point of fact been anticipated by Lunin so far back as 1881) suggested that there might be such

¹ *The Lancet*, 1902, vol. 1.

² Unpublished Report made to me.

things as 'deficiency diseases', and further that Beri Beri, Pellagra, Rickets, Scurvy and other forms of marasmus—which had all been attributed to poisoning—were in likelihood due to the absence from the patients' dietary of some one of the nutrient substances which Funk had named 'Vitamines'.

And some fourteen years later (1920) Szent-Gyorgi succeeded in identifying ascorbic acid as the vitamin whose withdrawal from the food conducts to the development of scurvy.

The next—and it was an all-important event in the history of scurvy—was the publication in 1907 of Holst and Fröhlich's classical paper on scurvy.¹ It is in that paper very clearly shown that symptoms absolutely identical with those of 'Sea' and 'Land Scurvy' were produced in guinea-pigs when they were put upon a diet consisting exclusively of cereals and water. And though mention is made by Holst and Fröhlich that it had been suggested that scurvy was probably an acidaemia the point is not directly examined.

As soon after Holst and Fröhlich's paper as I could do so, I repeated Holst and Fröhlich's experiments on guinea-pigs—supplementing them (because my immediate interest lay in the presence or absence of acidaemia in scurvy) by weekly titrations of the alkalinity of the serum of guinea-pigs placed upon a diet of cereals and water. The titrations in question satisfied me that there was in all these guinea-pigs progressive acidaemia. And when one picked out by eye from a set of guinea-pigs on Holst and Fröhlich's dietary those which were obviously very sick, one found in all these a very pronounced acidaemia.

On the other hand two of Holst and Fröhlich's observations weigh heavily against the interpretation that scurvy is an acidaemia. The first of these is that Holst and Fröhlich had reported—using a large number of animals for the experiment—that they had found that the administration of carbonate of lime did not prevent the supervention of scurvy in guinea-pigs placed upon the cereal and water dietary.

And the second significant fact reported by Holst and Fröhlich was that scurvy developed in a group of guinea-pigs which were fed wholly upon dried potatoes, a regimen which furnishes a definite alkali ash.

Clarification has been brought into this seeming conflict of facts by unpublished—but I hope soon to be published—experiments of L. B. Holt² carried out in this laboratory.

The first important point about the pathology of Holst and Fröhlich's scurvy which is brought out in Holt's experiments is that the dietary which produces this is definitely an acid dietary.

This is evidenced by the fact that the urine of the guinea-pigs becomes, when they are placed upon this diet, definitely acid, and continues so all the time they are on the dietary, and that the urine becomes always just before death regularly hyper-acid. The acidity then reached is always of the order of pH 6.0.

Holt's experiments further bring confirmation of the finding that the alkalinity of the serum of guinea-pigs begins, very soon after they are placed on Holst and

¹ *Journal of Hygiene*, vol. 7, 1907.

² L. B. Holt, Thesis for the M.Sc. degree, University of London.

Fröhlich's dietary, to decline and continues subnormal as long as they are kept on that dietary, and that this acidæmia is exacerbated in the four or five days before death.

The serum, which in all normal guinea-pigs contains enough alkali to neutralise an equal volume of $N/35$ H_2SO_4 , contains when a Holst and Fröhlich's guinea-pig is coming to the end of its tether only enough alkali to neutralise an equal volume of $N/100$ – $N/200$ H_2SO_4 .

This reduction of alkalinity in the blood is associated with a rapid diminution of weight and with the secretion of the hyper-acid urine already referred to.

This clearly demonstrated diminished-alkalinity of the serum and hyper-acidity of the urine not unnaturally convey to the mind the suggestion that scurvy is an acidæmia produced by an hyper-acid dietary.

When, however, we ponder the fact that the urine of starving guinea-pigs is always acid, and take, in connexion with this, account of the fact that guinea-pigs which are fed upon oats and water only, stop eating—as was correctly noted by Holst and Fröhlich—four or five days before they die, it becomes clear that famine may, in superaddition to the acid dietary, play its part in the lethal acidæmia of Holst and Fröhlich's scorbutic guinea-pigs.

Considerations of this kind led my fellow-worker Holt to titrate the alkalinity of the serum and to determine the acidity of the urine of fasting animals, in order to see how these titrations would compare with those animals who succumbed after they had been placed on a diet of oats and water.

The results arrived at were very interesting. It turned out that the urine which is secreted by starving guinea-pigs is quite as acid, and sometimes even more acid, than that of guinea-pigs on Holst and Fröhlich's dietary. Also it was found that the serum of the starving guinea-pigs, like that of guinea-pigs which succumb after being placed on a diet of oats and water, was completely neutralised by an equal volume of $N/100$ – $N/200$ H_2SO_4 .

Two other important facts emerge from Holt's work—the first relates to the effect of adding 5 mgm. a day of ascorbic acid to Holst and Fröhlich's regimen; and the second to the effect of adding to the same regimen a mixture of alkalies (lactates of soda and potassium, and carbonate of lime).

Holt found that the administration of sufficient ascorbic acid to keep guinea-pigs healthy on Holst and Fröhlich's dietary does not to any appreciable extent reduce the acidity of the urine, though it does effectively prevent the supervention of any serious acidæmia.

This latter fact throws an unsuspected sidelight on the *modus operandi* of ascorbic acid.

Passing from that to the effect exerted by adding alkali to the dietary, it was shown in Holt's experiments that the animals which are so treated live appreciably longer, maintain their weight appreciably longer, and also retain the alkalinity of their serum appreciably longer than untreated animals. And at the same time, as might have been anticipated, the urine which these animals secrete remains alkaline and never becomes acid until they go completely off their food.

And another important fact about the administration of alkali is that the

animals who receive this addition to their cereal dietary, although they all ultimately die of scurvy, do not develop any of that fragility of the bones which is so striking a feature of Holst and Fröhlich's scurvy, and which figures so largely in the clinical reports on 'sea scurvy'.

It became, on giving thought to these findings, impossible to shut one's eyes to the finding that acidaemia plays an important role in the production of 'Holst and Fröhlich's Scurvy', and it is also impossible to doubt that it plays a similar role in the pathology of 'Sea' and 'Land Scurvy'.

Independently, of course, of these experimental results, it is shown in the second of the papers which are here reprinted, which deals with a group of cases of scurvy in soldiers who had been beleaguered in Ladysmith, that the alkalinity of the serum was in all these cases greatly diminished, and that instant improvement was obtained from the administration of lactate of soda.

In view of these findings it would seem imperative for the clinician to measure the alkalinity of the blood in every case of scurvy.¹

And I may add to what has been said above that I have found in the half a dozen or more cases of infantile scurvy which I have had the opportunity of examining marked acidaemia. And in one of these cases—that of an infant daughter of a relative who developed scurvy on a diet of proprietary foods—an instant and striking improvement (this was before there was any vitamin treatment of scurvy) was obtained by the administration of lactate of soda.

¹ A convenient 'stop-gap' method of measuring is the following. Get some very sensitive *red* litmus paper, and some normal human serum. A 20-fold dilution of this last ought to change the red of the litmus paper into a violet, and if it is found that the patient's serum wont do this in higher dilutions than 1 in 10 or 1 in 5 that serum may be taken to be definitely acidaemic.

ON THE PATHOLOGY AND THERAPEUTICS OF SCURVY

(Reprinted from the *Scientific Appendix to the 'Report of the Royal Army Medical Service*
—1895. Published March, 1897)

We shall do well to commence our study of scurvy by considering, first, the facts in connexion with the aetiology, symptoms, and treatment of scurvy which are known to us by clinical experience; and, secondly, the questions connected with the pathology, diagnosis, and treatment of the disease which still await solution.

We may deal first with the facts that have been learned by clinical experience.

Causation.—Clinical experience has shown that scurvy is produced by a dietary which is poor in fresh vegetables and rich in cereals and preserved meats. It has further demonstrated that scurvy is aggravated by all exposure to cold and damp.

Symptoms.—Clinical experience has shown that this disease manifests itself, first, in a marked lassitude and in an extreme enfeeblement of the constitution; secondly, in 'actual haemorrhages', such as bleeding from the gums and other mucous membranes, purpuric eruptions, and sub-periosteal and intermuscular blood-extravasations; thirdly, in 'serous haemorrhages', such as oedema of the cellular tissue (especially of the legs and scrotum), joint effusions (especially in the ankles and knees), effusions into serous membranes (especially effusions into the pleura) and in intestinal effusions (clinically evidenced by diarrhoea); fourthly, in a marked tendency to every variety of suppurative processes.

Treatment.—Clinical experience has shown that the disease is alleviated by the free exhibition of green vegetables and fruit juices, by warmth and dry surroundings.

This is the sum and substance of our knowledge on the subject of scurvy. It will be recognised on reflection that it is incomplete in the following respects:

(1) *Our knowledge is incomplete, first, inasmuch as it does not furnish us with any explanation of the fact that a regimen consisting entirely of preserved meats and cereals, or of either of these separately, induces the symptoms of scurvy.*

Our ignorance on this heading hampers us very much in our selection of a 'non-scorbutic' dietary. Having no sort of scientific principle to work by in making our selection of food-stuffs, we have to guide ourselves entirely by the uncertain light of empiricism.

(2) *Our knowledge of scurvy is incomplete, secondly, inasmuch as it does not furnish us with any absolutely trustworthy criterion of scurvy.*

In view of the long train of symptoms which has been detailed above this statement may present a certain aspect of paradox. None the less, it may be absolutely depended upon, for all the symptoms, which have been enumerated above, manifest themselves in connexion with certain severe cases of haemophilia, and are rightly considered mere manifestations of a serious defect of blood-coagulability. They are not, therefore, as is commonly held, in any way pathognomonic of scurvy. It is obvious from this fact that a diagnosis of scurvy which is based solely upon the

presence of these symptoms cannot be absolutely depended upon. Such a diagnosis only becomes assured when it can be shown, either that these symptoms are directly traceable to a scorbutic dietary, or that relief is obtained from an anti-scorbutic treatment. Through failure to appreciate the necessity of attending to this point, cases of haemorrhagic marasmus with spongy gums, which are in reality dependent either upon tertiary syphilis or upon chronic malaria, are not infrequently mistaken for cases of true scurvy.

(3) *Our knowledge of scurvy is incomplete, thirdly, inasmuch as it does not furnish us with any thoroughly satisfactory method of treating scurvy.*

This statement also bears a paradoxical aspect. For it appears at first sight to be irreconcilable with the fact that sea scurvy has practically disappeared owing to the administration of lime-juice and a better provision of fresh vegetables on ship-board. The statement is, however, abundantly justified, *first*, by the fact that the overland transport of fresh vegetables and lime-juice involves great and at times perfectly insuperable difficulties; *secondly*, by the fact that lime-juice contains, in addition to an anti-scorbutic principle, a constituent which aggravates the defect of coagulability, which, as we have seen, exists in scorbutic blood; *thirdly*, by the fact that the scorbutic condition, when it is well pronounced, appears to be only very slowly and incompletely amended by the exhibition of lime-juice and fresh vegetables. The writings of the older clinicians are replete with testimony to these facts. It will suffice to quote the testimony of Lind, who notes (1) that some 10 to 20 per cent. of the cases of scurvy which were received into Haslar Hospital failed for a period of many weeks after landing to show any improvement under the influence of large quantities of lime-juice and fresh vegetables; (2) that even in the case of patients whose symptoms were rapidly alleviated by the exhibition of fresh vegetables and lime-juice, it was not by any means uncommon to see fresh crops of purpuric spots coming out for weeks after this treatment had been inaugurated; (3) that patients whose symptoms disappeared under the influence of the lime-juice and fresh vegetable treatment were extremely prone to relapse as soon as they were sent back to duty at sea. It is obviously legitimate to conclude from these facts that the scorbutic condition, and its accompanying defect of blood-coagulability, are only slowly and incompletely amended by the customary methods of treatment.

The lacunae in our present knowledge of scurvy having thus become manifest, we may now turn and consider the question.

1. *Why is it that a dietary consisting entirely of cereals and preserved meat induces the symptoms of scurvy?*

The answer to this question must be sought from physiological experiment.

Now it so happens that we have not far to seek for a body of physiological experiments, which, though they were not undertaken with any thought of elucidating the pathology of scurvy, are yet experiments which throw a very important light upon the pathology of this disease. The experiments in question were instituted by Walther under Schmiedeberg's direction. The object which the experimenters had in view was to determine the effect of administering mineral acids to animals.

Both dogs and rabbits were employed for these experiments.

We may deal, first, with the results which were obtained upon rabbits. These may be briefly summarised as follows :

It was found that when a mineral acid, such as hydrochloric acid, is administered to a rabbit the results vary according to the dose. When the amount of ingested acid is moderate the acid becomes completely neutralised by the surplus of alkaline salts which is normally present in the food. Under these circumstances the rabbit suffers no ill-effects from the acid ingestion. When, however, the quantity of acid is increased until the quantum of ingested acid is in excess of what can be neutralised by the alkaline salts of the food, it is found that the excess of acid neutralises itself by entering into combination with those alkaline salts upon which the alkalinity of the blood depends. Under these circumstances the rabbit begins to exhibit symptoms of acid-intoxication. If the amount of acid is considerably in excess of what can be neutralised by the alkalies of the food, the animal's condition becomes very serious. It refuses to eat and falls into a condition of extreme marasmus. Such a rabbit, if untreated, finally succumbs as a so-called '*acid rabbit*'. When the animal dies his blood is found to have lost nearly all its alkalinity. (Death invariably takes place before the blood becomes actually acid.) It is further found that the animal's blood has become extremely poor in carbonic acid. This is due to the fact that the blood loses its power of taking up carbonic acid from the tissues as soon as it is deprived of the alkaline salts, which under normal conditions function as the carriers of carbonic acid. Lastly, it is found that the blood of the acid-intoxicated animal has become almost incoagulable. This is no doubt due in part to the fact that the blood is impoverished in carbonic acid. In part it is also probably due to the fact that the hydrochloric acid which has been ingested has combined with the calcium salts of the blood, and has, by rendering them more soluble, favoured their excretion in the urine.

Entirely different results are obtained when mineral acids are administered to dogs.

In the first place, there can be no question in the case of the dog of any neutralisation of acid by the alkaline salts of the food. For the dog, like all other carnivora, feeds on animal food, which, as we shall presently see, contains an excess of acids over alkalies.

In the second place, the mode in which the ingested acid is neutralised in the dog's organism is found to be entirely different from the mode in which ingested acid is neutralised in the rabbit. In the rabbit, as we have seen, acid is neutralised at the expense of the alkaline salts of the blood. In the dog ingested acid is neutralised by ammonia. The difference is all-important. In the one case the alkali which is applied to the neutralisation of acid is abstracted from a comparatively small stock of alkaline salts, which forms an essential constituent of the blood, and which cannot consistently with safety be diminished. In the other case the alkali ammonia, which is applied to the neutralisation of acid, is a waste product, which, at any rate in the dog, is always available in sufficient quantity to meet all the demands that are made upon it.

In consequence of this faculty of applying the waste products of the body to the neutralisation of mineral acid, the dog, unlike the rabbit, bears up perfectly well against even a very considerable acid-ingestion. Contrary to what happens in

the rabbit the ingested acid does not in the dog either rob the blood of its alkaline salts or diminish its coagulability.

Man occupies with respect to his power of neutralising acid a position which is intermediate between that of the dog and the rabbit. He differs from the rabbit in possessing a certain faculty of neutralising acid by means of ammonia. He is, therefore, able to bear up without injury against a moderate degree of acid-intoxication. He differs, on the other hand, from the dog in the fact that there is a very definite limit to his power of neutralising acid by ammonia. If he is plied with acids beyond this point the alkalinity and coagulability of his blood will diminish, and will finally succumb to the acid-intoxication.

In order to see the particular application of this fact to the pathology of scurvy, we must now turn aside and consider the question of the acidity and alkalinity of our more common food-stuffs.

Our food-stuffs may be broadly classified for present purposes into three categories: (1) *Alkaline food-stuffs* (i.e. food-stuffs which leave upon incineration a distinctly alkaline ash): (2) *neutral food-stuffs* (i.e. food-stuffs which leave upon incineration a neutral or almost neutral ash): (3) *acid food-stuffs* (i.e. food-stuffs which leave upon incineration a distinctly acid ash).

In the class of *alkaline food-stuffs* may be ranged all the vegetable substances which are commonly grouped together under the title of 'fresh vegetables', i.e. all green vegetables, and further all tubers and roots. Again we may range under the alkaline food-stuffs all fruits and fruit juices. Even such eminently acid fruits as limes and lemons fall into the category of alkaline food-stuffs, inasmuch as the constituent vegetable acids of these fruits are entirely resolved into carbonic acid and water in the heat of the flame, and have therefore no influence on the character of the ash. Further, we may range under the alkaline food-stuffs the blood and milk of all mammals, especially the milk of the herbivora.

The most important food-stuffs which fall into the category of the *neutral food-stuffs* are the various sugars and the vegetable and animal fats and oils.

In the category of the *acid food-stuffs* may be ranged all cereals and all meats, for these food-stuffs contain considerably more mineral acid than can be neutralised by the alkaline bases which enter into their composition.

When we reflect upon these facts we see that they furnish us with an explanation of the differences in the faculty of acid-neutralisation which are found in the animals which feed on these various classes of food-stuffs.

We have in the first place a class of *herbivora*. In these, as we have seen, there is no special provision for the neutralisation of acid. We now see that this is in conformity with the fact that these animals, so long as they feed exclusively upon herbage, have no need for any such provision, seeing that they are feeding upon alkaline food-stuffs which continually replenish the blood with alkaline salts.

We have further a class of *carnivora*. In these animals, as we have seen, there exists a very effectual provision for neutralising acid by means of the waste ammonia of the body. Without some such provision as this for keeping the blood alkaline a class of carnivora could not well have come into existence.

Lastly, we have the case of *man*. In man, as we have seen, the same sort of provision for neutralising acid exists as exists in the carnivora. We can now appreciate that this is in conformity with the fact that man under normal circumstances feeds on a dietary in which the acid food-stuffs preponderate over the alkaline food-stuffs. But, on the other hand, that in man the provision which exists for neutralising acid is not by any means as effective as in the carnivora. We now see that this is in conformity with the fact that under ordinary circumstances there is in our dietary a comparatively small preponderance of acids over alkalies. This is due to the fact that we are continually neutralising some of the excess of acid, which we ingest in the form of acid food-stuffs, by the excess of alkali, which we ingest in the form of alkaline food-stuffs.

Our next step, after we have thoroughly digested these facts, must be to consider carefully what would inevitably happen if this process of setting off the alkalies of our vegetable food against the acids of our animal food were to be forcibly interrupted by the omission of all fresh vegetables and fruits from our dietary.

It is obvious to reflection that under these conditions we should inevitably lapse into a condition of acid-intoxication.

But, again, experience shows that it is precisely under these conditions that man falls a victim of scurvy.

We may, therefore, at least provisionally conclude that scurvy is a condition of acid-intoxication.

This conclusion has a very important bearing upon its differential diagnosis and upon its treatment.

Before, however, proceeding to base either a method of diagnosis or a method of treatment upon this theory of scurvy, it will be expedient further to test the correctness of our inferences by considering whether this theory of scurvy will suffice to explain all the symptoms which come under observation in cases of scurvy.

It will hardly be necessary in this connexion again to point out, for I have already pointed it out in the introduction to this paper and also elsewhere, that, on the one hand, purpura, bleedings from mucous membranes, intramuscular extravasations, and such like ; and, on the other hand, oedema of the cellular tissue, pleural and serous effusions into joints, serous cavities and intestinal tract, are generally nothing more nor less than manifestations of an existing defect of blood-coagulability. Neither will it be necessary again to point out that a tendency to suppuration is often only one of the manifestations of a condition of extremely defective blood-coagulability.¹

We have merely to note here that the occurrence of one and all of these symptoms in scurvy is readily explicable on the assumption that scurvy is an acid-intoxication which eventuates in a defect of blood-coagulability.

In connexion with the suggestion that defect of blood-coagulability may be due

¹ I may, however, note in passing that in a case of defective blood-coagulability which came under my notice, not only was there severe oedematous urticaria, but there was also such a pronounced tendency to suppuration, that every accidental scratch gave rise to suppuration, and every blister that was raised on the hands by rowing filled up with pus instead of with clear serum.

to a deficiency of lime salts in the blood, it is perhaps worth noting that the excessive erosion of bones, the absorption of already calcified callus, the spontaneous separation of rib cartilages from the sternum, and, finally, the deficient post-mortem rigidity which are recorded by the older writers as occurring in exceptionally severe cases of scurvy, are one and all suggestive of an extraction of lime salts from both bone and muscle under the influence of an acid-intoxication. The frequent association of infantile scurvy with rickets is another fact which points in this direction.

Again, it is worth noting the fact that cold which, as we have seen, aggravates all the symptoms of scurvy, also aggravates the defect of blood-coagulability in haemophilic patients, and in others who suffer from diminished blood-coagulability, and thus predisposes to bleedings and to 'serous haemorrhages'.¹

It will thus be seen that all the symptoms of scurvy without exception are perfectly consistent with the theory that scurvy consists essentially in an acid-intoxication.

We may further test this theory by considering whether the therapeutic results which have been obtained in scurvy are or are not consistent with this explanation. For obviously, if our theory of scurvy is correct, such methods of treatment, as have been employed in connexion with scurvy, ought to be effectual or ineffectual, just according as they are appropriate or inappropriate to the treatment of a condition of acid-intoxication.

The first of these methods which suggests itself for consideration is the *treatment of scurvy by the exhibition of fresh vegetables*.

We need not, however, delay long over this method. It will suffice us to note in the first place that this method of treatment is eminently effectual in practice, and in the second place that it is a method which is appropriate to the relief of acid-intoxication, inasmuch as the vegetable substances which are exhibited are substances which contain an excess of alkalies over acids.

We may next consider the *treatment of scurvy by lime-juice*. Here, again, we have a method which renders undeniable service in the prophylaxis, and to some extent also in the treatment, of scurvy. And here, again, in consonance with the theory of scurvy which has been enunciated, we find that lime-juice is a substance which upon incineration yields an alkaline ash.

In reality this fact sufficiently disposes of the whole question of the anti-scorbutic influence of lime-juice.

None the less, it may be well not to dismiss the subject without considering some of the issues that have been raised in connexion with this question.

We may note, first, the fact that lime-juice is something more than a mere alkaline food-stuff. It is a substance which contains as essential constituents, in the first place, some 7 to 8 per cent. of citric acid, and further some 0.3-0.4 per cent. of ash (chiefly potash).

In view of this preponderance of the citric acid over alkaline bases, the objection may not unnaturally suggest itself, that we are perhaps not justified in referring

¹ Chilblains are perhaps the most common example of a serous haemorrhage which is conditioned by cold.

the anti-scorbutic properties of the natural lime-juice to the alkaline potash salts instead of to the citric acid. This objection is, however, invalidated by the fact that clinical experience has definitely shown that citric acid taken by itself is of no avail whatever against scurvy.¹ When this has once been established it would appear inevitably to follow by exclusion, that the anti-scorbutic effect of lime-juice must be referred to the potash salts which enter into its composition.

But even this argument by exclusion, in spite of its all but absolute conclusiveness, appears to be of no avail against the fact that it has been established, not only by the experience of North American lumberers, who feed on meat which has been corned with nitrate of potash, but also by the results of experiments with nitrate of potash (which were instituted with the direct object of testing Dr. Garrod's theory of the causation of scurvy by a paucity of potash salts in the blood), that *potash salts as such* have no anti-scorbutic power. It is, however, hardly necessary to point out that nothing that may be either proved or disproved in connexion with *mineral acid salts* of potash has any application whatever to the *vegetable acid salts* of potash which are contained in lime-juice. For mineral acid salts, such as chlorides, nitrates, and sulphates, differ absolutely in their physiological relations to the organism from vegetable acid salts. Mineral acid salts (as our experience of sodium chloride teaches us) pass through the system unaltered. Vegetable acid salts are, as is well known, converted in the system into carbonates. The only interest which these nitrate of potash experiments have for us at present lies, therefore, in the fact that they establish that salts of potash, which upon incineration yield a neutral ash, are of no avail against scurvy. It is to be observed that this is a fact which is, not only not in contradiction, but is in reality in strict consonancy with the inference that lime-juice owes the anti-scorbutic properties which it possesses to the vegetable acid salts of potash which enter into its composition.

Lastly, we may consider the question of the *treatment and prophylaxis of scurvy by administration of blood, or of fresh meat with the blood in it.*

This method of treatment appears to be extensively employed by the Samoyedes, who have great faith in the anti-scorbutic powers of draughts of reindeer blood. Of late it has come prominently under notice in connexion with the experiences in the Arctic of Dr. Nansen, Mr. Jackson, and also of the crew of the *Eira* (detailed by Dr. Veale in the *Practitioner*, of June 1896). It would, in the light of these recent and well-authenticated experiences, appear to be no longer open to doubt that the ingestion of blood, or of meat with the blood in it, is by itself, quite independently of any aid from vegetable diet, perfectly effectual in warding off scurvy.

We have consequently to examine this new and important clinical fact, and to see whether it can be explained upon the theory that scurvy is an acid-intoxication.

We need not hesitate to reply to this question with an emphatic affirmative. For, on turning back to our classification of food-stuffs, it becomes perfectly clear

¹ It was hardly necessary to wait for clinical experience to establish the fact, for it is obvious to reflection that a substance, such as citric acid, which is resolved in the body exclusively into carbonic acid and water, could not by any possibility contribute any remedial element to the blood of a scorbutic patient.

not only that the blood is an alkaline food-stuff, but that it is comparable in its alkalinity to lemon and orange juice. We have obviously here a simple explanation of the utility of blood in warding off scurvy. Further, when we consider these explorers' dietaries we see a further explanation of their immunity from scurvy. We perceive that the carbohydrate material, which we in our ordinary dietary ingest in the form of acid cereal food-stuffs, was replaced in the explorers' dietaries by fats which were ingested in the form of neutral seal and walrus blubber.

We thus see that the acid-intoxication theory of scurvy furnishes us with a complete explanation of the fact that these explorers remained perfectly free from scurvy, although they fed on an exclusively animal dietary.

We may now briefly sum up the conclusions which have been arrived at in the course of our survey of the different methods of treating scurvy. We have on the one hand seen that there are only three methods which have been definitely shown to exert an influence in warding off and ameliorating the scorbutic condition. Each of these methods consists essentially in the administration of an alkaline food-stuff (we have seen that blood, fresh vegetables, and lime-juice all come under this denomination). Of each of these methods it may, therefore, be asserted that it is a method which is calculated to ward off and ameliorate a condition of acid-intoxication.

On the other hand, we have incidentally considered two other methods of treating scurvy, which have been tried, and have been discarded as useless. The methods in question are, first, the treatment of scurvy by citric acid, and further, the treatment by mineral salts of potash. Each of these methods has been shown to be a method of treatment which would be of no possible avail against an acid-intoxication.

We are consequently definitely confirmed in our belief that scurvy is a condition of acid-intoxication.

ON THE PATHOLOGY AND THERAPEUTICS OF SCURVY¹

(Reprinted from 'The Lancet', 25th August, 1900)

I propose here to place on record the results of a series of examinations of the blood, instituted with the view of testing the correctness of the inferences with regard to the nature of scurvy which were set forth by me in a paper on the 'Pathology and Therapeutics of Scurvy', printed in the *Army Medical Report* for the year 1895 (published in March, 1897).¹ The line of thought which runs through the paper in question was briefly as follows.

The scorbutic condition is a pathological condition which is induced by a dietary consisting of meat and cereals to the exclusion of green vegetables, tubers, and fruits. Inasmuch as the food-stuffs which are excluded from the dietary in question are food-stuffs which contain an excess of bases over mineral acids, while the food-stuffs (meat and cereals) which remain are food-stuffs which contain a large excess of mineral acids over bases, it is obvious that the scorbutic condition is one which supervenes upon the ingestion of a considerable excess of mineral acids over bases. It would, in view of this consideration, seem probable that scurvy is a condition of acid-intoxication, very similar to the acid-intoxication which can be experimentally produced in herbivora by the ingestion of a surplus of mineral acids. The theory that scurvy is essentially a condition of acid-intoxication would appear to be in harmony with the circumstance that the rapidity with which the scorbutic condition supervenes depends, apparently, upon the degree to which the mineral acids are in excess in the dietary. The condition is apparently more rapidly superinduced by a dietary of corned meat (i.e. meat which has been rendered hyperacid by the removal in the process of corning of the alkaline salts of the blood and lymph) than by a dietary of fresh meat (i.e. meat which still contains these alkaline salts). Similarly infantile scurvy would seem to be generally dependent upon the substitution of more acid food-stuffs (preparations of cereals sold under the designation of 'infant foods') for the less acid food-stuff, milk. Justification for the identification of scurvy with a condition of acid-intoxication would appear to be afforded also by the consideration that the scorbutic condition is remedied or alleviated by the addition to the scorbutic dietary of any one of a whole series of different substances—tubers, green vegetables, decoctions of leaves and growing shoots, blood (used for this purpose by the Lapps), fruits, and fruit juices—substances which have apparently in common only the circumstance that they all contain an excess of bases over mineral acids. It was pointed out in the conclusion of the paper whose argument has just been summarised that, given the correctness of the above view of the origin and nature of scurvy, the proper prophylaxis and treatment of the condition would consist in the administration of salts of oxidisable organic acids, inasmuch as such treatment would lead by the most direct means to the retention or restoration of the normal alkalinity of the blood.

¹ *Vide excerpt supra*, pp. 42-49.

Enough will now have been said to place the reader in possession of the ideas which dictated the line of inquiry and the therapeutic measures which were adopted in the following cases of scurvy which came under observation in the wards of the Royal Victoria Hospital, Netley.

The question of the presence or absence of a condition of acid-intoxication was in each case investigated by the method of haemalkalimetry. The haemalkalimetric method employed was the method which was described by me in a previous communication to *The Lancet*.¹ As estimated by that method, the alkalinity of the normal blood is represented by the formula N/35. In other words, the alkalinity of the blood is under ordinary conditions of health such that the addition of one volume of a normal acid, 35 times diluted, to an equal volume of serum, just suffices to deprive that serum of its power of blueing sensitive red litmus paper.

The particulars of the cases of scurvy which were examined are as follows.

CASE 1.—Private A. Patient was examined on 1st May, 1897, when considerable subcutaneous ecchymoses were found interspersed with smaller purpuric spots on the legs and arms. There was general yellowish discoloration of the skin and brawny discoloration and oedematous effusion of the right foot and ankle. There was no noticeable sponginess of the gums. The alkalinity of the blood was N/100. On the 10th three three-gramme (45-grain) doses of acetate of potash were prescribed. There was some resultant diarrhoea. On the 12th the alkalinity of the blood was N/100. In lieu of previous treatment two grammes (30 grains) daily of acetate of soda were prescribed. On the 14th the alkalinity of the blood was N/70. The same treatment was continued. On the 18th the alkalinity of the blood was N/70 and the treatment was persisted in. On the 21st the alkalinity of the blood was N/70, and four grammes (60 grains) daily of tartrate of soda were prescribed. On the 24th the alkalinity of the blood was N/55 and the treatment was continued. On the 26th the alkalinity of the blood was N/45. The patient, who had previously, on a regimen of lime juice, had several recurrences of the purpuric eruption and of the swelling in the foot, became perfectly well.

CASE 2.—The patient, a sergeant, developed typhoid fever on the transport returning from South Africa. On 12th June, 1900, his condition was as follows. There was a characteristic earthy yellow complexion; the gums were spongy, deeply ulcerated, and covered with blood; and the mouth, in spite of treatment with antiseptic washes, was so sore that the patient could hardly speak or drink. The alkalinity of the blood was N/100. Four grammes of lactate of soda daily were prescribed. On the 17th the complexion and condition of the mouth were found to be much more satisfactory. The patient could speak and swallow without pain. The alkalinity of the blood was N/35. The patient afterwards succumbed to typhoid fever.

CASE 3.—The patient, seen for the first time on 5th May, 1900, was a private soldier and was one of the beleaguered garrison at Ladysmith. He had a history of dysentery, complicated by frequent epistaxis. Since the raising of the siege his dietary had consisted exclusively of milk. The patient was seen to be in a very

¹ *The Lancet*, 18th September, 1897, p. 719.

precarious condition. He was extraordinarily emaciated and was too feeble to raise his head from the bed. His complexion was of a dark greenish-yellow colour, like that of a corpse which had been buried. His mouth was very foul, the gums being covered with blood-stained sordes. A thin bloody fluid oozed at times from the nostrils. He had frequent serous motions, especially at night, the calls being so often repeated and so sudden as to prevent sleep. The alkalinity of the blood was N/200. One gramme of bicarbonate of soda three times a day was prescribed. On the 7th the blood coagulation time (estimated at the standard temperature of 18.5° C., in coagulation tubes of the standard calibre of 0.25 millimetre), was seven minutes. The quantitative estimation of calcium salts in the blood (estimated by mixing in capillary tubes one volume of pure neutral oxalate of soda solution with an equal volume of blood) showed that the minimum addition of oxalate of soda which sufficed to keep the blood liquid was 1 in 800. The treatment was continued. On the 9th five grammes of lactate of soda were prescribed. On the 10th the lactate of soda was reduced to 2.5 grammes daily. On the 11th the alkalinity of the blood was N/40. After this the patient improved in an extraordinarily rapid manner, his complexion becoming healthy and his dysenteric symptoms amending. He left the hospital about eight weeks afterwards looking robust and well nourished, every trace of scurvy having passed away.

CASE 4.—The patient, who also was seen for the first time on 5th May, 1900, had arrived by the same transport as the patient in Case 3. He had been in Ladysmith during the siege. The patient was found to be in an extremely emaciated and very precarious condition. There was the characteristic yellowish-green complexion noticed in the last case and the body was covered with the remains of a (? purpuric) eruption. There was a large sore under the tongue. There were frequent dysenteric stools associated with great pain. The alkalinity of the blood was N/150. Two grammes of citrate of potash daily were prescribed. On the 7th the blood-coagulation time was eight minutes. The quantitative estimation of lime salts in blood showed that an addition of 1 in 600 of oxalate of soda was the minimum addition which sufficed to keep the blood liquid. The alkalinity of the blood was N/55. The same treatment was continued on the 8th and on the 9th five grammes of lactate of soda were ordered. On the 10th the lactate of soda was reduced to 2.5 grammes daily. On the 11th the alkalinity of the blood was N/35. The patient made a good but gradual recovery. He is now well nourished and has a clear healthy complexion, but he still suffers periodically from severe intestinal pain.

CASE 5.—The patient was a private soldier who arrived from Ladysmith by the same transport as the patients in Case 3 and Case 4. The diagnosis was dysentery complicated with phthisis. There was no history of bleeding or of purpuric eruption. He was not so reduced as the last two patients, being strong enough to sit up in bed. There was no sponginess of the gums, but the characteristic yellowish discoloration of the skin was present. There were large cavities in both lungs. The alkalinity of the blood on 5th May, 1900, was N/80. Three grammes of sodium bicarbonate daily were prescribed. On the 9th five grammes of lactate of soda were given, the dose being reduced on the 10th and following days to 2.5 grammes daily.

On the 12th the alkalinity of the blood was N/35. The patient died on the 16th. The necropsy showed widespread destructive changes in the lungs and extensive ulceration of the intestine.

CASE 6.—The patient, seen first on 17th June, 1900, was a private soldier, aged 22 years, who had been one of the beleaguered garrison of Ladysmith and had suffered from enteric fever during the siege. He was found to be in a most extreme condition of emaciation, being reduced to skin and bone. Both buttocks were the seat of enormous bed-sores. At times he appeared to be almost exanimate, the whites of the eyes being alone visible. A fluctuating abscess of the size of a small orange occupied the left side of the cheek over the jaw. Watery blood oozed from the gums and a quantity of yellow serous discharge came from the nose. In spite of hot bottles and thick blankets the patient felt stone cold. His feet were considerably swollen and were covered with extensive ecchymoses; there were ecchymoses also on the legs and arms. The patient at times yelled with the pain of the bed-sores and of the frequent cramps in his legs. His intelligence was disordered and he begged for his legs to be cut off. His motions were passed under him in bed. The alkalinity of the blood was N/110. Four grammes daily of lactate of soda were prescribed. There was no noticeable change in his condition on the 18th, his mind still rambling. The treatment was continued. On the 20th his condition had much improved; he felt warm and the oedema of the feet had somewhat subsided. He said that the cramps were less frequent and that the bed-sores were not so painful. The abscess in the cheek had burst into the mouth. The alkalinity of the blood was N/35. The treatment was continued. On the 22nd the patient declared himself much better and asked to be allowed to smoke. On the 24th his temperature rose, the curve assuming a characteristic septic type, and the bed-sores were found to have assumed a gangrenous appearance. He succumbed on the 28th. The necropsy disclosed a certain amount of thickening, pigmentation, and congestion of the intestine. There was no effusion into the serous membranes. A colourless gelatinous substance occupied the medulla of the long bones. In spite of frequent examination directed to this point no trace of rigor mortis was detected.

CASE 7.—The patient was a private soldier and was also one of the beleaguered garrison of Ladysmith. He was brought into hospital from the transport on 18th June, 1900, in an extremely emaciated and moribund condition. The whole front of the body, from the neck to the umbilicus, was occupied with an extensive blood extravasation. In places where the epidermis had peeled off the surface resembled that of dried raw meat, and there were copious ecchymoses over the limbs and other parts of the body. Five grammes of lactate of soda were administered in milk. He succumbed a few hours after admission. Beyond the appearances described above and a complete absence of rigor mortis nothing characteristic was discovered at the necropsy. The alkalinity of the blood which was taken from the heart 22 hours after death¹ was N/100.

¹ Observations made specially to determine whether any alteration of alkalinity occurs after death appear to show that there is in the case of blood taken from the heart only a very slight diminution of alkalinity within 24 hours after death.

The fact that in all these cases the alkalinity of the blood was so strikingly reduced, and the fact that in every case (with the exception of the last where there is reason to suppose that the drug was not absorbed) a very striking amelioration of the condition followed upon the exhibition of lactate of soda and other similar substances, seems to me to establish beyond doubt that scurvy is—as was suggested in the paper referred to above—a condition of acid-intoxication.

The following subsidiary points would appear to be deserving of notice: 1. Cases 3, 4, and 5, in which dysenteric symptoms were prominent, were well marked off from cases of ordinary dysentery, not only by their characteristic clinical features, but also by the fact that the alkalinity of their blood was diminished. The alkalinity of the blood in the uncomplicated cases of dysentery was not found to differ from the normal. 2. It was found that there was neither a notable reduction of blood-coagulability nor a diminution of the lime salts of the blood in Cases 3 and 4, where these points were specially investigated. Nor were there in any of the three cases which succumbed any effusions into the serous cavities such as are described in the older records as constituting a characteristic feature in pronounced cases of 'sea scurvy'.¹ 3. Case 2 would seem to be of interest as showing that the scorbutic condition may supervene and complicate the course of a specific fever. This point would seem to deserve attention, not only in connexion with the fact that a patient admitted for specific fever may previously have been subsisting on a scorbutic dietary—as will not unfrequently be the case in soldiers on active service—but also in connexion with the circumstance that a scorbutic condition may be induced during the course of a fever by the restriction of the patient to a dietary consisting of 'acid food-stuffs'.² 4. A comparison of the course of events in Case 1 with the course of events in Cases 3, 4, 5, and 6 (all of which were much more severe) would seem to indicate that the desired increase of alkalinity can be more rapidly achieved by the administration of lactate of soda than by the administration of the salts of the less easily oxidizable organic acids. This is in conformity with what might *a priori* have been expected.

NETLEY HOSPITAL.

¹ The absence of any features pointing to a notable reduction of blood-coagulability and the presence of lime salts in the blood in normal quantities in the two cases examined are possibly associated with the fact that the patients who were under observation had, so far as was known, been continuously upon a diet of milk, which though it would do nothing to correct the condition of diminished blood alkalinity would probably efficiently correct any tendency to diminished coagulability.

² It need hardly be pointed out that a condition of diminished alkalinity, even when it is not sufficiently pronounced to induce the characteristic symptoms of scurvy, may not be without influence in the course of a specific fever.

ON THE TREATMENT OF THE HAEMORRHAGES AND URTI- CARIAS WHICH ARE ASSOCIATED WITH DEFICIENT BLOOD-COAGULABILITY

(Reprinted from 'The Lancet', 18th January, 1896)

I have in previous communications¹ directed attention to the fact that the coagulability of the blood can be increased (1) by calcium salts, (2) by carbonic acid, and (3) by solutions of cell nucleo-albumins (Wooldridge's tissue-fibrinogens). I propose in the present communication first to amplify certain statements I have made upon these subjects; secondly, to direct attention to a simple method of administering carbonic acid; and, thirdly, to suggest that calcium chloride may prove useful in the treatment of urticaria, wherever the urticarious eruption is associated with a condition of diminished blood-coagulability.

The following cases may be of interest as showing the increase of blood-coagulability which can be obtained in haemophilia by the internal administration of calcium chloride.

Patient	Age	Date of antecedent blood examination	Coagulation time in standard tube (temp. 18.5° C.)	Amount of CaCl ₂ administered	Date of subsequent blood examination	Coagulation time in standard tube (temp. 18.5° C.)
Boy (very severe haemophilia)	9 years	April 13th, 1894	Exceeds 54 minutes	Two 2 gramme doses	April 14th, 1894	25 minutes
				Two 2 gramme doses	April 15th, 1894	13½ minutes
		Sept. 28th, 1894	14 minutes	Two 0.6 gramme doses	Sept. 29th, 1894	6½ minutes
Brother of above (less severe haemophilia)	7 years	April 13th, 1894	7 minutes	Two 2 gramme doses	April 14th, 1894	4 minutes
		Sept. 28th, 1894	9½ minutes	One 0.6 gramme dose	Sept. 29th, 1894	5½ minutes

It is to be noted that the augmentation of coagulability which is here recorded is neither a constant nor a permanent augmentation of coagulability. In these, as in all other cases of haemophilia which have come under my observation, a continued administration of twenty- to thirty-grain doses of calcium chloride (cryst.) resulted in a diminution of coagulability below the original norm. There is evidently in the haemophilic, just as there is in the normal, patient a maximum of lime addition which ought not to be exceeded. For the purposes of the arrest of haemorrhage this subsequent diminution of coagulability may, however, generally be left out of

¹ Vide pp. 15 *et seq.*, and pp. 26 *et seq.*

account, for when the maximum of coagulability is reached haemorrhage will generally be arrested by the sealing of the wound by clot. I have seen this result follow upon the internal administration of calcium chloride in several cases of haemophilic haemorrhage. I am also indebted to Dr. Newcombe of Gateshead-on-Tyne, to Mr. Horace Potts, to Dr. A. H. Jones of Northampton, and to Surgeon-Lieutenant J. N. Macleod, I.M.S., for notes of cases in which haemophilic haemorrhage was arrested by the internal administration of calcium chloride. The less soluble calcium salts may also be usefully applied in the form of local applications to the bleeding surfaces. I have obtained very satisfactory results from the application of finely powdered chalk mixed into a paste with a $\frac{1}{2}$ per cent. solution of calcium chloride. Dr. N. F. Surveyor had previously been good enough to send me the notes of a case under his care in which an arrest of severe haemophilic bleeding from the gums was obtained by an application of calcium phosphate. In Dr. Surveyor's case escharotic styptics had previously been applied with unsatisfactory results.

Hypodermic administration of calcium chloride is a method which I have forborne to apply upon man, as I have seen extensive (apparently aseptic) sloughing to result from a subcutaneous inoculation of calcium chloride into a dog. I have also in a haemophilic boy seen scars of extensive sloughing which had been produced by a hypodermic injection of calcium chloride employed for the arrest of haemorrhage.

Before dismissing the topic of the effect of calcium salts in haemophilia it may not be out of place to put upon record the fact that I have been able to convince myself of the truth of Dr. Wickham Legg's statement that haemophilic children are not infrequently addicted to eating plaster, mortar, and similar substances. For instance, the sole surviving maternal uncle of the two haemophilic boys, who have already been dealt with in this paper, spontaneously volunteered the statement that he had in his boyhood a constant craving for lime and plaster. This man is the subject of moderate haemophilia, and has an ankylosed joint. Again, I was informed that a maternal first cousin of these same boys "could not be kept off from eating plaster". This boy, a child aged four years, who is the subject of severe haemophilia (blood-coagulation time twenty-nine minutes), used to pick out the mortar from between the bricks when he was sent out of doors to prevent his eating plaster off the wall. I was shown a large portion of wall denuded of plaster as evidence of the child's plaster-eating propensities, and I was informed, that his craving for plaster was most marked before his haemorrhagic attacks.

I will now pass on to consider the other means which are at our disposal for combating haemophilic haemorrhage. The internal and external administration of calcium salts does not always result in the arrest of haemorrhage. Even so large an increase of blood-coagulability as that which I have recorded in the case of the first boy (*vide* Table *infra*) would not necessarily have resulted in an arrest of haemorrhage. A blood-coagulability of $6\frac{3}{4}$ minutes¹ is no bar to the occurrence of very severe capillary haemorrhages. In cases of severe haemorrhage it will, therefore, always be judicious to supplement the treatment by calcium salts by the

¹ Normal blood coagulates in from two to four minutes in the standard capillary tube at a temperature of half blood heat (18.5° C.).

inhalation of carbonic acid. I have employed this treatment upon two occasions in the treatment of haemophilic haemorrhage. Upon both occasions I obtained a comparatively prompt cessation of haemorrhage. I have also obtained very satisfactory results from the application of the method in the case of a patient in the Royal Victoria Hospital, Netley, whose blood-coagulability was seriously diminished by prolonged tropical fever, and who was reduced to an extremely precarious condition by perpetually recurring epistaxis. In the case of this patient all the ordinary methods of arresting haemorrhage had been resorted to unavailingly. He had been treated successively with ferric chloride, with turpentine, with calcium chloride, with hypodermic injections of ergot, with alum insufflations, and with ice applications. His coagulation period varied during the whole of this period of treatment between eight and four and a half minutes. The number of his white blood corpuscles, though increased under the influence of the turpentine, often fell below 1000 per cubic millimetre. Under these circumstances administrations of carbonic acid were resorted to whenever the epistaxis recurred. The administration of the gas was invariably followed by a prompt arrest of haemorrhage. The method of administration which was adopted consisted in leading a stream of carbonic acid into the nose through an india-rubber tube passed up well into the nostril. The carbonic acid was supplied from an ordinary Kipp's gasogene, such as can be purchased at any chemical apparatus dealer's for a few shillings. The patient was directed to hold his head forward in order that the blood should run out of the nostril along the india-rubber tube instead of trickling down the posterior nares. The coagulative effect of the carbonic acid was gauged by noting the rate at which the blood dripped from the tube. On several occasions this treatment was supplemented by a previous syringing out of the nostrils with $\frac{1}{2}$ per cent. calcium chloride solution. In the case of epistaxis it is not necessary that the patient should inhale the gas: the local effect of the gas at the seat of haemorrhage will suffice. The same statement would hold good of a possible treatment of metrorrhagia by an administration of carbonic acid. It is, however, necessary to insist upon the fact that an excess of carbonic acid must be avoided if the method is to be effectual. My experiments upon animals¹ have shown that the accelerating influence of carbonic acid gas upon blood-coagulation is manifested only in presence of a sufficiency of oxygen. When this fact has been realised it becomes evident that the inhalation of carbonic acid gas would be applicable to the treatment of haemoptysis. It is not necessary that the patient should be in any degree asphyxiated. Asphyxiation would militate against the efficacy of the method. The stream of gas should first be turned on very gently so as to induce anaesthesia of the mucous membranes. As soon as this has been effected very large quantities of the gas can be tolerated without discomfort. I have not had an opportunity of testing the method in a case of haemoptysis: it would appear, however, to be deserving of a trial, for it is a method which might result in an immediate arrest of haemorrhage. If the administration of carbonic acid were not effectual by itself, its coagulative effect might be enhanced by a previous administration of calcium chloride. It might, for instance,

¹ *Vide pp. 15 et seq.*

be applied an hour after the administration of thirty grains of calcium chloride cryst. by the mouth.

Finally, before dismissing the subject of the arrest of haemorrhage, it may be well to advert to the employment of solutions of cell nucleo-albumins as local applications to bleeding surfaces. The employment of physiological styptics of this kind would appear to be especially indicated in the treatment of haemophilia, for I have convinced myself by a somewhat extensive series of observations on the blood of haemophilic families that the blood of haemophilic patients and of their female ascendants is characterised by a notable paucity of white blood corpuscles, and especially by a relative paucity of the polynuclear white blood corpuscles. In other words, haemophilic blood is deficient in the cellular elements which contribute the nucleo-albuminous element to the formation of fibrin. An addition of nucleo-albumins is, therefore, essential to the formation of a sound clot. The practitioner can always readily obtain a supply of these by mincing up a thymus gland, a testicle, or (if these cannot be obtained) a piece of gastric mucous membrane, in a little 1 in 500 solution of carbonate, and by filtering off the infusion, either immediately or after the lapse of a few minutes, through a piece of calico. I have employed such solutions of cell nucleo-albumins in two cases of haemophilic haemorrhage; in both cases the haemorrhage was taking place from cuts upon the hand. The result of the application of this physiological styptic was in each case the formation of an enormous mass of clot round the wound. In one of the cases bleeding continued for days under the clot (this was no doubt due to some dislodgment of the clot), and the skin became extensively macerated. I had in this case to clear away the clots and to arrest the haemorrhage by inhalations of carbonic acid combined with an application of lime salts. It is, perhaps, not too much to say that with these three methods of arresting haemorrhage at our disposal very few, if any, cases of haemophilia ought to be allowed to succumb to their capillary haemorrhages.

I have now to deal very shortly with the question of the treatment of urticarias, which are associated with deficient blood-coagulability. It is probable that most urticarias fall under this category. Instances in point are the urticarias which result from eating unripe or acid fruit. These, as I have elsewhere pointed out,¹ may almost certainly be attributed to a diminution of blood-coagulability due to the abstraction of calcium salts from the blood by the vegetable acids. Again, the urticaria which supervenes upon the eating of certain molluscs and crustaceans is, if one may judge by the analogy of what happens in animals, associated with a diminution of blood-coagulability. There is yet another example of the association of diminished blood-coagulability with urticaria in the case of the urticarious eruption which, as Shore first showed, occasionally occurs in dogs whose blood has been deprived of its coagulability by an injection of peptone. I was led by the analogy of these facts to inquire whether the urticaria which frequently supervenes upon an injection of antidiphtheritic serum is also associated with a diminished blood-coagulability. In the few cases which have come under my personal observation I have found that the blood-coagulability is really notably diminished. A practical point in the treatment of urticaria would appear to result from these considerations.

¹ *Brit. Med. Journ.*, 14th July, 1894.

Whenever we are dealing with an urticaria which is associated with a diminished blood-coagulability any method of treatment which will augment blood-coagulability will, in all probability, exert a favourable influence upon the course of the eruption. Acting upon this assumption, I have treated the few cases of post-antitoxin urticaria which have come under my notice with 15- to 30-grain doses of calcium chloride. This treatment was apparently very successful. In one typical instance the coagulation-time of the patient who was suffering from acute urticaria stood at *eight minutes*. Within a few hours after the administration of the calcium chloride it had come down to *four minutes*, and the rash had entirely disappeared. This method of treatment would appear, therefore, to deserve investigation at the hands of those who have frequent opportunities of observing this form and other forms of urticaria.¹ The treatment of urticaria by carbonic acid inhalations would hardly appear to be a practical method. Its results would, however, have a certain theoretical interest, as it seems probable that the nocturnal supervention of urticaria, like the nocturnal supervention or aggravation of haemophilic haemorrhages, must have some relation to the diminished nocturnal output of carbonic acid.

In all cases of urticaria associated with diminished blood-coagulability, just as in all cases of haemophilic bleeding, it is of the utmost importance to avoid diminishing the blood-coagulability by the administration of wine. Wines, especially the more acid ones, diminish blood-coagulability by virtue both of the alcohol² and the free citric and tartaric acids they contain, which abstract lime salts from the blood. In a case which came under my notice incidentally even the smallest quantity of any wine, except port wine, produced a slight oedema of the fingers and an urticarious eruption. The urticaria in this case was a mere unregarded incident in a case of incipient tuberculosis which was being treated with creosote. If, however, the urticaria was really referable to a deficiency of lime salts in the blood, it was a therapeutic indication of the utmost importance, for the supervention of the urticaria would be the equivalent of a call for lime. Now, a demand for lime on the part of a tuberculous organism is a demand which ought to be carefully attended to, for Metchnikoff has shown that one of the methods of defence which is employed by the organism is the encapsulation of the intracellular tubercle bacilli in capsules of lime.

NETLEY.

¹ I have elsewhere (*Brit. Med. Journ.*, 12th Oct., 1895) pointed out that post-antitoxin urticarias appear to be much rarer after the injection of antitoxic plasma than after the injection of antitoxic serum.

² *Vide supra*, p. 37 and Postscript.

ON CERTAIN GRAVE DEFECTS IN THE SYSTEM OF ARTIFICIAL RESPIRATION

AS ORDINARILY APPLIED TO THE TREATMENT OF CHLOROFORM COLLAPSE AND ASPHYXIA

(Reprinted from the 'British Medical Journal', 25th January, 1896)

A somewhat large experience of the results of the application of unassisted artificial respiration to the treatment of animals whose respirations and heart beats have ceased under the influence of an overdose of an anaesthetic has convinced me that this method of treatment gives very unsatisfactory results. Experience upon animals is, in this respect, in perfect accord with clinical experience upon man. I therefore wish to direct attention to a method of treating such cases of chloroform collapse, which has proved itself extremely efficacious in the case of the ordinary laboratory animals. The method consists in opening a major artery before proceeding to apply artificial respiration. At least nine out of every ten dogs may be resuscitated from a condition of apparent death from chloroform by the application of this method of combined arterial bleeding and artificial respiration. On reflection it becomes intelligible why this should be so. The essentials of a successful treatment of cases of chloroform collapse are evidently the following: First, we must have a proper ventilation of the chloroform-charged venous blood in the lungs; and, secondly, we must have a rapid distribution of this duly ventilated blood through the arterial system. Now, unassisted artificial respiration undoubtedly makes provision for the ventilation of the blood in the lungs. It, however, makes no effective provision for the immediate feeding of this aerated blood into the left heart and the arterial system.

The method, in fact, fails to take into account two important facts.

It fails to take into account the fact that the passage of the duly aerated blood into the arterial system is blocked by the venous and chloroform-overcharged blood, which passed through the pulmonary capillaries before artificial respiration was resorted to, and now occupies the left heart.

It further fails to take into account the other equally important fact that no blood (or at most only a minimal quantity of blood) can be expelled from the left heart into the arterial system until sufficient pressure has been got up in the ventricle to distend the walls of the collapsed arteries to something approaching their original size.

When, therefore, we set to work with the ordinary methods of artificial respiration to re-establish the circulation we place ourselves under very distinct physiological disadvantages. We not only undertake to drive on in front of the aerated blood a considerable volume of hyper-vitiated blood, but we set ourselves to overcome a very considerable mechanical resistance in the arteries.

By opening an artery, we immediately place ourselves under infinitely more

advantageous conditions. In the first place, we provide an outlet through which we can evacuate the greater part of the vitiated blood (in the dog a very considerable quantity of such venous and chloroform-charged blood comes away); and in the second place we reduce the resistance in the arterial system sufficiently to allow of the enfeebled heart resuming its beat. This method of combined artificial respiration and arterial bleeding would appear to be applicable not only to the treatment of chloroform collapse in man, but possibly also to the treatment of carbonic oxide poisoning, drowning, and asphyxia. In the case of man, it would be well to divide both temporal arteries, and to allow the haemorrhage to go on unchecked until a certain amount of arterialised blood had run away.

In conclusion, it may not be inappropriate to direct the earnest attention of the practitioner to the eminent utility of preliminary injections of atropine as a means of preventing the fatalities which occur in the early stages of chloroform administration. This method, which was recommended originally by Dr. J. Harley,¹ but which was first placed on a scientific basis by Dastre and Morat, does not appear to have come into general use yet. The method is based upon perfectly sound physiological principles, inasmuch as it is directed to the prevention of the heart stoppage, which in the case of early chloroform collapse appears generally to be brought about by the inhibitory action of the vagus. The atropine² removes this source of danger by paralysing the nerve endings of the inhibitory fibres in the heart. In the case of dogs and rabbits, this atropine method is of almost absolute efficacy against the otherwise frequent fatalities of the early stage of chloroform administration.

¹ *British Medical Journal*, vol. i, 1868, p. 320.

² For use in man Dastre (*Les Anesthésiques*, Paris, 1890) recommends the injection of 1 milligramme (= *circ.* $\frac{1}{60}$ grain) of sulphate of atropine combined with 1 centigramme (= *circ.* $\frac{1}{60}$ grain) of hydrochlorate of morphine twenty minutes before the administration of the chloroform.

NOTES ON TWO CASES OF URTICARIA TREATED BY THE ADMINISTRATION OF CALCIUM CHLORIDE

(Reprinted from the 'British Journal of Dermatology', No. 89, vol. 8)

The theoretical considerations which appear to me to justify the administration of calcium chloride in case of urticaria may be very briefly adverted to.

In all conditions of diminished blood-coagulability there is not only a tendency to actual haemorrhage, but there is also a tendency to what we may conveniently call 'serous haemorrhage', i.e. to an increased transudation of the fluids of the blood into the tissues.

For instance, the haemophilic patient is not only liable to haemorrhages in the ordinary sense of the term, but he is liable to joint effusions and to the development of haematomata which contain an inordinate amount of transudation fluid as compared with the number of red blood corpuscles.

Again, persons whose blood-coagulability is diminished appear to be particularly liable to urticaria, i.e. to 'serous haemorrhage'¹ into the skin. I myself am an example in point. I have produced urticaria upon myself on one occasion recently by diminishing my blood-coagulability by taking inordinate doses of calcium chloride. I have also, when a boy, often developed urticaria after eating acid fruits which diminish² the blood-coagulability by abstracting lime salts from the blood.

These facts suffice to show that an increased transudation may be due to a diminished blood-coagulability.

Where this holds true we may reasonably hope to control the transudation by correcting the defect of blood-coagulability.

With this object in view I have employed calcium chloride in the treatment of the joint effusions which occur in haemophilic patients. As far as I can judge the treatment appears to control these effusions. The two cases which are subjoined are illustrations of the application of the same therapeutical principle to the treatment of urticaria.

CASE I.—W. M., *aet.* 84 years.

January 26th, 1896 (5 p.m.).—For the last six weeks patient has suffered from severe and persistent urticaria, accompanied by insomnia and by great cardiac

¹ If experimental proof be required that urticaria is due to increased transudation into the skin, such experimental proof is to hand in the fact that all the lymphagogues which produce increased transudation from the blood occasionally produce an urticarious eruption in animals. Such urticarias are, for instance, occasionally seen in dogs after the intravascular injection of peptone or leech-extract, or crab or mussel-extract.

² I have little doubt that the severe attacks of oedematous urticaria from which I suffered as a boy were associated with a diminished blood-coagulability. I base this opinion (*a*) upon the fact that I was at that time subject to frequent attacks of epistaxis; (*b*) upon the fact that I was growing rapidly (i.e. that I was depositing considerable quantities of lime salts in my bones); (*c*) upon the fact that in the few cases of epistaxis in growing children that I have examined, I have invariably found blood-coagulability to be diminished.

weakness. At the outset the eruption of urticaria was associated with severe asthma and extreme cardiac irregularity. During this time patient was in an extremely precarious condition.

There is no history of any previous attacks of urticaria or asthma, and the present attack cannot be referred to any definite cause. It supervened upon a condition of vague ill-health which resulted from a severe cold contracted sometime in the late autumn of last year.

Patient, who till recently was marvellously vigorous and robust, has lost a great deal of flesh, and looks very seriously ill. Appetite is much impaired, and his hand trembles when he holds it out.

The patient suffers so much from itching that he finds himself, in his own words, 'at the end of a long life, reduced to scrubbing himself night and day like one of his poor relations in the Zoo'.

Arms and legs are thickly covered with an urticarial eruption. The eruption is, for the most part, papular. Here and there large white wheals are interspersed among the papules. The eruption and the itching become more pronounced with every change of temperature. The itching is particularly intolerable after going to bed. For the last six weeks patient has never closed his eyes till after 4 a.m. The insomnia is attributed in large part to the itching.

Temporary relief from the itching is obtained by sulphuret of potash baths. Digitalis and sulphonal are being administered internally.

In view of the possibility of this case of urticaria being due to an abnormally diminished blood-coagulability, the condition of blood-coagulability was tested in the usual way with the coagulometer.

The coagulometer showed a blood-coagulation time of 4 min. 20 sec.

Seeing that the patient's hands were very cold when the samples of blood were withdrawn for examination, the coagulability estimation was repeated after immersing the hands in hot water.

The coagulometer again showed a blood-coagulation time of 4 min. 25 sec. It was thus evident that we were here dealing with a case of severe urticaria, unaccompanied by any considerable defect of blood-coagulability.

None the less, I decided to administer calcium chloride. I reflected that, since calcium chloride will control haemorrhage in the man who has no defect of blood-coagulability in precisely the same manner as it will control haemorrhage in the haemophilic, it would be legitimate to expect that it would control 'serous haemorrhage' in the man who has no defect of blood-coagulability in precisely the same way as it will control 'serous haemorrhage' in the man whose blood-coagulability is seriously reduced.

Thirty grains of calcium chloride were therefore administered. Instructions were left that the dose should be repeated at bedtime (11 p.m.), and again the next morning at 9 a.m.

All other medicine, except the sulphonal, was discontinued.

January 27th, 1896 (11.30 a.m.).—Patient is reported to have passed a decidedly better night. His wife is quite certain that there was much less itching. The patient himself is not so certain on this point.

Blood-coagulation time, 2 min. 30 sec. No notable change in the rash. Twenty-grain doses of calcium chloride were prescribed—the doses to be taken at 6 p.m., 11 p.m., and 9 a.m.

January 30th, 1896.—In addition to the 20-grain dose of calcium chloride which was administered at 9 a.m. an additional 20-grain dose was administered at 2 p.m., in order to ensure that the patient should be under the influence of the drug when he was seen at 5 p.m.

5 p.m.—Patient looks wonderfully better, and has a much better pulse-beat. The eruption has almost disappeared from the arms, but still persists on the front of the thighs. Itching is very much less, there being no itching whatever during the day, and one good scrub down with the clothes-brush sufficed to make the patient comfortable for the night. The arms can now be bared and exposed to the cold without bringing on any itching. Patient had previously been compelled to swathe his arms in bandages.

Blood-coagulation time, 3 min.

Calcium chloride to be administered in 20-grain doses t.d.s. as heretofore.

February 4th, 1896.—Skin has now become soft and smooth. Itching has practically disappeared, and patient sleeps satisfactorily under the influence of small doses of sulphonal. Patient has been out for a walk and is rapidly regaining strength.

Blood-coagulation : estimation omitted.

Calcium chloride to be continued in 20-grain doses t.d.s. as heretofore.

February 8th, 1896 (5 p.m.).—There has been more irritation these last two nights. Itching has continued for one to two hours after retiring to rest, but there is no rash or irritation during the day.

Blood-coagulation time, 2 min. 30 sec.

In view of the fact that blood-coagulability stood at $2\frac{1}{2}$ min. at 5 p.m., eight hours after the administration of the last dose of calcium chloride, it was surmised that there might be an excess of calcium salt in the blood during the night. The doses of calcium chloride were therefore reduced to 10 grains t.d.s.

February 11th, 1896.—Patient is reported to have passed two perfectly quiet nights.

Dose of calcium chloride was now reduced to 5 grains t.d.s.

February 18th, 1896.—The reduction of the dose of calcium chloride to 5 grains appears to have been followed by a slight increase of irritation. Patient has, therefore, for the last four days, been taking 10 grains t.d.s., and expresses himself perfectly free from all itching. Rash has practically all disappeared. Patient appears to have regained a great deal of his accustomed vigour.

Remarks.—The first point that is to be noted is that large doses of calcium chloride may be administered at the outset, in order to supply the deficiency of lime in the system, and to bring the patient rapidly under the influence of the drug. Afterwards it will be wise to reduce the doses so that excessive quantities of lime shall not accumulate in the system.

The second point which is to be noted is that lime salts may prove useful in urticaria, even when the urticaria is not associated with any notable defect of blood-coagulability. If this fact is confirmed by further experience lime salts may be

found useful in the treatment of insect bites and of other irritable eruptions. It may also be found useful in the treatment of 'weeping' eczema.

A third point of interest is the effect of calcium chloride upon the heart. Lime salts are as essential to heart-muscle as they are to blood or to milk.

CASE II.—Private H., in hospital, under treatment for secondary syphilis.

February 5th, 1896.—Developed a sore throat which proved to be diphtheritic.

February 6th, 1896.—25 c.c. of diphtheria antitoxin injected.

February 14th, 1896.—Diphtheria bacilli have disappeared from the throat.

February 15th, 1896.—Patient awoke this morning with violent itching. A well-marked eruption, consisting of raised wheals and erythematous patches, came out during the night over the trunk, but especially on the thighs, arms, and on the dorsum of left hand. Patient has no joint-pains.

11.45 a.m. Blood-coagulation time, 8 min.

12 noon. Administered 30 grains of calcium chloride.

2.40 p.m. Blood-coagulation time, 5 min.

2.50 p.m. Administered another 30-grain dose of calcium chloride.

4.40 p.m. Blood-coagulation time, 5 min. 10 sec.

February 16th, 1896.—No calcium chloride has been administered since 2.50 p.m. yesterday.

There has been no itching whatever since early yesterday morning. The rash is, however, said to have 'come out' in the early morning. There is hardly a trace of it to be seen now (10.30 a.m.).

Blood-coagulation time, 4 min. 10 sec.

Thirty grains of calcium chloride administered at 10.45 a.m.

1.15 p.m. Blood-coagulation time, 3 min. 30 sec.

Ordered another 30-grain dose of calcium chloride to be administered at 6 p.m.

February 17th, 1896.—No further trace of rash.

Blood-coagulation time, 2 min. 45 sec.

Remarks.—In view of the association of serum-disease with diminished blood-coagulability, which is evidenced by this and several cases which previously came under observation, the following questions suggest themselves.

(1) Is the urticaria, which develops in a percentage of cases after the administration of antitoxic horse serum, invariably associated with a diminished blood-coagulability?

(2) Do all the patients in whom a diminution of blood-coagulability takes place after an injection of horse serum, suffer from urticaria, or does some other factor come into play?

(3) Does an injection of horse serum always produce a diminution of blood-coagulability?

No answer is as yet forthcoming to the first two of these questions. The third may probably be answered in the negative, as the following observation shows:

Private J., who shares the diphtheria ward with Private H., and who is now convalescent from diphtheria, was injected on the same day as Private H. with the same quantity of the same antitoxin. He has not developed any urticaria. His blood-coagulation stood at 3 min. on the ninth day after the injection of the antitoxin.

ON THE ASSOCIATION OF SEROUS HAEMORRHAGES WITH CONDITIONS OF DEFECTIVE BLOOD-COAGULABILITY

(Reprinted from 'The Lancet', 19th September, 1896)

In previous papers I have pointed out that, on the one hand, excessive haemorrhages from trifling wounds, and, on the other hand 'spontaneous haemorrhages', are in almost all cases attributable to a defect in blood-coagulability. The epistaxis and haemorrhage from the bowel in typhoid fever, the epistaxis of growing children, and the excessive haemorrhages of haemophilic patients are typical instances of haemorrhages which are due to this cause. Conditions of deficient blood-coagulability do not, however, manifest themselves only in a tendency to 'actual haemorrhages'. They manifest themselves also in a tendency to increased transudation of plasma through the capillary wall—i.e. in a tendency to '*serous haemorrhages*'. I propose here to review the more important varieties of such '*serous haemorrhage*' and to draw attention to the association of each of these forms of serous haemorrhage with conditions of diminished blood-coagulability.

Serous haemorrhage in the skin.—I have elsewhere¹ shown that urticaria or serous haemorrhage into the skin is often associated with, and is probably dependent upon, a condition of defective blood-coagulability. In particular I have pointed out that this holds true (*a*) of the urticarias which supervene upon the injection of diphtheria antitoxin; (*b*) of the urticarias which supervene upon eating acid fruit; and (*c*) in all probability also of the urticarias which supervene after eating crabs or shellfish.² Two other urticarias—i.e. the urticarias which supervene occasionally after eating rhubarb and the urticaria which supervenes, more exceptionally, after the administration of soap enemas—are also almost certainly referable to a condition of diminished blood-coagulability, depending upon an abstraction of lime salts from the blood. This abstraction of lime salts occurs in the first case under the influence of the oxalates of the rhubarb, and in the second case under the influence of the fatty acids of the soaps. To this list of urticarias, which are almost certainly referable to defects of blood-coagulability, we may probably also add the urticarias which occur not infrequently in haemophilic patients. Several instances of these urticarias have come under my observation.

In connexion with the general question of the etiology of urticaria it may be well to point out that serous haemorrhage under the skin, like every other variety of serous haemorrhage, may be due either (*a*) entirely to a condition of diminished blood-coagulability or more commonly (*b*) to a combination of causes—i.e. to a local injury superadded to a condition of diminished blood-coagulability.

¹ *Vide supra*, pp. 55-59 and pp. 62-65.

² Since writing the above this inference has been confirmed by observations made by Dr. Wm. John Scott on a case of shell-fish urticaria, which was successfully treated by him with calcium chloride.

As an instance of an urticaria which is referable to this combination of causes I may instance the local urticaria which so frequently manifests itself at the site of injection after the administration of antitoxic serum. I have recently had instructive experience of such an urticaria in my own person, having suffered from a severe local urticaria after an inoculation of 1 c.c. of tetanus antitoxin. This urticaria, which had been very troublesome for three days, disappeared in two or three hours under the influence of one 30-grain (2-gramme) dose of calcium chloride. The disappearance of this urticaria was coincident with an increase of blood-coagulability from *five minutes* (to which it had declined under the influence of the antitoxin) to its normal of *three minutes*. It may, therefore, be reasonably inferred that this urticaria was not attributable only to the local injury which resulted from the injection, but also in part to the state of diminished blood-coagulability.

Serous hæmorrhage into the subcutaneous and muscular tissues.—The best example of this variety of serous hæmorrhage is found in the serous hæmatomata which are so commonly seen in cases of hæmophilia. These serous hæmatomata may be distinguished from subcutaneous blood effusions by the fact that they leave a very trifling amount of discolouration behind. Other instances of oedemas which are referable to a condition of diminished blood-coagulability are the widespread oedemas which occur after the inoculation of viperine poison,¹ and in all probability also the oedema of the feet which occurs in patients whose blood-coagulability has been seriously reduced by prolonged tropical fevers. Again, it would be well worth investigating whether chilblains are or are not dependent upon a diminished blood-coagulability. The following facts speak in favour of an association between the two phenomena: (1) in a case of aggravated chilblains which has recently come under my notice (a case in which the puffiness and blueness of the hands persists even in summer) I find that there is a notable defect of blood-coagulability (blood-coagulation time seven and a half minutes instead of from two to four, or at most five, minutes); (2) I have noted the occurrence of aggravated chilblains in one of the families of 'bleeders' I have under observation; (3) I have frequently noted the association of chilblains with a tendency to epistaxis and to urticaria; and (4) chilblains are in many respects comparable to a deep-seated urticaria. For instance, the itching that accompanies chilblains, like the itching that accompanies urticaria, is most troublesome in the evening and is aggravated by every change of temperature.

Serous hæmorrhage into the tubules of the kidney.—The association of so-called 'cyclic albuminuria' with a tendency to epistaxis has been noted by Marie,² and is suggestive of a connexion between low blood-coagulability and albuminuria. The connexion between the two phenomena is suggested also by the fact that albuminuria occurs independently of any verifiable kidney disease in persons whose blood-coagulability has been reduced by tropical fevers. I have not as yet met with any albuminuria in 'bleeders'. I have, however, not as yet sufficiently examined for it.

¹ Dr. C. J. Martin (*Proceedings of the Royal Society of New South Wales*, July, 1895; *Journal of Physiology*, vol. xv) has shown that when viperine poison does not produce instantaneous vascular coagulation it produces an extreme diminution of blood-coagulability, which is quite comparable to the 'negative phase' of coagulability obtained after an injection of Wooldridge's tissue-fibrinogens.

² *Semaine Médicale*, January, 1896.

Serous haemorrhage into joints and serous cavities.—That effusions into joints may be dependent upon a defect of blood-coagulability is evident from the fact that next to actual haemorrhages joint effusions constitute the most characteristic clinical manifestations of haemophilia. Effusions into other serous membranes do not appear to have been specially noted in cases of haemophilia. Probably, however, attention has not been directed to this point. In a case I have under observation symptoms which are suggestive of a serous haemorrhage into the brain—i.e. stupor followed by 'fits'—have several times occurred simultaneously with effusions into joints. Again, quite independently of haemophilia, the possible dependence of serous effusions upon a defect of blood-coagulability is often suggested by the fact that pericardial and pleural effusion are often in the post-mortem room found associated with signs of haemorrhages from mucous membranes, and with defective clotting of blood in the larger blood-vessels. The joint pains which occasionally supervene upon injections of antitoxic serum are also suggestive of a dependence of serous haemorrhages into joints upon defects of blood-coagulability. For these joint-effusions, like the urticaria which they so frequently accompany, may be reasonably referred to the defect of diminution of blood-coagulability which, as I have pointed out, is frequently induced by the injections of antitoxin. In view of these facts it would be well worth investigating whether cases of hydrocele and pleural and joint-effusions for which no other sufficient cause can be detected are, or are not, dependent upon defects of coagulability. In this connexion it would also be interesting to examine the condition of blood-coagulability in beri-beri.

Serous haemorrhage into the intestinal canal.—In my experience haemophilic patients very seldom suffer from constipation. Their bowels are usually free and there is often a history of frequently recurring diarrhoea. These diarrhoeas seem to be coincident with periods of abnormally diminished blood-coagulability. For instance, in one of the 'bleeder' boys I have under observation blood-coagulation time stood at over twenty-five minutes at a time when he was suffering from a persistent attack of diarrhoea. This boy's blood had in previous observations been found to clot in periods varying between seven and ten minutes. It seems a probable inference from these facts that diarrhoea may be caused by serous haemorrhage, depending upon a defect of blood-coagulability. The association of a defect of blood-coagulability with diarrhoea may also be inferred from Osler's observations on the frequent association of diarrhoea and vomiting with cases of morbus maculosus Werlhofii¹—i.e. with a disease which is plainly associated with a serious defect of blood-coagulability. The same association of serous haemorrhage into the bowel with serous haemorrhage into the skin and deeper tissues may be noted in the case of the urticaria which results from eating crab or shellfish. Again, the occurrence of diarrhoea after croupous pneumonia at a time when peptone (albumose) is being excreted in the urine is also probably referable to a serous haemorrhage into the bowel induced by a defect of blood-coagulability. This inference is based upon the fact that diarrhoea due to serous haemorrhage is invariably seen in dogs whose blood-coagulability has been diminished by an injection of peptone (albumose).

In addition to the facts just adverted to, a series of pharmacological facts seem

¹ *Johns Hopkins Hospital Reports*, vol. v.

to point to the existence of a relation between the state of blood-coagulability and the condition of the stools. In the first place non-irritant hydragogue cathartics appear, if I may judge from a very few experiments made with magnesium sulphate and bitartrate of potash, to owe some part of their efficacy to their power of diminishing blood-coagulability. Again, the marked constipating power of lime salts (e.g. chalk and calcium chloride) may quite probably be due to a diminution of serous haemorrhage into the intestine dependent upon an augmentation of blood-coagulability. In like manner the notoriously constipating effect of a milk diet may be in part due to the large percentage of calcium salts contained in cow's milk. This last inference is to some extent confirmed by the fact that obstinate infantile constipation will often (I speak, however, from a very small experience) disappear when the child is put upon a diet of citrated milk (i.e. milk which has been deprived of its excess of lime salts by an addition of 1-400th of citrate of sodium). It will be obvious that the lines of thought which are opened up by the above series of facts are too numerous, and, in some instances, too far-reaching to be followed up within the compass of a paper like the present. The following up of these lines of thought will, however, present no difficulty to anyone who takes as his starting-point the generalisation that a defect of blood-coagulability tends to manifest itself, not only in 'actual haemorrhages', but also (according to the particular idiosyncrasy of the patient) on some one or more of the forms of 'serous haemorrhage' which have been adverted to. As testimony to the truth of this generalisation we have the case of haemophilia, where every one of these forms of serous haemorrhage (with the as yet doubtful exception of albuminuria) comes under observation.

The bearing of this generalisation upon the question of treatment is obvious. Methods of treatment which augment blood-coagulability will be methods of treatment that will be appropriate, not only to the prevention and treatment of 'actual haemorrhage', but also to the prevention and treatment of 'serous haemorrhage'. The more important of these therapeutical measures appear to be the following: (a) the exhibition of calcium chloride (or other soluble lime salt) in suitable quantities; (b) the avoidance of such vegetable acids as citric, malic, tartaric, and oxalic acids, which form insoluble salts with lime; (c) the concentration of the blood either by diaphoretics or by such purgatives as do not owe their efficacy to a power of reducing blood-coagulability; (d) the restriction of the amount of fluid ingested; (e) the increase of the amount of carbonic acid in the blood, either by direct inhalation of the gas or by other methods; and (f) the avoidance of alcohol.

The object of this paper will have been attained if it should lead to a trial of such of these therapeutic measures as may not already be in use, both in the treatment of actual haemorrhage and also in the treatment of the various forms of serous haemorrhage which have been enumerated. Even where, as probably in a large majority of cases, these clinical symptoms are dependent upon something more than a mere defect of blood-coagulability, an augmentation of coagulability may be expected to alleviate the clinical symptoms by limiting the transudation through the capillary wall.

As an example of what can be done in controlling serous haemorrhage I may subjoin the following protocols of experiments, which show that the serous

haemorrhage, which is associated with the hypodermic inoculation of typhoid bacilli can be controlled by the exhibition of calcium chloride.¹

Horse—Typhoid Vaccination

Aug. 6th.—Receives a hypodermic injection of 20 c.c. of virulent typhoid culture. (This is the seventh injection to which the horse has been subjected.)

Aug. 7th.—Yesterday's injection, like all previous injections, has given rise to an enormous local oedema. The horse now receives 1 ounce (30 grammes) of calcium chloride in a bran mash.

Aug. 8th.—The oedema, which has on all previous occasions lasted for some considerable number of days, has practically disappeared, leaving behind two small, sharply circumscribed abscesses at the site of the inoculations.

Aug. 20th.—Horse receives a hypodermic injection of 50 c.c. of the same virulent typhoid culture. He at the same time receives one ounce (30 grammes) of calcium chloride in a bran mash.

Aug. 21st.—No noticeable oedema. Only a slight fulness can be detected when the hand is passed over the site of the inoculation.

Aug. 22nd.—No further local symptoms whatever.

Sept. 7th.—50 c.c. of virulent typhoid culture hypodermically on right side of the neck. No calcium chloride.

Sept. 8th.—Painful tense swelling (size of inverted soup-plate) at site of inoculation. Oedema of dependent parts of the neck. Pain on moving fore-leg.

Sept. 9th.—Swelling at seat of injection still very tense and painful. Oedematous swelling at lower part of the neck practically unaltered.

Sept. 11th.—The swelling at the seat of injection which has been threatening to suppurate appears now to be slowly resolving itself. The oedema has, if anything, a little increased. It has now passed down from the neck on to the front of the chest.

M.D., an Officer of the Indian Medical Service—Typhoid Vaccination

July 31st.—Inoculated hypodermically in flank with one-twentieth of a tube of dead typhoid bacilli.

Aug. 1st.—Extensive oedema extending from site of inoculation to pubis and for four or five inches upwards over the front of the abdomen.

Aug. 4th.—Swelling and redness gradually disappearing.

From Aug. 4th to Aug. 11.—Several 1- to 2-gramme doses of calcium chloride.

Aug. 14th.—3 p.m. : three-twentieths of a tube of more virulent typhoid bacilli inoculated into flank. 6 p.m. : a small amount of swelling has developed at seat of inoculation. 20 grains (1.25 grammes) of calcium chloride. 11 p.m. : swelling not noticeably increased. Another 10 grains (0.6 gramme) of calcium chloride.

Aug. 15th.—No increase in the oedema.

¹ I would here again warn against injecting calcium chloride solutions hypodermically. I find that the injection of perfectly aseptic 10 per cent. solutions of calcium chloride in animals followed by widespread sloughing of the subcutaneous tissues. *Vide p. 56.*

Aug. 16th.—All swelling and tenderness have disappeared.

Sept. 5th.—One-quarter of a tube of dead typhoid bacilli hypodermically. 45 grains (3 grammes) of calcium chloride by the mouth.

Sept. 6th.—No oedema whatever. Considerable redness and tenderness of skin disappearing towards evening.

Sept. 7th.—No further local symptoms.

J.S., an Officer of the Indian Medical Service—Typhoid Vaccination

Aug. 19th.—12 noon : receives a hypodermic inoculation of one-twentieth of a tube of dead typhoid bacilli (culture the same as that employed in the second inoculation of M.D. above). Blood-coagulation time—7 min. 6 p.m. : considerable fulness has developed round site of inoculation. Blood-coagulation time—9 min. Receives 45 grains (3 grammes) of calcium chloride in half a tumbler of water. 8 p.m. : blood-coagulation time—5 min. 10 sec. ; no increase of oedema.

Aug. 20th.—No trace of oedema, no further local symptoms, except a little redness and tenderness at site of inoculation.

These facts would appear to have an importance altogether beyond that which attaches to this particular vaccination process. They have, for instance, an obvious application in connexion with the prevention and treatment of the serous haemorrhages, which are associated with Haffkine's anti-cholera inoculations. (I need hardly point out that these anti-cholera inoculations have served as a pattern for the typhoid vaccinations detailed above.) They have a further application in connexion with the treatment of insect bites and of the oedematous arms which are sometimes seen after small-pox vaccinations. And, lastly, a more general therapeutical importance accrues to these facts when we consider that oedematous conditions not only lower the resistance of the organism to bacterial infection, but they also, if we may judge from what occurs in the case of bad chilblains and in the case of the traumatic oedemas of the bleeders, sometimes lead on directly to suppuration and mortification. Possibly the favourable results which are said to be obtained by the exhibition of calcium chloride in the treatment of boils, of croupous pneumonia, and of some cases of phthisis with considerable expectoration, may be due to the fact that any drug which controls serous haemorrhage will, by virtue of that property, exert a favourable influence also upon suppurative processes.

NETLEY.

ON THE PATHOLOGY AND TREATMENT OF CHILBLAINS

(Reprinted from 'The Lancet', 30th January, 1897)

I have in a recent issue of *The Lancet*¹ dealt with the general question of 'serous haemorrhage' (i.e. of increased transudation of the blood-fluids into the tissues), and I have pointed out (a) that this condition is very often dependent upon a defect of blood-coagulability, and (b) that serous haemorrhage can to a large extent be controlled by increasing the coagulability of the blood.

I had also in a previous paper² dealt with this question of serous haemorrhage in its special relation to urticaria, and had demonstrated not only that urticaria is very often dependent upon a condition of defective blood-coagulability, but also that this affection can often be relieved in a very striking manner by increasing the patient's blood-coagulability.

I propose in this paper to adduce evidence to show that what holds true of urticaria holds true also of that very familiar form of serous haematomata which we denote by the name 'chilblain'.

Association of chilblains with a condition of defective blood-coagulability.—I have investigated the condition of blood-coagulability in ten cases of chilblains.

Two of these cases were cases of aggravated chilblains occurring in adult males. The blood-coagulation times of these patients were respectively *nine minutes*, and *nine and a quarter minutes*. Four of these cases were cases of aggravated chilblains occurring in adult females. The respective blood-coagulation times of these cases were respectively *thirteen minutes*, *eleven minutes*, *eight and three-quarter minutes*, and *seven and a half minutes*. Lastly, four of these ten cases were mild cases of chilblains occurring in schoolboys. The coagulation times of these cases were respectively *eleven minutes*, *nine and a quarter minutes*, *seven and three-quarter minutes*, and *four and a half minutes*.³

It is obvious, therefore, when we consider that the normal blood-coagulation time varies between *three and four minutes*, that all these cases of chilblains, with the exception of the last case, were associated with a very notable defect of blood-coagulability.

This fact stands in relation with certain other facts which obtrude themselves more directly upon the clinician's attention. These facts are—(a) the superior liability of children to chilblains; (b) the fact that chilblains are prone to occur in persons who give a history either of nose-bleeding or of urticaria; (c) the occurrence of chilblains in persons who are characterised by a 'lymphatic habit' of body; (d) the not unfrequent occurrence of chilblains in persons who are the subjects of

¹ *Vide supra*, pp. 66 *et seq.*

² *Vide supra*, pp. 79 *et seq.*

³ All these coagulation estimations were made with coagulation-tubes of 0.25 m.m. internal diameter at the standard temperature of 18.5° C. (half blood heat).

malarial cachexia ; and (c) the not unfrequent occurrence of chilblains in haemophilic families. We may briefly consider each of these predisposing causes.

Childhood.—The notorious liability of children to chilblains is no doubt in part referable to the fact that the influence of cold makes itself felt more upon the relatively small extremities of the child than upon the relatively large extremities of the adult. Another probable factor in the etiology is the fact that the lime salts upon which the coagulability of the blood depends are in the growing child being continually removed from the blood in order that they may be deposited in the bones.

Predisposition to urticaria and epistaxis.—There is an obvious relation between the predisposition to epistaxis, the predisposition to urticaria, and the predisposition to chilblains, inasmuch as these predispositions have been shown to depend upon a defect of blood-coagulability. In two cases which have recently come under my observation I have seen urticaria alternate with chilblains. Both these forms of serous haemorrhage were apparently brought on in susceptible patients by exposure to cold.

'Lymphatic habit' of body.—We shall understand the relation between 'the lymphatic constitution', and a predisposition to chilblains if we consider, *first*, that the essence of the lymphatic constitution is to be found in a water-logging of the tissues which is dependent upon an excessive transudation of lymph ; *secondly*, that it will require only a very slight increase of transudation to convert water-logged tissues into perfectly definite 'sero-haematomata' such as we see in chilblains ; and *thirdly*, that in all probability both chilblains and the water-logged condition of the tissues which we meet with in the lymphatic patient are ultimately referable to a defect of blood-coagulability.¹

Malarial cachexia.—The subjects of malarial cachexia are not unfrequently also the subjects of chilblains. It is even possible, as I am assured by a medical officer who has experience of the truth of this fact in his own person, to suffer from chilblains on the West Coast of Africa after a severe attack of malarial fever. This liability of the malarious subject to chilblains is in absolute conformity with the fact that the blood of patients who are the subjects of malarial cachexia is characterised by a defect of blood-coagulability which is dependent upon a great paucity of leucocytes,² especially of polynuclear leucocytes.

Haemophilic constitution.—I have pointed out in previous papers that the chilblains are of very frequent occurrence in haemophilic families. This stands in connexion with the fact that haemophilic blood is, as I have previously shown, characterised by an extreme defect of blood-coagulability which is dependent upon an extreme and hereditary paucity of leucocytes and, in particular, upon a paucity of polynuclear leucocytes.

Treatment of chilblains.—In view of the aetiological facts which are thus disclosed, the obvious indication for treatment in a case of chilblains is to take steps

¹ It is customary to impute the liability of the lymphatic patient to chilblains to the patient's bad circulation. But in many cases it is, in all probability, not the bad circulation which produces the oedema. It is rather the oedema which impedes the circulation of the blood in the tissues, especially in the tissues of the extremities.

² There may in malarial cachexia be as few as 400 white blood corpuscles in a c.mm. of blood.

to augment the patient's blood-coagulability. In conformity with these indications I placed my patients upon a regimen of calcium chloride (after duly cautioning them against lowering their blood-coagulability by the ingestion of sour fruits, alcohol, or excessive quantities of fluid).¹ Of the eight cases which are particularised below, six cases (Cases 1, 4, 5, 6, 7, and 8) responded to this treatment with a marked increase of blood-coagulability. These cases were all completely cured as soon as a sufficient augmentation of coagulability had been achieved. In one of the remaining cases (Case 2) no good whatever resulted from the treatment. In this case, owing perhaps to the non-absorption, or the maladjustment of the dose of calcium chloride, no augmentation of coagulability was obtained. Finally, in Case 3 only transient and uncertain amelioration was obtained from the treatment. And here, again, only a very transient augmentation of coagulability was obtained.

CASE 1.—The patient was a woman aged twenty-seven years. She suffered every winter from very bad chilblains. On Oct. 31st, 1896, the mean temperature of the air for the day was 38·2° F. The patient's hands were very red and swollen and the skin had a very glazed appearance, especially over the proximal joints of the fingers. The blood-coagulation time was *thirteen minutes*.² Twenty grains (1·3 gramme) of calcium chloride cryst.³ were prescribed night and morning. On Nov. 11th the mean temperature for the day was 44·2° F. The chilblains were almost gone. The skin was no longer glazed, but a certain amount of redness and thickening still persisted. Calcium chloride was ordered to be continued in the same doses. The blood-coagulation time was *nine minutes*.⁴ On Nov. 3rd the mean temperature for the day was 40·2°. No notable change occurred in the condition of the hands since the day previous. The blood-coagulation time was *eight minutes, forty-five seconds*. Calcium chloride was ordered to be continued in the same doses until the chilblains absolutely disappeared. The treatment was to be resumed as soon as the chilblains threatened to reappear. On Nov. 11th the mean temperature for the day was 35·1°. The chilblains absolutely disappeared. The fingers are now quite thin and white.

CASE 2.—The patient was a man aged thirty-five years. He suffered very severely from chilblains every winter and was very subject to attacks of urticaria every summer. On Nov. 3rd, 1896, the mean temperature for the day was 40·2° F. Every finger on both hands was markedly stiff and oedematous. The skin over the fingers was reddened and glazed. There was, in addition to the chilblains on the

¹ I find that it is quite unnecessary to caution a lymphatic patient against ingesting excessive quantities of fluid, for the typical lymphatic patient, owing probably to that water-logging of the tissues which has been referred to above, is apparently never thirsty. The lymphatic young woman contrasts markedly in this respect with the wizened elderly woman, whose dry tissues seem to require to be irrigated with perpetual draughts of tea.

² It is a point worth noting that in connexion with the diminution of blood-coagulability a patient who bleeds freely from the pin-prick which is made in the finger is a patient whose blood-coagulability is considerably abnormal. In such a case it will be unnecessary to examine the condition of the contents of the first capillary coagulation tube until an interval of at least from five to six minutes has elapsed.

³ It is important in prescribing calcium chloride to specify either calcium chloride cryst. or calcium chloride desicc., for the first of these preparations is exactly half the strength of the second. I have invariably, unless where otherwise specified in my papers, employed calcium chloride cryst.

⁴ In this and in all the following cases the determinations of blood-coagulability were, in order to secure accuracy, made almost at exactly the same hours on successive days.

fingers, a tense and painful sero-haematoma on the hypothenar margin of the right hand. The blood-coagulation time was *nine minutes, twenty seconds*. A forty-grain (2.6 gramme) dose of calcium chloride cryst. at night followed by a 20-grain (1.3 gramme) dose on rising and by another 20-grain dose at midday was prescribed. The mean temperature for the day was 36.2° F. On the 11th the patient reported that the chilblains were better yesterday and that they were as bad as ever to-day. The appearance of the hands bore out the patient's statements. The blood-coagulation time was *ten minutes ten seconds*. Twenty grains (1.3 gramme) of calcium chloride cryst. were ordered three times a day. Owing to a misunderstanding, the patient, however, now took only 20 grains at night and another 20 grains in the morning. On the 9th the mean temperature for the day was 39.1° . The chilblains were said to be no better; they looked rather worse than they were before treatment was begun. The blood-coagulation time was *twelve minutes, thirty seconds*. Owing to external circumstances the observations on this case were now abandoned.

CASE 3.—The patient was a woman aged twenty-five years. She was lymphatic-looking and had suffered severely from chilblains every winter since she was an infant; she had also suffered severely from epistaxis. She had for some time past been taking calcium chloride (30 grains) twice a day somewhat irregularly and with little result. On the whole, however, the chilblains were said to have improved somewhat under the influence of the drug. On Nov. 11th, 1896, the mean temperature for the day was 44.2° F. The fingers were still somewhat swollen and the skin was red and glazed. The blood-coagulation time was *eight minutes, forty-five seconds*. Thirty grains (2 grammes) of calcium chloride cryst. twice a day were prescribed. On the 5th the mean temperature for the day was 41.1° F. There was no appreciable change in the chilblains. The blood-coagulation time was *six minutes, twenty seconds*. Thirty grains (2 grammes) of calcium chloride cryst. three times a day were prescribed. On the 7th the mean temperature for the day was 32.2° . The chilblains were said to be somewhat better. The blood-coagulation time was *ten minutes*. The treatment was continued for some days longer without producing any definite result. It was then abandoned.

CASE 4.—The patient was a woman, aged twenty-seven years, and was a very lymphatic-looking subject; she had suffered very severely from chilblains every winter since her infancy. On Nov. 9th the mean temperature for the day was 36.1° F. The patient's hands presented a very curious parti-coloured appearance, the hand from the wrist to the knuckles being very pallid and all below the knuckles being of a bright boiled lobster colour. The fingers were very swollen and stiff. The blood-coagulation time was *eleven minutes*. Twenty grains (1.3 gramme) of calcium chloride cryst. three times a day were prescribed. This treatment was continued for a week without any marked change either in the blood-coagulability or in the chilblains. The patient, however, insisted that she was better and suffered less from itching. After this time the treatment was owing to external circumstances very irregularly carried out. On Dec. 21st the mean temperature for the day was 32.2° . The patient presented herself again for treatment. The hands were much in the same condition as before, but were somewhat less swollen. The blood-

coagulation time was *eight minutes, forty seconds*. Twelve grains (0.8 gramme) of calcium chloride desicc. three times a day were prescribed. On the 22nd the mean temperature for the day was 32.2° . The fingers appeared not to be so congested. The blood-coagulation time was *seven minutes, thirty-five seconds*. Eighteen grains (1.2 gramme) of calcium chloride desicc. three times a day were prescribed. On the 23rd the mean temperature for the day was 35.2° . The chilblains were said to be rather worse. There was no observable change in the condition of the hands. The blood-coagulation time was *seven minutes, forty-five seconds*. Nine grains (*circ.* 0.6 gramme) of calcium chloride desicc. three times a day were prescribed. On the 26th the mean temperature for the day was 41.2° . The chilblains were very markedly better. The blood-coagulation time was *six minutes, twenty-five seconds*. Nine grains of calcium chloride desicc. three times a day were prescribed. On the 28th the mean temperature for the day was 43.2° . The chilblains were now practically well. Only a very little redness and a trace of oedema remained. The blood-coagulation time was *six minutes, twenty seconds*. Six grains of calcium chloride desicc. three times a day were prescribed. On the 30th the mean temperature for the day was 39.3° . The fingers had now become perfectly thin and redness had to a very great extent disappeared. The patient expressed herself as perfectly well. The blood-coagulation time was *six minutes*. Six grains of calcium chloride desicc. three times a day till all redness had disappeared were prescribed. Treatment was then to be discontinued and to be resumed on the first re-appearance of the chilblains.

CASE 5.—The patient was a boy aged eleven years. On Nov. 30th, 1896, the mean temperature for the day was 33.1° F. He had chilblains on the feet. The little toes on both feet were found to be oedematous and congested. The blood-coagulation time was *eleven minutes*. Fifteen grains (1 gramme) of calcium chloride cryst. morning and evening were prescribed. On Dec. 2nd the mean temperature for the day was 42.1° . The chilblains had quite gone. The blood-coagulation time was *five minutes, fifteen seconds*.

CASE 6.—The patient was a man aged twenty-two years. He had suffered severely from chilblains every winter. On Dec. 17th, 1896, he had extremely swollen and livid hands; the skin over the chilblains was everywhere peeling off, leaving deep and painful chaps. In addition to the chilblains on the fingers there was a large, tense chilblain of about the size of a walnut over the hypothenar margin of the hand. The blood-coagulation time was *nine minutes, five seconds*. Twenty-three grains (1.5 gramme) of calcium chloride cryst. three times a day were prescribed. On the 18th the mean temperature for the day was 30.2° F. The chilblains were less swollen. Itching was said to have been much better than on the previous night. The blood-coagulation time was *eight minutes*. On the 19th the mean temperature for the day was 30.5° . The chilblains were much the same in appearance. The itching is said to have been nearly as bad as before. The blood-coagulation time was *eight minutes, twenty seconds*. Fifteen grains (1 gramme) of calcium chloride cryst. three times a day were prescribed. On the 20th the mean daily temperature was 34.1° . The fingers were no longer so swollen. The skin over the chilblains had become quite loose and wrinkled. This was particularly noticeable

over the hypothenar margin of the hand. There was no itching whatever the previous night. The blood-coagulation time was *four minutes, ten seconds*. Ten grains (0.6 gramme) of calcium chloride cryst. three times a day were prescribed. On the 21st the mean temperature for the day was 32.2° . There was more itching the previous night; the chilblains were decidedly tenses. The blood-coagulation time was *ten minutes*. Fifteen grains (1 gramme) of calcium chloride cryst. three times a day were prescribed. On the 22nd there had been very little itching the previous night and the chilblains looked very much better. The blood-coagulation time was five minutes, forty-five seconds. Eighteen grains (1.2 gramme) of calcium chloride cryst. three times a day were prescribed. On the 24th the mean daily temperature was 34.3° . The chilblains were almost quite well. There was now no swelling and very little lividity to be seen. The blood-coagulation time was *six minutes*. The patient considered himself perfectly well and considered it unnecessary to pursue the treatment.

CASE 7.—The patient was a boy aged eleven years. On Dec. 19th, 1896, the mean temperature for the day was 30.5° F. He had chilblains on the feet. There was not much to be made out on inspection except a little swelling and lividity. Great complaints were, however, made of intolerable itchiness, and the father said that the boy cried every morning from the pain when he was putting on his boots. The blood-coagulation time was *seven minutes, forty-five seconds*. Ten grains (0.6 gramme) of calcium chloride cryst. three times a day were prescribed. On the 20th the mean temperature for the day was 34.1° . The chilblains were said to be much better and there was no pain on putting on his boots. The blood-coagulation time was *six minutes, fifteen seconds*. Ten grains (0.6 gramme) of calcium chloride cryst. three times a day were prescribed. On the 21st the mean temperature for the day was 32.2° . There had been no further pain or itching. The blood-coagulation time was *six minutes, thirty seconds*; 7.5 grains (0.5 gramme) of calcium chloride cryst. three times a day were given. On the 22nd the mean temperature for the day was 35.2° . The chilblains had absolutely disappeared. The blood-coagulation time was *four minutes, twenty seconds*.

CASE 8.—The patient was a boy aged eleven years. On Dec. 20th, 1896, the mean temperature for the day was 34.1° F. The chilblains on his feet looked very trifling, but great itching was complained of. The blood-coagulation time was *four minutes, thirty seconds*. Twelve grains (0.8 gramme) of calcium chloride cryst. three times a day were prescribed. On the 21st the mean temperature for the day was 32.2° . The chilblains were said to have been less itchy. The blood-coagulation time was *five minutes*. Six grains (0.3 gramme) of calcium chloride cryst. three times a day were prescribed. On the 22nd the mean temperature for the day was 35.2° . There was some itching last night. The blood-coagulation time was *five minutes, five seconds*. Twelve grains (0.75 gramme) of calcium chloride cryst. three times a day were prescribed. On the 23rd the mean temperature for the day was 35.2° . The chilblains were stated to be perfectly well. The blood-coagulation time was *four minutes*.

In conclusion, I would point out that the importance of the facts which have been put on record does not consist solely in the fact that calcium chloride has been

shown to be a palliative for chilblains. It consists rather in the fact that these observations contribute to further establish the principle that serous haemorrhages are often dependent upon a defect of blood-coagulability, and that they may be relieved or prevented in exactly the same way as actual haemorrhages can be by augmenting the coagulability of the blood.

NETLEY.

A NOTE ON THE CAUSATION AND TREATMENT OF THROMBOSIS OCCURRING IN CONVALESCENCE FROM TYPHOID FEVER

(Reprinted from the 'Medico-Chirurgical Transactions', vol. 86, 1903; and 'The Lancet', 6th December, 1902)

BY THE AUTHOR AND H. H. G. KNAPP, M.D., LIEUT. INDIAN MEDICAL SERVICE

We have recently, in the hope of learning something of the causes of the thrombosis which is met with during convalescence from typhoid fever, addressed ourselves to the task of making a series of comparative observations on the blood in (a) typhoid-fever patients in the acute stage of the disease, (b) convalescents from typhoid fever, and (c) in normal persons. Led by considerations which will presently appear, we measured in each case the coagulation time of the blood and its content in lime salts.

Methods employed for measuring the Coagulation Time and the Calcium Content of the Blood.

The account of the methods employed is here omitted, because they were practically identical with those which are described in the Author's TECHNIQUE OF THE TEAT AND CAPILLARY TUBE, 2nd Edition, Constable, London, 1921.

Results of the Blood Examinations.

Results of the blood examinations undertaken on normal men.—In Table I will be found arranged in tabular form the results of a series of blood examinations undertaken upon normal men. A consideration of these brings out the fact that there is as between different individuals, and, we may add, between the blood drawn off at different times from the same individual, a considerable difference not only with respect to the blood-coagulation time, but also with respect to the content in lime salts. We find that the coagulation-time, determined as explained above, may, in the normal male adult, vary between three and a half minutes and eleven minutes, and the minimum strength of oxalate of ammonium solution required to avert coagulation from 1 in 800—this being altogether exceptional—to 1 in 2000.

Of importance in connexion with the method of measuring the content of the blood in lime salts is the fact, which is brought out in Table I, and more clearly in the subsequent tables, that a blood which contains less calcium salts than a control blood is not always less coagulable; nor, again, is a blood which contains more lime salts necessarily more coagulable than the control. The content of a blood in lime salts as estimated by this method is, in fact, far from being an index of its coagulability.

Results of the blood-examinations undertaken upon typhoid-fever patients during the acute stage of the disease.—These results are presented in Table II. The most

noteworthy feature here is the general diminution of blood-coagulability.¹ Let it be observed also that the diminished coagulability furnishes an explanation of the profuse haemorrhages which may occur from comparatively small lesions in the typhoid intestine. Exceptions to the prevailing rule of the association of a condition of diminished blood-coagulability with the acute stage of typhoid fever are furnished by Cases 8, 9, and 10. The former of these was a very mild case. And in case 9—a case which was complicated with pneumonia and bronchitis—femoral thrombosis supervened. The symptoms had manifested themselves only a few hours before the blood was withdrawn for examination.

Results of the blood-examinations undertaken upon convalescents from typhoid fever.—The results we have obtained are incorporated in Table III. The salient feature in connexion with these results is the marked increase of blood-coagulability which accompanies convalescence from typhoid fever. Taking the first eight cases—all cases which were examined both during the course of the pyrexia and after the return of the temperature to the normal—the coagulation time of the blood was, on the average, four and a half times shorter in the convalescent stage than during the course of the fever— $4\frac{1}{2}$ as compared with 20 minutes.

In Cases 1, 4, and 14, and to these may be added Case 9 from Table II, blood-coagulation was abnormally rapid. In each of these cases femoral thrombosis had supervened—these being the only cases among those studied in which it occurred. Exceptional, though not standing entirely by itself, is Case 13. Here the diminished coagulability, which has been shown to be a feature of the acute stage of the disease, is seen to have persisted into the convalescent period. On the thirteenth day after the return of the temperature to the normal, the blood-coagulation time was found to be thirty-five minutes, and this in spite of the fact that the blood contained more than the normal quantum of lime salts. On the fortieth day the coagulation time was still somewhat prolonged.

Turning our attention now more particularly to the results of the calcium-salt estimations, we see that the average content of the blood in lime salts, as estimated by the oxalate method, is, in the case of these typhoid convalescents, rather more than twice that of the normal blood, the average strength of oxalate solution required for decalcification being 1 in 900 as compared with 1 in 2000.

Therapeutical significance of the above facts.—Limiting ourselves here to the consideration of the question of the therapeutics of thrombosis, we may, as a preliminary to setting forth the treatment we adopted, direct attention to a fundamental point in connexion with intra-vascular coagulation. Arguing from what occurs *in vitro*, we might expect that in the case where a thrombus forms in a vein, the patency of the vessel would be rapidly restored by the contraction of the clot. We do, as a matter of fact, see this happening in connexion with the intra-vascular thrombosis, which supervenes upon the injection of cell-nucleo-albumens (Woolbridge's 'tissue-fibrinogens'). If the animals survive this thrombosis for a few hours, we find the thrombus, which previously blocked the vessel, represented by a mere filament of clot. But the conditions are here quite special. As pointed out by

¹ It may be remarked that a comparable diminution in the coagulability of the blood supervenes upon the inoculation of large doses of 'anti-typhoid vaccine'.

Wooldridge, there supervenes here upon the 'positive phase' of increased coagulability which culminates in the thrombosis a 'negative phase' of diminished or abolished blood-coagulability. By reason of the supervention of this 'negative phase', the thrombus, when once formed, does not receive any further accretions of fibrin from the circulating blood.

Quite different are the circumstances when the blood maintains its original coagulability. Here, as soon as any blood-flow is re-established past the clot, additional fibrin will be deposited,¹ and the thrombus will grow larger and firmer until at last it is converted into a solid plug of 'white blood-clot', which definitely blocks the vessel. Probably in this way are sown the seeds of the permanent trouble so often seen after typhoid thrombosis, and we may add after phlegmasia alba dolens.

Recognising the practical importance of the after-deposition of fibrin upon the thrombus, the coagulation time of the patient's blood subsequent to the development of thrombosis is a matter of concern. A reference to Table III will show that in each of the cases of thrombosis—and these were examined respectively eight, twenty-one, and forty-five days after the date of the original thrombosis—the blood was found to be abnormally coagulable. The blood conditions were thus, at these dates, still favourable to a deposition of fibrin upon the clot.

We proposed to ourselves, both in these cases and in the case of acute thrombosis referred to above as having occurred during the pyrexial stage of the fever, to place an obstacle in the way of this deposition of fibrin by diminishing the patient's blood-coagulability. With this view we administered a decalcifying agent²—citric acid.

In Table IV will be found details of the amount of citric acid given, and of the effect of the treatment. It will be seen that in each of the seven patients observed the exhibition of citric acid was followed by a decalcification of the blood and a corresponding diminution of its coagulability. Hand-in-hand with the blood changes went, notably in the case of acute thrombosis already referred to, a rapid alleviation of the symptoms.

Inferences with regard to the causation of the thrombosis which occurs in connexion with typhoid fever.—Turning, in conclusion, to the problem as to what is the cause of the thrombosis so frequently seen in connexion with typhoid fever, and scrutinising the results of the blood-examinations to see whether they shed any light upon this problem, our attention fastens on the fact that the quantum of lime salts in the blood of the typhoid convalescents examined was greatly in excess of that in the normal blood. This fact suggests that the increased coagulability during the convalescent stage may be dependent upon the excess of lime salts present.

Evidence pointing in the same direction is afforded by the circumstance that though the blood-coagulation times of our typhoid patients were, as compared with the normal, much reduced, the content of their blood in lime salts (as is brought out by a comparative study of Tables IV and I) was much in excess of that of normal bloods.

When we consider whence the *excess of lime salts* in the blood of the typhoid patient and convalescent can be derived, we recognise that it may reasonably be

¹ *Vide infra*, pp. 34–35.

² *Vide supra*, pp. 34 *et seq.*

supposed to derive from the milk which, for the most part, constitutes the exclusive dietary of the patient.¹ Cow's milk, be it noted, contains 1 part in 600 of CaO as compared with 1 part in 800 contained in lime water.

If we have, in the milk dietary of the typhoid patient,² the key to the problem of the frequency of thrombosis in the period of convalescence, we have probably obtained a clue also to the resolution of certain other problems ; in particular the problem of the frequently beneficial effect of a milk dietary on ' serous haemorrhage ' from the kidney, and the comparative rarity of thrombosis after acute fevers such as Malta fever, where a milk dietary is not imposed upon the patient.

We obtain at the same time indications for the *prophylaxis and after-treatment of thrombosis*, both when it occurs in connexion with typhoid fever and when it occurs in connexion with other diseases. The remedial measure which would seem indicated is the exhibition of *citric acid*. The same treatment, initiated as soon as the danger of intestinal haemorrhage has been surmounted, would be appropriate for prophylaxis of typhoid thrombosis.

Or, as an alternative, we might, with a view to restricting the intake of lime salts, appropriately undertake a partial decalcification of the milk. One of us has already pointed out that a partial decalcification such as is here contemplated is advisable also from the point of view of rendering the milk more easily digestible, and of preventing constipation. The partial decalcification which would be appropriate *in such cases* in question can be readily effected by adding to the milk 0.25 to 0.5 per cent. of citrate of soda (20 to 40 grains per pint).

¹ In the case of our particular patients milk formed a very important element of their dietary for a period of many weeks after convalescence.

² For an investigation of this question see *infra*, pp. 109-111.

TABLE I.—*Normal Men.* Showing the blood-coagulation time and the strengths of neutral ammonium oxalate solution which respectively averted and failed to avert coagulation when added to the blood in equal volume.

Initials of the persons who furnished the blood	Coagulation time estimated in capillary tubes of the new standard size at 18.5° C. (half blood-heat).	Concentration of the solutions of oxalate of ammonium solution which were mixed with the blood for the purpose of estimating its content in calcium salts					
		1 in 800 (5 in 4000)	1 in 1000 (4 in 4000)	1 in 1333 (3 in 4000)	1 in 1600 (2.5 in 4000)	1 in 2000 (2 in 4000)	1 in 4000 (1 in 4000)
A. W.	6' 30"	0	0	Trace	—	Clot	Clot
C. K.	7' 10"	0	0	"	—	"	"
R. C.	11'	0	0	Clot	—	"	"
G. E. V.	8' 15"	0	0	"	—	"	"
A. A.	7' 30"	0	0	0	—	"	"
S. D.	5' 45"	0	0	0	—	"	"
R. W.	6' 10"	0	0	0	—	"	"
J. S.	9' 15"	0	0	0	—	"	"
J. R.	8' 10"	0	0	0	—	"	"
B. S.	10' 15"	0	0	0	—	"	"
R. E. S.	9'	0	0	Trace	—	"	"
J. B.	10' 10"	0	0	Clot	—	"	"
O. N.	8'	0	0	"	—	"	"
W. B. L.	4'	0	0	Trace	—	"	"
G. E. V.	8' 45"	0	0	0	0	"	"
N. M.	8'	0	Clot	Clot	Clot	"	"
N. C.	6'	0	0	0	0	"	"
J. M.	8'	0	0	0	Clot	"	"
C. P.	9'	0	0	Trace	"	"	"
D. B.	6' 30"	0	0	Clot	"	"	"
W. R. ¹	8'	Clot	Clot	"	"	"	"
P. L.	7'	0	0	0	"	"	"
T. Y.	8' 20"	0	0	0	"	"	"
M. M. ²	6'	0	0	0	"	"	"
M. M. ²	3' 30"	Clot	Clot	Clot	"	"	"
W. R. ¹	6' 30"	"	"	"	"	"	"
T. H.	6'	0	0	"	"	"	"

¹ The observations here in question were made at an interval of a few days.

² The observations here in question were made at an interval of about forty-eight hours.

TABLE II.—*Typhoid Patients in the Acute Stage.* Showing the results of the blood-examinations undertaken on typhoid-fever patients (soldiers) in the acute stage of the disease.

Serial number	Notes with regard to the clinical features of the case and the stage of the disease at the date of the observation	Coagulation time	Measurement of the calcium content of blood—i.e. concentration of oxalate of ammonium solution, which (added to the blood in equal volume) just sufficed to avert coagulation
Case 1	Fourth week of pyrexia ; case has been complicated by epistaxis and pleural effusion	30'	1 in 2000
Case 2	Beginning of fourth week of pyrexia	12'	1 in 750
Case 3	Eleventh day of relapse - - -	15'	1 in 900
Case 4	About seventeenth day of pyrexia -	22'	1 in 2000
Case 5	Uncomplicated case ; temperature falling by lysis	15'	1 in 2500
Case 6	About fourteenth day of pyrexia -	30'	1 in 1500
Case 7	Tenth day of relapse - - -	30'	1 in 900
Case 8	Tenth day ; very mild case - -	5'	1 in 900
Case 9	Fourth week of pyrexia ; complicated by pneumonia, capillary bronchitis, and on day of observation by acute femoral thrombosis	1' 45"	1 in 700
Case 10	Uncomplicated case ; beginning of fourth week	5'	1 in 600
Case 11	Fourth day of relapse ; history of haemorrhages in primary attack	17'	1 in 1000
Case 12	Beginning of fourth week of pyrexia ; much bronchitis	16'	1 in 900

TABLE III.—Showing the results of the blood-examinations undertaken on soldiers convalescent from typhoid fever.

Serial number	Notes with regard to the clinical features of the case and the stage of convalescence at which the patient had arrived at the date of the observation	Coagulation time (followed in brackets by the coagulation time as previously determined in the stage of pyrexia)	Estimation of content of the blood in calcium salts, i.e. concentration of ammonium-oxalate solution, which (added to the blood in equal volume) just sufficed to avert coagulation
Case 1	Fourteenth day of apyrexia : three weeks subsequent to development of slight femoral thrombosis	2' [30']	1 in 900
Case 2	Twenty-fourth day of apyrexia -	4' 15" [12']	1 in 700
Case 3	First day of apyrexia - - -	4' 30" [15']	1 in 1500
Case 4	Seventh week of apyrexia ; eight days after development of slight femoral thrombosis	1' 10" [22']	1 in 700
Case 5	Twentieth day of apyrexia ; after taking citric acid 2.5 grammes t.i.d. for six days	4' [15']	1 in 1500
Case 6	Second day of apyrexia - -	4' [30']	1 in 700
Case 7	Seventh day of apyrexia - -	10' [30']	1 in 1500
Case 8	First day of apyrexia - - -	5' [5']	—
Case 13	Thirteenth day of apyrexia - -	35'	1 in 700
	Fortieth day of apyrexia - -	11'	1 in 900
Case 14	Fifty-fifth day of apyrexia ; forty-fifth day after development of thrombosis	1' 30"	1 in 700
Case 15	Third week of apyrexia - -	3' 15"	1 in 700
Case 16	Fourteenth week of apyrexia -	9'	1 in 550
Case 17	Third week of apyrexia - -	9' 30"	1 in 700
Case 18	Third week of apyrexia - -	10'	1 in 800
Case 19	First day of apyrexia - - -	7'	1 in 700
Case 20	Fifth day of apyrexia - - -	4' 30"	—
Case 21	Fifth day of apyrexia - - -	5'	—
Case 22	Tenth day of apyrexia - - -	9' 30"	—

TABLE IV.—Exhibiting the effect of the decalcifying treatment adopted in the case of typhoid convalescents possessing an unduly coagulable blood.¹

Initials of patient	Date of observation	Notes with regard to dietary and treatment	Notes with regard to clinical symptoms at date of observation	Blood-coagulation time in standard tubes, at 18.5° C.	Estimation of content of blood in calcium salts.				
					$\frac{\text{part}}{\text{part}}$ Concentration of ammonium-oxalate solution which, when added in equal volume to the blood, respectively averted and failed to avert coagulation	$\frac{\text{part}}{\text{part}}$	$\frac{\text{part}}{\text{part}}$	$\frac{\text{part}}{\text{part}}$	$\frac{\text{part}}{\text{part}}$
J. B.	8-7-02	Milk diet	Typhoid fever, fourth week, complicated by pneumonia and capillary bronchitis; to-day acute development of femoral thrombosis	1' 45"	0	0	Clot	Clot	Clot
	10-7-02	Ditto + citric acid 4 grms. (5j) t.i.d. (since 8-7-02)	Pain and swelling in limb less; fever continues	6'					
	11-7-02	" "	No change	7' 30"	0	0	"	"	"
	13-7-02	" "	Oedema and pain in the limb have quite disappeared; fever continues	7' 15"	0	0	"	"	"
	14-7-02	" "	No change	5' 45"	0	0	0	"	"
B. D.	7-7-02	Convalescent diet, including milk (circ. 2 pints)	Fourteenth day of apyrexia; twenty-second day after slight thrombosis	2'	0	0	Clot	Clot	Clot
	14-7-02	Ditto + citric acid 2.5 grms. (circ. 36 grs.) t.i.d. (since 12-7-02)	—	3' 45"	0	0	Trace	"	"
	19-7-02	" "	—	over 15'	0	0	0	"	"

C. D.	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Fifty-fifth day of apyrexia; forty-fifth day after thrombosis	1' 30"	0	Clot	Clot	Clot	Clot	Clot
C. D.	14-7-02	Ditto + citric acid 2.5 grms. t.i.d. (since 12-7-02)	—	3' 15"	0	Trace	"	"	"	"
	19-7-02	" "	—	10'	0	0	"	"	"	"
	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Seventh week of apyrexia; seventh day after thrombosis	1' 10"	0	Clot	Clot	Clot	Clot	Clot
J. A.	15-7-02	Ditto + 2.5 grms. of citric acid t.i.d. (since 12-7-02)	—	5'	Trace	"	"	"	"	"
	20-7-02	" "	—	over 20'	0	0	"	"	"	"
	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Third week of apyrexia	3' 15"	0	Clot	Clot	Clot	Clot	Clot
D. R.	15-7-02	Ditto + 2.5 grms. of citric acid t.i.d. (since 12-7-02)	—	4' 45"	0	0	Trace	"	"	"
	19-7-02	" "	—	13' 30"	0	0	Clot	"	"	"
	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Fourteenth day of apyrexia	9'	Clot	Clot	Clot	Clot	Clot	Clot
R. D.	15-7-02	Ditto + citric acid 2.5 grms. t.i.d. (since 12-7-02)	—	9' 30"	0	0	0	"	"	"
	19-7-02	" "	—	10'	0	0	Clot	"	"	"
	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Third week of apyrexia	9' 30"	0	Clot	Clot	Clot	Clot	Clot
F. D.	16-7-02	Ditto + citric acid 2.5 grms. t.i.d. (since 12-7-02)	—	over 13' 30"	0	0	"	"	"	"
	19-7-02	" "	—	over 30'	0	0	0	"	"	"
	8-7-02	Convalescent diet, including milk (<i>circ.</i> 2 pints)	Third week of apyrexia	9' 30"	0	Clot	Clot	Clot	Clot	Clot

¹ It would seem from the fact that the point is not mentioned in our notes that we are not sure the milk was cut out from the dietary of these patients when they were placed on the citric acid treatment.

ON THE EFFECT EXERTED ON THE COAGULABILITY OF THE BLOOD BY AN ADMIXTURE OF LYMPH

(Reprinted from the 'Journal of Physiology', vol. xxviii, No. 6, 1902)

It was pointed out by Delezenne¹ in a very suggestive paper that the blood of fowls, currently supposed to be a highly coagulable blood, will, if rigorous precautions are taken to keep it from contact with the *tissues* and *foreign matter generally*, remain uncoagulated for prolonged periods; while it will clot with extreme rapidity if in drawing off it has come in contact with the tissues, or if failing this it is brought in contact *in vitro* with a piece of freshly extirpated muscular tissue. In the case of mammalian blood a similar acceleration of coagulation was observed. It had already been observed by Halliburton,² in connexion with experiments on the effect of the addition of muscle-juice or of fresh muscle to salt plasma, that the coagulation time of this plasma was by these means considerably reduced.

Before dealing, as I propose to do here, with the cause of this accelerated coagulation, I may conveniently adduce certain experiments which bring clearly before us the phenomenon which is in question.

Rabbit 1. Ether.

Approximately equal volumes of blood were allowed to flow from the carotid artery directly into a series of carefully cleaned test-tubes. The progress of coagulation in the samples of blood was tested by inclining the test-tubes at half-minute intervals. The interval which elapsed between the time of drawing off blood and the time at which test-tubes could be inverted without disturbing the contents was taken as the 'coagulation time'.

First series of experiments

Tube 1.	Empty (to serve as a control)	-	-	-	Coagulation time	4 mins.
Tube 2.	Contains a loose pledget of cotton-wool (to serve as a further control)	-	-	-	,,	,, 4 mins.
Tube 3.	Contains small piece of muscle	-	-	-	,,	,, 2 mins.

(Note. Volume of muscle estimated at $\frac{1}{7}$ th of volume of blood.)

A considerable amount of blood is now drawn off for other purposes.

Second series of experiments (10 mins. after)

Tube 1.	Empty	-	-	-	Coagulation time	2 $\frac{1}{2}$ mins.
Tube 2.	Contains a loose pledget of cotton-wool	-	-	-	,,	,, 2 $\frac{1}{2}$ mins.
Tube 3.	Contains a piece of muscle	-	-	-	,,	,, 1 min.

¹ *Archives de Phys. norm. et pathol.*, 1897.

² *Journal of Physiology*, vol. viii, p. 175, 1887.

Rabbit 2. Ether. Same procedure as in Rabbit 1.

Tube 1.	Empty - - - - -	Coagulation time	7½ mins.
Tube 2.	Contains a piece of muscle - - - - -	„ „	3½ mins.
Tube 3.	Contains 0.75 per cent. NaCl extract of muscle (volume of extract employed approximately ½th of blood-volume) - - - - -	„ „	3½ mins.
Tube 4.	Contains a piece of muscle - - - - -	„ „	3½ mins.
Tube 5.	Empty - - - - -	„ „	7½ mins.

Dog 1. Chloroform and Ether. Procedure exactly the same as above.

First series of experiments

Tube 1.	Empty - - - - -	Coagulation time	3½ mins.
Tube 2.	Contains a loose pledget of cotton-wool - - - - -	„ „	3½ mins.
Tube 3.	Contains a piece of muscle - - - - -	„ „	1½ mins.

A considerable amount of blood drawn off for another purpose.

Second series of experiments

Tube 1.	Empty - - - - -	Coagulation time	1½ mins.
Tube 2.	Contains cotton-wool - - - - -	„ „	1½ mins.
Tube 3.	Contains a small piece of muscle - - - - -	„ „	1 min.

The acceleration of coagulation obtained by the contact of the blood with the tissues is manifestly a very notable one; and nothing comparable to it is obtained by the mechanical effect of foreign matter (cotton-wool).

Passing to enquire what is the element which induces the accelerated coagulation obtained when the blood is allowed to pass over the tissues of the wound or to come in contact *in vitro* with a piece of tissue, confirmation was readily obtained of the correctness of Delezenne's statement that the property of accelerating coagulation is not specific to muscular tissue. It was found that the accelerating influence was exerted, and apparently in an equal degree, by pieces of subcutaneous tissue, spleen, liver, kidney, lungs, and suprarenal body.

Two alternative hypotheses suggest themselves. Either the coagulative element in question is an actual component element of each and every tissue, or it is something extraneous to the tissues but found in association with them.

The first hypothesis wins little support from considerations of what actually occurs. It does not appear probable that any constituent element could be dissolved out of the tissues during the very fugitive contact of the blood with the tissues of the wound. Again, as has been just stated, no indication was obtained of any difference as between the different tissues from the point of view of their effect in accelerating coagulation.

The second hypothesis resolves itself into the hypothesis that the coagulative element is supplied by the lymph.

That the lymph might be the active agent in the acceleration of the blood-coagulation was rendered probable by the work of Shore. Shore,¹ following up Wooldridge's work on intravascular thrombosis, had found that the intravascular

¹ *Proc. Camb. Phil. Soc.*, vii, Pt. vi.

injection of lymph collected from the thoracic duct frequently, but not invariably, produced the phenomenon in question.

With a view to further investigating the effect of lymph on blood-coagulation, the following series of experiments were instituted.

1. In a first series of experiments, so far as possible equal weights of washed and unwashed muscular tissue were introduced into equal samples of blood drawn from the carotid.

Two typical experiments may be adduced.

Dog. Anaesthetised with ether and chloroform.

A piece of gluteal muscle was extirpated, and was divided into four portions of equal weight. Two of these pieces were separately washed by shaking them in test-tubes half filled with normal salt solution. This operation was in each case repeated three times with fresh portions of normal salt solution.

A cannula was then introduced into the carotid artery and so far as possible equal samples of blood were filled without contact with the tissue into a series of small carefully cleaned test-tubes.

Tube 1.	Empty. (To serve as a control)	-	-	-	Coagulation time	3 mins.
Tube 2.	Contains a piece of washed muscle	-	-	-	" "	2 mins.
Tube 3.	Contains a piece of unwashed muscle	-	-	-	" "	1 m. 30 s.
Tube 4.	Empty	-	-	-	" "	3 m. 15 s.

Second series of experiments. (Same procedure adopted)

Tube 1.	Empty	-	-	-	Coagulation time	2 mins.
Tube 2.	Contains a piece of washed muscle	-	-	-	" "	2 mins.
Tube 3.	Contains a piece of unwashed muscle	-	-	-	" "	1 m. 30 s.
Tube 4.	Empty	-	-	-	" "	2 mins.

Fowl. (Same experimental procedure as above)

Tube 1.	Empty	-	-	-	Coagulation time	about 20 mins.
Tube 2.	Contains a piece of washed muscle	-	-	-	Coagulation time	6 mins.
Tube 3.	Contains a piece of unwashed muscle	-	-	-	" "	3 mins.

Second series of experiments

Tube 1.	Empty	-	-	-	Coagulation time	20 mins.
Tube 2.	Contains a piece of washed muscle	-	-	-	" "	4 mins.
Tube 3.	Contains a piece of unwashed muscle	-	-	-	" "	2 m. 30 s.

The effect of unwashed muscle is thus seen to be greater than the effect of washed muscle, a result which is in harmony with the assumption that the acceleration of coagulation obtained by contact of blood and tissue is due to the admixture of lymph to blood. The fact that the muscle still exerts after washing an accelerating influence may in all probability be referred to the presence of a residue of lymph in the muscle.

2. The next step which was taken was to determine the effect of addition of lymph to blood.

The lymph required for this purpose was obtained in various ways. In the first series of experiments a supply of clear lymph was obtained from blisters raised

in some cases by the application of a heated glass rod, and in other cases by the application of blistering fluid. The lymph thus obtained was mixed with blood in capillary 'coagulation tubes' of a standard calibre. The results obtained were as follows.

EXP. I. Human blood (supplied by A.B.). 23-2-98.	
Coagulation time of blood flowing spontaneously from puncture in finger (determined at the temperature of the air, 13° C.) - - - - -	9 mins.
Coagulation time of same blood mixed with $\frac{1}{3}$ rd its volume of perfectly clear human blister fluid (determined as above at temperature of air) -	2 mins.
EXP. II. Human blood (supplied by X.Y.) 23-2-98.	
Coagulation time of unmixed blood (determined at temperature of air) -	14 $\frac{1}{2}$ mins.
Coagulation time of blood mixed with $\frac{1}{3}$ rd volume of fresh human blister fluid - - - - -	2 $\frac{3}{4}$ mins.
EXP. III. Human blood (supplied by B.C.). 9-6-98.	
Coagulation time of unmixed blood - - - - -	5 mins.
Coagulation time of blood mixed with mere <i>trace</i> of human blister fluid -	2 $\frac{1}{2}$ mins.
Coagulation time of blood mixed with $\frac{1}{3}$ rd volume of human blister fluid	2 mins.
EXP. IV. Rabbit's blood. 22-2-98.	
Coagulation time of unmixed blood (determined at temperature of air) -	5 $\frac{1}{2}$ mins.
Coagulation time of blood which had received an addition of half its volume of fresh rabbit's blister fluid - - - - -	2 $\frac{1}{2}$ mins.

In a further series of experiments, additions of pericardial fluids and of lymph obtained from the thoracic duct were made to the blood. The results of these are as follows.

EXP. I. ¹ Dog's blood. 8-6-98.	
Coagulation time of unmixed blood from heart - - - - -	6 mins.
Coagulation time of same blood which had received an addition of $\frac{1}{6}$ th its volume of human pericardial fluid - - - - -	1 min.
Coagulation time of same blood which had received an addition of $\frac{1}{6}$ th of its volume of lymph from this dog's thoracic duct - - - - -	3 $\frac{1}{4}$ mins.
EXP. II. ¹ Human blood. 8-3-98.	
Coagulation time of blood from finger at temperature of air - - - - -	13 mins.
Coagulation time of same blood mixed with $\frac{1}{3}$ rd its volume of human pericardial fluid - - - - -	6 mins.
EXP. III. Dog's blood. 10-6-98.	
Coagulation time of blood from carotid - - - - -	1 $\frac{1}{4}$ mins.
Coagulation time of same blood which had received an addition of about $\frac{1}{20}$ th of its volume of lymph from this dog's thoracic duct - - - - -	$\frac{1}{2}$ min.
EXP. IV. Dog's blood. 15-6-98.	
Coagulation time of blood from carotid - - - - -	7 $\frac{1}{2}$ mins.
Coagulation time of same blood which had received an addition of a trace of lymph from this dog's thoracic duct - - - - -	1 $\frac{1}{4}$ mins.

¹ Experiments 1 and 2 of this series are manifestly in harmony with the classical experiments of Buchanan and Alexander Schmidt, which showed that a coagulum is obtained by bringing in contact with each other albuminous elements isolated respectively from a transudation-plasma (hydrocele fluid) and serum.

It will be seen that an addition of lymph, from whatever source that lymph has been obtained, brings about a notable acceleration of blood-coagulation.

There can, therefore, hardly be any doubt that the acceleration of coagulation observed when blood has come in contact with the wound, or when a piece of muscle is introduced into shed blood, is an acceleration due to an intermixture of lymph.

The last question which may be considered is the question as to what is the element of the lymph which produces the acceleration of coagulation. With a view to determining this, the influence of an addition of lymph serum to blood was compared with the influence exerted by an addition of freshly drawn lymph. It was found that while the influence of freshly drawn lymph was, as has already been shown, very striking, the influence of an addition of lymph serum was either slight or altogether insensible. This point is brought out in the following experiments.

EXP. I. Human blood drawn from the finger.

Coagulation time - - - - -	8 m. 30 s.
Coagulation time of the same blood mixed with $\frac{1}{3}$ rd of its volume of serum obtained from lymph which had been drawn off six hours previously -	8 m. 30 s.

EXP. II. Human blood drawn from the finger.

Coagulation time - - - - -	14 m. 30 s.
Same blood mixed with $\frac{1}{3}$ rd of its volume of serum from lymph drawn off 5 hours previously, coagulation time - - - - -	8 m. 45 s.
Same blood mixed with $\frac{1}{3}$ rd of its volume of lymph freshly drawn off from a blister, coagulation time - - - - -	2 m. 40 s.

The inference which we may base on these experiments, i.e. the inference that the effect of the lymph is attributable to the coagulative albuminous element which is removed by clotting, is further confirmed by the result of such experiments as the following.

Rabbit. Anaesthetised with ether. Cannula was placed in carotid. So far as possible equal quantities of blood drawn off directly from the artery into a series of test-tubes.

Tube 1. (Control) - - - - -	Coagulation time 7 m. 30 s.
Tube 2. Contains a 0.75 per cent. NaCl extract of boiled muscle, amounting in volume to $\frac{1}{7}$ th of the blood - - - - -	„ „ 4 mins.
Tube 3. Contains the same quantity of a similar extract of unboiled muscle - - - - -	„ „ 2 m. 45 s.
Tube 4. (Control) - - - - -	„ „ 7 m. 30 s.
Tube 5. Contains a similar extract of unboiled muscle amounting to $\frac{1}{3}$ rd of the volume of the blood - - - - -	„ „ 2 m. 15 s.
Tube 6. Contains the same quantity of extract of boiled muscle - - - - -	„ „ 7 mins.

In conclusion, brief reference may be made to the fact that the acceleration of coagulation which results from an addition of lymph to blood is in point of fact constantly obtruding itself upon the attention. It comes under observation in a very characteristic manner in the course of post-mortem examinations, it being quite common to see the blood suddenly coagulate on issuing from the heart and

mixing with the pericardial fluid. A similarly accelerated coagulation comes under observation also when we make pressure on the tissues and drive the lymph into a bleeding wound. We may, for instance, contrast the short coagulation time of the mixture of blood and lymph obtained from a small or almost occluded puncture on the finger with the much longer coagulation time of the blood issuing spontaneously from a free puncture. The same phenomenon—we may conveniently speak of it as the phenomenon of Delezenne—comes under observation also when blood from a ruptured vessel exudes on to a raw surface which is bathed with lymph, such, for instance, as a weeping eczematous surface or the floor of an ulcer.

ON A NEW METHOD OF TESTING THE BLOOD AND THE URINE

WITH SPECIAL REFERENCE TO THE DETERMINATION OF THE EXCRETORY EFFICIENCY OF THE KIDNEY

BY THE AUTHOR AND J. NEWPORT KILNER, M.B. LOND.

(Reprinted from 'The Lancet', 2nd April, 1904)

The examination of the urine for albumin is a very indirect, ineffective, and often fallacious method of obtaining information with regard to the excretory efficiency of the kidney. While it is capable of revealing leakage of the albuminous substances from the blood into the urine it tells us nothing with regard to the excretion of the salts and products of metabolism generally into the urine. This information is furnished by comparative cryoscopic examinations of the urine and of the blood from which that urine has been elaborated. These examinations, involving as they do not only resort to complicated and delicate apparatus but also the employment of a comparatively large quantity of blood, are impracticable in connexion with ordinary clinical work. The difficulties which are associated with cryoscopic work may be avoided by the method described below. The information which it furnishes seems likely to be of value alike to the clinician, the operating surgeon, and the medical officer who has to deal with life insurance.

Principle of the method.—Dilutions are made of the patient's serum, of his urine and of a salt solution of a standardised strength, until we arrive in each case at a dilution of which 2 volumes completely haemolyse 1 volume of normal blood.

The different degrees to which the serum and urine have to be diluted furnishes the *excretory quotient*; and the degree to which these fluids have to be diluted gives us a basis for calculating the salt content of the haemolysing dilutions of the serum and urine.

Precautions to be observed in collecting the serum and urine which are to be compared.—In each case the samples of blood and urine are obtained from patients who have not drunk anything for a period of hours. Where accurate comparisons are required the bladder is emptied before commencing operations. A sample of blood is thereupon withdrawn, and as soon as possible afterwards a sample of newly secreted urine is passed.

Instructions.—The instructions given below will be sufficient for any one who can carry out very simple glass-working operations, and has mastered the '*Technique of the Teat and Capillary Tube*'.

Apparatus required.—The apparatus required consists of (a) *Ordinary*, or better, *long-stemmed*¹ capillary pipettes provided with rubber teats; (b) distilled water for making graduated dilutions of the serum, urine and salt solution; (c) a standard salt solution made by taking 1 c.c. of a saturated solution of saline and adding to it 25 c.c. of distilled water; (d) three or four paraffined slides upon which to arrange

¹ Vide Author's *Technique of the Teat and Capillary Tube*, 2nd Edition, pp. 29-31, Constable, London.

the 2-volume drops of diluted serum, urine, and 1 per cent. salt solution ; (d) 'sliver prickers'¹ for obtaining from the operator's finger the blood which is to supply the red blood corpuscles required for haemolysis.

Details of the procedure.—Making use of distilled water as a diluting agent prepare a 2-, 3- and 4-fold dilution of the patient's serum and arrange a series of 2-volume drops of these graduated dilutions in order upon a paraffined slide.

Make then a 2-, 4-, 8-, 12- and 16-fold dilution of the patient's urine, and again arrange a series of 2-volume drops of these graduated dilutions in order upon a paraffined slide.

Finally make 2-, 3-, 4- and 5-fold dilutions of the 1 per cent. salt solution, and again arrange 2-volume drops of these dilutions in order upon a paraffined slide.

Now puncture your own finger and collect blood upon a paraffined slide. And, taking in hand again the same graduated pipette in which the 2-volume drops of the three diluted fluids were measured off, add one volume of blood to each of the drops, taking care to mix intimately. This done, take three capillary pipettes, preferably long-stemmed pipettes, and fill into these, labelling as you go along, and commencing in each case with the smallest dilution and ending up with the highest, an aliquot volume of each of the urine and blood dilutions, separating the different dilutions in each case by a bubble of air.

Having sealed up the ends of the capillary pipettes, put them side by side in the incubator and leave them there for, let us say, one quarter of an hour. Then take the tubes out and examine them, and note that you have in each pipette in the proximal end of each tube a clot without haemolysis, and further down the stem clots showing haemolysis, and further down again clots which are completely haemolysed.

Compare now the amount to which each of the three fluids required to be diluted to give complete haemolysis. And it will not be an absolutely simple matter to express the result in the form of an excretory quotient and to say how much salt taken as sodium chloride is contained in the patient's serum and urine.

TABLE I.—*Setting forth the Concentration (expressed in terms of NaCl) of the Serum and Urine and the Excretory Quotient of Normal Adult Men.*

No.	Date	Concentration of :		Excretory quotient
		Serum	Urine	
		Per cent.	Per cent.	
1	5-2-04	0.78	1.56	2
	6-2-04	0.78	1.56	2
2	6-2-04	0.78	1.56	2
	11-2-04	0.78	1.56	2
	13-2-04	0.78	1.56	2
	24-2-04	0.78	1.56	2
3 ²	5-2-04	0.78	3.0	4
	8-2-04	0.78	3.0	4

¹ *Vide Proceedings Royal Society of Medicine*, Jan. 1942, p. 161 ; also Vol. IV of these Collected Researches.

² The subject of these observations perspires a great deal and excretes proportionally less urine.

TESTING THE BLOOD AND THE URINE

TABLE I—*Continued.*

No.	Date	Concentration of :		Excretory quotient
		Serum	Urine	
		Per cent.	Per cent.	
	9-2-04	0.78	3.0	4
	11-2-04	0.78	3.9	5
	12-2-04	0.78	1.56	2
	13-2-04	0.78	3.0	4
	16-2-04	0.78	4.7	6
	22-2-04	0.78	1.56	2
4	18-2-04	0.78	1.56	2
5	26-2-04	0.78	3.0	4
6	26-2-04	0.78	3.0	4
7 ¹	26-2-04	0.78	1.2	1.5
8	26-2-04	0.78	1.56	2

¹ The subject of this observation had drunk freely some hours before. In association with this it may be mentioned that the subject of Observation Number 1 was successful in reducing the concentration of his urine to less than 0.1 per cent. NaCl by drinking 1500 cubic centimetres (*circ.* three pints) of water upon an empty stomach.

It will be seen that the concentration of the serum is a very constant function in health and that the excretory quotient is, if we except the first observation made in the case of the man denoted by the serial number 7, always two or more than two.

TABLE II.—*Setting forth the Concentration (expressed in terms of NaCl) of the Serum and Urine and the Excretory Quotient in the Case of Patients suffering from Renal Disease.*

Serial number of case	Clinical data	Concentration of :		Excretory quotient
		Serum	Urine	
		Per cent.	Per cent.	
1	Patient, a woman, aged 54 years, has suffered for two months from oedema of the feet and legs. Urine contains half its volume of albumin.	2.0	1.56	0.76
2	Patient, a woman, aged 52 years, contracted scarlet fever in childhood. Urine erstwhile passed in large quantities has recently become scanty. Vomiting and headache seven days ago. Has considerable thickening of arteries and a high arterial tension.	0.97	1.2	1.2
3	Patient, a woman, aged 35 years, dates back her illness to an attack of scarlet fever in childhood. An exploratory incision has revealed extensive destructive changes in the right kidney. Patient suffers from headache and incapacity for exertion. Urine is free from albumin. Coli bacilli are present in pure culture in urine.	0.78	0.78	1.0

TABLE II—*Continued.*

Serial number of case	Clinical data	Concentration of :		Excretory quotient
		Serum	Urine	
4	Patient, a child, aged about 11 years, is the subject of enlarged liver and spleen, fibrosis of the base of the right lung, and swelling of the legs. Urine contains half its volume of albumin.	Per cent. 0·97	Per cent. 0·97	1·0
5	Patient, a woman, aged about 50 years, who is now lying in a semi-comatose condition, has suffered from giddiness, twitching, and vomiting. Hypertrophy of the heart and arterio-sclerosis are well marked. Double optic neuritis. Urine contains one-fifth volume of albumin.	0·97	0·48	0·5
6	Patient, a woman, aged about 30 years, the subject of extensive swelling of the legs and face, suffers from headache and vomiting. Had scarlet fever when two years of age. Has lately been confined and has suffered from dropsy with each of three former pregnancies. Vascular changes slight. Large quantity of albumin in the urine.	1·56	0·78	0·5
7	Patient, aged 26 years, dated back her illness to five years ago, when she suffered from headache and vomiting. Since that date she has had several subacute attacks, with anasarca, headache and vomiting. Her symptoms are now passing off.	1·56	3·0	2·0
8	Patient, aged 17 years, has recently suffered from oedema of the face and legs, with occasional vomiting, headache, and traces of blood in the urine. The symptoms have now all disappeared.	1·56	1·56	1·0
9	Patient, aged 22 years, is suffering from epistaxis, pain in back, frequency of micturition, headache, twitching, and vomiting, with some drowsiness and anasarca.	1·0	2·0	2·0
10	Patient, an elderly man, is suffering from oedema, anasarca, and ascites, with albumin in the urine.	0·78	0·29	0·37
11	Patient, a middle-aged man, suffering from headache, incapacity for exertion and albuminuria.	1·2	0·78	0·66
12	Patient is a boy with ascites and albuminuria.	0·97	0·97	1·0
13	Patient with tubercle bacilli in the urine, suffering from frequent micturition.	0·92	1·15	1·2
		1·1	1·1	1·0
14	Patient with pain and tenderness and sensible swelling of both kidneys, frequent micturition, very large number of tubercle bacilli in the urine.	1·4	1·1	0·79
		1·1	1·1	1·0

Remarks

CASE 1.—Diagnosis : parenchymatous nephritis. CASE 2.—Diagnosis : interstitial nephritis. CASE 3.—Extirpation of kidney is under consideration. CASE 4.—Diagnosis : amyloid disease. CASE 5.—Diagnosis : interstitial nephritis. CASE 6.—Diagnosis : Parenchymatous nephritis. CASE 7.—Diagnosis : parenchymatous nephritis. CASE 8.—Diagnosis : subacute nephritis. CASE 9.—Diagnosis : chronic parenchymatous nephritis. CASE 10.—Diagnosis : chronic parenchymatous nephritis complicated by cirrhosis of the liver. CASE 11.—Diagnosis : chronic parenchymatous nephritis. CASE 12.—Diagnosis : acute nephritis. CASE 13.—Tubercle of kidney. The second of the estimations was made five days after the first. CASE 14.—Tubercle of kidney. The second estimation was made four days after the first.

TABLE III.—Setting forth the Concentration (expressed in terms of NaCl) of the Serum and Urine and the Excretory Quotient in the Case of the Subjects of Pernicious Anaemia and Chlorosis.

Serial number of case	Clinical data	Concentration of :		Excretory quotient
		Serum	Urine	
		Per cent.	Per cent.	
1	Patient is suffering from advanced <i>pernicious anaemia</i> . Examination of the blood films shows marked poikilocytosis and the presence of nucleated red blood corpuscles.	0.78	—	—
2	Patient, aged 35 years, is suffering from <i>pernicious anaemia</i> . Red blood corpuscles, 1,700,000 ; marked poikilocytosis. No nucleated red blood corpuscles.	2.4	—	—
3	Patient, aged 19 years, is suffering from well-marked <i>chlorosis</i> associated with amenorrhoea, constipation, shortness of breath, and cramp.	1.0 1.56 1.56	—	—
4	Patient, aged 21 years, is suffering from <i>chlorosis</i> associated with oedema of the legs, constipation, and dyspepsia.	3.0 1.2 1.56	3.0	2
5	Patient, aged 18 years, is suffering from <i>chlorosis</i> , irregularity of the bowels, and clavus hystericus.	1.0	—	—
6	Patient is suffering from <i>gastric ulcer with profound anaemia</i> .	1.0 0.78	—	—
7	Patient, aged 25 years, is suffering from <i>gastric ulcer and anaemia</i> dating back nine years.	2.4 1.2 1.56	3.0	1.7
8	Patient, aged 25 years, has suffered from anaemia complicated with thrombosis, first of the left and then of the right leg.	2.44	—	—

It is brought out in the cases tabulated above that the serum is modified in a characteristic way. The improvement which appears in the successive observations made in Cases 4, 6, and 7 may, perhaps, be referred to the treatment. It will be observed that the excretory quotient in the two cases where it was tested is approximately normal.

Concluding remarks and question as to the precise significance of the method of testing here recommended.—We have seen above that the investigation of the *haemolytic index* of the serum or, as the case may be, the comparative estimation of the haemolytic indices of the serum and urine is likely to prove of utility in connexion with clinical work. It may clear up a diagnosis, it may tell us whether a patient is in a condition to undergo a surgical operation, it may give warning of the approaching advent of uraemic symptoms, it may assist the physician in selecting the proper dietary for a patient who is suffering from Bright's disease, and it may serve to distinguish between so-called functional and organic albuminuria. While it is, perhaps, not essential to the achievement of these practical ends that the exact significance of the test should be cleared up it is obviously a desideratum that we should know so far as possible what it is that we are measuring. It seems probable that what is measured by the haemolytic index is the general salt content of the fluid. This is not the place to go into the consideration of the grounds upon which this inference is made. It will suffice to bring out the following. The presence of urea in a fluid is, so far as this test is concerned, a matter of indifference, haemolysis being obtained at precisely the same point when diluting with a 5 per cent. solution of urea as when diluting with distilled water. The *specific electrical conductivity* of the fluids which we have, by the kindness of Dr. A. D. Waller, been able to test in the physiological laboratory of the University of London was found to be roughly ¹ proportional to the salt content of the fluids as estimated by the method here in question. This is exhibited in the table below (Table IV).

TABLE IV

Fluid tested	Relative concentrations of the fluids in salts as determined by the haemolytic method	Relative concentrations of the fluid in salts as determined by the specific electric conductivity
Ascitic fluid from patient with acute nephritis -	100	100
Urine from same case - - - - -	75	89
Urine from case of parenchymatous nephritis -	50	57
Urine from case of interstitial nephritis - -	50	40

In conclusion attention may be drawn to the fact that *specific haemolysins*, such as are found in the blood of animals which have been immunised by injections of red blood corpuscles, do not come into consideration in connexion with the haemolytic method as here applied. This is shown by the fact that the 'haemolytic index' of serum, or as the case may be of urine, which has been exposed to a temperature of 65° C. for ten minutes is exactly the same as that of the unheated serum or urine. Attention may be drawn also to the at present quite unexplained fact that the haemolytic index of serum, or as the case may be of urine, which contains

¹ It will be manifest that in the case of the haemolytic method we multiply our error of observation in each case by the factor which corresponds to the dilution we have arrived at.

a considerable quantity of albumin, is represented by a higher fraction after it has been raised to the boiling point. It is to be noted that this alteration of the haemolytic index is not associated with any comparable alteration in the specific electric conductivity of the fluid.

TABLE V.—*Setting forth the Dilutions with which a Complete Haemolytic Effect was obtained in the Case of Serum and Urine tested before and after Exposure to a Temperature of 100° C.*

Nature of fluid whose haemolytic index was examined	Haemolytic index of the unheated fluid	Haemolytic index of fluid after exposure to a temperature of 100° C.
Serum from normal man - - - - -	1-8th	1-16th
Serum from another normal man - - - - -	1-8th	1-16th
Serum from patient suffering from amyloid disease of the kidney, etc. - - - - -	1-8th	1-32nd
Serum from patient suffering from interstitial nephritis -	1-8th	1-16th
Serum from patient suffering from parenchymatous nephritis - - - - -	1-16th	1-32nd
Serum from another patient suffering from parenchymatous nephritis - - - - -	1-16th	1-32nd
Non-albuminous urine from normal man - - - - -	1-32nd	1-32nd
Urine with trace of albumin derived from a patient suffering from cystitis due to infection by the bacillus coli -	1-16th	1-16th
Urine with trace of albumin derived from a case of renal disease - - - - -	1-32nd	1-32nd
Urine with trace of albumin derived from a case of renal disease - - - - -	1-16th	1-16th
Highly albuminous urine from a case of renal disease -	1-8th	1-32nd
Urine containing a considerable amount of albumin -	1-5th	1-16th

ON CERTAIN POINTS IN CONNEXION WITH THE EXALTATION AND REDUCTION OF BLOOD-COAGULABILITY BY THERAPEUTIC MEASURES

AND IN PARTICULAR ON THE EFFECT PRODUCED UPON THE BLOOD BY THE INGESTION OF CALCIUM CHLORIDE, CALCIUM LACTATE, MAGNESIUM CARBONATE, COW'S MILK, AND OTHER MEDICINAL AGENTS

BY THE AUTHOR AND W. ERASMUS PARAMORE, M.B.

(Reprinted from 'The Lancet', 14th October, 1905)

Feeling that real advances in therapeutics will be made only when the effects of medicinal agents shall have been followed out on man by the aid of accurate quantitative methods, we have recently—carrying on a line of research already opened up by one of us—made a more detailed study of the accelerating or, as the case may be, retarding action which is exerted by certain medicinal agents upon blood-coagulation. We have investigated in particular the accelerating effect which is, as one of us has previously shown, exerted by calcium chloride and by milk¹ respectively. Further, we have drawn into the scope of this investigation also the lactate of calcium and the carbonate of magnesium. Lastly, we have carried a step further the investigation of the effect exerted upon blood-coagulation by the ingestion of decalcifying agents.

Method employed for measuring the content of the blood in calcium and magnesium salts.—The method we have employed in the researches reported below was the same as was employed in the paper just referred to.²

Points to which attention was directed in connexion with the calcium salts and other medicinal agents here experimented with.—We have in the experiments recorded below sought an answer to the following questions: (a) How soon after the ingestion of each medicinal agent the coagulability of the blood is sensibly increased? (b) What is the maximum acceleration of coagulation which can be achieved by the ingestion of a single dose of the calcium salt or other medicinal agent employed? (c) Is the increased coagulability of the blood associated with a definite increase in the calcium or, as the case may be, magnesium salts in the blood? and (d) How long is the condition of exalted coagulability in each case maintained? These questions are to some extent resolved by the subjoined protocols.

Calcium Chloride cryst.

Observation 1.—H. S. A healthy man. 4 p.m.: Coagulation time, 2 minutes 10 seconds. Complete decalcification with a 1 in 1800 solution of ammonium oxalate.

¹ *Vide supra*, pp. 26–28, and 82.

² *Vide supra*, pp. 79–87.

4.10 p.m. : Four grammes (60 grains) of calcium chloride *cryst.* were administered.
 5.10 p.m. : Coagulation time, 35 seconds. A solution of 1 in 800 of ammonium oxalate was required for complete decalcification.

Observation 2.—M. G. A patient suffering from furunculosis. Feb. 20th, 1905 :—3.20 p.m. : Coagulation time, 1 minute 35 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 3.35 p.m. : Four grammes of calcium chloride *cryst.* were administered. 5.5 p.m. : Coagulation time, 45 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification.

Observation 3.—De V. K. A healthy man. May 16th, 1905 :—2.30 p.m. : Coagulation time, 2 minutes. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 2.45 p.m. : Four grammes of calcium chloride *cryst.* were administered. 3.35 p.m. : Coagulation time, 30 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 17th : Coagulation time, 40 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 18th : Coagulation time, 40 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete decalcification. 19th : Coagulation time, 30 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 20th : Coagulation time, 30 seconds. A solution of 1 in 900 of ammonium oxalate was required for complete decalcification. 23rd : Coagulation time, 45 seconds.

Observation 4.—W. E. P. A healthy man. May 9th, 1905 :—4 p.m. : Coagulation time, 1 minute 50 seconds. A solution of 1 in 1050 of ammonium oxalate was required for complete decalcification. 4.15 p.m. : Four grammes of calcium chloride were ingested. 5.15 p.m. : Coagulation time, 55 seconds. A solution of 1 in 750 of ammonium oxalate was required for complete decalcification. 10th : Coagulation time, 1 minute. A solution of 1 in 750 of ammonium oxalate was required for complete decalcification. 11th : Coagulation time, 1 minute. A solution of 1 in 600 of ammonium oxalate was required for complete decalcification. 12th : Coagulation time, 1 minute. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 13th : Coagulation time, 1 minute. A solution of 1 in 1200 ammonium oxalate was required for complete decalcification. 15th : Coagulation time, 1 minute 30 seconds. A dilution of 1 in 1800 of ammonium oxalate was required for complete decalcification.

Observation 5.—X. Y. A patient who was suffering from oedema of the eyelids and lips and aggravated urticaria. July 5th, 1905 :—2 p.m. : Coagulation time, 2 minutes 15 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 3.50 p.m. : Four grammes of calcium chloride were administered. 5.55 p.m. : Coagulation time, 45 seconds. A solution of 1 in 750 was required for decalcification. 13th : The patient reported that the urticaria had completely disappeared. Coagulation time, 48 seconds. A solution of 1 in 900 was required for decalcification.

Observation 6.—A. E. W. A healthy man who had as a boy frequently been the subject of aggravated giant urticaria on the ingestion of decalcifying agents (acid fruits, etc.). Feb. 30th, 1905 :—1.30 p.m. : Coagulation time, 1 minute

45 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete decalcification. 1.45 p.m.: Four grammes of calcium chloride were ingested. 2.45 p.m.: Coagulation time, 1 minute 30 seconds. A solution of 1 in 1500 of ammonium oxalate was required for complete decalcification.

Observation 7.—A. E. W. (*vide* Observation 6 *supra*). May 12th, 1905:—2.30 p.m.: Coagulation time, 2 minutes 10 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification. 2.50 p.m.: Four grammes of calcium chloride were ingested. 3.50 p.m.: Coagulation time, 1 minute 50 seconds. A solution of 1 in 1200 of ammonium oxalate was required for complete decalcification.

Summary of Results obtained with Calcium Chloride.

(a) *Time required for the achievement of increased blood-coagulability.*—The observations show in a very concordant manner that the full accelerating effect of calcium chloride is achieved within the first hour after its administration.

(b) *Extent to which the coagulability of the blood is increased by the administration of calcium chloride.*—The data obtained in this series of observations are as follows. With a single dose of four grammes (60 grains) of calcium chloride *cryst.* the coagulation time of the blood (measured at 37° C.) was reduced:

In Observation 1 from 2 minutes 10 seconds to 35 seconds—i.e. in the ratio of 1 to $\frac{1}{4}$.

In Observation 2 from 1 minute 35 seconds to 45 seconds—i.e. in the ratio of 1 to $\frac{1}{2}$.

In Observation 3 from 2 minutes to 30 seconds—i.e. in the ratio of 1 to $\frac{1}{4}$.

In Observation 4 from 1 minute 50 seconds to 55 seconds—i.e. in the ratio of 1 to $\frac{1}{2}$.

In Observation 5 from 2 minutes 15 seconds to 45 seconds—i.e. in the ratio of 1 to $\frac{1}{3}$.

In Observation 6 from 1 minute 45 seconds to 1 minute 30 seconds—i.e. in the ratio of 1 to $\frac{6}{7}$.

In Observation 7 from 2 minutes 10 seconds to 1 minute 50 seconds—i.e. 1 to $\frac{3}{4}$.

(c) *Absorption of calcium salts into the blood.*—In Observations 1, 3, and 5 satisfactory evidence was obtained of the absorption of calcium salts into the blood. In the second of these cases, where the observations were extended over a week, the lime salts in the blood were seen to diminish contemporaneously with the return of coagulability to the normal.

(d) *The period during which the effect of the single dose of calcium was maintained.*—In Observations 3, 4, and 5 where this point was investigated the increased blood-coagulability was found to be maintained in Observation 3 for five days, in Observation 4 for eight days, and in Observation 5 for eight days.

Comment.—It is brought out in the results tabulated under (b) *supra* that there are as between different individuals conspicuous differences in their capacity of responding to calcium chloride. These differences may, in view of the facts

summarised under (c); further in view of the fact that results altogether similar to those recorded in Observations 6 and 7 in connexion with A. E. W. had previously been obtained upon him on quite a number of different occasions; and lastly, in view of the case of a bleeder¹ whose blood-coagulation was quite uninfluenced by large doses of calcium chloride given by the mouth, while it was conspicuously increased by hypodermic injection of a suitable calcium salt; be referred to constitutional differences in the matter of the absorption of calcium chloride.

A constitutional incapacity, or partial incapacity, of this nature may perhaps underlie the 'idiosyncrasy' of certain persons to suffer from those forms of urticaria which one of us has denoted 'decalcification urticarias'.² We might quite reasonably expect that the absorption into the blood of decalcifying agents (soap from soap enemas; oxalic acid from rhubarb; citric, tartaric, and malic acid from sour fruits, fruit juices, and acid wines) would induce a condition of diminished blood-coagulability, and in association with this 'serous haemorrhages' in persons who happened to be unable to maintain their store of calcium salts at a high level, or to replenish it rapidly when encroached upon.

It is interesting in this connexion to bring into relation with the defective power of absorption for calcium chloride demonstrated to exist in A. E. W. the fact that he suffered for a period of years during boyhood from aggravated giant urticaria whenever any decalcifying agent was ingested. Again, it is perhaps deserving of passing mention that in his case, contrary to what was shown³ by him to obtain in other cases of urticaria produced by serum, the exhibition of calcium chloride neither warded off nor relieved a severe attack of urticaria engendered by an injection of an anti-Malta fever serum.

Whatever may be the view taken with regard to these suggested explanations it will not be questioned that it became desirable, in view of the facts disclosed above, to see whether an effective substitute could be obtained for calcium chloride for employment in those cases where this latter drug by reason of its non-absorption fails to increase the coagulability of the blood.

We selected for purposes of study the lactate of calcium, a salt which had already for some time past been employed by one of us with very satisfactory results in the control of actual and serous haemorrhage. This salt recommends itself for use, firstly, by the fact that it is devoid of unpleasant taste, sufficiently soluble (about 1 in 10) in water, and suitable for administration in the form of powders, and, secondly, by the fact that the salts of organic acids, and more particularly of lactic acid, are known to be readily oxidised in the system, with the result that their bases are placed more fully at the disposal of the organism than these would be the case when the corresponding mineral acid salts are exhibited.

¹ It is to be noted that a deficient power of absorbing calcium salts is not by any means a common feature in haemophilia. One of us, in recommending the employment of calcium chloride in haemophilic haemorrhages, has given examples of the notable acceleration of coagulation time which may generally be obtained in these patients by the exhibition of calcium chloride. (*Vide supra*, pp. 27-28, also p. 55.)

² *Transactions of the Pathological Society*, vol. li, part 3, 1900.

³ *Vide supra*, p. 59.

Calcium Lactate.

Observation 1.—M. G. A patient suffering from furunculosis.¹ April 18th, 1905 :—3.10 p.m. : Coagulation time, 1 minute 50 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 3.30 p.m. : Four grammes of calcium lactate were administered. 4.20 p.m. : Coagulation time, 45 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 6 p.m. : Coagulation time, 30 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification.

Observation 2.—De V. K. A healthy man.² Feb. 20th, 1905 :—5.10 p.m. : Coagulation time, 2 minutes. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 5.15 p.m. : Four grammes of calcium lactate were ingested. 6 p.m. : Coagulation time, 50 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 9.15 p.m. : Coagulation time, 40 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 21st : Coagulation time, 50 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 22nd : Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 23rd : Coagulation time, 50 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 24th : Coagulation time, 37 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 25th : Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 26th : Coagulation time, 45 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 27th : Coagulation time, 48 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. March 6th : Coagulation time, 55 seconds. A solution of 1 in 1000 was required for complete decalcification.

Observation 3.—F. M. The patient was suffering from phthisis. Feb. 7th, 1905 :—2.30 p.m. : Coagulation time, 1 minute 50 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 8th : 2 p.m. : Coagulation time, 1 minute 55 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 2.15 p.m. : Four grammes of calcium lactate were administered. 3 p.m. : Coagulation time, 22 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 9th : Coagulation time, 1 minute 35 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification.

Observation 4.—A healthy man. Feb. 6th, 1905 :—2 p.m. : Coagulation time, 1 minute 50 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 2.20 p.m. : Four grammes of calcium lactate were administered. 2.30 p.m. : Coagulation time, 1 minute 50 seconds. 2.40 p.m. : Coagulation time, 1 minute 20 seconds. 3.50 p.m. : Coagulation time, 25 seconds.

¹ A previous observation had been made upon this patient with calcium chloride (*vide* under Calcium Chloride, Observation 2).

² An observation was subsequently made upon this 'patient' with calcium chloride (*vide* under Calcium Chloride, Observation 3).

A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 7th : Coagulation time, 1 minute 25 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification. 10th : Coagulation time, 45 seconds. A solution of 1 in 800 of oxalate of ammonium was required for complete decalcification.

Observation 5.—A healthy man. Feb. 21st, 1905 :—3 p.m. : Coagulation time, 1 minute 40 seconds. A solution of 1 in 1800 of ammonium oxalate was required for complete decalcification. 3.15 p.m. : Four grammes of calcium lactate were administered. 4 p.m. : Coagulation time, 45 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 22nd : Coagulation time, 35 seconds. 24th : Coagulation time, 45 seconds. March 1st : Coagulation time, 1 minute 20 seconds.

Observation 6.—A. E. W. A healthy man.¹ May 15th, 1905 :—2.45 p.m. : Coagulation time, 2 minutes 5 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 3 p.m. : Four grammes of calcium lactate were ingested. 4 p.m. : Coagulation time, 1 minute 5 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification.

Observation 7.—W. E. P. A healthy man.² Feb. 3rd, 1905 :—2 p.m. : Coagulation time, 1 minute 45 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 2.15 p.m. : Four grammes of calcium lactate were ingested. 3 p.m. : Coagulation time, 1 minute 15 seconds. A solution of 1 in 1000 of oxalate of ammonium was required for complete decalcification. 6 p.m. : Coagulation time, 1 minute 20 seconds. 9 p.m. : Coagulation time, 1 minute 20 seconds. 4th : Coagulation time, 1 minute 35 seconds. A solution of 1 in 2000 of oxalate of ammonium was required for complete decalcification.

Summary of Results obtained with Calcium Lactate.

(a) *Time required for the achievement of increased blood-coagulability.*—As in the case of calcium chloride the effect of the drug is very rapidly manifested. Increased coagulability may, as shown in Observation 4, be registered within 20 minutes of the administration of the drug. The full effect is in practically every case achieved within the course of three-quarters of an hour.

(b) *The extent to which the coagulability of the blood is increased.*—With a single dose of four grammes (60 grains) of calcium lactate the coagulation time of the blood was reduced :

In Observation 1 from 1 minute 50 seconds to 30 seconds—i.e. in the ratio of 1 to $\frac{1}{4}$.

In Observation 2 from 2 minutes to 40 seconds—i.e. in the ratio of 1 to $\frac{1}{3}$.

In Observation 3 from 1 minute 50 seconds to 22 seconds—i.e. in the ratio of 1 to $\frac{1}{5}$.

In Observation 4 from 1 minute 50 seconds to 25 seconds—i.e. in the ratio of 1 to $\frac{1}{5}$.

¹ Two previous observations made upon this man with calcium chloride are recorded above.

² A previous observation made upon this man with calcium chloride is recorded above.

In Observation 5 from 1 minute 40 seconds to 45 seconds—i.e. in the ratio of 1 to $\frac{1}{3}$.

In Observation 6 from 2 minutes 5 seconds to 1 minute 5 seconds—i.e. in the ratio of 1 to $\frac{1}{2}$.

In Observation 7 from 1 minute 45 seconds to 1 minute 15 seconds—i.e. in the ratio of 1 to $\frac{5}{7}$.

(c) *Absorption of calcium salts into the blood.*—In four out of the seven observations satisfactory evidence of the dependence of the increased coagulability upon the absorption of calcium salts was obtained (Observations 1, 2, 4, and 7).

(d) *Period during which the effect of a single dose of calcium lactate is maintained.*—This question was investigated only in connexion with Observations 2 and 4. In the former case the effect was maintained for a minimum of 17 days and in the latter for a minimum of four days.

Comment.—The data set forth above under (b) show very clearly that the acceleration of blood-coagulability achieved by the ingestion of four grammes of calcium lactate is, if anything, greater than that achieved with the same dose of calcium chloride. It would seem probable from a comparison of the data set out under (c) with the corresponding data obtained with calcium chloride that this more satisfactory result is referable to a readier absorption of the lactate. With regard to the question as to whether the difficulties in connexion with the absorption of lime are solved by the substitution of the lactate for the chloride it will be obvious that no certain conclusions could be arrived at from the limited data as set forth above. At the most these data suggest that the lactate is in the case of one of us (W. E. P.) less well resorbed than the chloride, while in the case of the other of us (A. E. W.) the contrary appears to be the case. We have, however, in the case of the haemophilic patient already referred to conclusive evidence that the difficulty in connexion with the resorption of calcium is not disposed of by the substitution of the lactate for the chloride. Reserving the further exposition of this case for a subsequent section of this paper we may here pass on to consider a third series of protocols relating to the effect exerted upon blood-coagulability by the ingestion of magnesium carbonate.

Magnesium Carbonate.

Observation 1.—A. E. W. A healthy man. June 20th, 1905 :—Coagulation time, 2 minutes. 4.30 p.m. : Four grammes of magnesium carbonate were ingested. 21st : Coagulation time, 45 seconds. 22nd : Coagulation time, 1 minute 15 seconds. 23rd : Coagulation time, 1 minute 15 seconds.

Observation 2.—W. E. P. A healthy man. June 19th, 1905 :—12.30 p.m. : Coagulation time, 1 minute 5 seconds. Coagulation averted when the blood was mixed with an equal volume of a 1 in 1800 solution of oxalate of ammonium. 3.35 p.m. : Four grammes of magnesium carbonate were ingested. 4.45 p.m. : Coagulation time, 30 seconds. 20th : Coagulation time, 28 seconds. Coagulation not averted until the blood was mixed with an equal volume of a 1 in 600 solution of oxalate of ammonium. 21st : Coagulation time, 25 seconds. Coagulation not

averted until the blood was mixed with an equal volume of a 1 in 900 solution of oxalate of ammonium. 22nd: Coagulation time, 33 seconds. Coagulation not averted until the blood was mixed with an equal volume of a 1 in 600 oxalate of ammonium solution. 23rd: Coagulation time, 42 seconds. Coagulation averted when the blood was mixed with a 1 in 1200 solution of oxalate of ammonium.

Observation 3.—R. A healthy man. June 19th, 1905:—4.30 p.m.: Coagulation time, 40 seconds. Coagulation averted when the blood was mixed with an equal volume of a solution of 1 in 2400 of oxalate of ammonium. 5 p.m.: Four grammes of magnesium carbonate were ingested. 7 p.m.: Coagulation time, 1 minute 10 seconds. Coagulation only incompletely averted when the blood was mixed with an equal volume of a solution of 1 in 2400 of oxalate of ammonium. 20th: Coagulation time, 25 seconds. Coagulation not averted till the blood was mixed with an equal volume of a 1 in 1200 oxalate of ammonium solution. 21st: Coagulation time, 50 seconds. A 1 in 1500 solution was the minimum concentration of oxalate of ammonium which averted coagulation. 22nd: Coagulation time, 33 seconds. A 1 in 1500 solution of ammonium oxalate was the minimum dilution which sufficed to avert blood-coagulation. 23rd: Coagulation time, 25 seconds. A 1 in 1200 solution of ammonium oxalate was the minimum dilution which sufficed to avert coagulation. 24th: Coagulation time, 30 seconds.

Observation 4.—F. A healthy man. June 19th, 1905:—1.5 p.m.: Coagulation time, 35 seconds. Coagulation averted when the blood was mixed with an equal volume of a 1 in 1800 solution of oxalate of ammonium. 4.15 p.m.: Four grammes of magnesium carbonate were ingested. 6.30 p.m.: Coagulation time, 35 seconds. Coagulation was averted when the blood was mixed with an equal volume of a 1 in 2500 solution of oxalate of ammonium. 20th: Coagulation time, 33 seconds. Coagulation was not averted until the blood had been mixed with an equal volume of a 1 in 1200 oxalate of ammonium solution. 22nd: Coagulation time, 33 seconds. Coagulation was averted when the blood was mixed with an equal volume of a 1 in 1500 oxalate of ammonium solution.

Observation 5.—C. A patient suffering from cystitis. June 13th, 1905:—4 p.m.: Coagulation time, 1 minute 40 seconds. A 1 in 900 oxalate of ammonium solution was the minimum dilution which averted blood-coagulation. 4.20 p.m.: Four grammes of magnesium carbonate were administered. 5.30 p.m.: Coagulation time, 45 seconds. Coagulation was not averted until the blood had been mixed with an equal volume of a 1 in 750 solution of oxalate of ammonium.

Summary and Comment.

In the case of the experiments reported above which were conducted by administering in each case 60 grains of magnesium carbonate the blood-coagulation time was accelerated:

In Observation 1 from 2 minutes to 45 seconds—i.e. in the ratio of 1 to $\frac{1}{3}$.

In Observation 2 from 1 minute 5 seconds to 25 seconds—i.e. in the ratio of 1 to $\frac{5}{13}$.

In Observation 3 from 40 seconds to 25 seconds—i.e. in the ratio of 1 to $\frac{5}{8}$.

In Observation 5 from 1 minute 40 seconds to 45 seconds—i.e. in the ratio of 1 to $\frac{1}{2}$.

In Observation 4 the blood-coagulation time, which was already very short, remained at 35 seconds.

In the case of two of these observations the acceleration of blood-coagulation time was registered in an hour from the time of administration of the drug. In Observations 2, 3, 4, and 5 distinct evidence was obtained of an absorption of magnesium salts into the blood.

The evidence furnished above that magnesium salts exert when ingested an effect which is quite comparable to that exerted by calcium salts is exactly what might have been expected in view (*a*) of the close chemical affinities which obtain as between magnesium and calcium, and (*b*) of the original experiments of Arthus and Pagès, which showed that magnesium salts induced coagulation in oxalated blood *in vitro* in exactly the same manner as calcium salts. The disclosure of the effect which magnesium salts exert on blood-coagulation is of therapeutic interest as explaining the *rationale* of the employment of magnesium carbonate in the treatment of urticaria and the special efficacy of the drug—as one of us has learned by experience on his own person—in the treatment of that form of urticaria which supervenes upon the ingestion of decalcifying agents. The specific remedial action here exerted is obviously not, as the pathology of a pre-scientific age assumed, the result of a neutralisation of acid properties in the blood, but the result of the replenishment of the blood with the salts which render the plasma coagulable and viscid.

From the study of the effect produced upon the blood by the ingestion of calcium and magnesium salts we pass on to study the effect which is exerted upon the blood-coagulation by the ingestion of cow's milk. The line of thought which prompts to this inquiry will immediately suggest itself to the reader who is familiar with the observations made by one of us in conjunction with Knapp,¹ which show that the thrombosis which so frequently occurs in connexion with convalescence from typhoid fever almost certainly stands in relation with an excess of calcium salts furnished to the typhoid fever patient in the exclusively milk dietary which is so generally imposed upon him.

Cow's Milk.

Observation 1.—H. K. A healthy medical student. May 15th, 1905 :—Coagulation time, 2 minutes 22 seconds. A solution of 1 in 1800 of oxalate of ammonium added to the blood in equal volumes effected complete decalcification. Two pints of milk a day were now added to the dietary, which remained in other respects unaltered. 17th : Coagulation time, 45 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification. 18th : Coagulation time, 45 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 20th : Coagulation time, 30 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. 22nd : Coagulation time, 50 seconds. A solution of 1 in 900 of oxalate of ammonium was required

¹ *Vide supra*, pp. 81-82.

for complete decalcification. 23rd : Coagulation time, 1 minute. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. 24th : Coagulation time, 30 seconds. A solution of 1 in 1500 of oxalate of ammonium was required for complete decalcification. 25th : Coagulation time, 20 seconds. A solution of 1 in 1800 of oxalate of ammonium was required for complete decalcification. 26th : Coagulation time, 45 seconds. A solution of 1 in 1200 of oxalate of ammonium was required for complete decalcification.

Observation 2.—B. A healthy medical student. May 17th, 1905 :—Coagulation time, 1 minute 25 seconds. A solution of 1 in 900 of oxalate of ammonium was required for complete decalcification. Two pints of milk a day were now added to the dietary, which remained the same in other respects. 18th : Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 19th : Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. 20th : Coagulation time, 1 minute. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. 23rd : Coagulation time, 40 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. 24th : Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. 25th : Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1050 of oxalate of ammonium. 27th : Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 29th : Milk left off. 31st : Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium. June 6th : Coagulation time, 33 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 7th : Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 750 of oxalate of ammonium. 10th : Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 900 of oxalate of ammonium.

Observation 3.—L. A patient suffering from pleurisy with effusion. Feb. 10th, 1905.—Coagulation time, 1 minute 20 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium. Two pints of milk were now added to the patient's dietary. 11th : Coagulation time, 1 minute 40 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 12th : Coagulation time, 55 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 13th : Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 14th : Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 200 of oxalate of ammonium. 15th : Coagulation time, 40 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 16th : Coagulation time, 45 seconds. Complete decalcification with a dilution of 1 in 800 of oxalate of ammonium.

In addition to these observations, where the blood was examined both before and after the addition of milk to the dietary, we have made also a certain number of observations upon adults who happened to be taking a considerable quantity of milk and also upon infants. The data obtained in this manner are tabulated below.

Serial number of observation	Description of patient	Particulars with respect to amount of milk in dietary	Minimum concentration of oxalate of ammonium solution required for complete decalcification of an equal volume of blood	Coagulation time
				Seconds
4	Phthisical patient	1 to 1½ pints of milk daily -	1 in 1500	30
5	"	" "	1 in 800	35
6	"	" "	1 in 800	50
7	"	" "	1 in 800	20
8	Healthy man -	1 pint of milk on 4 preceding days	1 in 800	30
9	"	1 to 2 pints of milk regularly -	1 in 1500	35
10	"	1½ pints of milk regularly - -	1 in 1500	55
11	"	1 to 2 pints of milk regularly -	1 in 1200	50
12	Infant aged 6 months	Dietary of cow's milk - -	1 in 600	25
13	Infant aged 4 months	Dietary of cow's milk and barley water	1 in 750	25
14	Infant aged 4 months	Fed on human milk supplemented by cow's milk	1 in 1200	37
15	Infant aged 6 weeks	Fed on human milk - - -	1 in 750	30
16	Infant aged 19 months	½ pint of cow's milk daily - -	1 in 900	25
17	Infant aged 2 months	Fed on human milk - - -	1 in 600	25

It will be seen that the above observations—which are in close agreement with those made by one of us in conjunction with Knapp on typhoid fever convalescents—show in a consistent manner that the coagulability of the blood is increased by the ingestion of milk, and that this increased coagulability is associated with the presence of large quantities of calcium and magnesium salts in the blood. It follows that milk is much more than a food-stuff. It is also in an eminent degree a medicinal agent. As such it may exert, according to circumstances, either a beneficial or a prejudicial effect. While advantage may accrue from the prescription of milk in connexion with haemorrhage, aneurysm, physiological albuminuria, and the oedema of Bright's disease, it is practically certain that in many other cases the medicinal effect of milk is exerted to the prejudice of the patient. The importance of this aspect of the matter will not need to be enforced upon anyone who will let it come home to him that every patient—or rather let us say, every adult patient—who is placed on a dietary of milk is thereby brought into a condition which predisposes to thrombosis. We would throw it out as a suggestion that it would be profitable to make a systematic inquiry into the frequency with which thrombosis supervenes in hospital patients placed on a dietary of milk.

We pass now to the consideration of certain final points relating to the therapeutic exploitation of the medicinal agents which are available for increasing and diminishing the coagulability of the blood.

Dosage to be employed where calcium or, as the case may be, magnesium salts are exhibited for the purpose of achieving as rapidly as possible a considerable exaltation of blood-coagulability.—The experiments which have been detailed above make it clear that a rapid increase of blood-coagulability such as is desired for the arrest of actual or serous haemorrhage can, unless in the case where we are dealing with a person who is defective with respect to his power of absorbing calcium salts, be achieved by the administration of a single 60-grain dose of either calcium lactate or, as the case may be, calcium chloride or magnesium carbonate.

Dosage to be employed where calcium salts are to be exploited for the purpose of maintaining a permanently high level of blood-coagulability.—Success in maintaining the blood-coagulability at a high level involves adjusting successive doses of calcium salts in such a manner as to avoid introducing into the blood such excess of these salts as would effect a retardation of blood-coagulation time.

Observation.—R. Healthy man. Feb. 23rd, 1905 : Coagulation time, 1 minute 35 seconds. Complete decalcification with a dilution of 1 in 1800 of oxalate of ammonium. 15 grains of calcium lactate were given three times a day. 24th : Coagulation time, 30 seconds. Complete decalcification with a dilution of 1 in 1500 of oxalate of ammonium. 25th : Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 27th : Coagulation time, 35 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. 28th : Coagulation time, 25 seconds. Complete decalcification with a dilution of 1 in 1500 of oxalate of ammonium. March 1st : Coagulation time, 50 seconds. Complete decalcification with a dilution of 1 in 1000 of oxalate of ammonium. 2nd : Coagulation time, 47 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium. The drug was discontinued on the 3rd. 6th : Coagulation time, 55 seconds. Complete decalcification with a dilution of 1 in 1200 of oxalate of ammonium.

The next protocol we owe to our fellow-worker, Dr. George W. Ross. Dr. Ross kindly undertook to investigate here in association with the primary question at issue also the subsidiary question as to whether the presence of an excess of calcium salts in the blood would betray itself on examination of the patient's serum. The protocol refers to a case of aneurysm of the arch of the aorta under the care of Dr. E. C. Beale.

First period, April 12th to 16th, 1905.—In this period, which preceded the administration of calcium salts, the patient's blood was tested on two occasions. The results of the blood examinations were as follows :—April 12th : Blood-coagulation time, 1 minute 50 seconds. Concentration of oxalate of ammonium solution required for complete decalcification, 1 in 1350. 16th : Blood-coagulation time, 1 minute 50 seconds. Concentration of ammonium oxalate required for complete decalcification, 1 in 1350.

Second period, April 18th to 25th, 1905.—During this period 20 grains of calcium lactate were administered three times a day. The results of the blood examinations made during this period were as follows :—April 19th : Blood-coagulation time, 1 minute 20 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 1200. 21st : Blood-coagulation time, 1 minute 25 seconds.

Concentration of ammonium oxalate required for complete decalcification 1 in 1000. 23rd : Blood-coagulation time, 1 minute 35 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 800. 25th : Coagulation-time, 1 minute 50 seconds. Concentration of ammonium oxalate required for complete decalcification 1 in 1000.

The patient's serum was now tested for calcium salts on the idea that these would when present in excess in the blood remain in solution in the serum instead of disappearing, as is normally the case, in the course of the chemical changes associated with blood-coagulation. It was found in accordance with what was expected that the presence of calcium salts could be demonstrated in the patient's serum.¹

Third period, May 1st to 13th, 1905.—After an interval of four days, during which no calcium salts were exhibited, 20 grains of calcium lactate were again administered three times a day. The results of the blood examinations made during this period were as follows. May 2nd : Blood-coagulation time, 1 minute 20 seconds. 4th : Blood-coagulation time, 1 minute 15 seconds. 6th : Blood-coagulation time, 1 minute 20 seconds. 8th : Blood-coagulation time, 1 minute 35 seconds. 10th : Blood-coagulation time, 1 minute 50 seconds. 12th : Blood-coagulation time, 1 minute 50 seconds.

Fourth period, May 14th to June 24th, 1905. During this period ten grains of calcium lactate were administered three times a day. The following results were obtained. May 26th : Blood-coagulation time, 1 minute. 30th : Blood-coagulation time, 1 minute 15 seconds. June 3rd : Blood-coagulation time, 1 minute 10 seconds.

¹The method employed for testing for the presence of calcium salts in the serum was as follows. Two series of progressive dilutions of oxalate of ammonium were made up, the menstruum employed for the dilution being, in the one case, the patient's serum and, in the other case, a solution of chemically pure sodium chloride. The calcium salts of the observer's blood were now measured in duplicate, first with the one and then with the other series of progressive dilutions. The results obtained are exhibited in tabular form below :

Table showing the Concentrations of Oxalate of Ammonium which when dissolved in Serum and Salt Solution respectively effected the Complete Decalcification of or (as the case may be) just failed completely to decalcify a Test Blood.

Date of examination	Oxalate of ammonium dissolved in the patient's serum		Oxalate of ammonium dissolved in physiological salt solution	
	Dilution which effected complete decalcification of an equal volume of the observer's blood	Dilution which failed to effect complete decalcification of an equal volume of the observer's blood	Dilution which effected complete decalcification of an equal volume of the observer's blood	Dilution which failed to effect complete decalcification of an equal volume of the observer's blood
25-4-05	1 in 600	1 in 800	1 in 1350	1 in 1500

It will be seen that more concentrated solutions of oxalate of ammonium in the patient's serum were required to effect the same decalcifying effect which was exerted by less concentrated solutions of oxalate of ammonium in a menstruum of sodium chloride. The difference must be ascribed to the presence of calcium salts in the patient's serum.

10th : Blood-coagulation time, 1 minute 20 seconds. 24th : Blood-coagulation time, 1 minute 20 seconds.

On the possibility of introducing calcium salts into the blood by hypodermic injection in the case where they are not absorbed when given by the mouth.—Our personal experience of hypodermic injection of calcium salts in man is limited to a single case—that of a bleeder before referred to who appears to be incapable of absorbing any calcium salts administered by the mouth. The particulars given below represent the unfortunately in some respects incomplete observations which were made (many of these observations were kindly made for us by Dr. J. B. Nias) upon this bleeder on four successive occasions when he presented himself, as is his wont, at this laboratory to see whether anything could be done for the relief of the haemorrhages which, in his case, occur on each occasion from roots of the upper teeth.

Observation 1.—H. G., a man, suffering from haemophilia. Feb. 8th, 3 p.m. : Coagulation time, 2 minutes 15 seconds. 3.10 p.m. : 4 grammes of calcium lactate were given by the mouth. 3.50 p.m. : Coagulation time, 2 minutes 15 seconds. No effect was exerted upon the haemorrhage.

Observation 2.—Feb. 17th, 2.30 p.m. : Coagulation time, 2 minutes 50 seconds. 2.40 p.m. : 4 grammes of calcium lactate were administered. 3.25 p.m. : Coagulation time, 2 minutes 45 seconds. No effect was exerted on the haemorrhage.

Observation 3.—Feb. 24th, 4 p.m. : Coagulation time, 2 minutes 50 seconds. 4.10 p.m. : Subcutaneous injection of 0.5 gramme of calcium lactate in 10 cubic centimetres of water. 4.55 p.m. : Coagulation time, 2 minutes 10 seconds. No marked effect was exerted on the haemorrhage.

Observation 4.—March 3rd, 2.10 p.m. : Coagulation time, 2 minutes 5 seconds. There was continuous haemorrhage from the gums. 2.30 : Hypodermic injection of 0.6 gramme of calcium lactate. 2.45 : Haemorrhage from the gums has ceased. 3.30 p.m. : Coagulation time, 40 seconds. 4.30 p.m. : Coagulation time, 35 seconds. March 6th : Coagulation time, 50 seconds. 16th : Coagulation time, 2 minutes 10 seconds.

In publishing this case we would venture to add a warning against employing calcium chloride for hypodermic injection, and we would suggest that if the hypodermic injection of lactate of calcium is resorted to the maximum concentration of the drug employed should be a 1 in 20 solution.

On the therapeutic measures to be employed for diminishing the coagulability of the blood and for maintaining a condition of diminished coagulability.—It was pointed out a good many years ago by one of us that it was possible to decalcify the blood and diminish blood-coagulability by the administration of citric acid. The practical importance of this therapeutic measure in connexion with the treatment of thrombosis was further pointed out by one of us in conjunction with Knapp in a paper already referred to. We come back upon the subject here to supplement what was said in the paper last referred to in the light of experience recently gained in connexion with the examination of certain cases of haemorrhage into the vitreous which were under the treatment of Mr. Leslie Paton in the out-patient department of this hospital. After it had been ascertained by a blood examination that the coagulation times of these three patients were respectively 1 minute 10 seconds,

50 seconds, and 1 minute 35 seconds, citric acid was in each case prescribed with intent to reduce the blood-coagulability and to keep it throughout the course of the treatment at a low level. In each case the former but not the latter object was achieved. In the first case the coagulation time was reduced within a week to 2 minutes 25 seconds and was maintained at that level or thereabouts for a further month. But after this time, in spite of the fact that the citric acid had been persisted in throughout, the blood-coagulation time came up to 1 minute 37 seconds. In the second case exactly the same thing happened. Under the influence of the citric acid the blood-coagulability diminished step by step until the coagulation time reached 2 minutes 25 seconds six weeks after the inception of the treatment. Within the next month, in spite of the fact that the citric acid was still persisted in, the coagulability increased step by step till the coagulation-time reached 55 seconds. In the third case the event was again the same. After a month's exhibition of citric acid a blood-coagulation time of 2 minutes 40 seconds was reached. Within the next fortnight the coagulation time diminished to 55 seconds and continued high from this date. The interpretation of these facts is for the present obscure. It would, however, appear from the data obtained by the measurement of the calcium salts of the blood in these cases that the decalcification of the blood which is achieved by the exhibition of citric acid is followed after an interval by an increase in the calcium salts of the blood. This last may very probably depend upon the bringing into solution again of calcium salts precipitated and eliminated from the blood by citric acid but not excreted.

ON THE DISCRIMINATION OF 'PHYSIOLOGICAL' ALBUMINURIA FROM THAT CAUSED BY RENAL DISEASE

AND ON THE MEANS OF CHECKING THE ALBUMINURIA WHERE IT OCCURS INDEPENDENTLY OF SUCH DISEASE

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(Reprinted from 'The Lancet', 21st October, 1905)

WE propose here to consider in connexion with physiological albuminuria (1) the question as to how it can be discriminated from the albuminuria which is dependent upon organic disease; (2) the question as to the conditions which are favourable to its occurrence; and (3) the question as to how it can be checked.

Introductory.—The idea that the presence or absence of albumin in the urine furnishes a trustworthy criterion of the competence or incompetence of the kidney belongs already to the antiquities of medicine. The question as to whether the renal function is impaired can, as the important work of von Koranyi has made clear, be much more justly adjudicated upon by determining whether the kidney is, or is not, competent to elaborate out of the blood a concentrated saline solution. Taking this as our criterion of renal competency we have recently investigated in a series of cases of physiological albuminuria (a) the percentage of salts in the urine and (b) the excretory quotient.¹

Method employed for measuring the salt content of the urine.—One of us working with Kilner showed some time ago² that it is possible to substitute for the cryoscopic method introduced by von Koranyi a much simpler method of estimating the salt content of a fluid. The consideration upon which the suggested method was based was the consideration that we can obtain a measurement of the salt content of any fluid by determining the extent to which it must be diluted before it completely dissolves a definite quantum of red blood corpuscles. All that is required for the purposes of the test is to take in each case a measured volume of any normal blood and to mix with it two volumes of the progressive dilutions of the fluids which are examined.

Method employed for the determination of the excretory quotient.—The 'excretory quotient' was in the paper already referred to defined as the expression for the efficacy of the kidney which is obtained by dividing in accordance with the following scheme, the salt content of a patient's blood into the salt content of his urine. Each of these dilutions is mixed by the technique described in accordance with the formula:

Minimum dilution of the urine which effects complete haemolysis.

Minimum dilution of the serum which effects complete haemolysis.

¹ The signification which we attach to this term will appear below.

² *Vide supra*, pp. 94–100.

Discrimination of 'physiological albuminuria' from the albuminuria of organic disease by the aid of the methods described above.—It will be seen on referring to Table I, which summarises the results of examinations of the blood and urine which we have carried out on a series of seven typical cases of physiological albuminuria and in one further case which would seem also to fall into that category, that the excretory quotient is in each case high, and that the salt content of the urine has approximated to or exceeded 2 per cent. NaCl, while it has in some cases largely surpassed that figure. These results, which are fully equal to any obtained upon healthy persons, contrast in a very marked manner with those obtained in connexion with renal disease,¹ and thus furnish what is in our judgment conclusive evidence that the renal function is in cases of 'physiological albuminuria' entirely unimpaired.

Conditions which are favourable to the transudation of lymph into the urinary tubules.—When we reconsider the pathology of 'physiological albuminuria' in the light of the data incorporated in Table I, we are led almost inevitably to the conclusion that we have to deal in this condition with a transudation of lymph into intact urinary tubules. This inference wins support from the consideration that the conditions which are favourable to the occurrence of serous haemorrhage in general—to wit, increased hydrostatic pressure in the capillaries of a particular region, and diminished blood-coagulability—are favourable also to the appearance of albumin in the urine in the cases we have here in view. We may recall to mind in this connexion that the appearance of albumin in the urine in physiological albuminuria is influenced by active exercise, by nervous disturbances, and by the assumption of the erect posture; and we may note that under all of these conditions the hydrostatic pressure in the renal capillaries would be increased. We may further in this connexion take cognisance of the fact that a condition of diminished blood-coagulability was found in many of our cases of physiological albuminuria; and that the output of albumin in cases of physiological albuminuria can, as is shown in the next section of this paper, be restrained by increasing the coagulability of the blood. It must be left for future experiment to determine whether in physiological albuminuria, as in urticaria, the exudation can be increased by the ingestion of decalcifying and lymphagocic agents—we have in view here in particular those lymphagocic agents which are contained in shell-fish, crustacea, and strawberries. Pending the carrying out of such experiments it is of interest to note that in one of the cases which we have included in Table I albuminuria was associated with giant urticaria and recent hydrocele, while in another case occasional puffiness under the eyes was a marked feature.

Observations on the possibility of restraining the output of albumin in physiological albuminuria by increasing the coagulability of the blood.—On following up the line of thought which has been indicated in the foregoing it occurred to us that it ought to be possible to check the excretion of albumin in physiological albuminuria by increasing the coagulability of the blood by the administration of calcium salts. The data set forth in Table II show that this line of treatment which is effective in many cases of chilblains and urticaria, in weeping eczema, and also in many cases of general oedema due to Bright's disease, is effective also in the case of physiological albuminuria.

¹ *Vide supra*, pp. 96-97, Table II.

TABLE I.—*Giving Summary of the Results of Examination of the Blood and the Urine in Eight Cases of Physiological Albuminuria*

No. of case	Initials, age, and date	Clinical data	General character of the urine	Excretory efficiency of kidneys as determined by the method of haemolysis		
				Salt content of the serum	Salt content of the urine	Excretory quotient
1	A. B., aged 19 years, March 23rd, 1905	The patient had had no illness predisposing to nephritis. He had always been well and strong, and was so at the time of examination. The albumin was discovered when the patient went up for medical examination. There were no signs of nephritis, either renal or cardiac, other than the presence of albumin in the urine	Good colour; acid; specific gravity, 1018; albumin $\frac{1}{2}$ by boiling, absent in early morning specimen, present in afternoon specimen	1.75 per cent. NaCl	3.90 per cent. NaCl	2.2
2	C. D., aged 21 years, a medical student, March 24th, 1905	Similar to Case 1. Albumin was discovered accidentally	Good colour; acid; specific gravity, 1022; albumin, a pronounced trace, absent in early morning specimen, present in afternoon specimens.	March 24th, 1905: 1.17 per cent. NaCl June 7th, 1905: 0.67 per cent. NaCl	2.34 per cent. NaCl 1.74 per cent. NaCl	2.0 2.6
3	E. F., aged 28 years, April 14th, 1905	Similar to Cases 1 and 2, except in the respect that the patient is an extremely nervous subject. Albumin was discovered accidentally	Good colour; acid; specific gravity, 1018; albumin, 0.04 per cent. (by Esbach), absent in morning specimen, present in afternoon specimens	March 14th, 1905: 1.36 per cent. NaCl June 7th, 1904: 0.96 per cent. NaCl	2.73 per cent. NaCl 3.3 per cent. NaCl	2.0 3.4
4	G. H., aged 15 years, May 11th, 1905	Similar to Cases 1, 2, and 3. Albumin was discovered when the patient presented himself for medical examination	Good colour; acid; specific gravity, 1018; albumin, 0.15 per cent. (by Esbach), absent in morning specimen, present in afternoon specimens	1.56 per cent. NaCl	3.12 per cent. NaCl	2.0
5	I. J., aged 12 years, April 14th, 1904	Puffiness developing beneath the eyes led to examination of the urine and detection of albumin. Albuminuria was notably increased by active exercise. The patient was robust and in perfect health	Albumin, a pronounced trace present in specimen collected some hours after rising	1.0	2.0	2.0
6	K. L., aged 45 years, March 22nd, 1904	The patient, a robust artisan, came to hospital suffering from giant urticaria and recent hydrocele	Albumin present; one-eighth by boiling	0.7	1.8	2.5
7	M. N., aged 17 years, March 22nd, 1904	Similar to Case 1. Albumin present, especially after severe exercise (shooting)	Albumin, a pronounced trace, present in specimen collected some hours after rising	0.85	1.87	2.2
8	O. P., aged 55 years	Similar to Case 1. No atheroma or increased arterial tension	Colour good; specific gravity, 1018; no casts; no blood; quantity normal; albumin absent in early morning specimens; generally a trace of albumin in specimen collected a few hours after rising; a pronounced trace practically always after active exercise	—	1.94	—

In connexion with the results given in Table II and those set down in a previous paper¹ with regard to the effect of a milk dietary upon the coagulability of the blood and its content in lime salts, it is interesting to one of us to recall the medical history of one of his pupils who had passed into the Indian Medical Service. This

¹ *Vide supra*, pp. 101-115.

officer, who was the son of a medical man, related that both he and a succession of his brothers had on reaching the period of early adolescence—i.e. the period at which lime salts would be taken out of the blood in connexion with the processes of

TABLE II.—*Showing the Restraining Influence which is exerted by Calcium Salts on the Output of Albumin in Physiological Albuminuria*

—	Period at which observation was made	Blood-coagulation time	Minimum concentration of oxalate of ammonium required for decalcification of an equal volume of blood.	Quantity of albumin in the urine and method employed for precipitation of albumin	
A. B. -	Before the administration of calcium salts	1 min. 40 secs.	1 in 1500	$\frac{1}{4}$ volume, boiling	
	60 grains of calcium lactate administered				
	One and a half hours after the administration of calcium salts	1 min. 20 secs.	1 in 1000	$\frac{1}{2}$ th volume, boiling	
	Two 20-grain doses of calcium lactate administered				
	24 hours after the first administration of calcium salts	1 min. 20 secs.	1 in 1200	None	
C. D. -	Before the administration of calcium salts	1 min. 25 secs.	1 in 1350	Pronounced trace	
	60 grains of calcium lactate administered				
	One hour after the administration of calcium salts	1 min.	1 in 1200	None	
E. F. -	Before the administration of calcium salts	—	1 in 1350	0.04 per cent., Esbach	
	60 grains of calcium lactate administered				
	One hour and three-quarters after the administration of calcium salts	—	1 in 1200	Slight haze, boiling	
	20 grains of calcium lactate administered three times a day				
	Six days after the first administration of calcium salts	—	—	Trace	
20 grains of calcium lactate administered three times a day					
19 days after the first administration of calcium salts	—	1 in 800	None		

	Period at which observation was made	Blood-coagulation time	Minimum concentration of oxalate of ammonium required for decalcification of an equal volume of blood	Quantity of albumin in the urine and method employed for precipitation of albumin
G. H. -	Before the administration of calcium salts	1 min. 55 secs.	—	0.15 per cent., Esbach
	60 grains of calcium lactate administered			
	Two hours after the administration of calcium salts	1 min. 20 secs.	—	0.05 per cent., Esbach
	24 hours after the administration of calcium salts	—	—	None
K. L. -	Before the administration of calcium salts. While the patient was suffering from giant urticaria	—	1 in 1200	$\frac{1}{8}$ th volume, boiling
	20 grains of calcium chloride administered three times a day			
	Four days after the first administration of calcium salts, the urticaria having completely disappeared	—	1 in 750	None
O. P. -	Before the administration of calcium salts and after walking several miles	2 mins. 15 secs.	1 in 1000	Definite trace
	24 hours' interval; then the ingestion of 60 grains of calcium chloride			
	After the administration of calcium salts followed by same walk as before	1 min. 40 secs.	—	None

growth—developed albuminuria which had in each case been permanently arrested by rest in bed combined with a dietary of milk.¹

On the possibility of discriminating the albuminuria which occurs independently of renal disease from the albuminuria which is due to such disease by noting the effect produced upon the output of albumin by the exhibition of calcium salts.—Having found, as has been shown above, a method by which physiological albuminuria can be abolished, the next point which suggested itself for investigation was the question as to whether calcium salts were competent also to abolish the excretion of albumin in albuminuria dependent upon renal disease. The data set forth in Table III furnish the answer to this question. It will be seen that in spite of the fact that

¹ We learn from a paper by Dr. Clement Dukes (*Brit. Med. Journ.*, 7th Oct., 1905) published while this was in the press that he has seen physiological albuminuria disappear under a regimen of milk even apart from rest in bed. Such results would be in all points comparable to those in Table II above obtained by the exhibition of calcium salts.

TABLE III.—*Showing that the Albuminuria of Renal Disease is not abolished by the Exhibition of Calcium Salts*

Initials, age, and date	Clinical data	General character of the urine	Dates of examination	Excretory efficiency as determined by the method of haemolysis			Effect of the administration of calcium lactate
				NaCl content of the serum	NaCl content of the urine	Excretory quotient	
C. W., aged 15 years, April 18th, 1905.	Patient has been ill for at least nine months and presents typical symptoms and signs of parenchymatous nephritis — oedema, headaches, thickened arteries, increased arterial tension, and hypertrophied heart.	Smoky; acid; specific gravity, 1016; albumin; granular epithelial casts and blood, about 25 ounces per diem.	Nov. 18th, 1904.	1.17 per cent. NaCl	1.17 per cent. NaCl	1.0	Jan. 1st, 1905.— <i>Before the Administration of calcium salts</i> : coagulation time of blood, 1 minute 50 seconds; minimum concentration of ammonium oxalate required for decalcification, 1 in 1750; albumin, 1.6 per cent. by Esbach. 40 grains of calcium lactate administered. 2½ hours after the administration of calcium salts: coagulation time of blood, 1 minute; minimum concentration of ammonium oxalate required for decalcification, 1 in 1200; albumin, 0.9 per cent. by Esbach.
			Nov. 19th, 1904.	1.56 per cent. NaCl	0.78 per cent. NaCl	0.5	
			Nov. 29th, 1904.	0.97 per cent. NaCl	0.585 per cent. NaCl	0.6	
T. S., aged 17 years, May 3rd, 1905.	Patient is the subject of a typical parenchymatous nephritis following exposure to cold and wet. Signs and symptoms as in Case 1 and in addition ascites.	As in Case 1; specific gravity, 1012; albumin; from 20 to 30 ounces per diem.	Nov. 16th, 1904.	0.82 per cent. NaCl	0.819 per cent. NaCl	1.0	Jan. 1st, 1905.— <i>Before the administration of calcium salts</i> : coagulation time of blood, 1 minute 45 seconds; albumin ½ths by boiling. 60 grains of calcium lactate administered. Two and a half hours after the administration of calcium salts: coagulation time of blood, 1 minute 25 seconds; albumin ½ths by boiling.
			Nov. 20th, 1904.	0.78 per cent. NaCl	0.78 per cent. NaCl	1.0	
			Nov. 29th, 1904.	0.97 per cent. NaCl	0.78 per cent. NaCl	0.8	
			Dec. 12th, 1904.	0.97 per cent. NaCl	0.78 per cent. NaCl	0.8	
W. W., aged 49 years, shipwright, May 5th, 1905.	Patient has been ill for one year. Oedema of the eyelids, the conjunctiva, and the legs; severe headaches, anaemia, loss of appetite, thickened arteries, high arterial tension, and hypertrophied heart.	Colour, pale; specific gravity, 1010; acid; albumin; hyaline casts; quantity, from 80 to 100 ounces per diem.	Dec. 5th, 1905.	1.36 per cent. NaCl	1.36 per cent. NaCl	1.0	Jan. 1st, 1905.— <i>Before the administration of calcium salts</i> : coagulation time of blood, 30 seconds; concentration of ammonium oxalate required for decalcification of blood over 1 in 800; albumin, ½ by boiling; 0.68 per cent. by Esbach. 60 grains of calcium lactate administered. Two and a half hours after the administration of calcium salts: coagulation time of blood, 25 seconds; concentration of ammonium oxalate required for decalcification of blood over 1 in 600; albumin, ½ by boiling; 0.76 per cent. by Esbach.
A. B., aged 21 years.	Albuminuria associated with a coli infection of the urinary passages which has persisted for years.	Turbid with bacteria; no casts; much bladder epithelium; some polynuclear white blood corpuscles. Albumin; quantity normal.	Feb. 6th, 1905.	0.6 per cent. NaCl	0.85 per cent. NaCl	1.4	Feb. 6th, 1905.— <i>Before the administration of calcium salts</i> : coagulation time, 1 minute 50 seconds; minimum concentration of oxalate of ammonium required for decalcification of blood, 1 in 1000; albumin, 0.17 per cent. 60 grains of calcium lactate administered. 45 minutes after administration of calcium salts: coagulation time, 25 seconds; minimum concentration of oxalate of ammonium required for decalcification of blood, 1 in 750; albumin, 0.66 per cent.

the coagulability of the blood was in each case increased the output of albumin was not diminished. We have here, as reflection will show, a fact which may with advantage be exploited in the differential diagnosis of albuminuria dependent on kidney disease from physiological albuminuria or, as the case may be, in the determination of the question as to whether albuminuria is or is not in part referable to a simple transudation.

Conclusions.—We venture to suggest, in view of the observations which are set forth in this paper, that it will no longer be justifiable to take, in connexion with examination for insurance or for entry into the public services, the serious view of physiological albuminuria which has hitherto been taken by most clinicians. Where it is found that a patient possesses a normal excretory quotient, and that his albuminuria can be abolished by diminishing the hydrostatic pressure on the renal capillaries and by increasing the coagulability of the blood, there is, we submit, every reason to conclude that the kidney is free from organic disease and that life is no more endangered than it would be if the patient were the subject of urticaria.

HAEMOPHILIA

Definition.

Haemophilia is a disorder depending on a congenital defect in the coagulating power of the blood, and characterised by immoderate spontaneous and traumatic haemorrhages, 'seromata', and recurrent effusions into the joints.

Incidence.

The disease, as defined above, is restricted to the male sex, and is nearly always associated with a family history of bleeding. It is met with in all classes of society and occurs in persons of every kind of physique.

The Symptoms may be most conveniently discussed under the following headings :

Sub cutaneous Haemorrhages and 'Seromata'.—That a child is destined to be a 'bleeder' is generally first shown by the occurrence in the subcutaneous tissue of 'seromata', which appear either as superficial bruises or as deeper diffuse swellings. They may be 'spontaneous' or may follow in the train of quite insignificant injuries. The swellings are always tender to the touch, and may, when the effusion has been considerable, be extremely painful. As these seromata are the result not only of an increased transudation of blood-fluids through the capillary walls into the tissues, but also of the diapedesis of the red blood corpuscles, a play of colours such as is seen in connexion with ordinary subcutaneous haemorrhages may be seen around them. In those cases in which there has been considerable effusion of all the elements of the blood, a definite blood clot may form in the tissues. Seromata are not confined to the subcutaneous tissue, but may take place into the sheaths of the muscles, and give rise to very considerable pain. This condition appears to be analogous to the painful intramuscular effusions which were common in 'land-' and 'sea'-scurvy, and are still seen in infantile scurvy. Like the other active manifestations of the haemorrhagic diathesis, seromata occur pre-eminently in early childhood, and become less frequent as age advances.

Articular Effusions constitute another manifestation of the liability to 'serous haemorrhage' which is characteristic of the bleeder. Effusions into joints occur in practically all cases of haemophilia, generally appearing as soon as active exercise throws a strain upon the joints. These joint-effusions, like the seromata come on either 'spontaneously' or in the train of injuries which in healthy persons would usually be too trifling to attract attention. Judging from the analogy of what

occurs in the subcutaneous tissues, the fluid effused into the joints would generally seem to be clear lymph, but sometimes the lymph may contain a large admixture of red blood corpuscles. As a rule the fluid is only incompletely absorbed, and the joint remains more or less permanently waterlogged with blood-stained lymph. The repeated articular effusions are followed by adhesions and by degenerative changes resembling those in osteo-arthritis. Partial ankylosis often supervenes, and the patient generally becomes more or less seriously crippled. The knees are most generally affected, next in order of frequency come the ankles and elbows. Articular effusions become rarer and rarer as the boy grows up, but they may occur in adult life when the joints are subjected to strain, or when the coagulability of the blood has been seriously reduced by supervening disease. I know a late naval surgeon whose two knee-joints spontaneously filled with blood when he had an attack of malaria.

Spontaneous Haemorrhages from Mucous Membranes.—In addition to these transudations into the tissues the bleeder practically always suffers from immoderate haemorrhages from mucous membranes; of these the commonest is severe epistaxis, and next in frequency haemorrhage from the gums. In other cases blood escapes from the kidney or the bowel. In all these forms of haemorrhage, bleeding may persist as a capillary oozing until the patient succumbs to loss of blood; but more often—in association with that ‘haemorrhagic increase of blood-coagulability’ to which attention was called by Cohnheim in connexion with bleeding experiments conducted upon animals—the blood-flow ultimately stanches. In the bleeder, however, this may only result after the blood has been oozing away for weeks, and has become so impoverished in red corpuscles as to leave hardly more than a rusty stain upon the linen.

In connexion with all such haemorrhages continuous headache and racking thirst are prominent symptoms. The cases of bleeding from the nose or mouth are perhaps the most distressing. Here, when after hours or days, the blood commences to clot, coagula collect on the teeth and tongue, and hang down in long strings from the posterior nares, interfering with respiration, and fouling all the food with blood. In addition to blood swallowed with the food, blood here continually trickles into the stomach, and becoming putrid in the intestinal canal, gives rise to a very distressing colic. The clots which adhere to the teeth and obtrude from the nostrils also putrefy, and poison the patient with their stench. It is little wonder that, after going through all this repeatedly the bleeder should, as he so often does, fall into marasmus and succumb.

Traumatic Haemorrhages.—The bleedings following injuries—and these injuries may be such as would in healthy persons not be of the slightest moment—differ from the spontaneous haemorrhages just described, only in being more serious. The gravest are perhaps those in which a boy cuts his lip or bites his tongue as the result of a fall. Small skin abrasions are seldom of much account: vaccination, for instance, is said to be comparatively free from danger. Deeper cuts, of course, and surgical incisions, are perilous. The opening of abscesses, or haematomas, and the major operations of surgery have often been followed by fatal results. Among minor operations the extraction of a tooth is perhaps the most dangerous. It has

time and time again been followed by death. There is, however, no risk in drawing blood from an ordinary finger-prick. It would seem that the elasticity of the skin here arrests the bleeding. Blood may also, it would seem, be drawn with impunity from a prick in a vein.

Very noticeable in connexion with all these haemorrhages of the bleeder is their nocturnal incidence. Subcutaneous haemorrhages often come on at night during sleep. The same applies in connexion with traumatic haemorrhages. Here it is the rule for the bleeding which supervenes immediately after the infliction of the wound to be comparatively trifling. But it will often break out again as soon as the patient has fallen asleep. In such a case if the boy sleeps on uninterrupted, and no one watches over him, the bed may be soaked with the blood until it drips upon the floor. The perfectly desperate condition that things get into in the houses of the poor when such bleeding as this occurs is more easily imagined than described. I have seen a room look like a shambles; and know a case where a mother, finding her boy bleeding in his sleep, had to wrap him in the blood-soaked blanket, and to wheel him on a coster's hand-cart, in the middle of the night, bleeding, all the way from a suburb to one of the London hospitals.

Periodic Exacerbation of the Symptoms and the Question whether the Bleedings are preceded by Prodromal Symptoms.—I see no room to doubt that the serous haematomas, and the spontaneous haemorrhages from mucous membranes, are only the most conspicuous manifestations of some periodical change in the condition of the blood. I have satisfied myself by repeated blood examinations, and by observation and inquiry from the patient's relatives, that there are in the life of every bleeder recurrent periods, during which the coagulability of his blood is reduced far below its mean value, and during which all the symptoms of his disorder are aggravated. The clinical manifestations of such a blood-change, if noticed before the onset of spontaneous haemorrhage, would not improperly be described as 'prodromal symptoms'. These may amount to little more than slight puffiness of the face, a feeling of lassitude, and an increased fullness in the joints. Or again the blood-change may induce hysterical irritability, persistent headache, or, as in a case which I had under observation, a quasi-comatose condition. The periodical attacks from which the bleeder boy in question suffered were described by his relatives as 'fits'. All these nervous symptoms may perhaps be provisionally referred to serous haemorrhages into the nervous system. The headache may be classed with the type of headache described by Dr. G. W. Ross¹ in chlorotic girls who have a diminished blood-coagulability; and the hysterical symptoms and fits may be paralleled with those met with in some aggravated cases of urticaria, in which again there is generally a diminished coagulability of the blood.

Further Points in connexion with the Symptomatology of Haemophilia.—A few other points in connexion with the symptomatology of haemophilia deserve attention either because they are of cardinal importance to the haemophilic patient, or because they may ultimately serve to illuminate the obscure pathology of the disease. The first of these is the very frequent association of early and extensive dental caries with the haemorrhagic diathesis. Seeing the risk attached to the

¹ *The Lancet*, 1906, i, 143.

extraction of teeth this disposition to dental caries constitutes a serious calamity. Of less direct practical interest is the frequency with which a depraved appetite, as shown by the eating of grit and chalk, has been observed in haemophilia; this was specially noted by Dr. Wickham Legg,¹ and I have seen notable instances of it. In one case when questioning the mother of a bleeder on the subject I was, for answer, conducted through the front room to the kitchen, the wall of which had been completely cleared of its plaster—and it was very thick plaster—over an area of about three feet by one foot. This had been done by the bleeder boy of three years old, who could not be prevented from picking off and eating the plaster. When, in order to prevent this, the boy was shut out into the yard, he set to work upon the mortar between the bricks, which he picked out and ate. His mother saw in this morbid craving something uncanny, but his uncle, also a bleeder, told me that he had behaved in the same way when a boy. One cannot help suspecting that there may be at work in these cases an imperious craving for calcium. I have very frequently met with chilblains and urticaria in connexion with bleeders; both these disorders occur, as I have pointed out, in direct connexion with diminished blood-coagulability.² Inasmuch as physiological albuminuria is also, as I have shown in association with Dr. Ross,³ a disorder which occurs in connexion with diminished coagulability of the blood, it would be interesting to see whether it occurs frequently in bleeders; but I have not investigated this point.

Differential Diagnosis.

When the appearance of some one or more of the symptoms enumerated above calls for a decision of the question whether we have to deal with the congenital defect which is properly described as haemophilia, or with some other non-congenital disorder which favours immoderate haemorrhage, the following points, in addition to the history, should be taken into consideration: the subcutaneous haemorrhages of haemophilia may be distinguished from ordinary ecchymosis and purpura by their generally being associated with a certain amount of swelling and by not being of the same deep inky purple as purpuric eruptions. This is in consonance with the idea that we have in haemophilia to deal with haemorrhages *per transudationem et diapedesin* as distinguished from haemorrhages *per rhexin*. The less superficial haematomas may be distinguished from those of infantile scurvy by their occurring in the subcutaneous tissue, as distinguished from the periosteum; and by the absence of any general tenderness or any implication of the gums. Nor are they, if we may generalise from an observation by Sahli and a similar one by myself, associated with that defect of blood-alkalinity which is in my experience a characteristic feature of scurvy.⁴

¹ *A Treatise on Haemophilia, sometimes called the Hereditary Haemorrhagic Affection*, London, 1872; and *System*, 1st ed., 1898, v, 548.

² *Vide supra*, p. 67.

³ *Vide supra*, pp. 116 *et seq.*

⁴ *Vide supra*, pp. 38–54.

Prognosis.

The outlook for the bleeder would seem to be specially unfavourable when the disorder appears in early infancy. But even in these—the worst cases—the danger to life is not by any means so serious as was once supposed; for we have now, as will be shown in discussing the treatment of haemophilia, methods for the arrest of haemorrhage which will practically always prove successful. It must also be borne in mind that the risk of fatal haemorrhage diminishes as the bleeder boy grows up, not only because, as he learns caution, injury is carefully avoided, but also because, as it would seem, the coagulability of the blood improves as age advances, with the result that when adult life is reached the spontaneous haemorrhages generally cease, and the traumatic haemorrhages become less formidable. A similar improvement is seen as regards the serous haemorrhages, which can also be held in check by the measures available for increasing the coagulability of the blood.

But when every possible allowance has been made for these more hopeful elements in the clinical picture, it must be recognised that the outlook in haemophilia is very depressing. Quite apart from all considerations of the serious risk to life from haemorrhage, and of the miseries which are associated with such haemorrhage (both for the patient and his relatives), the recurrence of serous haemorrhages into the joints means constant invalidism, and almost inevitably goes on to partial ankylosis, which incapacitates the patient for many kinds of work.

Data with regard to the Manifestation of the Bleeding Diathesis in the Female Members of Bleeder Families and Exceptional Fertility of the Women in such Families.

The female members of bleeder families do not show the symptoms of the disorder; they never suffer from seromata, from the characteristic effusions into the joints, and only very rarely from immoderate spontaneous or traumatic haemorrhages. Nor as a rule do they lose an excessive amount of blood at the menstrual periods or at their confinements. Epistaxis, flooding after labour, and menorrhagia at the menopause, are not infrequently recorded. I have myself seen severe recurrent epistaxis in a young woman, the daughter of a bleeder: and in a girl of eight or nine, the sister of a bleeder, serious haemorrhage occurred after the extirpation of a nasal polypus. Although, as I have just insisted, manifestations of the bleeding diathesis are exceptional in women of bleeder families, some of the anomalous features which are found in the blood of their bleeder sons may be also detected in their blood (see. pp. 130–132).

A characteristic point about bleeder women is their exceptional fertility. The family tree of the bleeder family Mampel which has been published by Lossen furnished, as he points out, striking instances of such fertility. The pedigree shows 4 families with 19 children each, 2 with 13 children each, 2 with 11 children, and several with 10, 9 and 8 children each. The genealogies of the three bleeder stocks which are given on pp. 136 and 137 also supply evidence of this fertility. The *first* genealogy shows in the first generation a family of 9, and in the second generation one of 6. The third generation cannot be considered from this point of view, for limitation of the family is continually present to the minds of its female members

—one of the sisters absolutely refusing to marry and become the mother of bleeders. In the *second* genealogy there is in the first generation a family of 13, in the next generation families of 9 and of 11, and in the third generation one family of 7, which has been numerous added to since the pedigree was compiled. The *third* genealogy shows in the older generation a family of 18, and in the present generation a family of 7. The nature of the nexus between descent from a bleeder stock and exceptional fertility in the female is an unsolved and perhaps an insoluble problem. And yet when we consider how the discovery of this nexus might throw a light on the complicated phenomena of inheritance through an apparently unaffected parent, and further how the elucidation of this problem of exceptional susceptibility to impregnation might assist in the treatment of sterility, it becomes clear that it is a problem which might fittingly attract attention. Consideration will, I think, lead to the conviction that it is wholly gratuitous to suppose that a woman of bleeder stock would, as compared with a normal woman, be less liable to suffer from mechanical hindrances to impregnation, or that her fluids would contain less of those products of immunisation (spermato-tropic elements) which from analogy must probably be produced in the organism by the absorption into it of the sexual products of the male. The cause of the exceptional fertility of the woman of bleeder stock might more reasonably be sought for in those features of the blood which are special to haemophilia. Now the special characters of the blood of bleeder families, so far as is at present known, are, as we shall see in more detail in a subsequent section, a diminished content in leucocytes, and diminished blood-coagulability. The diminished number of leucocytes, and of polymorphonuclear leucocytes in particular, might at first appear not to possess any special significance: it may, however, have a bearing on the question of fertility, for spermatozoa when brought in contact with leucocytes in the presence of the blood-fluids are actively phagocytosed. It would seem, therefore, that spermatozoa in the course of their passage along the uterine and tubal mucous membranes may have to run the gauntlet of the leucocytes before they can effect a junction with the ovum, and it is just conceivable that there may be fewer phagocytes to evade when there are fewer leucocytes in the blood-stream. In like manner the diminished blood-coagulability and correspondingly increased transudation of fluid from the blood-vessels into the mucous membrane of the genital passages, which would accompany it, might quite well be a factor of dominating importance for the successful passage of the spermatozoa along the mucous membranes. When we call up a mental picture of the muscular, nearly amenorrhoeic woman, whose blood is highly coagulable, and whose tissues are correspondingly dry and parchments; and contrast her with the muscularly lax type of woman, whose blood is somewhat deficient in coagulability, and whose tissues are correspondingly lymphatic and succulent, we immediately realise that the latter is incomparably the more fertile type. Now the woman of bleeder stock, to my mind, belongs eminently to this latter type. Is there not perhaps here a hint that it might be reasonable in the case in which we desire to facilitate impregnation in the former type of woman—the type of the sterile virago—to administer citric acid,¹ with a view to diminishing the coagulability and viscosity of her blood?

¹ *Vide supra*, pp. 34–37.

Pathology.

Although consideration of the problem of haemophilia would suggest that there must be some defect in the coagulating power of the blood in this disease, this view has not been universally accepted.

Since blood-clots are in haemophilia, after free and persistent bleeding, a very striking feature in the clinical picture, it has often been contended that there cannot possibly be any fault in the coagulating power of the blood. The supporters of this argument, being obliged to provide an explanation for the excessive haemorrhages of the bleeder, have relied on Virchow's report of hypoplasia of the aorta and arterial system in the necropsy of a bleeder, and on the reported occurrence of enlargement of the left side of the heart in bleeders, to justify the hypothesis that the excessive haemorrhages depend on increased arterial blood-pressure, or the hypothesis that they depend on a defect in the coats of the blood-vessels. To my mind these hypotheses do not rest upon a sufficient logical basis to deserve serious refutation; in the first place, it does not follow from the fact that the blood of bleeders clots that its clotting proceeds in normal time; in the second place, the data invoked to prove that the defect must lie in the mechanics of the circulation or in some abnormality in the walls of the blood-vessels are isolated observations; and lastly, the slow capillary oozing which is the characteristic feature of haemophilia is not explained by the thinning out of the walls of the arteries, and no one, I imagine, would be prepared to contend that the capillary walls of the bleeder can be thinner than they are in a normal man. Still as Sahli¹ in his careful study of haemophilia, and subsequently Morawitz and Lossen,² have thought it worth while to refute these speculative views, it may in passing be noted that Sahli brings forward evidence from his four cases to show that a low arterial pressure obtains in bleeders, and that Morawitz and Lossen adduce a comparative experiment made with dry cupping respectively on a bleeder and on a normal person to prove that the capillary walls are not more permeable in the hæmophilic than they are in the normal person. It will thus be clear that we may with advantage turn our attention to the blood and more especially to its coagulability, bearing in mind that for the arrest of haemorrhage it is essential that blood-clot should form in the orifice of the cut blood-vessel, and that it is, so far as the arrest of haemorrhage is concerned, a matter of indifference whether the blood clots, or does not clot, after it has flowed away from the bleeding-point.

Coagulation time.—The first measurements of the coagulation time in bleeders were published by me in 1893 and 1894,³ and showed that the coagulation times in three bleeders were 60, 20 and 10 minutes respectively, as compared with about 5 minutes, which is the coagulation time of the normal blood when drawn up into capillary tubes of similar calibre, and maintained under the same conditions of temperature. My note-books for the years 1893–1896 contain records of five other bleeders—all belonging to bleeder stock No. 1 (see pp. 132 and 138)—with coagulation times of 54 minutes, over 20 minutes, 17 minutes, 17 minutes, and 26 minutes respectively; and also of two unrelated bleeders with coagulation times of 11 and 70

¹ *Ztschr. f. klin. Med.*, 1905, lvi, 264.

² *Deutsches Arch. f. klin. Med.*, 1908, cxiv, 110.

³ *Vide supra*, p. 28.

minutes. Sahli while quoting and confirming, by examination of the bloods of his four bleeders, my published results, insists, and very properly, that during and for some time after haemophilic haemorrhages, coagulation times are obtained which are as short as or shorter than those of normal blood. The existence of this 'haemorrhagic increase of the blood-coagulability' in bleeders I had already reported.¹ More than that, I had pointed out that it was a physiological phenomenon which was already familiar in connexion with blood-letting in animals.² In order to avoid this fallacy, the blood examinations I reported (and the same applies to those recorded above) were always made in inter-haemorrhagic periods.

Leucocytes.—In the series of papers just been referred to I drew attention also to the leucocytes in haemophilic blood. The aggregate result of 55 enumerations and of about double that number of differential counts shows that bleeders and the female ascendants of bleeders almost always have a subnormal number of leucocytes, and in particular a subnormal percentage of polymorphonuclear leucocytes. In connexion with the percentage count of polymorphonuclear leucocytes in children, it must be remembered—though, unfortunately, exact data on this subject are not yet available—that it is the rule for the percentage of polymorphonuclears to be less in early infancy than in childhood, and less in childhood than in adult life—ranging it would seem from perhaps 25 per cent. in early infancy to 70 per cent. in adult life. The more interesting of my observations, almost all of which date back to the years 1893–1896, on the leucocyte-counts of bleeders are the following :

(1) *Observations relating to the Leucocytes of Adult Bleeders*

	Leucocytes per c.mm.	Polymorphonuclear Leucocytes per cent. per c.mm.
No. 1, aged about 25 years	6600	56 = 3700
No. 2, " " 45 "	7400	52 = 3850
No. 3, " " 30 "	4300	70 = 3000

With these may be compared recent observations by Sahli on three bleeders, and by Weil :

	Leucocytes per c.mm.	Polymorphonuclear leucocytes per cent. per c.mm.
Sahli's cases		
No. 1, aged 17 years -	6200	63 = 3800
No. 3, " 17 " -	6700	55 = 3700
No. 4, " 21 " -	3600	45 = 1600
Weil's case		
Aged 45 years - - -	2600	57 = 1500
" " - - -	4000	60 = 2400

¹ *Vide supra*, p. 32.

² Cohnheim, *Vorlesungen über allg. Pathologie*, Berlin, 1882, Bd. I, s. 387.

(2) *Observations relating to the Leucocytes of entire Bleeder Families:* My observations on the leucocytes of entire bleeder families are presented below in tabular form. As already indicated above, low leucocyte-counts in haemophilic families are not confined to the bleeders. Evidence bearing on this is furnished in the tables below.

BLEEDER STOCK NO. 1. *Synopsis of Results presented in the Table below.*—The observations tabulated below show that a subnormal number of leucocytes, and in particular of polymorphonuclear leucocytes, was a constant feature in all the bleeder boys of this stock. It was found also in two of the mothers of bleeder boys (the observation relating to the third bleeder mother may probably be neglected, as the results were obtained in the ninth month of pregnancy). Two of the fathers of bleeders presented a deficiency of polymorphonuclear leucocytes similar to that found in the mothers of bleeders. A comparison of the bleeder boys with their maternal uncle, also a bleeder, and a comparison of the leucocyte-counts obtained in two of the bleeder boys at an interval of three years, show that some improvement has taken place with age :

Name	Relationship to the bleeders H. H. and T. H.	Age	Number of leucocytes per c.mm.	Number of polymorpho- nuclear leucocytes per c.mm. or per- centage	Blood-coagulation times at 18.5° C. (circa.)
Henry G.	- Maternal grandfather -	72	—	61%	7' 10"
Jesse H.	- Father - - - - -	38	8,200	3,100	3' 40"
Emma H.	- Mother - - - - -	36	4,000	1,700	3' 30"
Jessie H.	- Sister - - - - -	10½	12,400	7,500	2' 45" : 5'
Harry H. (bleeder)	—	9 12	6,000	2,600 47%	54' : 14'
Tommy H. (bleeder)	—	7 10	5,800	2,800 54%	6' 45" : 9' 15" over 20'
John G.	- Maternal uncle - -	45	7,400	3,850	17'
Ellen G.	- Maternal uncle's daughter	19	2,700	1,350	9' 30"
Jane B.	- Maternal aunt - -	32	6,400	2,900	4' 45"
Frederick B. (bleeder)	- Maternal first cousin -	5	6,800	2,400	7' 30" : 17'
Ethel B.	- Maternal first cousin -	3	8,800	4,000	7' 30"
Wilfred K.	- Maternal aunt's husband	31	4,970	3,000	2'
Kate K.	- Maternal aunt - -	27	—	78%	3' 30"
Percy K. (bleeder)	- Maternal first cousin -	3	—	34%	26'

BLEEDER STOCK NO. 2. *Synopsis of Observations set forth in the Table below.*—The table shows that the mother and grandmother of the bleeder boy—women through whom the haemorrhagic diathesis was inherited—present when contrasted with the father and grandfather, who were sound men, of non-bleeder stock, a

notable inferiority in the number of leucocytes, and in particular in the number of polymorphonuclear leucocytes. The observations which relate to the leucocytes of the bleeder boy himself do not confirm the general rule which applies to bleeder boys. On the other hand, it is to be noted that the leucocytic observations on this boy here tabulated were made at a time when he was just recovering from an alarming haemorrhage which had almost proved fatal. The observations which relate to the three married sisters, the eldest of whom (Esther) had had a family of perfectly healthy sons, whilst the two younger (Caroline and Kate) had had bleeder sons, show that the first had a normal number of polynuclears, whilst the two latter had a subnormal number. The female children of this bleeder stock show striking differences with respect to their leucocyte-counts which do not stand in relation with ages, and which recall the conditions found in their maternal aunts :

Name	Relationship to bleeder G. C.	Age	Number of leucocytes per c.mm.	Number of polymorphonuclear leucocytes per c.mm.	Blood-coagulation time
Peter H.	- Maternal grandfather -	70	10,800	6,900	5' 10" (13° C.)
Caroline H.	- Maternal grandmother -	68	7,600	4,000	11' 30" (13° C.)
George C.	- Father - - - -	45	12,200	7,500	2' 30" (14° C.)
Kate C.	- Mother - - - -	28	8,400	4,200	6' 50" (16° C.)
Esther C.	- Maternal aunt - -	48	12,300	7,400	7' 30" (5° C.)
Caroline M.	- Maternal aunt - -	46	9,000	5,100	5' (9° C.)
Eliza G.	- Maternal aunt - -	44	8,600	4,100	5' 20" (5° C.)
Lily C.	- Sister - - - -	10	7,800	2,400	11' 45" (13° C.)
Ellen C.	- Sister - - - -	7	8,300	4,000	8' (15° C.)
Ethel C.	- Sister - - - -	6	16,400	7,500	6' (13° C.)
Maysie C.	- Sister - - - -	5	12,200	6,700	6' 45" (13° C.)
George C. (bleeder)	- — - - - -	3	15,800	6,900	25' (18.5° C.)
Jane C.	- Sister - - - -	1½	9,200	2,500	12' 45" (13° C.)
Willie C. (not a bleeder)	- Brother - - - -	2½	—	35%	4' 20" (18.5° C.)
Frank H. (not a bleeder)	- Maternal first cousin -	12	10,200	4,400	8' 30" (13° C.)

BLEEDER STOCK NO. 3. *Synopsis of the Data in the Table below.*—There is a diminished number of leucocytes and of polymorphonuclears in the bleeder and in the mother of the bleeder, and a diminished number of leucocytes in the father. A brother, who has not inherited the tendency to bleed, has a large number of leucocytes and a normal percentage of polymorphonuclear leucocytes. The girls of the bleeder family present striking differences in the leucocytic counts, which do not stand in any relation to the individual ages :

Name	Relationship to bleeder W. G.	Age	Number of leucocytes per c.mm.	Number of polymorphonuclear leucocytes per c.mm.	Blood-coagulation time at 18.5° C. (<i>circa</i>)
W. S. G.	Father - - - -	45	5,800	4,200	3' 50"
Janet G.	Mother - - - -	42	4,400	3,100	6' 45"
Willie G.	—	11½	7,600	2,600	4' 30"
(bleeder)	—	14	6,200	3,100	20' 0"
Maggie G.	Sister - - - -	10½	4,250	2,300	1' 50"
Mary G.	Sister - - - -	9	8,600	5,500	3' 30"
Thomas G.	Brother - - - -	6	10,200	5,500	2' 30"
		8½	7,000	4,900	3' 45"
Florrie G.	Sister - - - -	3½	8,600	2,300	2' 15"

How far does the foregoing account of the pathology of haemophilia furnish an explanation of that disorder?—Even if all that has been set down above had been placed beyond the reach of doubt, it could not be contended that anything in the nature of a complete solution of the problem of haemophilia had been arrived at. The ultimate causes of the defect of blood in the bleeder and of the limitation of the manifestations of this disorder to the male sex are left unexplained.

There are two ways of viewing this situation. There is the point of view of the man who is always concerned about getting down to the very foundation of things. A theory of haemophilia such as he asks for will no doubt be forthcoming when we have completely solved the general problem of blood-coagulation, and when we have discovered how it is that differences of sex are correlated not only with profound intellectual differences, but with such completely mysterious differences as are encountered here and there in connexion with the inheritance of colour-blindness. But there is also the point of view of the man who has no ambition to go out of his depth, who can acquiesce in a knowledge of proximate as distinguished from ultimate causes, provided only there follows from a knowledge of proximate causes a power of controlling events, and who can in connexion with a disease content himself with a provisional theory provided it calls up before the mind the essential clinical features of the disorder, and suggests at the same time a useful line of treatment.

Now the hypothesis that haemophilia depends upon a defect in the coagulability of the blood—and the existence of this defective coagulation in haemophilia is, as we have seen, attested by a considerable body of observations—supplies the mental picture the practical man requires. It explains the persistent and excessive haemorrhages of haemophilia. It explains also the articular effusions of the bleeder. For, as I have pointed out, defective blood-coagulability—presumably because a blood which is deficient in coagulability is deficient also in viscosity—goes hand in hand with a tendency to serous haemorrhages. The nocturnal incidence and aggravation of the haemorrhages which is such a striking feature in haemophilia also fits in with this conception. Since the coagulability of the blood increases when CO₂ accumulates in the blood, and diminishes when the CO₂ diminishes, it might on *a priori* grounds

alone be expected that an existing defect of blood-coagulability would be exaggerated when the patient is at rest in bed and the output of CO_2 from the tissues is diminished.

Two further points must now be considered. The first is the question whether the subnormal number of leucocytes, and especially of the polymorphonuclears, is or is not related to the defect in the coagulability of the blood. It would appear that such a connexion exists; for generally speaking pathological conditions associated with a polymorphonuclear leucocytosis are characterised by an increase in the coagulability of the blood, and, *vice versa*, conditions characterised by a diminution in the number of the polymorphonuclear leucocytes are associated with a diminished blood-coagulability. The reason of this is unknown, but it has often been surmised that destruction of the white blood-corpuses—and I would suggest more especially of the polymorphonuclear leucocytes—supplies the blood with a fibrino-plastic element. There remains a point which has been considered both by Sahli and after him by Morawitz and Lossen. This is the oozing which takes place from under the clot in haemophilic wounds, and the persistence of this oozing when as the result of the haemorrhagic increase of blood-coagulability the blood coagulates in normal time or less than normal time. In explanation of this it is suggested by Sahli that the tissues and the vascular wall may, in the case of the bleeder, fail to contribute to the blood some element which is essential to the effective plugging of the vessel. This may well be; for Delezenne's observations show that the coagulability of avian blood is accelerated in an extraordinary way when, as it flows from the blood-vessel, it comes in contact with the tissues; and working on the same lines I have found that 'Delezenne's phenomenon', if I may so denote it, manifests itself also in a marked manner in connexion with mammalian blood, and that an equally marked acceleration of coagulation is obtained when a trace of lymph is added to the blood, showing that admixture with lymph is probably here the operative factor.¹ It is therefore conceivable that this factor which contributes to the thrombogenic power of the blood may in some way fail to come into operation in the case of the bleeder. But the oozing which persists after the haemorrhage has been arrested by clotting can be even more simply explained. Since the wound does not become sealed with clot until bleeding has continued for many hours or days, when the volume of red blood-corpuses in the blood has been seriously reduced, and since the clot shrinks more and more as the blood becomes impoverished in corpuses, until in extreme anaemia it floats as a mere thread in the serum, it is not surprising that in the case of the exsanguine bleeder the clot contracts upon itself in such a way as to reopen the mouths of the cut vessels.

Whatever the explanation, it is clear that the problem of the failure of haemophilic blood to furnish an effective plug for the bleeding vessels must not be allowed to divert attention from the means at our disposal for arresting the haemorrhage by increasing the coagulability of the blood and at the same time diminishing the retractability of the clot.²

¹ *Vide supra*, pp. 88-93.

² *Vide text and illustration, infra*, pp. 159-160.

Problems for Consideration in connexion with the Inheritance of the Haemophilic Diathesis.

The well-known law that the haemorrhagic diathesis is handed down through a female, who does not herself suffer, to her male offspring is strikingly exemplified in the pedigree of the Mampel bleeder stock already referred to.¹ This remarkable family tree, published by Lossen in 1905, covers one hundred years, and embraces five generations with a total of 212 persons.

From this pedigree and the three Family Histories of Bleeders given below, pp. 131 and 132, and 136 and 137, we may endeavour to elucidate certain further points in connexion with the law of haemophilic inheritance. The following questions may with advantage be asked: (a) Does every female who comes of a bleeder stock transmit the diathesis to her offspring, and do mothers who transmit the diathesis present a different blood-picture when compared with the mothers who do not transmit this diathesis? (b) Does a transmitting mother convey the diathesis in an overt form to all or to some only of her sons, and does she transmit the inheritance in a 'recessive' form to all or to some only of her daughters? (c) Do the males who inherit the bleeder diathesis transmit the disease to their descendants, and do the males who do not show any sign of the disease hand it down? (d) Have the characters of the blood of the male who mates with a female of bleeder stock any bearing on the transmission of the diathesis, and apart from a bleeder heredity can the disease arise *de novo* in the offspring of a male and female who have a predisposition to bleeding? These questions will now be considered seriatim.

(a) *Is the haemorrhagic diathesis transmitted by every mother who comes of bleeder stock?*—Analysis of the pedigree of the Mampel bleeder stock shows that the haemorrhagic diathesis was there transmitted by 11 out of a total of 16 women of bleeder stock who became mothers of male children.

In the Tables and Family Histories here set out there were in the first generation, reckoned in the ascending line from the bleeder boys, 3 out of 3 mothers transmitted the diathesis to their sons. In the previous generation, if the records can be trusted, only 1 of the 3 mothers transmitted the diathesis. In Family History 2, again going up in an ascending line from the bleeders, 2 out of 3, and in the foregoing generation 3 out of 3 mothers of sons transmitted the diathesis. Adding all these together we find that 20 out of 28 mothers of sons transmitted the diathesis. Whether the mothers who transmit the diathesis differ in their blood-pictures from the mothers who do not transmit is a question upon which we are still very ill-informed.

(b) *Does a transmitting mother transmit the bleeder diathesis to all or to some only of her sons?*—In relation to this question we find that in the Mampel stock only 37 out of 82 sons of mothers who transmitted the haemophilic diathesis were bleeders. In the first of the Family Histories here recorded we find that in the present generation of 5 boys all are bleeders, and that in the next older there were 5 males all bleeders. In Family History 2 we have, in the youngest generation among the offspring of the mothers who transmitted the disease, 4 boys, of whom 2 inherited the disease. In the previous generation we have in one family 6 out of 7 sons bleeders,

¹ *Deutsche Ztschr. f. Chir.*, 1905, lxxvi, 1.

in another family 2 out of 2 sons bleeders, and in the third family 1 out of 4 sons a bleeder. In Family History 3, out of 3 sons 2 were bleeders. By adding together the figures relating to these three bleeder stocks we find that 24 out of 31 sons were bleeders, as compared with 37 out of 82 sons in the Mampel bleeder stock.

(c) *Is the haemophilic diathesis transmitted through the male?*—The Mampel stock contains seven instances of (male) bleeders marrying and producing male offspring, one of whom was a bleeder. In an eighth instance a bleeder married his first cousin of bleeder stock and had a bleeder son. In estimating the weight of this evidence it is, however, important to note that a scrutiny of the clinical details set forth by Lossen shows that 1 only out of the 8 bleeders in the Mampel stock could be classed as a severe bleeder.

Turning now again to bleeder stocks which form the subjects of Tables on pp. 131 and 132 (*supra*) and of the Family Histories on pp. 138 and 139 (*infra*), Family History 1 shows an instance of a bleeder transmitting a bleeding diathesis to one of his daughters, and Family History 2 an instance of a woman who had, in addition to a bleeder son, one who was not a bleeder. The inference from the data would therefore appear to be—and here as elsewhere it is probably advisable to discard incompletely reported cases—that the bleeding diathesis is seldom inherited through the male, even when he is himself a bleeder. In other words, that the influence exerted upon the blood of the offspring by the father is quite subordinate to that exerted by the mother. It would be extremely interesting to determine whether this inference also holds good with respect to the inheritance of chilblains, urticaria, and physiological albuminuria, all of which are, as I have shown, correlated with a condition of diminished coagulability of the blood.¹

(d) *Do the blood-characters of the male influence the transmission of the bleeding diathesis to the offspring, and does the disease arise de novo from the conjunction of male and female when both have a predisposition to bleeding?*—The possibility thus formulated as a question is suggested by the following data. In Family History 1, 3 out of 3 male ascendants examined (i.e. the fathers of two of the families of bleeders, and the maternal grandfather common to these two families) gave in each case a strikingly subnormal count of polymorphonuclear leucocytes; in Family History 2 a similar subnormal count of polymorphonuclear leucocytes was obtained neither in the father of the bleeder boy nor in his maternal grandfather; and in Family History 3 exactly the same holds good in connexion with the father of the bleeder family. These data obviously suggest that the influence of the father, even though it would seem to be quite subordinate to that of the mother, may sometimes be a factor of moment in connexion with the inheritance of haemophilia. Continuing this line of thought we naturally inquire whether in the absence of a definitely haemophilic ancestry the disease may not originate *de novo* from the conjunction of a male and female both predisposed to bleeding, whose blood has in each case the characters associated with the haemophilic predisposition. Cases of haemophilia without any haemophilic ancestry are not rare; 4 have come under my personal observation. In the case of two of these families—and in each there had been one case of fatal haemophilic bleeding, with evidence of haemophilia in other members—I investi-

¹ *Vide supra*, pp. 66–68.

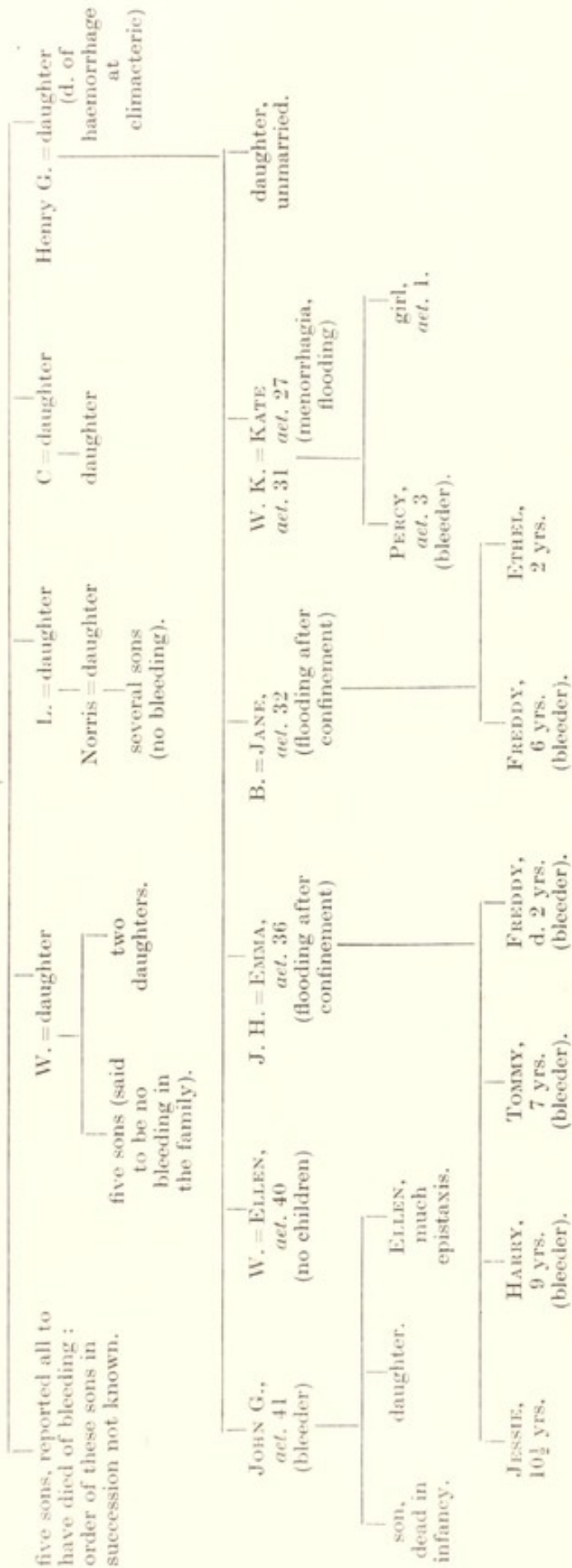
gated, in addition to the surviving bleeder members of the family, the bloods of the father, mother, sisters and brothers. In the one family, that of a tanner whose eldest son, a guardsman, died of bleeding after the extraction of a tooth, the blood of the father gave a total leucocytic count of only 3100 with 1700 polymorphonuclear leucocytes, whilst the mother, who suffered from menorrhagia, gave a leucocytic count of 7200 with only 3900 polymorphonuclear leucocytes. In the other family, that of a London policeman who had lost a son from bleeding at the age of eight and who had another bleeder son, the father had a leucocyte count of 5800 and the mother, who suffered from menorrhagia, one of 5400 with 3800 polymorphonuclear leucocytes.

Question as to the Practical and Theoretical Consequences which may be deduced from the Evidence reviewed above.—The data considered above have a direct practical bearing on the question of the restrictions the male and female members of a bleeder stock might with advantage impose upon themselves as regards marriage, or rather reproduction. It is obvious that in the absence of any proof to the contrary, every woman of bleeder stock should be regarded as a potential mother of bleeders. In future, however, it may be possible by examining the blood to distinguish between the women likely to become mothers of bleeders and those who would be likely to bear healthy children. As it is probable that the male parent exerts some influence on the disposition of the offspring with respect to bleeding, it would further be desirable, if it were practicable, that women of bleeder stock should mate only with men whose blood is free from any sign of bleeder predisposition. As regards men of bleeder stock, the history of the Mampel family would suggest that male bleeders do not transmit the disease. But this history cannot be regarded as conclusively settling what would happen in the case of a conspicuous bleeder, since only 1 out of the 8 male bleeders in that stock who married and had male offspring could be classified as such. It would, probably, be a counsel of perfection that in the case of both the partners in a marriage, the male no less than the female, the blood should be irreproachable as regards its coagulability and its leucocytic content.

Passing from matters of direct practical importance to those of speculative interest, we may now inquire whether these data do or do not support the Mendelian theory of inheritance, and whether they throw any light on the general question of genetics. In connexion with the first question, it may be pointed out that whilst the Mendelian terms 'recessive' and 'dominant' may be convenient formulas for expressing the rule that in haemophilic stocks the males become bleeders and the females transmit the disease, it is not by any means certain that the particular properties of the blood which determine the tendency to bleed are really, in the female, recessive in the sense of being present only in the germ-cells. Inasmuch as the females of bleeder stocks appear to have the same character of blood as their bleeder descendants, it would seem that the disease in females was not really recessive, but only masked. Again the figures with respect to the inheritance of the haemophilic diathesis show that it is largely in excess of the Mendelian expectation. We have seen that in the offspring there is among males a large excess of bleeders over non-bleeders, and among the females a large excess of mothers who transmit, over those who do not transmit the disorder.

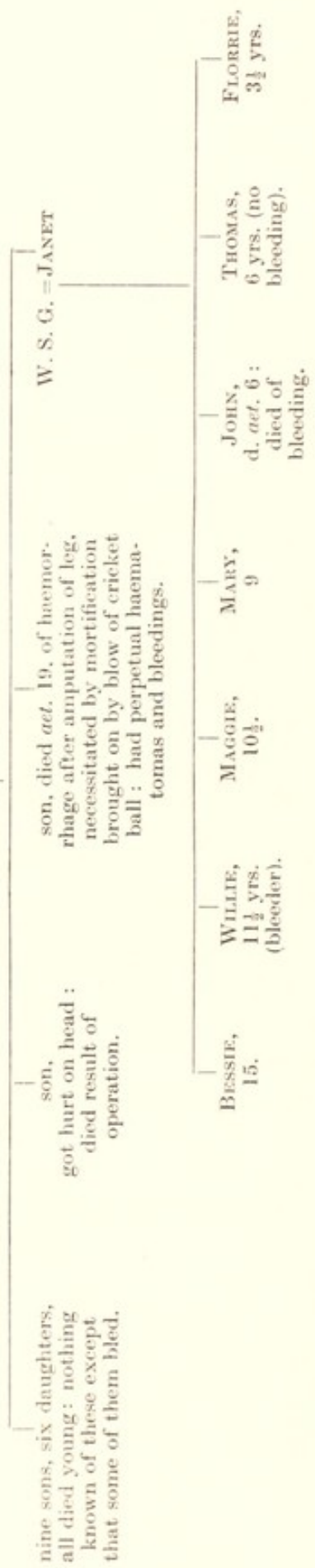
FAMILY HISTORY OF BLEEDER STOCK, No. 1

Mrs. H.



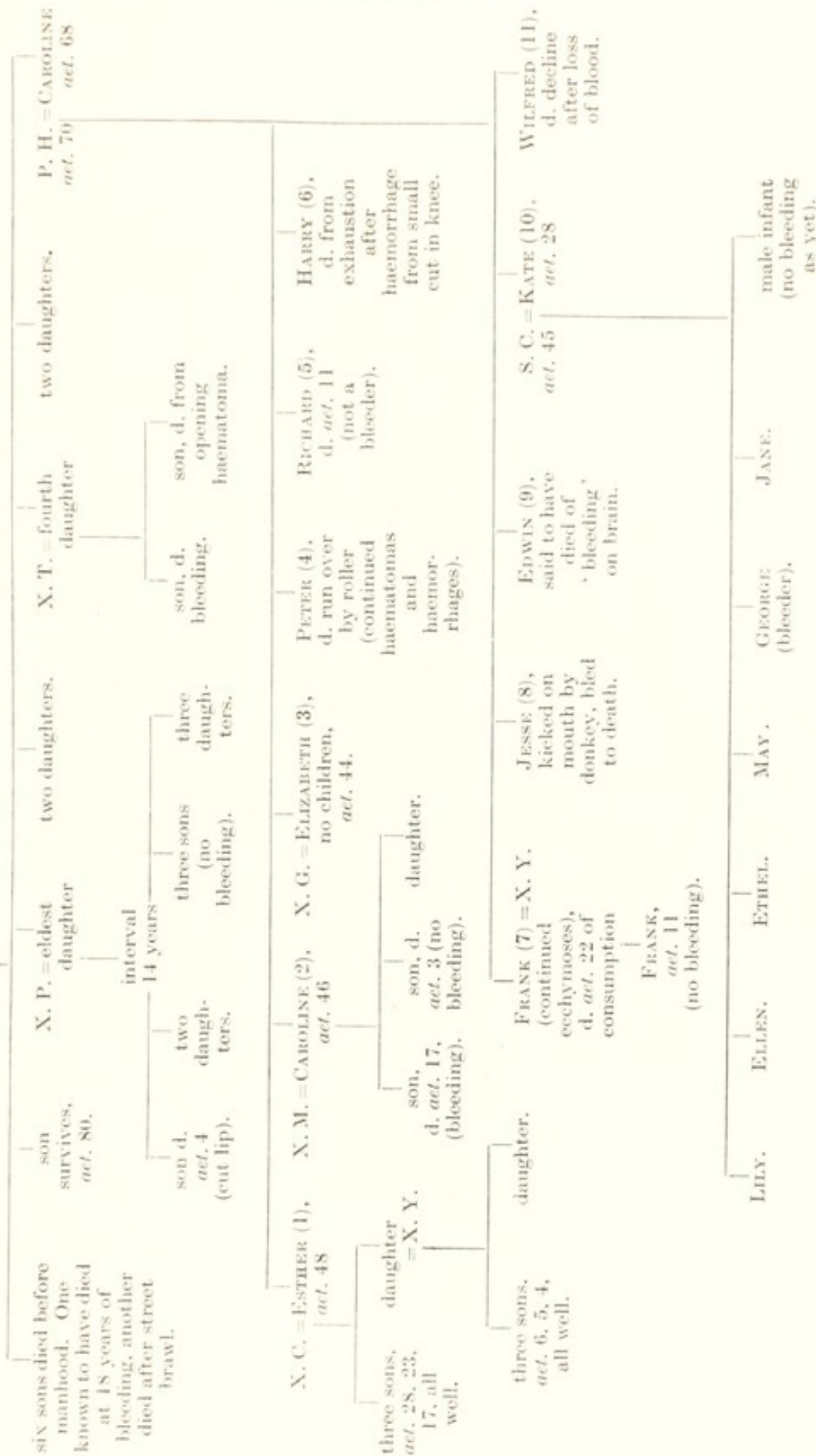
FAMILY HISTORY OF BLEEDER STOCK No. 3

Mrs. McN.



FAMILY HISTORY OF BLEEDER STOCK No. 2

X. C. = Y. Z. (one of her cousins known to have died of bleeding)



Treatment.

Had not modern medicine been evolved, as it has been almost exclusively, by the method of random trial and empiricism, or had it disengaged itself from these, I might have stated as a self-evident proposition that no effective system of therapeutics could be expected in any branch of medicine except as the outcome of experimental research or of personal familiarity with, as distinguished from a purely literary study of, the results of such research. And in particular I might have laid it down as an axiom that the treatment of haemophilia must be based on a study of the physiology of the blood and blood-coagulation as a whole, supplemented by experimental research, undertaken upon bleeders. As it is, I find in the literature of haemophilia, instead of an assertion of this principle, much random trial, many purely empirical judgments, only very little evidence of a personal study of the physiology of the coagulation of the blood, much neglect of the generalisations already arrived at, much rediscovery of, and much insistence on details which are covered by those generalisations. All the more must I reiterate that the treatment of haemophilia can only be successfully attacked from the standpoint of the physiological laboratory.

The three issues to be considered in connexion with the treatment of haemophilia are: (1) Are there any means of amending the congenital defect which lies at the root of the haemophilic diathesis? (2) Failing these, are there any other therapeutic agents which when given internally will restrain the haemorrhages and serous haemorrhages of the bleeder, and which can be given as a prophylactic measure to patients before surgical operations? (3) Are there any therapeutic agents which when applied locally to the bleeding point will arrest haemophilic haemorrhage?

Under (1) two suggestions will be briefly referred to. The first of these is that it might be worth while to administer ovarian extract to male bleeders with a view to endowing them with the mysterious physiological advantages which, in bleeder families, attach to the female sex. As one who toyed with this speculation long before encountering it in print I may perhaps insist that, although such ideas may have a certain fascination for the intellect, the practical man would do well to treat them, until they have been controlled by serious experimental work, as mere will-o'-the-wisps.

The second suggestion is that nucleo-albumin, its derivative nuclein, or substances which contain nucleo-albumin—and these last are available in the form of thymus tabloids, and various preparations of yeast—should be administered to bleeders with a view to remedying directly that deficiency of leucocytes, and indirectly the associated defective coagulability, which characterise the blood of the bleeder. This suggestion, whatever its value may prove to be, is not without some experimental support. I have satisfied myself both that the number of leucocytes can be increased in haemophilia by the ingestion of nuclein¹ and thymus tabloids, and that the tendency both to serous haemorrhages and actual haemorrhages is often held in check by the administration of these remedies.

(2) Passing now to consider whether there are any other available therapeutic agents which can be employed to increase the coagulability of the blood, it will

¹ *Brit. Med. Journ.*, 1893, ii, 223.

perhaps be advantageous to retrace the road originally followed in the search for such remedies. We may consider here (*a*) the administration of the salts of calcium and magnesium, (*b*) the administration of CO_2 , and (*c*) the inoculation of serum.

(2) As soon as Arthus and Pagès proved that the coagulability of the blood could be abolished by decalcification and that its coagulability could be restored by the addition of calcium salts, it became obvious that the next step for the physician was to investigate the effects of making graduated additions of calcium salts to blood *in vitro*, to study upon animals the effect of the internal administration of calcium salts upon the rapidity of coagulation, and finally, after devising a clinical method of measuring the coagulation time of human blood, to investigate the effect of the administration of calcium salts to the normal man and to the haemophilic. Confining myself here to what has direct relation to haemophilia, I extract from my published papers and from my notebooks the following illustrations of the effects produced by the administration of calcium chloride to bleeders :

Serial	Patient's initials	Age	Date	Treatment	Coagulation time at 18.5° C.
1	S. W.	11	June 1, 1893	Nil. 1 gramme CaCl_2 cryst. at bedtime	10½ minutes
			June 2, 1893	1 gramme CaCl_2 cryst. t.i.d.	5½ „
			June 3, 1893	1 gramme CaCl_2 cryst. b.i.d.	5½ „
			June 5, 1893	1 gramme CaCl_2 cryst. b.i.d.	Over 1 hour
2	H. H.	9	April 13, 1894	Nil. 2 grammes CaCl_2 cryst. at bedtime	54 minutes
			April 14, 1894	2 grammes CaCl_2 cryst. on rising	27 „
			April 15, 1894	2 grammes CaCl_2 cryst. on rising	13 „
3	„	„	Sept. 28, 1894	Nil. 0.6 gramme CaCl_2 cryst. at bedtime	14 „
			Sept. 29, 1894	Two doses of 0.6 grammes CaCl_2 cryst. at bedtime	6¾ „
4	T. H.	7	Sept. 30, 1894	CaCl ₂ cryst. at bedtime	25 „
			April 14, 1894	Nil. 2 grammes CaCl_2 cryst. at bedtime	6¾ „
5	„	„	April 15, 1894	2 grammes CaCl_2 cryst. this morning	4 „
			Sept. 28, 1894	Nil.	9¼ „
6	N. R.	26	Sept. 29, 1894	Two doses of 0.6 gramme CaCl_2 since Sept. 28	5¾ „
			Mar. 22, 1894	Nil. 2 grammes CaCl_2 cryst. at bedtime	7½ „
			Mar. 23, 1894	2 grammes CaCl_2 cryst.	5¾ „

These observations, which are in complete accordance with many others made on normal blood, show that the coagulability of the blood of the bleeder can be increased by the administration of calcium salts. These experimental results are in harmony with the fact that calcium salts have approved themselves to be a mainstay in many cases of haemophilia, both in checking serous haemorrhage and

in rendering the blood coagulable and so arresting actual haemorrhage. Calcium salts, however, are not invariably helpful. Nor indeed could they be. For we have in calcium salts not a directly fibrinoplastic element, but only a chemical agent which acts upon the fibrinoplastic elements of the plasma in such a way as both to promote coagulation and to increase the viscosity of the blood. Moreover, these effects will be exerted (*a*) only when the drug is absorbed, (*b*) only when the patient has not already in his blood the optimum of calcium salts, and (*c*) only so long as the blood is not overloaded with calcium salts. A few words may be devoted to each of these questions. Estimations of the coagulation time, and of the combined calcium and magnesium content of the blood before and after the administration of calcium salts, show that in some normal persons calcium salts are only very indifferently absorbed.¹ This condition is also present in a bleeder whom I have had under observation for years for recurrent haemorrhages from the gums—haemorrhages which have often lasted for weeks, leaving the patient completely blanched. The characteristic features of this bleeder's case are that his haemorrhage is confined to the gums, that he has never suffered from articular swellings, that no heredity can be traced, and that his blood does not show any conspicuous defect of coagulability—although he suffers from a deficiency in 'thrombogenic' power which seems to depend on a deficiency of fibrinogen in his plasma. The following observations refer to this patient :

Observation 1. H. G., a man suffering from haemophilia. February 8, 3 p.m. : Coagulation time, 2 minutes 15 seconds. 3.10 p.m. : 4 grammes of calcium lactate were given by the mouth. 3.50 p.m. : Coagulation time, 2 minutes 15 seconds. No effect was exerted upon the haemorrhage.

Observation 2. February 17, 2.30 p.m. : Coagulation time, 2 minutes 50 seconds. 2.40 p.m. : 4 grammes of calcium lactate were administered. 3.25 p.m. : Coagulation time, 2 minutes 45 seconds. No effect was exerted upon the haemorrhage.

Observation 3. February 24, 4 p.m. : Coagulation time, 2 minutes 50 seconds. 4.10 p.m. : Subcutaneous injection of 0.5 gramme of calcium lactate in 10 c.c. of water. 4.55 p.m. : Coagulation time, 2 minutes 10 seconds. No marked effect was exerted on the haemorrhage.

Observation 4. March 3, 2.10 p.m. : Coagulation time, 2 minutes 5 seconds. There was continuous haemorrhage from the gums. 2.30 p.m. : Hypodermic injection of 0.6 gramme of calcium lactate. 2.45 p.m. : Haemorrhage from the gums has ceased. 3.30 p.m. : Coagulation time, 50 seconds. March 16 : Coagulation time, 2 minutes 10 seconds. (The coagulation times here were measured at 37° C.)

When the power of absorbing calcium salts is so defective as it was in this patient, no result can be anticipated from moderate doses, and at the most we can expect but slight results from large doses. But in such cases, as I have shown in conjunction with Dr. Paramore,² salts of magnesium (the carbonate and lactate were employed), may be well absorbed, and may have quite as good an effect as the calcium salts, as was shown in a striking fashion by the case of the bleeder just mentioned. His haemorrhages, which previously were never controlled by calcium salts, are now almost invariably checked by the magnesium salts. In order to

¹ Delezenne, *Arch. de physiol. norm. et path.*, 1897, s. 5, ix, 646.

² *Vide supra*, pp. 101 et seq.

guard against possible failure due to deficient absorption of calcium salts, it would, therefore, be advisable to prescribe as a routine measure in every case of haemophilic haemorrhage a mixture of calcium and magnesium salts.

It may be here incidentally noted that the subcutaneous inoculation of calcium chloride is quite inadmissible. I have seen extensive sloughing follow upon its subcutaneous injection into a dog, and know of a case in which it was directly tried on a bleeder with a like result. The injection of calcium lactate on man must also be very cautiously resorted to, for, although the lactate has no escharotic properties, very severe pain may follow upon its injection in too concentrated a form.

We must now consider the risk of overloading the blood with calcium salts. It is to be noted here that a retardation of coagulation similar to that which is observed *in vitro*¹ when an excess of calcium salts is added to the blood also appears *in vivo* after excessive doses of calcium (*vide* Table, p. 141, Case I). Where, as in haemophilic haemorrhage, a question of life or death may hang in the balance, it would therefore be well before persisting in the administration of large doses of calcium and magnesium salts, first to determine upon the patient's blood *in vitro* whether an addition of calcium salts will accelerate or retard the coagulation time. In connexion with Experiment 1 in the Table on p. 141, it had been determined before administering the calcium chloride that the coagulation time of the blood drawn from the finger was diminished by half by additions of 0·2 to 0·1 per cent. of calcium chloride to the blood *in vitro*.

Conclusions with respect to Administration and Dosage of Calcium and Magnesium Salts.—When it has been clearly realised that it is impossible in any particular case to tell, apart from experiment, either that magnesium and calcium will be absorbed from the alimentary canal, or that the patient's blood may not already contain the optimum of calcium and magnesium, it becomes obvious that in connexion with these drugs no absolute rule can be laid down as to dosage, the interspacing of the doses, nor as to what number of doses should be administered. The following, however, may serve as general indications. Where, as in the presence of active haemorrhage, it is desired to obtain the most rapid and marked effect upon blood-coagulation, an initial dose of 1 gramme or somewhat less of calcium chloride cryst. or lactate, or of a mixture of magnesium carbonate or lactate with calcium chloride or lactate, may be administered to young children, and fully 4 grammes to an adult. In order to keep up the effect of the initial dose, 2 grammes daily may be administered to adults, and proportionately smaller doses to children.

(b) *Administration of CO₂.*—As in the case of the administration of calcium salts, in order to increase the coagulability of the blood, so also here with regard to the administration of CO₂ with the same object, the rationale of the proposed treatment will be most clearly brought out by explaining the origin of the suggestion. In researches² undertaken in connexion with the study of intravascular coagulation, which is obtained when a solution of nucleo-albumin (Wooldridge's tissue-fibrinogen) is injected into the circulating blood, I found that it was possible to increase or diminish the amount of intravascular thrombosis by increasing or diminishing the venosity of the blood in the general circulation, and that thrombosis could be in-

¹ *Journ. Path. and Bacteriol.*, 1893, i, 434.

² *Vide supra*, pp. 2-9.

duced in any particular vascular area by increasing the venosity of the blood there. I suggested in connexion with those results that the accumulation of CO_2 in the blood would probably prove to be the casual factor.

The hypothesis that an accumulation of CO_2 in the blood would act in the direction of increasing the coagulability of the blood was afterwards examined by me in a research which was published in March, 1894.¹ I showed there—and these results tallied with those obtained by Mathieu and Urbain with other methods—that when animals are made to breathe out of a reservoir containing a mixture of 80 per cent. of CO_2 and 20 per cent. of O_2 , a very notable increase in the coagulability of the blood is induced.

The next and obvious step was to turn these physiological results to therapeutic uses. In addition to utilising them in the treatment of aneurysm and epistaxis I made my first trial of CO_2 ² in haemophilic haemorrhage on the bleeder boy G. C., whose family history is set out on page 138. The details of the case and the result of the administration of the CO_2 are described in the following extract from my paper :

The child is at present nearly four years old, and has suffered from an almost continuous succession of subcutaneous seromas. In September, 1893, haemorrhage set in as a result of a fall upon the forehead, which left a scar which was visible for months after. The haemorrhage was treated by ordinary palliative measures, and finally ceased after lasting some six weeks. The blood is said to have shown no tendency whatever to clot, except when the wound had been tightly bandaged up for several days at a time. The coagulation time of this child (taken at temperatures ranging between 42° and 57° F.) oscillated between 45 minutes and 1 hour. On February 2, 1894, the child had another fall against a chair, and hurt the fraenum of his upper lip, and bled a little at the time. Haemorrhage came on profusely at night, and his pillow was soaked with blood and a great deal of blood was swallowed. When this was discovered the parents, according to directions previously left by me, administered 0.6 gramme of calcium chloride, and they state that the blood, which had previously shown no sign whatever of clotting, began to clot firmly in two or three hours after the administration of the lime. Bleeding recurred the next day, and in the evening, after the child had fallen asleep, his mouth was found quite filled with blood-clot. On February 4, 5 and 6, bleeding recurred at intervals (probably owing to the frequent dislodgment of the clot). Calcium chloride had been administered all this time in 0.6 gramme doses twice daily. The child was seen by me on February 6, and I found on the fraenum of the upper lip a scratch about one-eighth of an inch long, covered over by coagulated blood. There was no oozing from the wound. A drop of blood was drawn off from the child's finger, and coagulation time (determined at 37° C.) was found to be 2 minutes 25 seconds, and the addition of calcium chloride to the extravascular blood was found not to effect any acceleration of coagulation time. The calcium chloride already taken appears, therefore, to have done all that could have been expected of it, and yet there had been frequent recurrences of the haemorrhage when the clot became dislodged. In view of these facts I determined to administer

¹ *Vide supra*, pp. 14–25.

² *Vide supra*, pp. 31–32.

carbonic acid gas in order still further to increase blood-coagulability. I hoped in this way to cause the blood to clot, not only on the surface of the wound, but also some distance up the lumina of the ruptured vessels. Guided by these considerations I inserted a soft india-rubber tube into the child's mouth, and connected it with a Kipp's gas apparatus which I had brought with me. I determined the coagulation time of the child's blood while the carbonic acid was being administered to him, and found that it was accelerated to 1 minute 40 seconds (determined at 37° C.).

The child was not seen by me again till February 12, when I received another urgent summons saying that the haemorrhage, which had ceased for 24 hours after the inhalation of the carbonic acid, had broken out afresh and had continued ever since. Calcium chloride had been administered twice daily in 0.6 gramme doses from the 7th to the 11th, when the child vomited and refused to take it. On arrival I found the child absolutely blanched, and tetchy to a painful degree. Determinations of coagulability were, therefore, out of the question. Blood was found to be oozing from the fraenum of the upper lip, and there was a trace, but only a trace, of clot around the wound. Carbonic acid was immediately administered in the same manner as before, and under its influence bleeding broke out copiously. When, however, the child came more under the influence of the gas, and his struggles ceased, the blood clotted instantaneously, so that even the film of blood which was drawn out between the upper and lower lips when the mouth was opened instantly congealed into a clot. I proceeded to remove the large clot of blood which had formed round the gum, and found it to be of extraordinary firm texture. A small clot instantly reformed round the wound, the haemorrhage ceased, and the child fell asleep. The administration of the gas was continued for half an hour. The gasogene was then recharged and was left under the parents' charge. Haemorrhage recurred two or three times in the course of the night, when the clots became dislodged, but clotting is reported to have taken place as soon as the inhalation of the gas was renewed. After this there was no further return of haemorrhage, and convalescence took place."

Suggestions with regard to the Administration of CO₂.—A Kipp's apparatus filled in with marble and hydrochloric acid, and fitted with a wash-bottle and a length of rubber tubing to serve as a delivery tube, is all that is necessary for the production and administration of CO₂. In default of a Kipp's apparatus a gasogene can be extemporised by knocking a hole in the bottom of a Winchester quart bottle, filling it with pieces of chalk, stretching muslin over the hole to serve as a false bottom and then lowering the bottle into a large jug containing vinegar or any other weak acid, after fitting into the neck a cork perforated by a glass tube with a length of rubber tubing attached. The output of gas can then be regulated by compressing the rubber tube. In administering the gas care must be taken to deliver it only in a small stream so as to avoid the acceleration and deepening of the respiratory movements which is produced by excess of CO₂.

(c) *Inoculation with Serum.*—P. Emile Weil suggested injection of serum with the object of increasing the coagulability of the blood in haemophilia. In the course of investigations on a non-hereditary, and in many respects a very atypical, bleeder,

he recounts that the addition of normal serum made the blood clot more rapidly *in vitro*. (This result is obtained only if the serum is quite fresh.) In order to determine whether this same effect could be obtained by an intravascular injection of serum, Weil injected his patient on three successive occasions with serum; and on withdrawing blood from a vein at intervals of several days he found that his expectations were realised. These observations are interesting, and Weil's suggestion has since been repeatedly acted upon. But I do not see in his published results—for the shortest interval between the injection of the serum and his subsequent examination of the blood was 48 hours—any proof that an injection of serum will effect that rapid increase in the coagulability of the blood which would be desirable in haemophilic haemorrhage.

This point can only be settled by clinical observations undertaken in conjunction with estimations of the coagulation time of the blood. Until such data become available Weil's work may be dismissed as work which completely lacks scientific basis.

(3) *Is there any Local Treatment for the Arrest of Haemophilic Haemorrhage?*—Since direct surgical means for the arrest of haemorrhage, such as the use of ligatures and compresses, are in haemophilic haemorrhage nearly always inapplicable, ineffective, or dangerous, and since ergot and adrenalin are of doubtful or temporary utility only, the question of the arrest of haemorrhage by local treatment is narrowed down to a discussion of what can be done by styptic applications. I must now revert to the distinction, which I emphasised many years ago,¹ between an *escharotic* and a *physiological styptic*. An escharotic styptic, like the red-hot iron of the Middle Ages, produces its effect by charring the tissues in the neighbourhood of the bleeding point and by forming a plug out of the eschar. This form of styptic is an obvious anachronism in any civilised system of therapeutics, and, it may be noted, is specially unsuitable in haemophilia, for in this disease the falling off of the eschar would generally be followed by an outbreak of bleeding from a larger area of denuded surface.

Physiological Styptics, which exert their effect by accelerating the coagulation of the blood upon the bleeding wound, are, in contrast to escharotic styptics, quite painless in application, and are free from the risks which attach to the use of escharotic styptics in bleeders. The only risk which comes into consideration in connexion with physiological styptics is the liability of the clot to be brushed off or loosened in such a way as to furnish opportunity for fresh haemorrhage.

Preparation of Physiological Styptics and Data with regard to their Potency.—So far as I know, the idea of turning to account, for the arrest of haemorrhage, the knowledge which had been won of the process of blood-coagulation occurred first to Wooldridge. I remember his meditating, shortly before his premature death, the problem of injecting a solution of his 'tissue-fibrinogens' into an aneurysm which was pointing through the thoracic wall and was threatening to give way. Whilst this particular application of a physiological styptic holds out, as I think, very little promise, Wooldridge's suggestion is, if I mistake not, destined to bear fruit in many other directions.

¹ *Brit. Med. Journ.*, 1891, ii, 1306; *The Lancet*, 1893, i, 435.

When I first set about making a physiological styptic (this was in 1891¹), I used a watery extract of fibrin (such extracts were, and perhaps still are, spoken of as solutions of fibrin ferment), reinforced by 1 per cent. of calcium chloride. This was, except in respect in the calcium chloride, an example of regressive invention, for, in contrast with that which Wooldridge had proposed to use, this styptic contained no fibrinoplastic element. This defect, however, was soon afterwards rectified by substituting a much more potent extract of thymus gland for the watery extract of fibrin.² The styptic thus obtained is so powerful that it can arrest the haemorrhage from the cut femoral artery of a dog, provided that the cut artery is compressed for a minute or two to allow of the consolidation of the clot. This styptic is capable of rendering conspicuous services in connexion with haemophilic blood. By its means I have formed round the cut finger of a bleeder boy a clot so dense and hard as to resemble a ball of clay which a gardener binds round a branch when he is fixing a graft in position. As this preparation acts both by accelerating the rate of blood-coagulation, and by increasing the density of the clot, it is, I believe, beyond all comparison the most potent physiological styptic at present available.

Recently the idea of adding fibrinoplastic elements to the blood with a view to checking haemorrhage has suggested itself also to medical practitioners on the Continent. It has been proposed that human blood should be applied to the wound in haemophilic haemorrhage and should be allowed to clot there. It has also been proposed—and this proposal appears to have been made first by Weil—that serum should be applied to the wound. I have no personal experience of these methods, but I can hardly imagine any one who has had experience of the physiological styptic described above accepting them as substitutes for it. It may perhaps be well to subjoin some details as to the preparation of this physiological styptic.

The Preparation of the Physiological Styptic.—Take a thymus gland (known to butchers in England as the chest-sweetbread) of a calf or lamb, carefully remove all the fat and comminute it on a chopping board, or pass it through a sausage-machine, then place it in a jar and cover it over with a 0.5 to 1.0 per cent. saline solution to which a mere trace of sodium carbonate has been added, using about 10 parts of the solution to 1 part of comminuted gland substance. If time presses, filter off immediately through fine calico and complete by adding 0.25 per cent. or less of calcium chloride (weighed as crystals) and 1 per cent. of carbolic acid. When time does not press, the extraction may be continued for 12 to 24 hours, the 1 per cent. of carbolic acid being added *ab initio*, the calcium being introduced as before, only after filtering. If a thymus gland cannot be procured, a testis will serve the purpose equally well, but a pancreas should not be used. When neither a thymus gland nor a testis is available, an efficient styptic can be made from the epithelial cells of the gastric mucous membrane.

Suggestions with regard to the Employment of Physiological Styptics.—As has already been pointed out, incidentally, there is the drawback in connexion with all physiological styptics that the clot thus formed is liable to be brushed away or loosened, with the result that bleeding breaks out afresh. In other words, invaluable as are physiological styptics, the control of haemorrhage thus obtained is only a

¹ *Brit. Med. Journ.*, 1891, ii, 1306.

² *The Lancet*, 1893, i, 435.

temporary arrest. What is wanted is a clot extending into the lumina of the open vessels. With this object in view it is always advisable to supplement the action of the styptic by measures which increase the coagulability of the intravascular blood.

Another important point is that even with the most potent physiological styptic we cannot hope to obtain the instantaneous arrest of haemorrhage which is provided by an escharotic styptic. It follows that if the styptic be merely poured upon the bleeding point without being kept for some time in contact with it, the blood will clot at a distance from the bleeding orifice, and the wound will remain free from clot, with the result that the bleeding will continue. We must, therefore, always plug the wound with wool or lint soaked in the styptic and apply pressure.

Thirdly, since an excess of calcium salts diminishes the coagulability of the blood it is advisable, when using a styptic which contains 0.5 per cent. of CaCl_2 , to regulate the quantity of styptic, using it in the proportion of 1 part of the styptic to about 2 to 3 parts of blood.

Summary of the Methods of Treatment available for the Control of Haemophilic Haemorrhage.

We have thus seen that, excluding from consideration the method of inoculating serum until it has been scientifically tested, there are four methods which may be employed to control haemophilic haemorrhage; it is, indeed, often necessary to call all four to our aid. Tabloids of thymus gland (B. W. & Co., 5 grains each), administered up to 20 a day will supply the blood with the nucleo-albuminous element which it probably needs. A mixture of calcium and magnesium salts, administered in appropriate doses, will increase the coagulability of the intravascular blood and will favour thrombosis inside the open blood-vessels. And carbonic acid will serve to reinforce this action. The physiological styptic described above applied locally in the manner indicated will at least temporarily obstruct the mouths of the blood-vessels. With these methods at disposal all cases of haemophilic haemorrhage should prove controllable.

EXCERPTS FROM THE AUTHOR'S 'TECHNIQUE OF THE TEAT AND CAPILLARY TUBE'¹

EXCERPT I.—ON THE PHYSIOLOGICAL SIGNIFICANCE OF THE ANTI-TRYPTIC FUNCTION OF THE BLOOD; AND ON THE PROCEDURES FOR OBTAINING AN ANTI-TRYPTIC WOUND EXUDATE, AND ON THOSE FOR SETTING FREE, WHERE TRYPTIC DIGESTION IS WANTED, TRYPSIN FROM PUS

(1) *Introductory*—(2) *The anti-tryptic power of the blood as an element of the protective machinery of infection*—(3) *The anti-tryptic power of the blood as a protection against tryptic attack upon the blood-fluids and digestive erosion of the tissues*—(4) *Experiment showing that trypsin is inactivated by serum*—(5) *Practical application of this in the treatment of digestive erosion*—(6) *Experiment showing that serophytic microbes implanted into blood overcome its anti-tryptic power by elaborating tryptic ferments*—(7) *Experimental observations showing that an addition of trypsin reduces the coagulability, and also the bactericidal and opsonic power, of the blood, at the same time converting the blood-fluids into a medium which grows non-serophytic microbes freely and also serophytic microbes much more freely than the normal blood*—(8) *Verification of the above in vitro observations by experiments carried out on wounds*—(9) *'Lymph leech' experiment*—(10) *Practical application of the information obtained from the lymph leech experiment, and procedure to be employed for restricting microbial growth in wound discharges*—(11) *Procedure for setting free additional trypsin in wounds and other foci of infection, and so promoting the digestive separation of sloughs and the resolution of inflammatory products.*

(1) *Introductory.*—The anti-tryptic or trypto-tropic—or, if we would be perfectly precise, diastaso-tropic—element in the blood-fluids has the function of neutralising ferments derived from leucocytes, and microbes, and digestive glands.

By so doing it renders two important services to the organism: (1) It hinders bacterial growth in the blood-fluids, and (2) it protects the blood and the tissues against digestive erosion.

(2) *The anti-tryptic power of the blood as an element of the protective machinery of infection.*—The plasma and lymph would appear to provide no ready-made bacterial pabulum, but only a raw material of native proteins from which such pabulum can be procured. In other terms, bacterial growth in the blood-fluids becomes possible only when the albumens of these fluids have been broken down by digestive action. Before this can be done the anti-tryptic power has, at any rate in the environment of the microbes, to be overpowered.

That condition of things can be brought about by the ferments secreted by the

¹ Wright and Colebrook, *Technique of the Teat and the Capillary Tube*, Second Edition, Constable, London, 1921.

microbes themselves. But it will in many cases be brought about by ferments derived from disintegrating leucocytes.

It will be clear that the necessary tryptic change will, when the general anti-tryptic power is high, with difficulty be effected; and will, when the general anti-tryptic power is low, relatively easily be effected. In other words, the greater the anti-tryptic power of the blood, the more difficult will it be for microbes to establish themselves, or for leucocytic ferments to attack the tissues; and the lower the anti-tryptic power, the more easily will these things happen.

(3) *The anti-tryptic power of the blood as a protection against tryptic attack upon the blood-fluids and digestive erosion of the tissues.*—In the normal man digestive attack on the tissues, in the form of erosion of wound surfaces, abscess cavity formation, the burrowing and tracking of pus, the resolution of inflammatory products, the disintegration of blood clots obtruding the mouths of arteries, the separation of sloughs, and cavitation, manifest themselves only after the setting free of considerable quantities of leucocytic trypsin—such quantities as can overpower the potent anti-tryptic resistance offered by the normal blood. In certain very rare conditions—conditions which are, as was ascertained by our late colleague Dr. Beaton, associated with a general reduction of the anti-tryptic power of the blood—every accumulation of leucocytes is prone to lead to tryptic digestion. Here inoculations of very small quantities of sterilised vaccines, and even of sterilised salt solution, though undertaken with meticulous antiseptic precautions, are followed by abscess formation. Here also every superficial suppuration-producing infection gives rise to excessive digestive erosion—the patients ascribing this to their not having ‘good healing flesh’.

In another category of cases—that in which the anti-tryptic power of the blood is higher than the normal—the digestive effects described above will be restrained or completely arrested.

In pneumonia, the anti-tryptic power of the blood is conspicuously increased. The same holds true also in a number of other bacterial infections—in particular in staphylococcal and streptococcal infections. The anti-tryptic power of the blood is also markedly increased in malignant disease—no doubt here as the result of the septic infection which is an early accompaniment of malignant growth. Further, the anti-tryptic power of the blood is markedly increased in patients suffering from war wounds, the rise being already well marked within forty-eight hours after wounding. The inoculation of bacterial vaccines is followed by a rise in the anti-tryptic power of the blood. Intravenous inoculations of trypsin leave, as Dr. Beaton has found, this power unaltered; while subcutaneous inoculations (working possibly through the agency of the local leucocytic reaction) increase the anti-tryptic power.

Where we have an increase of anti-tryptic power this will generally be of advantage to the organism. It will, on the one hand, restrain microbial invasion, and on the other hand protect the tissues against erosive digestion. For example, in pneumonia it is without doubt the highly anti-tryptic blood which protects the lung, preventing the formation of abscesses and cavitation. But there are also occasions where increased anti-tryptic power may incidentally be of disadvantage. The

digestive separation of sloughs and resolution of inflammatory products may be conspicuously retarded.

The general significance of anti-tryptic power having now been explained, it will be well to illustrate by experiment the points already adverted to together with certain others, and further to indicate some principles of treatment which emerge from the experimental facts.

(4) *Experiment showing that trypsin is inactivated by serum.*—Take a couple of tubules and place in each a little of 0.5 per cent. carbonate of soda solution; and either a shred of well-washed fibrin or a small cube of hard-boiled white of egg. To one of the tubules add a little fresh serum. Now introduce into each tubule a little trypsin, then cap with plasticine, and incubate at 50° C. It will be found that tryptic digestion is completely inhibited in the tubule which has received an addition of serum.

The same holds true also of peptic digestion. In this case, however, it will be found that excess of acid will abolish the anti-fermentative properties of the serum.

(5) *Practical application of this in the treatment of digestive erosion.*—The erosion which calls most loudly for treatment is that aggravated digestive erosion of the skin of the abdomen seen in connexion with duodenal fistula. Here the tryptic pancreatic fluid which is the source of the trouble can be rendered inert by laying upon the wound lint soaked in anti-tryptic serum. Fresh horse serum serves the purpose admirably.

The same procedure—but here, of course, we have the alternative of bringing into therapeutic application the patient's own blood-fluids—can be employed in the treatment of ulcers whose discharges are tryptic.

Minor degrees of tryptic erosion, such as are met with in neglected wounds, are treated simply by washing and redressing.

(6) *Experiment showing that serophytic microbes implanted into blood overcome its anti-tryptic power by elaborating tryptic ferments.*—Fill a little blood from the finger into a paraffined pipette. Then centrifuge and pipette off the plasma, and deposit it in the form of separate drops upon a paraffined slide. Then make, using broth as the diluent, 'a wash-volume dilution' of a staphylococcus or streptococcus broth culture. This done, take a long-stemmed pipette furnished with a teat, inscribe a fiducial mark, and aspirate into it, first, an implanting volume of the diluted culture, and then, separating off by air-bubbles, ten to fifteen volumes of plasma. These, of course, will all speedily clot.

On examining these after forty-eight hours' incubation it will be found that we have now in the lightly implanted, more distal volumes definite cylinders of clot, and in the thickly implanted, proximal volumes only shreds of fibrin. Further, in the distal volume it will be found that each separate colony has, by the tryptic ferment it generates, excavated for itself a distinct cavity in the clot; in the proximal volumes these cavities have coalesced, leaving only remnants of a clot.

Consideration will show that microbes will be furnished with favourable conditions for overcoming the anti-tryptic resistance of the blood-fluids, *first*, when as here they are tied down to one and the same spot in a blood-fluid that remains stationary; *secondly*, when they are confined in narrow crevices in a wound or

'artificial wound' where they have to cope only with a minimal quantity of anti-tryptic fluid; and, *thirdly*, where a number of microbes are, by the fact that they are assembled together, enabled to co-operate.

These inferences are confirmed by the fact that it has been shown by the author, and afterwards, by a number of ingenious experiments by Douglas, Fleming and Colebrook,¹ that we can by taking advantage of these mechanical factors obtain a growth of non-serophytic microbes in serum, and cultures also of all sorts of microbes in definitely uncongenial media.

It is interesting also in this connexion to reflect that the movements of the circulation must, by maintaining the anti-tryptic power everywhere in the vessels at a constant level, largely defeat the tryptic activity of serophytic bacteria, and so minister to protection against infection.

(7) *Experimental observations showing that an addition of trypsin reduces the coagulability, and also the bactericidal and opsonic power, of the blood, at the same time converting the blood-fluids into a medium which grows non-serophytic microbes freely and also serophytic microbes much more freely than the normal blood.*—When we diminish, or nearly neutralise, the anti-tryptic power by an addition of trypsin we produce very profound changes in the blood.

As the anti-tryptic power is gradually neutralised, the coagulability of the blood is progressively diminished and finally abolished. Hand in hand with this, the bactericidal power of the blood for the typhoid bacillus (and probably for other microbes), and also the opsonic power (certainly for some and probably for all microbes), are progressively reduced and finally abolished.

Again, hand in hand with this go also other changes. The blood-fluids, which in their normal condition refuse to grow any but the few species of serophytic microbes, become now an eminently favourable culture medium for all kinds of microbes. Again, the blood-fluids now grow serophytic organisms with quite extraordinary facility. In an experiment of our colleague, Dr. A. Fleming, a 6,000-fold more luxuriant growth of streptococcus was obtained by neutralisation of the anti-tryptic power.²

All these effects are produced not only when trypsin is directly added to the blood, but also when pus is implanted in it, or it is very heavily implanted with trypsin-producing microbes.

(8) *Verification of the above in vitro observations by experiments carried out on wounds.*—Whenever septic discharges are long confined within a wound, and the leucocytes of the pus disintegrate, the originally anti-tryptic exudate becomes tryptic. It now furnishes an eminently favourable culture medium for every species of microbe. And with that the wound becomes definitely foul. The dependence of this corruptive change upon the overpowering of the 'anti-trypsin' of the exudate by trypsin derived from the leucocytes was established by washing out a series of foul wounds with physiological salt solution; applying to the infected wall a 'lymph leech' (i.e. a small cupping apparatus); drawing into this exudate from the deeper

¹ Douglas, Fleming and Colebrook, *The Lancet*, 1917, vol. ii, p. 530. Also *vide* vol. i, pp. 48 and 118 of these *Collected Researches*.

² Fleming, *British Journal of Surgery*, 1919, vol. vii, No. 25.

tissues ; cultivating this exudate in the lymph leech left attached to the wound ; and comparing together this culture with that obtained from the cavity of the wound.

The lymph leech experiment is described in Vol. I, pp. 4-5 and 123, of these *Collected Researches*.

(10) *Procedure for setting free additional trypsin in wounds and other foci of infection, and so promoting the digestive separation of sloughs and the resolution of inflammatory products.*—Consideration will show that the way to effect this will be to break down more leucocytes and set free more trypsin.

(a) We can here disintegrate the leucocytes by a direct application of 5 per cent. salt solution to the leucocyte infiltrated tissue.

(b) We can also break down the leucocytes by inoculating bacterial toxins, superadding these to those already in operation in the focus of infection.

Experiments showing that trypsin can be liberated from pus in this manner, and that artificial sloughs are then loosened from their foundation, are described in Vol. I, pp. 151 and 152, of these *Collected Researches*.

This method was discovered by Koch and was used by him in his original tuberculin inoculations for the purpose of breaking down and getting rid of old tubercular foci. That procedure led, as is well known, to extensive dissemination of tubercle bacilli and to disastrous results. The method has none the less in cautious hands a useful application.

In localised tubercular infection of glands the inoculation of tubercle vaccine may often with advantage be applied for the purpose of breaking down the products of inflammation. And in less dangerous infections the method may be employed with a much freer hand. Large doses of a staphylococcus vaccine may, for instance, be advantageously given in carbuncle for the purpose of breaking down the induration and getting rid of the sloughs.

EXCERPT II.—ON THE CLINICAL SIGNIFICANCE OF INCREASED AND DIMINISHED BLOOD-COAGULABILITY, AND ON THE METHOD OF CORRECTING THESE CONDITIONS

(1) *Introductory.*

SECTION I.—PROPHYLAXIS AND TREATMENT OF THROMBOSIS

(2) *Pathology of thrombosis—(3) Therapeutics of thrombosis—(4) Method of combating conditions of hyper-coagulability, and preventing the reinforcement of a thrombus by secondary clottings.*

SECTION II.—ARREST OF HAEMORRHAGE AND RESTRICTION OF 'SEROUS HAEMORRHAGE'

(5) *Factors which come into consideration in haemostasis—(6) Treatment of haemorrhage in the case where the number of red corpuscles in the blood is seriously diminished—(7) Treatment of haemorrhage where the number of red corpuscles in the blood is not seriously diminished—(8) Method of operating upon the blood so as to obtain accelerated coagulation: Administration of CO₂—(9) Method of operating on the blood so as to obtain a firmer and less contractile clot: Administration of calcium chloride or lactate or of magnesium salts—(10) Methods of demonstrating the augmentation of coagulability and the improved quality of clot obtained by the addition of graduated quantities of calcium chloride to blood—(11) Physiological styptics and preparation of these—(12) Association between abnormally increased transudation from the blood-vessels and defective blood-coagulability, and treatment of such serous haemorrhage by the administration of calcium salts.*

(1) *Introductory.*—Alterations in the coagulability of the blood have a very great practical importance: *increased coagulability*, because it conduces to thrombosis; *diminished coagulability*, because it interferes with haemostasis, and also because it conduces to serous haemorrhage¹—in other words, to increased transudation.

Section I.—Prophylaxis and Treatment of Thrombosis

In connexion with the prevention of thrombosis it is important to keep in view not only that typhoid fever in the convalescent period and certain other infections may conduce to a condition of hyper-coagulability, but also that a dietary of milk—i.e. a dietary which is very rich in lime salts—may conduce to this condition. It will consequently in these cases be proper to safeguard the typhoid patient who is to be fed on milk against thrombosis by a regular administration of citric acid.² And where a dietary of milk is being administered this may, both on the ground of

¹ *Vide supra*, pp. 66–68.

² *Vide supra*, pp. 79–87.

digestibility, but also as a possible prophylactic against thrombosis, be decalcified by adding to it $\frac{1}{4}$ to $\frac{1}{2}$ per cent. of citrate of soda.¹

(2) *Pathology of thrombosis.*—In connexion with the treatment of thrombosis it is essential to regard its pathology and to appreciate the normal evolution of events.

A general survey of the subject teaches us the following :

When drawn blood clots in a tube, the immediate result is the complete blocking of the lumen with a clot. This has normally the approximate composition of : corpuscles, 55 per cent. ; serum, 45 per cent. ; and fibrin, 0.3 per cent.

After a short interval the clot commences to contract, and when detached from the wall it contracts up to the point at which the corpuscles are tightly jammed up one against the other. The clot then occupies 55 per cent. of the lumen of the tube, and 45 per cent. are occupied by serum. That means 45 per cent. of the lumen is reopened.

That completes stage 1 in the process of shrinkage.

There supervenes then another train of events. The superficial meshes of the fibrin meshwork, unable to support the weight of the contained corpuscles, and the elastic pull of the contracting fibrin, tear through in many places. An appreciable number of the corpuscles then escape from the clot as sand does through tears in the walls of a sack.

In vitro we have, as a result of this, a 'haemorrhage of red corpuscles from the clot'. In other words, a deposit of red corpuscles accumulates upon the floor of the containing vessel. In the interior of the circulation the blood-current would carry away these corpuscles as they escape, and would tear away others out of the meshes of the fibrin, with the result that the clot would gradually be reduced in size and would become firmer—being now made up of a smaller and smaller proportion of corpuscles with a correspondingly larger proportion of fibrin.

Pari passu with the haemorrhage from the clot more and more of the lumen of the vessel would be reopened. Finally, all that remains of the original obstruction would be a shrivelled skeleton of fibrin corresponding in weight and volume to $\frac{1}{300}$ th of the original clot. When that stage is finally reached the $\frac{299}{300}$ ths of the lumen of our blood-vessel would have been opened up again.

When a soft clot—meaning by that a clot containing only its original 0.3 per cent. meshwork of fibrin—carries away from its moorings and lodges in the heart or one of the larger blood-vessels, it is within a very few moments reduced to a bare meshwork of fibrin—the red corpuscles being, by the pumping action of the heart and the scour of the blood, dislodged and sent adrift. In other words, when an embolus consisting of soft clot becomes lodged in the heart or a large blood-vessel, the fairway is (as can be seen after intravascular coagulation produced by the intravenous injection of Wooldridge's 'tissue-fibrinogen') within a few minutes reestablished. With an embolus constituted by a solid bullet of white clot—i.e. of accreted layers of fibrin, the vessel is, of course, completely and irretrievably blocked.

We have been following out up to this only one train of events in the history of the thrombus in the blood-vessels. But its narrative is not simply a chronicle

¹ *Vide supra*, pp. 10-13.

of shrinkage. Instead of that, it is largely a chronicle of additions made to the original fabric of clot, such additions being made both in the torrent of the blood-current and in the stagnant backwaters produced by the blockage of the stream.

In the former case the new material accreted is white clot—that is to say, principally fibrin. In the latter case it is a fibrinous meshwork carrying its full quota of red corpuscles.

It is in particular this latter form of accretion which claims our attention when we are considering the ordinary thrombus—i.e. the thrombus which remains fixed in the vein in which it is formed.

The evolution of such a thrombus would be that represented in a diagrammatic manner in Fig. 1. In *a* we have soft clot, *A*, obtruding the whole lumen of the

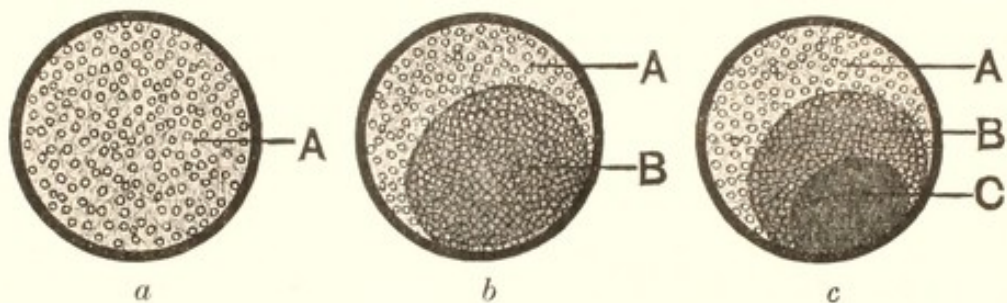


FIG. 1.

vessel. In *b* this clot has begun to contract, and has shrunk away from the wall in such a way as to leave a semilunar chink. The vessel is now again pervious. But it is only temporarily reopened. For when fresh blood from the circulation finds its way into the gap it coagulates there, *b*, *A*; and with that the vessel is resealed. Further shrinkage now takes place both in the primary and secondary clot, with the result that the vessel again becomes pervious; and we have thus, as indicated in *c*, as the result of a succession of clottings, a series of superimposed coagula, each of which condenses as the fibrin contracts and the corpuscles are washed out. It is in this way that a laminated clot is built up. A simple computation teaches that for the formation of a solid fibrinous clot that would completely fill in the lumen of the vessel there would be required 300 unit-volumes of blood—in other words, a total volume equivalent to 300 times the cubic content of the thrombosed vessel.

(3) *Therapeutics of thrombosis.*—When we recognise that in thrombosis we have to deal not with a single clotting but with a series of successive clottings, it becomes clear that effectual therapeutic intervention is possible. It will be possible to prevent further accretions of clot, and to provide that the vessel shall, when once opened up by the shrinkage of the clot, remain pervious.

The rapidity with which that shrinkage will take place will, of course, vary. It will depend on the proportion of non-condensed and shrinkable to condensed and unshrinkable clot.

Where we are dealing with a quite recent thrombosis and a clot which has

been furnished by one unit-volume of blood it will not be unreasonable to expect the clot to shrink within a very few hours to one-half of its bulk, and after that we may expect the corpuscles to be washed out little by little so as to leave the vessel again completely patent.

When the thrombosis is of very old standing, and the clot consists of fibrin furnished by very many unit-volumes of blood, we can expect very little diminution in size from shrinkage, and also very little from the washing out of corpuscles.

(4) *Method of combating conditions of hyper-coagulability, and preventing the reinforcement of a thrombus by secondary clottings.*—I pointed out in 1894¹ that citric acid administered in doses of 2 grammes t.i.d. diminished blood-coagulability; and the application of this drug in connexion with the treatment of thrombosis, following typhoid fever, was more closely studied by me in conjunction with Knapp in 1902.² It will be plain that the proper scientific method of conducting this citric acid treatment will be to measure as we proceed the calcium content of the blood and the resulting changes in the clotting by the methods described in that paper.

Where that is impracticable it will be advisable—and especially in the case where undue reduction of the coagulability of the blood would carry with it risk from haemorrhage—to keep at any rate some sort of watch upon the progress of events. We can do this by simply puncturing the finger and noting whether the blood flows freely or in niggardly fashion; whether it stanches slowly or rapidly; and whether pressure upon the punctured finger applied after the lapse of a few minutes restarts or fails to restart the haemorrhage. From these indications we can form an idea as to how far the object of our treatment has been attained.

Section II.—Arrest of Haemorrhage

(5) *Factors which come into consideration in haemostasis.*—These are precisely the same as those considered above in connexion with thrombosis. First we have a coagulation of the blood in and around the cut vessel. What that gives is only a purely provisional tamponing. That is followed, as soon as the clot begins to contract away from the wall, by a series of after-clottings. It is, of course, these that ward off recurrent haemorrhage and that give us the fortified tampon which permanently seals the vessel.

In the first and all the supplementary tampons which arrest haemorrhage it is, as consideration will show, the corpuscles caught up and held in position by the fibrin meshwork that really seal the vessel. Under normal circumstances, with 5 millions of corpuscles per cmm., there is enough of this filling material to make the uncontracted clot stanch; and enough, as we have seen, to furnish, when the fibrin network has contracted down upon the corpuscles, an absolutely solid tampon for $\frac{1}{2}$ ths of the lumen of the cut vessel.

In really serious haemorrhage—e.g. in the secondary haemorrhage of surgical sepsis and in the terminal stages of haemophilic bleeding—it is not defective blood-coagulability which is the danger. For even in those cases where the blood at the

¹ *Vide supra*, pp. 34–36.

² *Vide supra*, pp. 79–87.

outset may have clotted with extreme slowness, there invariably supervenes a 'haemorrhagic increase of coagulability'. The real source of danger is the reduced number of red corpuscles in the blood; in other words, the deficiency of packing material for the tampons of clot. Where we have, instead of 5 millions, let us say, only 2 or 1 million of corpuscles per cmm., there may perhaps be enough corpuscles caught up in the clot to arrest the outflow of blood, but there will not be enough to prevent oozing of blood-fluids through the clot. Moreover, there will be great risk of recurrent haemorrhage. For in view of the smaller load of corpuscles to be drawn together the clot will contract more rapidly, and will also shrink to much smaller dimensions—opening up in the case where we have only 2 or 1 million of corpuscles per cmm. in lieu of $\frac{1}{2}$, $\frac{1}{3}$ ths, or, as the case may be, $\frac{9}{10}$ th of the lumen of the vessel. And, of course, all the reinforcing tampons will be in the same proportion less effective than if they had been furnished by the normal blood.

(6) *Treatment of haemorrhage in the case where the number of red corpuscles in the blood is seriously diminished.*—Seeing that here the chief source of danger lies in the circumstance that there is not enough packing material of corpuscles to render the tampons of clot efficient, the obvious indication is to supply such material. The best way will, of course, be by transfusion of blood. Where transfusion cannot be carried out and the haemorrhage is from small vessels, blood drawn with a syringe from the vein of a normal man may be applied to the bleeding point. And possibly some filling material other than blood-corpuscles could be devised. Sterilised powdered chalk,¹ fortified by 1 in 1000 of calcium chloride, might perhaps serve.

In addition to supplying packing material for the tampons of clot, all the other lines of treatment indicated below may with advantage be followed.

(7) *Treatment of haemorrhage where the number of red corpuscles in the blood is not seriously diminished.*—Here we should aim at modifying the blood in the vessels so as to obtain accelerated blood-coagulation. By that means we may hope to obtain first a rapid provisional tamponing of the bleeding vessel, and then, when the original tampon of clot contracts, rapid supplementary coagulations. Or, again, instead of seeking only acceleration of coagulation we may aim at so modifying the blood in the vessels as to obtain a clot which will be firmer and will shrink less rapidly. Finally, when bleeding is external, we can employ *physiological styptics*—i.e. we can make such additions to the shed blood as will lead to more rapid and firmer clotting.

(8) *Method of operating upon the blood so as to obtain accelerated coagulation: Administration of CO₂.*—Of the methods of accelerating blood-coagulation the simplest and most immediately operative is the administration of CO₂.² The gas may be generated in a Kipp's gasogene, and may conveniently be delivered to the patient through a fine rubber tube inserted into the nostril, care being taken to cut down the supply of gas as soon as it excites unduly deep and frequent respirations. Where apparatus of this sort is not available we can take an ordinary rubber hot-

¹ Powders like chalk can be conveniently sterilised by heating them in a saucepan over a fire. A convenient thermometer is furnished by stirring in small pieces of white paper. The charring of these indicates a temperature of about 200° C.

² *Vide supra*, pp. 14–25.

water bottle, introduce into it the contents of a syphon of soda water, or a little water and a Seidlitz powder, or a little bicarbonate of soda and vinegar, and then get the patient to apply the funnel-shaped mouth of the bottle to his mouth and inspire the gas.

Experiment.—Prick the finger or, better, draw blood from a vein, and divide the blood into two equal portions, introducing these into two small paraffined test-tubes. Then, having placed ready to hand a Kipp's apparatus generating CO_2 , fill up the one test-tube with this gas.

This done, obtrude the mouths of both tubes by bringing down upon them the thumbs of the two hands. Keeping now the two thumbs in position invert the tubes so as to bring the one portion of blood in contact with the oxygen of the air, and the other in contact with the atmosphere of CO_2 . Repeat this inverting operation, let us say, every half minute.

It will be found that the CO_2 blood clots much more rapidly than the control blood.

(9) *Method of operating on the blood so as to obtain a firmer and less contractile clot: Administration of calcium chloride or lactate.*—Calcium chloride cryst. and lactate given in doses of about 2 grammes will also augment blood-coagulability. Under augmentation is here to be understood not necessarily an acceleration of coagulation time as measured by the interval between filling into a capillary and the first formation of fibrin, but an alteration of coagulability which leads to the production of a clot which differs from the normal, in being firmer, in adhering more tightly to the walls of a blood-vessel or capillary tube, in being less retractile, and in enveloping the red corpuscles more firmly¹ (i.e. in furnishing less haemorrhage from the clot). The augmentation of coagulability which is here in question can be demonstrated by comparing blood drawn before administering calcium salts with blood drawn off afterwards. In the latter case the result will, of course, be obtained only where the calcium is absorbed; and it is to be noted that there is, with respect to capacity for absorbing calcium salt, considerable individual variation.

The samples of blood taken before an ingestion of calcium salts can be tested by the methods described in the next subsection.

(10) *Methods of demonstrating the augmentation of coagulability and the improved quality of clot obtained by the addition of graduated quantities of calcium chloride to blood.*

Experiment 1.—Take a drop of 10 per cent. calcium chloride cryst. solution (sp. gr. 1040), and place this on a paraffin slide. Make from this a 5, 4, 3, 2, and a 1 per cent. solution. Then puncture the finger and let a large drop of blood fall on to another paraffin slide. Now take a pipette with a long stem of uniform calibre, place a fiducial mark on the stem, then draw up into it one volume of blood, then add to this a wash of the 5 per cent. calcium chloride; then another volume of blood and a wash of 4 per cent. solution; then proceed in this way until you have stored away in the pipette five volumes of calcified blood. Calculating the wash as equivalent to $\frac{1}{25}$ th volume, you will now have added to the

¹ Wright, *British Medical Journal*, 19th December, 1891; *Journal of Pathology and Bacteriology*, 1893; *British Medical Journal*, 29th July, 1893.

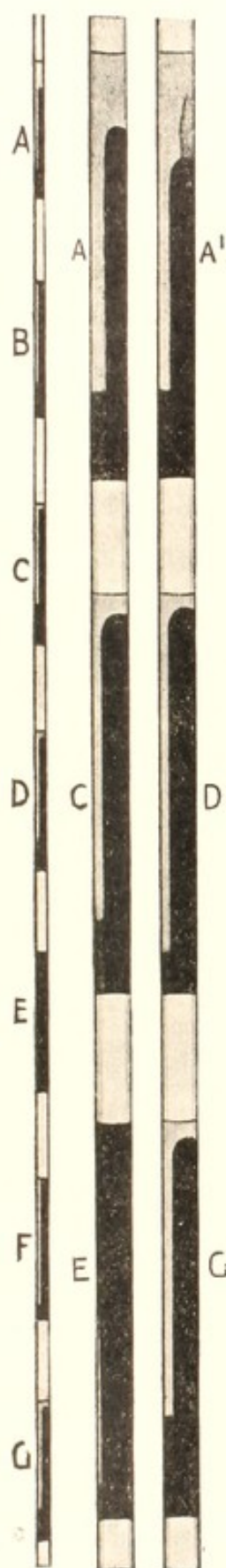


FIG. 2.

samples of blood 0.2, 0.16, 0.12, 0.08, and 0.04 per cent. of calcium chloride. Now follow on with two or three further volumes of blood, adding to these in each case a wash of 0.85 per cent. NaCl solution. This done, seal the distal end of the stem in the flame and block the neck of the pipette by introducing into it a little water or mercury. Then set the pipette up in vertical position, and then watch the result at laboratory temperature. Fix your attention first upon the settling of the corpuscles. If the blood has a slow coagulation time there will come into view in the control samples, before coagulation supervenes, a clear superficial band. The same appearance will be seen in the specimens of blood to which we have made an excessive addition of calcium. This clear superficial band will, of course, in both cases consist of plasma. At a later stage—twenty-four to forty-eight hours or earlier if we employ a hand lens—there will be seen in this position a white clot corresponding in depth to the clear band, and this white clot, owing to the fact that it has no filling of red corpuscles, will shrink in a characteristic way. This point is brought out by comparing at *A* and *A'* in the larger-sized tubes on the right hand of Fig. 84—*A'* representing the more or less pointed, white-tipped clot obtained with a blood which clots unduly slowly; *A* the type of blunt red clot obtained with a normal blood. Turning our attention now to the retraction of the clot, and to haemorrhage from this, it will be seen that in the samples of normal blood we have in every case (as shown in *A* and *B* in the small tube on the left, and in *A* and *A'* in the larger tubes on the right), after twenty-four hours in the cold, or two or three hours in the incubator, very considerable retraction, and along with this considerable haemorrhage from the clot. On running the eye down the tube, it will be found that both retraction of the coagulum and haemorrhage diminish until we come to the samples of blood which have received an addition of about 1 per 1,000 of calcium chloride. Here (as shown at *E* in the small tube on the left and at *E* in the middle tube) we have as good as no contraction and no haemorrhage from the clot. In the same way with excessive additions of calcium chloride, in particular with additions of 2 per 1,000 and over, we have again, as shown at *G* in the small tube on the left and at *G* in the large tube on the right, contraction and haemorrhage from the clot.

FIG. 2.—On the left-hand side a capillary pipette containing, as described in the text, in *G*, *F*, *E*, *D*, and *C* additions of 0.2, 0.16, 0.12, 0.08, and 0.04 per cent. of calcium chloride cryst.; and in *B* and *A* samples of blood without such admixture. On the right hand are shown on a larger scale the details described in the text.

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