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REPORT LXXXI.

THE COAGULATION TIME OF THE BLOOD IN PREGNANT AND PUERPERAL WOMEN SUFFERING FROM ALBUMINURIA AND ECLAMPSIA.

By CARSTAIRS DOUGLAS, M.D., B.Sc., F.R.S. EDIN.,
Professor of Medical Jurisprudence and Hygiene, Anderson's College
Medical School; and Pathologist, Maternity Hospital, Glasgow.

ALTHOUGH a study of the coagulability of the blood in pregnancy is one deserving attention, it is not my purpose to deal with it in this paper. It is being investigated at present by another worker at the Glasgow Maternity Hospital, and the results when published will, I trust, be a useful addition to our knowledge of the haematology of pregnancy and the puerperium. My own attention has been directed primarily to a consideration of the coagulation time of the blood in pregnant and puerperal women who were the subjects of eclampsia and albuminuria, and the investigation was undertaken for the special purpose of determining whether there was or was not on the part of such subjects a tendency for the blood to clot more rapidly than in health—whether, in short, such patients had a shortened coagulation time.

In April, 1901, Dr. Hey Groves read a communication before the Obstetrical Society of London in which he gave details (clinical and *post mortem*) of a case of eclampsia, and discussed in some fullness his own views as to the pathogenesis of the condition. He held that the essential lesion consisted in the formation of minute capillary thrombi, with haemorrhagic infarcts and necrosis of the surrounding cells. These thrombi occurred most frequently in the liver, the kidneys, and the brain, and by their presence gave rise to the fits and the coma. Dr. Hey Groves attributed the more ready formation of thrombi in eclampsia to an increased coagulability of the blood, this alleged increase in its turn being due to the presence of toxins which originate in the placenta, the fetus, and the alimentary canal.

That thrombi might be found at the necropsy in cases of eclampsia, and that these thrombi were situated chiefly in the liver, has been known for some time, attention having been directed to them a number of years ago by various observers, among whom may be mentioned Schmori,¹ Stumpf,² Gerdes,³ Klebs, and Dührssen.⁴ By some, however, their existence was attributed to the bruising of the liver which it undergoes during pregnancy and under the violent efforts of delivery. Klebs indeed inclined to the opinion that thrombi composed of multiple liver cells had something to do with the onset of the convulsions, and in this he was supported by Schmori; he held, however, that they arose, not from an increased coagulability of the blood, but, as already pointed out, from a bruising of the liver tissue itself.

Now, although I am at one with Dr. Hey Groves in regard to eclampsia as due to a toxæmia, I am not prepared to support his theory that multiple thrombi are very common in the disease, and that they are to be regarded as a causal factor in the production of convulsions and coma alike. I have had the opportunity during the past four years in my capacity as pathologist to the Glasgow Maternity Hospital of seeing a large number of cases of eclampsia patients, and of making the necropsy in seven or eight fatal cases. In most of these cases microscopic examination of the liver or kidneys or both was made, and I cannot say that the results obtained support the contention that in general thrombi occur as part of the pathological changes in eclampsia. The organ I have usually found most altered is the liver, and besides the macroscopic alterations, which have frequently been very striking, various microscopic changes have been noted, such as thrombi (occasional), haemorrhages, fine granular degeneration in the hepatic cells with enlargement of the nuclei, and areas of necrosis. These changes I am inclined to refer to the direct action of a toxin in the blood, just as the changes met with in the kidney in many instances are those of a toxic nephritis. There is,

however, a clinical method which one may employ in a matter of this kind, and that is the determination of the coagulation time of the blood during life by some such instrument as Wright's coagulometer. This has been done in the present instance, but before giving details of the method and the results obtained, it may not be out of place to consider briefly the general changes in the blood of the pregnant and puerperal woman.

In general terms it may be said that the total quantity of blood is raised in pregnancy; that the leucocytes, fibrin, and probably the haemoglobin are increased in amount, while the red cells are if anything diminished. Regarding some of these points the following are some of the results obtained by more or less modern observers:

1. The volume of the blood is increased during pregnancy. In 6 non-pregnant animals it was 7.8 per cent. of the body weight, while in 10 similar animals but pregnant it was 9 per cent. (Spiegelberg and Geschleiden⁵).

2. There is sufficient evidence from recent work to indicate that the old idea of poverty of haemoglobin in pregnancy is untenable. Fehling,⁶ Winckelmann, and Reihl (quoted by Buist⁷) all found that in the majority of pregnant women the haemoglobin was fully up to the average, while in a considerable number of cases it surpassed it. Schroeder⁸ actually found, out of 34 women examined during pregnancy, that over 70 per cent. of them gained in haemoglobin.

3. Observations recently carried out point to the fact that there is not nearly so great a diminution in the red cells as is frequently stated in textbooks; and, indeed, the ordinary pregnant woman has not much less than her full complement of erythrocytes. Bernhardt,⁹ for example, in healthy non-pregnant women found the average red-cell count to be 4,450,000 per c.mm., while in 32 pregnant women examined *ante partum* he had no average under 4,500,000, and even *post partum* the figures did not fall below 4,360,000. Henderson,¹⁰ working in this hospital, in 45 cases (during and just after delivery) obtained counts varying from 2,260,000 to 5,000,000 per c.mm., and having an average of close on 4,000,000. In the Edinburgh Maternity Hospital, Elder and Hutchison¹¹ obtained very similar figures from 16 women at parturition, their average being 3,978,000.

4. The leucocytes are normally increased in pregnancy, especially towards the latter months. Henderson¹² in 36 normal cases obtained at term figures ranging from a little over 10,000 to 36,600 per c.mm., the average being 21,365. Elder and Hutchison¹³ give figures varying between 8,000 and 25,000, with an average of 14,500, which is 33 per cent. lower than Henderson's.

5. The density of the blood was studied a good many years ago by Nasse,¹⁴ who found it always somewhat lowered in pregnancy, though not to any great extent. It receded most from the normal between the sixth and eighth months. The fibrin he found increased by nearly 4 per cent. The water and fat he also found increased, and the salts of the blood diminished. Nasse's observations would bear repetition.

6. The coagulation time in normal pregnant and puerperal women has hardly been worked at at all. As mentioned already this paper deals specially with the question of the alleged tendency of the blood in eclamptics to form thrombi readily, and the means adopted to try to settle the point clinically is by a determination of the coagulation time.

PROCEDURE.

The instrument employed was the latest form of Wright's coagulometer, as made by Hawksley, London, which consists of a numbered series of glass tubes, each being in calibre approximate to the measuring tube in the ordinary Gowers haemoglobinometer, and each having a mark of 5 c.mm. The observations should be made with the tubes at a temperature of 67° F., or that of an ordinary room on a summer day. In cold weather the tubes can be raised to the requisite temperature by standing them in a water bath, the entrance of water into the tubes being prevented by a small rubber cap drawn over the end of each.

In using the tubes the finger or lobe of the ear is pricked. I prefer the latter region. It is necessary that the blood should come somewhat freely, hence the puncture should be made with a fine sharp-pointed bistoury rather than with a needle. As the blood is flowing, tube after tube is filled in order up to the 5 c.mm. mark, though it does not signify if a little more or less is drawn in. Each tube should be wiped clean at the end after filling, and the column of blood should be aspirated up a little way from the end of the tube. This prevents early clotting of the blood, and the cushion of

air also serves to prevent the entrance of water and its touching the blood in case the tubes require to be replaced in the water bath (thus obviating the need of putting on the caps again).

The time of filling of each tube is carefully noted by the watch, and I have made it a point throughout to fill at intervals of a quarter or half minute, avoiding intermediate times and odd seconds. After, let us say, ten tubes are filled, the observer may remove them from the bedside and complete the matter at a window, table, or other convenient place. An effort is now made to blow the blood out of each tube in succession, noting carefully the time between filling and blowing, till at length a tube is found from which the blood cannot be expelled. The time that has elapsed between filling and blowing out of this particular tube gives the "coagulation time."

We begin, for example, with No. 1 after 5 minutes (the time always being counted from the moment of filling), and we find the blood slips out easily. We next try No. 2 at 6 minutes, and again we can readily dislodge the blood. A third attempt is made with No. 3 after 7 minutes, and noted that partial clotting has commenced. Accordingly No. 4 is tried at $7\frac{1}{2}$ minutes, and clotting is found to be complete. But it may be that $7\frac{1}{2}$ minutes is the time and not $7\frac{1}{2}$, so we go on forward a tube or two, and try one at $7\frac{3}{4}$, when we find clotting complete. We finally try another at the same interval, and obtain a like result, from which we state that the coagulation time is $7\frac{1}{2}$ or possibly a little less, but not so short as 7 minutes. I have regarded intervals of one-quarter of a minute as small enough. In the instance I have given, if we tabulate our results in the way I usually do, we get the following statement:

Example—Mrs. M., 1-para, aged 26. Severe eclampsia third day of puerperium. Fits *ante-partum*, and *inter-partum*, none *post-partum*. Albuminuria marked. Examined March 27th, 1902.

No. of Tube.	Time of Filling.	Interval.	Time for Blowing Out.	Coagulation.
1	11.5 a.m.	+ 5	11.10	Negative.
2	11.5 $\frac{1}{4}$ a.m.	+ 6	11.11 $\frac{1}{2}$	Negative.
3	11.5 $\frac{1}{2}$ a.m.	+ 7	11.12 $\frac{1}{2}$	Partial.
4	11.5 $\frac{3}{4}$ a.m.	+ 7 $\frac{1}{2}$	11.13 $\frac{1}{2}$	Complete.
*5	11.6 a.m.	—	—	—
6	11.6 $\frac{1}{4}$ a.m.	+ 7 $\frac{1}{2}$	11.13 $\frac{1}{2}$	Complete.
7	11.6 $\frac{1}{2}$ a.m.	+ 7 $\frac{1}{2}$	11.14	Complete.
8	11.7 a.m.	—	—	—
9	11.7 $\frac{1}{2}$ a.m.	—	—	—

* No. 5 is not used, as $7\frac{1}{2}$ added to its time of filling would give the same time for blowing out as No. 4, namely, 11.13 $\frac{1}{2}$ minutes.
Coagulation time = $7\frac{1}{2}$ minutes.

It does not always happen, of course, that the observation is ended so quickly. One or two precautions have to be observed.

1. The tubes must be quite dry inside when used otherwise the coagulability appears to be diminished. Drying of the interior of the tubes is accomplished in the usual way by first washing them through with absolute alcohol, then with ether, and then aspirating air through.

2. The tubes should be as near the temperature of 67° F. as possible; if much below this, for example, at 44° F., the coagulation time I found was delayed; if a little above it, for example, at 81° F., there was little difference.

3. The personal equation bulks largely in the use of a clinical instrument of this sort, and therefore in any given set of observations the same person must always perform the "blowing out" part.

4. After use the tubes must be cleaned at once by means of fine wire and then dried. If old blood is allowed to harden inside the tubes it is difficult to remove it sometimes. It may be got rid of by peptonization—done by placing the tube in a test tube of warm water containing a little liquor pepticus, acidulated by hydrochloric acid.

With these preliminary remarks we may now proceed to the consideration of the results obtained. Between 300 and 400 observations were made, and on the following groups of cases:—(1) Cases of albuminuria (pregnant and puerperal); (2) cases of eclampsia (pregnant, parturient, and puerperal); (3) cases of healthy puerperae; (4) cases of healthy pregnant women; (5) cases of healthy non-parous women. Unfortunately, the detailed reports of a considerable number of the earlier cases were lost through the accidental destruction of a notebook, but a large number still remained for arrangement. I have not given the figures for individual observations, but have collected the results of each group in a more condensed form.

I.—Cases of Albuminuria (Pregnant and Puerperal).

There were in all 16 cases observed, 6 in pregnancy (near full time) and 10 in the puerperium. Some of them were very severe. Of the 6 undelivered cases, the average coagulation time was 5.6 minutes, being the shortest found in any group of cases; the limits ranged from 4.7 to 7.5. Of the 10 albuminurics examined after delivery, the average period was 7 minutes, the numbers varying between 5.6 and 10. None of these patients developed eclampsia.

In looking over my notes of these cases I observe that one, a 2-para examined in the puerperium, suffered from eclampsia in her first confinement eighteen months previously. In another case of albuminuria with mitral stenosis it was noted at the time that the blood looked very watery. On two occasions in this the coagulation time was protracted to 9 minutes. I shall have occasion to refer to this group again.

II.—Cases of Eclampsia (Pregnant, Parturient, and Puerperal).

Of these no fewer than 22 were examined in the course of a little over two years. Many of them were very severe, and several proved fatal; 5 cases were obtained before delivery, and the average coagulation time obtained was 7.4 minutes, the figures extending from 4.5 to 9 minutes. In one of these, with *ante-partum* fits and a contracted pelvis, the coagulation time on admission was 4.5 minutes. A Porro operation was performed. The blood time on the second day of the puerperium was 4.7 minutes, while on the fourth it was 5 minutes. In addition to the 5 cases examined before delivery there were 17 where the first observation was possible only in the early puerperium. Of these the coagulation time varied from 4.5 minutes to 9.5, the average being 7. Some of the cases are worthy of short comment. That with the longest time (greatest diminution of coagulability) was a primipara of 18, who had severe eclampsia, *post partum* in incidence. She was transfused with 2 pints of normal saline solution. On the third day of the puerperium the time was 6.5 minutes, on the fourth day 8.75, on the sixth day (by which time she had developed jaundice) it was 8.5, and on the ninth day it was 9.5. In another case, where no fewer than 6 pints of saline solution had been given subcutaneously, the coagulation time was only 7.5 minutes, though one might reasonably have supposed it would be longer. We see from this not inconsiderable number of cases that there is nothing here to support the view that the blood clots more readily in eclampsia.

III.—Normal Puerperae (Non-albuminuric).

A large number of these were examined, and the average time was found to be 7.3 minutes, the shortest being 4.75 and the longest 9.5. Of three cases showing this lengthened time, one was a case of accidental haemorrhage, one had had severe bleeding at her last confinement, and the third was a normal case. In another case, a 2-para, aged 22, with a period of 7.25 minutes, bled freely at labour, while another, also 2-para, bled freely *post partum*, the coagulation time being extended to 9.25 minutes. Two other cases of *post-partum* bleeding were found to have a lessened coagulability, the times being 8 and 9.25 minutes respectively as maxima. As a rule, it was found that the coagulation time lengthened in the early days of the puerperium, attained a maximum, and then shortened again. This is what one would have expected, the loss of blood at labour being compensated for by lymph from the tissues (coagulating more slowly than normal blood), and this in its turn becoming more dense as regeneration of the various elements takes place.

IV.—Healthy Pregnant Women.

Seven cases were examined in this group, with the result that the coagulation time was found to average 7.4 minutes, the figures ranging from slightly below 5 in a full-time 1-para to 9 in a seven-month 3-para. Only one case showed anything of special interest, and that was a 2-para, aged 30, the subject of phlebitis; her coagulation time was 7.5 minutes, showing no shortening.

V.—Healthy Non-pregnant Women.

In addition to the examination of 7 healthy pregnant women, observations were made on 10 healthy non-pregnant females, with the result that an average period of 7.75 minutes was obtained, the shortest and longest times being 5 and 10 minutes respectively. The last is a prolonged coagulation time, and no explanation can be given as to why it should have occurred in this case, the subject being a healthy unmarried woman.

If we arrange these different groups in a table and compare

the coagulation times, we observe that in the main there is very little difference between them:

Group.	Average Coagulation Time in Minutes.	Shortest.	Longest.
I. Albuminurics:			
(a) Pregnant	5.60	4.70	7.5
(b) Puerperal	7.00	5.60	10.0
II. Eclampsias:			
(a) Pregnant	7.40	4.50	9.0
(b) Puerperal	7.00	4.50	9.5
III. Normal puerperal	7.30	4.75	9.5
IV. Healthy pregnant women...	7.40	5.00	9.0
V. Healthy non-pregnant women ...	7.75	5.00	10.0

Looking at the last six lots, we see that the average, the shortest, and the longest coagulation times are very near one another, the average periods being 7.0, 7.4, 7.0, 7.3, 7.4, and 7.75 respectively. A healthy pregnant woman and a pregnant woman with eclampsia show almost identical times, and there is not much difference between either of them and the healthy, non-pregnant women. There is nothing at all, so far, to support the theory of an increased coagulability in this special class of cases. When we turn, however, to the albuminurics in pregnancy, we do find that the time is shortened as compared with the other groups, being only 5.6 minutes on an average. But when the 6 cases that make up this class are scrutinized more carefully, it is found that 2 are cardiac cases and 1 hemiplegic, leaving only 3 as possible albuminurics of pregnancy and possible eclampsias. As a matter of fact, none of these 3 did develop convulsions.

I think, therefore, that we are entitled to say from these observations that there is little difference in the coagulation time of healthy pregnant and puerperal women and of eclampsia before and after delivery, and that there is nothing, as far as a study of the coagulability of the blood goes, to support the contention that the thrombi found in certain organs in fatal cases of eclampsia are due to an increased coagulability in these cases.

In conclusion, I should like to express my indebtedness to Dr. Robert Jardine and Dr. Munro Kerr, the Visiting Physicians of the hospital, for their kindness in permitting me to examine their cases.

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LEPROSY IN SOUTH AMERICA.—In a report from the United States Minister, Mr. Beaupré, from Bogotá, under date November 5th, 1903, reference is made to the prevalence of leprosy in Colombia. He says this is one of the gravest questions now confronting that commonwealth. The disease has invaded the country to an alarming extent, and extraordinary measures have become necessary to check its spread. He encloses a copy of a law enacted by Congress, under which lazarettos are to be established in each department of the republic, in which all the lepers are to be confined. Various other provisions are made, but the central idea is to isolate all those who are suffering from the malady. The department of Antioquia already has a lazaretto which has been erected at an expense of more than 3,000,000 pesos, and much other good work has been done in various districts by private efforts and contributions.

TWO CASES INVOLVING THE QUESTION OF THE SITE OF IMPREGNATION.

BY
HARRISON CRIPPS, and HERBERT WILLIAMSON,
F.R.C.S., and M.B., B.C.,
Surgeon. Demonstrator of Practical
Obstetrics.
St. Bartholomew's Hospital.

IN spite of the careful and valuable work which in recent years has been done upon the early history and development of the fertilized ovum, and in spite of the light which Peter's observations have thrown upon many previously obscure pathological conditions, we are still in ignorance of the site at which impregnation normally occurs and of all details of the journey of the ovum from the ovary to the uterus. The following two cases, which have occurred in the practice of St. Bartholomew's Hospital, have some bearing upon these points and are therefore worthy of being placed on record.

CASE I.

TUBAL GESTATION AFTER COMPLETE REMOVAL OF THE OVARY ON THE SAME SIDE.

B. D. was admitted into St. Bartholomew's Hospital on January 10th, 1903, under the care of Dr. Champneys, complaining of pain in the lower part of the abdomen and haemorrhage from the vagina. She had previously had five pregnancies, four children (the last of whom was born in January, 1902), and one miscarriage in 1898. Menstruation had always been regular; the periods commenced when she was 14 years of age; they recurred every 28 days, lasted four days, and the amount lost was not excessive. The last period ceased on November 9th, 1902. The patient stated that she underwent an operation in 1899, when Mrs. Scharlieb removed an ovarian tumour.

History of the Present Condition.—After the cessation of menstruation in November, 1902, there followed a period of six weeks' amenorrhoea. In Christmas week of that year the patient commenced to suffer from pain situated chiefly in the right iliac fossa; this pain came on suddenly, but without any symptoms of collapse; at the same time she noticed haemorrhage from the vagina. The pain and haemorrhage have persisted since that date, the haemorrhage being sufficient to necessitate the use of six diapers a day.

Condition on Admission.—A scar was seen reaching from the pubes to the umbilicus. On the right side of the hypogastrium, situated $2\frac{1}{2}$ in. above the pubes, was a fixed indurated mass the size of an orange. On vaginal examination the cervix was found to be displaced downwards, forwards, and to the right, so as to lie a fingerbreadth behind the right pubic ramus; behind this and occupying the rest of the pelvis was a fixed tumour partly solid, partly fluid and elastic. On bimanual examination the uterus could be felt lying behind the right Poupert's ligament, and not appreciably enlarged. The tumour itself reached to a point midway between the pubes and umbilicus. On examination by the rectum the tumour was observed to lie entirely in front of the bowel. The uterine sound passed, with its concavity forwards, for a distance of 4 in. in front of the tumour.

Operation.—On January 21st abdominal section was performed by Mr. Harrison Cripps. An incision 5 in. in length was made, nearly in the middle line and just to the right of the scar of the previous incision. A quantity of old blood clot was found in Douglas's pouch, and the right Fallopian tube was expanded and ruptured. No trace of the right ovary could be seen. The tube was drawn up into the wound (after separating adhesions) and the broad ligament transfixed and secured as a pedicle. The distended tube was then cut away. Nearly a pint of old blood clot was removed from Douglas's pouch. Careful search failed to reveal any trace of a right ovary.

After-history.—The patient made an uninterrupted recovery and was discharged on February 21st, 1903.

Microscopical Examination.—Sections of the tube wall and of portions of the clot found in the tube show the presence of numerous well-formed chorionic villi, so that there can be no doubt whatever that the case was one of tubal gestation.

Note by Mrs. Scharlieb.—I removed from Mrs. D. a right-sided ovarian tumour on May 9th, 1899. It contained much grumous material and a little coiled up hair. It was the size of a fetal head at full term. The uterus and appendages of the left side were healthy. The patient made a good recovery and went home on June 2nd.

The chief interest in this case centres in the fact that it affords clear proof of the possibility of gestation in a Fallopian tube after the ovary of the same side has been removed.

At the operation described above a careful search was made, but no trace of the organ could be discovered; further, the condition found at the previous operation—a dermoid cyst—renders it very improbable that any portion of the oöphoron could have been left behind. What was the source, then, of the ovum which gave rise to the tubal gestation? Was there an accessory ovary on the right side? This is improbable; the presence of a third ovary is one of the rarest abnormalities met with in the human body, if indeed it ever occurs. Cases have been recorded from time to time, but of