Hemorrhagic Diathesis Due to a Circulating Anticoagulant
Report of Case with Laboratory Observations

By Eduardo R. Pons, Jr., M.D. and Mercedes Vicente de Torregrosa, Ph.D.

Lozner, Jollife and Taylor first described, in 1940, a case of bleeding tendency resulting from the presence of an anticoagulant in the patient’s circulation. Since then the appearance of 11 additional case reports of this unusual hemorrhagic diathesis has given an opportunity to study previously unknown, abnormal mechanisms of blood coagulation. It has recently been pointed out that these cases may occur more frequently than heretofore suspected.

All the cases reported were in adults. Their ages ranged from 21 to 68 years, and all but 3 were males. In all patients the clinical course consisted in the appearance of multiple, spontaneous, hemorrhagic phenomena. The routine hematologic studies were essentially negative, except for a marked prolongation of the clotting time of venous blood, and for anemia following some of the hemorrhages. Minute amounts of the blood or plasma of these patients prolonged the clotting time of normal blood, indicating the existence of a circulating anticoagulant. In spite of frequent and, at times, dangerous periods of disability due to hemorrhage, 2 patients are thought to have had the disease for as long as nine and twenty years, respectively. No therapeutic measures have been reported that will alter the natural course of the illness.

In the present communication we report a case of this blood dyscrasia and present special studies on the properties and mechanism of action of the circulating anticoagulant.

CASE REPORT

Present illness: R. R. is a 43 year old divorced white woman who was hospitalized in August, 1948, because of hematuria and subcutaneous hemorrhage. Her past history is essentially negative. She underwent an appendectomy at the age of 19; she suffered a heavy blow to the nose at the age of 38; and had her tonsils and adenoids removed one year later. On none of those occasions was there prolonged bleeding, and she never suffered from easy bruising. The menses occurred regularly every 28 days, and lasted 3 to 4 days, with a normal amount of flow. The review of systems was negative.

Ten days before admission the patient had a tooth extracted under local anesthesia; the specific analgesic is not known. That night she awoke to find her pillow soaked in blood coming from the tooth socket. Throughout that night she lost an amount estimated at half a liter of blood, but the hemorrhage was controlled next morning with local hemostatics. Four days later, she felt pain in the right hypothenar region, and noted that the area underwent swelling and purplish discoloration. Next day she developed severe pain in the right...
which also presented diffuse swelling and purplish discoloration. Two days afterwards, similar swelling and discoloration developed on the left side of the neck, and she began to have painless, gross hematuria.

Family history: There was no recognized bleeding tendency in the patient's parents, maternal and paternal grandparents, and 7 siblings.

Physical examination: Temperature 98.6 F., pulse 92, blood pressure 120/70. The patient was a well developed, slightly obese woman. The skin was very pale. The left side of the neck was moderately swollen, and the overlying skin was purple. Several patches of greenish discoloration were seen in the skin of the right forearm, but no petechiae were noted.

The sclerae had a slightly icteric tinge. The optic fundi revealed no hemorrhages. The right lower second molar was markedly carious. The superficial lymph nodes were not palpable. The liver margin was felt at the level of the costal border, and was smooth and nontender. The anterior pole of the spleen was very soft, and extended for two fingerbreadths below the left costal border, but this was noted only while the patient was bleeding. The rest of the examination, including a pelvic exploration, was normal.

Laboratory findings: R.B.C. 4,010,000; Hgb. 81 per cent (Sahli) ; W.B.C. 12,000; P.M.N. 70 per cent (stabs 4 per cent, segmented 66 per cent), lymphs. 27 per cent, P.M.E. 3 per cent. Blood smears for malaria were negative. Urinalysis: traces of albumin; sediment loaded with red blood cells. Kahn test: negative. Hanger cephalin flocculation test: negative. Serum proteins: total 6.53 Gm.; albumin 4.38 Gm., globulin 2.15 Gm. Platelet count: 160,000. Bleeding time 3 minutes; venous clotting time (Lee-White) 25 to 87 minutes. Clot retraction: beginning retraction in 1 hour, complete retraction in 2 hours. Prothrombin time: (1) Squibb lung thromboplastin—patient 14 sec., control 14 sec. (2) Viper Venom—patient 25 sec., control 25 sec. Diluted prothrombin time (Squibb's lung thromboplastin): (1) with plasma 1:4; the patient was 19 sec. and the control 17 sec., (2) with plasma 1:8; the patient was 33 sec. and the control 31 sec. Plasma fibrinogen: 0.37 per cent. Capillary fragility (Rumple-Leede): normal. Blood calcium: 9.2 mg. Serum prothrombin conversion accelerator (by the method of De Vries, Alexander and Goldstein): normal.

Course: During a period of twenty months of hospitalization, the patient developed a variety of bleeding episodes, all of which subsided spontaneously. Some of these were mild, while others seriously threatened her life. The hematuria which she presented on admission to the hospital lasted for six weeks, and at one time caused a drop in the red cell count to 1.86 M. and of the hemoglobin to 46 per cent. With multiple transfusions and hematines, normal blood values were restored. During the fourth hospital week she had a massive hemorrhage into the tongue. For three days this organ was swollen to twice its normal size, and protruded from the mouth causing marked respiratory embarrassment and requiring the continuous use of oxygen through a nasopharyngeal catheter. In the second hospital month, a three day episode of nausea, vomiting, crampy abdominal pain, and generalized abdominal tenderness with the passage of tarry, guaiac positive stools, indicated bleeding from the gastro-intestinal tract.

However, subcutaneous hemorrhages were the most frequent bleeding phenomena observed, occurring almost continuously throughout the course. They ranged from ecchymoses about 2.5 cm. in diameter to extensive purpuric hemorrhages involving an entire arm or leg and causing severe pain and numbness of the affected limb. Hemorrhages into the scalp, subconjunctival tissues, breasts and anterior abdominal wall were also seen. The patient could always foretell their onset by a sensation of sudden pricking pain followed by a feeling of warmth in the involved area. On at least two occasions the development of severe pain and swelling in the thigh, followed in two days by the appearance of discoloration in the same area, suggested large intramuscular hemorrhages. The absorption of the extravasated blood invariably occurred without residual disability, deformity or peripheral nerve damage. The time of resolution of these hemorrhages varied from five days to as much as three weeks in the case of the more extensive ones. In the latter instances, transient scleral icterus often accompanied absorption of the extravasated blood.

It is interesting that no hemarthroses were seen, and that the menses were of normal frequency and duration throughout the period of observation. No episode of intracerebral bleeding was observed.
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All therapeutic agents utilized in the hope of shortening the clotting time or of controlling the bleeding tendency were unsuccessful. During the first week of illness, when the patient was very acutely ill, she received large doses of vitamins C and K, Koagamin, rutin, intramuscular thromboplastin, snake venom and antihistamines. Six transfusions of 500 cc. of type A, Rh positive citrated, fresh blood were given, each one within a half hour after collection from donors. Aside from the beneficial effect of replacement of blood lost from hematuria, there was no reduction in the venous clotting time and no change in the clinical signs of bleeding following transfusions. Three infusions of plasma (dry, Sharp and Dohme) were given in one week. The clotting time immediately after one of these was found to be 45 minutes. Antihemophilic globulin (Cutter) was given intravenously. Half an hour after the injection of 20 cc. of this substance the venous clotting time was 50 min-

### Table 1.—Effect of Patient's Blood on the Clotting Time of Normal Blood

<table>
<thead>
<tr>
<th>Clotting Time</th>
<th>1/15/49</th>
<th>1/28/49</th>
<th>2/8/49</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 cc. of pt's blood</td>
<td>66 min.</td>
<td>25 min.</td>
<td>51 min.</td>
</tr>
<tr>
<td>2.0 cc. of normal blood</td>
<td>5 min.</td>
<td>4 min. 15 sec.</td>
<td>5 min. 40 sec.</td>
</tr>
<tr>
<td>0.05 cc. pt's blood and 1.95 cc. normal blood</td>
<td>8 min. 15 sec.</td>
<td>13 min.</td>
<td></td>
</tr>
<tr>
<td>0.1 cc. pt's blood and 1.90 cc. normal blood</td>
<td>22 min.</td>
<td>10 min.</td>
<td>13 min.</td>
</tr>
<tr>
<td>0.2 cc. pt's blood and 1.80 cc. normal blood</td>
<td>32 min.</td>
<td>13 min. 40 sec.</td>
<td>13 min.</td>
</tr>
<tr>
<td>0.5 cc. pt's blood and 1.5 cc. normal blood</td>
<td>35 min.</td>
<td>13 min. 55 sec.</td>
<td>12 min. 30 sec.</td>
</tr>
<tr>
<td>1.0 cc. pt's blood and 1.0 cc. normal blood</td>
<td>31 min.</td>
<td>16 min. 30 sec.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2.—Effect of Recalcified Citrated Patient's Plasma on the Clotting Time of Normal Blood

<table>
<thead>
<tr>
<th>cc. Normal Blood</th>
<th>cc. Pt's Plasma</th>
<th>cc. 0.025M CaCl₂</th>
<th>Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>0</td>
<td>0</td>
<td>5 min. 48 sec.</td>
</tr>
<tr>
<td>1.8</td>
<td>0.1</td>
<td>0.1</td>
<td>16 min. 30 sec.</td>
</tr>
<tr>
<td>1.6</td>
<td>0.2</td>
<td>0.2</td>
<td>16 min. 30 sec.</td>
</tr>
<tr>
<td>1.2</td>
<td>0.4</td>
<td>0.4</td>
<td>15 min.</td>
</tr>
<tr>
<td>1.0</td>
<td>0.5</td>
<td>0.5</td>
<td>23 min.</td>
</tr>
</tbody>
</table>

utes, and after 40 cc., 45 minutes. When evidence was obtained of the presence of a circulating anticoagulant, protamine sulfate and toluidine blue were also tried without success, as will be described later. At the time of writing this report the patient is having short asymptomatic periods which are interrupted by the appearance of subcutaneous hemorrhages as before.

**Methods**

Venous blood was used for all the studies. The samples, drawn with sterile, chemically clean and dry syringes, were placed in clean and dry pyrex glass tubes. Citrated plasma was obtained by mixing fresh venous blood and 0.2 M sodium citrate in a ratio 9:1, and centrifuging at 2,000 r.p.m. for 10 minutes. Recalcification was done when necessary with 0.025 M CaCl₂ in volumes equal to those of the plasma used. Fresh plasma, not more than one hour old, was used in all experiments, excepting those that necessitated storage.

**Special Laboratory Studies**
The coagulation time of whole blood, of blood mixtures and of blood-plasma mixtures was done according to the Lee-White method. Speed in drawing blood and pipeting the various fluids resulted in completion of all the mixtures within one minute after blood had been drawn. The total volumes of these mixtures were uniformly kept at 2 cc., except in the experiments in which minute amounts of plasma had to be used. All samples of normal blood and plasma were obtained from the same subject, who belongs to the same blood group as the patient.

Results:

1. Demonstration of the presence of an anticoagulant in the patient’s blood. Effect of patient’s blood on the clotting time of normal blood.

The addition of small amounts of the patient’s blood to normal blood of the same group resulted in a definite prolongation of the clotting time (table 1). The anticoagulant action of the patient’s blood was thus demonstrated, and this action appeared to be stronger whenever the patient’s clotting time was more prolonged. The addition of increasing amounts of the patient’s blood in proportions higher than 1 part to 9 of normal blood, caused no further prolongation of the clotting time of normal blood. Mixtures of two normal bloods of the same type in similar proportions had a normal clotting time.

2. Demonstration of anticoagulant in the patient’s plasma. Effect of patient’s citrated plasma, both recalcified and unrecalcified, on the clotting time of normal blood.

The prolongation of the clotting time of normal blood by the patient’s plasma, recalcified and citrated, is shown in table 2. A control experiment with normal blood and normal plasma that had been similarly processed and recalcified, in identical proportions, showed some shortening of the clotting time of normal blood (table 3). This acceleration of clotting has been described by Quick after
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decalcification and recalcification. Mixtures of citrated, unrecalcified patient's plasma with normal blood showed prolongation of the latter's clotting time in proportions of 1 to 19 (table 4). Mixtures of the same proportions of citrated, unrecalcified normal plasma with normal blood showed no significant prolongation of the clotting time. The citrate effect, when recalcification was not done, prevented clotting in dilutions of 1 to 4 or less (tables 4 and 5). These results demonstrated the presence of an anticoagulant in the patient's plasma, irrespective of the effects of citrate and recalcification.

The anticoagulant effect of minute amounts of the patient's unrecalcified citrated plasma was also studied. Amounts of patient's plasma smaller than 0.1 cc. were brought to a total volume of 0.1 cc. with normal saline, and were then added to 2 cc. of fresh normal blood. The anticoagulant effect of the patient's plasma was evident in all dilutions up to 1:350 (table 6). Control observations using similar amounts of normal plasma and normal blood showed that the citrate contained in 0.1 cc. or less of normal plasma caused no demonstrable prolongation of the clotting time of normal blood.

3. Effect of heat, cold and storage on the anticoagulant effect of the patient's plasma.

Of three samples of the patient's plasma, one was heated in a water bath at 61 C. for 10 minutes, another was kept in a refrigerator for 24 hours and the third was stored at room temperature for 24 hours. The samples were then tested for anticoagulant activity using the same technic as that previously employed with minute amounts of the patient's plasma. Neither heat, cold nor storage at room temperature seemed to affect the anticoagulant action of the patient's plasma (table 7).

4. Tests for the presence of heparin: Since the presence of heparin-like sub-

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* All plasma dilutions brought to total volume of 0.1 cc. with normal saline.

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stances has been described in the blood of some patients with bleeding phenomena, tests for such an anticoagulant were carried out. Toluidine blue, which combines chemically with heparin, was added in vitro to 2 cc. samples of fresh whole blood from the patient in amounts ranging from 0.012 mg. to 2.5 mg. of the dye. No reduction in clotting time was obtained. The dye was then administered intravenously in doses of 2.0 mg. per Kg. body weight in 500 cc. of 5 per cent glucose in physiologic saline solution. The clotting time at the end of the infusion was 80 minutes. Protamine sulfate, which has a similar neutralizing effect on heparin, was administered once daily for four days in doses of 2.5 mg.

### Table 7. Effect of Heat, Cold and Storage on the Anticoagulant Action of Patient's Plasma

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>2</td>
<td>27 min. 20 sec.</td>
<td>24 min.</td>
<td>19 min.</td>
</tr>
<tr>
<td>0.05</td>
<td>2</td>
<td>28 min.</td>
<td>30 min.</td>
<td>45 min.</td>
</tr>
<tr>
<td>0.025</td>
<td>2</td>
<td>19 min.</td>
<td>18 min. 30 sec.</td>
<td>24 min.</td>
</tr>
<tr>
<td>0.012</td>
<td>2</td>
<td>12 min. 30 sec.</td>
<td>6 min. 30 sec.</td>
<td>14 min.</td>
</tr>
</tbody>
</table>

* All plasma dilutions brought to total volume of 0.1 cc. with normal saline.

### Table 8. Tests for Antithromboplastic Activity of Patient’s Blood Prothrombin Time (secs.)

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Human Thromboplastin</th>
<th>Rabbit Thromboplastin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Control</td>
<td>Patient Control</td>
</tr>
<tr>
<td>Undiluted</td>
<td>21 21</td>
<td>22 21</td>
</tr>
<tr>
<td>1:4</td>
<td>25 23</td>
<td>22.5 22</td>
</tr>
<tr>
<td>1:16</td>
<td>35 31</td>
<td>35 32</td>
</tr>
<tr>
<td>1:64</td>
<td>56 55</td>
<td>52 44</td>
</tr>
<tr>
<td>1:256</td>
<td>76 69</td>
<td>67 54</td>
</tr>
<tr>
<td>1:512</td>
<td>116 83</td>
<td>96 74</td>
</tr>
<tr>
<td>1:1024</td>
<td>135 100</td>
<td>135 110</td>
</tr>
</tbody>
</table>

per Kg. of body weight in a 500 cc. physiologic saline intravenous drip. Immediately after one of these injections, the clotting time was found to be 75 minutes. These findings suggest that the anticoagulant in this case was not heparin.

5. Determination of antithromboplastic activity of the patient’s plasma: Fresh thromboplastin from human and rabbit brains was prepared according to Quick’s method, and was diluted serially. Each dilution was tested for prothrombin activity with the patient’s and with normal plasma, using the Quick one-stage technic. It was found that the prothrombin time of the patient’s plasma was more prolonged than that of normal plasma when the higher dilutions of thromboplastin were used. This occurred with both types of thromboplastin (table 8).

These results suggest that the patient’s plasma possesses antithromboplastic activity for both human and rabbit brain thromboplastin.

6. Prothrombin consumption test: The prothrombin consumption during

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* Courtesy of Abbott Laboratories.
† Courtesy of Eli Lilly and Co.
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clotting of the patient's blood was studied following the technic described by Quick. Blood was allowed to clot in three tubes, the first of which was centrifuged 15 minutes after coagulation, the second 30 and the third 45 minutes after clotting had taken place. The prothrombin time of the sera was determined in each tube immediately after centrifugation and every 15 minutes for one hour after clotting. The results, shown in table 10, indicate that little prothrombin is consumed in the clotting of this patient's blood. Normal subjects are reported to show as much as 85 to 95 per cent consumption of prothrombin at the end of one hour after coagulation.

7. Effect of placental plasma on the clotting time of the patient's blood: Placental blood was aspirated with a 15 gauge needle and a 50 cc syringe from the umbilical cords of newborn infants before separation of the placenta had taken place. This blood was mixed in the syringe with 5 cc. 2.5 per cent sodium citrate and immediately centrifuged at 2,500 r.p.m. for 10 minutes. The supernatant plasma was then mixed with the patient's fresh whole blood in various proportions, and the clotting time was then estimated. It was found that in proportions as low as 1 part of placental plasma to 9 parts of patient's blood the clotting time of the patient's blood was reduced to 6 minutes from a previous value of 60 minutes (table 9). Normal plasma, prepared and treated in a manner similar to that with which placental blood was handled, and mixed with the patient's blood in proportions similar to those in which placental blood had been mixed, failed to shorten the patient's clotting time. In contrast with the high residual prothrombin activity in the patient's serum after spontaneous clotting, the serum that separated from the clotted mixtures of placental plasma and the patient's

**TABLE 9.—Effect of Fresh Placental Plasma on the Clotting Time of Patient's Blood* (No Recalcification Done)**

<table>
<thead>
<tr>
<th>cc. Placental Plasma</th>
<th>cc. Patient's Blood</th>
<th>Clotting Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20</td>
<td>1.80</td>
<td>6 min. 30 sec.</td>
</tr>
<tr>
<td>0.15</td>
<td>1.85</td>
<td>7 min. 20 sec.</td>
</tr>
<tr>
<td>0.10</td>
<td>1.90</td>
<td>13 min. 50 sec.</td>
</tr>
<tr>
<td>0.05</td>
<td>2.0</td>
<td>87 min.</td>
</tr>
</tbody>
</table>

* Normal blood plasma mixed with patient's blood in similar amounts failed to reduce the clotting time of patient's blood.

**TABLE 10.—Prothrombin Consumption Test**

<table>
<thead>
<tr>
<th>Tube</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15*</td>
<td>14</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>13*</td>
<td>13</td>
<td>12.5</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>13*</td>
<td>12.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Prothrombin assayed immediately after centrifugation.
blood had no residual prothrombin activity. It was also found that the clotting property of placental plasma was lost after storage in an ordinary electric refrigerator for twenty-four hours, but that it could be preserved for at least four weeks if the placental plasma was frozen immediately after collection and separation.

A total of 500 cc. of pooled placental plasma, obtained from 20 normal childbirths with sterile pyrogen-free equipment, and prepared and frozen in the above manner, was then administered intravenously to the patient over a 4½ hour period. The clotting time was reduced from 66 minutes to 33 minutes at the end of the plasma infusion, but returned to 66 minutes on the following day. There was no change in the appearance of the usual hemorrhagic phenomena after the administration of placental plasma.

**Discussion**

The clinical and laboratory findings in this case did not suggest any of the usual types of hemorrhagic diathesis. The sex, absence of family history and lack of response to fresh blood transfusions or to antihemophilic globulin ruled out hemophilia. The normal platelet counts, the normal clot retraction and the normal capillary fragility excluded thrombocytopenic purpura; the normal prothrombin time, hypoprothrombinemia; and the normal serum fibrinogen, fibrinopenia and afibrinogenemia. There were no morphologic abnormalities of the red or white blood cells. No indications of increased capillary fragility, of allergy, or of intercurrent disease were present.

On the other hand, a marked clinical resemblance existed with the cases of hemorrhagic diathesis due to a circulating anticoagulant. The inability to correct the clotting defect upon the addition—in vivo or in vitro—of normal blood, indicated that there was no deficiency of any of the factors involved in blood coagulation. The data presented established the presence of a circulating anticoagulant in this patient’s blood and plasma, and the lack of response to toluidine blue or protamine sulfate suggested that the anticoagulant was not heparin. Facilities were not available for electrophoretic studies on this patient’s plasma.

Although many details of the mechanism of blood coagulation are far from clear, it is generally accepted that the process takes place in three main stages, as follows: **Stage 1**: the activation of thromboplastin from its precursor, thromboplastinogen, by an enzyme found in platelets. **Stage 2**: the conversion of prothrombin into the enzyme thrombin, a process which involves the participation of “conversion factors” (thromboplastin, calcium, plasma prothrombin conversion factor) and “accelerators” (serum accelerator and platelet accelerator). **Stage 3**: the clotting of fibrinogen to fibrin by thrombin.

Some of the studies done, such as the normal prothrombin time and normal SPCA, as well as the calcium and fibrinogen determinations, suggest that the second and third stages of coagulation are normal in this patient, and that the clotting defect might be localized in the first stage. It seems plausible to think that the abnormal clotting results from interference with, or inhibition of, one or more of the factors involved in the first stage of coagulation which are thromboplastinogen, thromboplastin and the enzyme or “platelet” factor.

No tests were made for an inhibitor of thromboplastinogen, which is considered
identical with antihemophilic globulin.24 Craddock and Lawrence8 have reported 2 hemophilic patients who developed a circulating anticoagulant after receiving multiple blood transfusions. The anticoagulant was thought to be an antibody to antihemophilic globulin, and was believed to result from an immunity mechanism aroused by the repeated administration of antihemophilic globulin which the patients lacked. On clinical grounds we have no evidence for this type of an anticoagulant in our patient, since she does not have hemophilia or a history of having received blood transfusions before onset of the disease. Likewise, no evidence for any other type of immunization mechanism has been found in this case.

The presence of an inhibitor of the platelet enzyme factor that mediates the conversion of thromboplastinogen to thromboplastin has not been ruled out by us. However, the normal platelet count and clot retraction in our patient would point to normal platelet function.

We believe that our patient’s plasma has antithromboplastic activity, and that the anticoagulant concerned may be an antithromboplastin. This belief is based on the progressive prolongation of the clotting time of the patient’s plasma, over that of normal plasma, upon the addition of increasingly smaller amounts of thromboplastin. However, the anticoagulant does not seem to be identical with the antithromboplastin described by Tocantins,27 since its action persisted after heating to 61 C. and after other experimental manipulations described. Fantl and Nance7 report a case of bleeding tendency due to a circulating anticoagulant which was antithromboplastic for the thromboplastin of human brain but not for that of the rabbit. In our case the antithromboplastin does not seem to be species-specific.

The mechanism of correction of the patient’s clotting defect in vitro by the addition of fresh placental plasma is not known. The lack of such an effect with normal blood plasma would suggest that some factor, present in placental plasma, promotes accelerated clotting of the patient’s blood. Direct neutralization of the anticoagulant is a possibility. It would seem more likely however, that the addition of an excess of active thromboplastin, possibly contained in placental plasma, brought about normal coagulation in the test tube. The moderate reduction in clotting time after the administration of placental plasma to the patient must be interpreted with caution in light of the intrinsic errors of the clotting time determination, especially when coagulation is unduly prolonged.28 The administration of plasma is necessarily a slow process, and the possible thromboplastic substance, or the inhibitor of the anticoagulant, could have been destroyed or neutralized before effective concentrations were reached. Perhaps by plasma fractionation methods a more potent preparation could be obtained from placental plasma which would have therapeutic effectiveness in a case like this one. The effect of placental plasma in diseases such as hemophilia and thrombocytopenic purpura, in which the first phase of coagulation is affected, deserves investigation.

Some clinical observations on this patient deserve mention. A severe dental hemorrhage appears to have been the precipitating factor in her illness. The regularity and normalcy of the menses in the presence of continuous hemorrhagic episodes and of a prolonged clotting time were extraordinary. We have no adequate explanations for these phenomena.
This condition is probably commoner than appears from the number of cases reported to date, since they are progressively increasing. Even prior to the recognition of circulating anticoagulants as a cause of bleeding tendency, there were reports of cases with similar clinical pictures in which no specific search for anticoagulants was made.\(^29\),\(^30\) Recent refinements in technics for the detection of these anticoagulants have facilitated the study of this problem.\(^11\) A better understanding of this disease, or group of diseases, and a rational therapeutic approach await a fuller knowledge of the fundamentals of blood coagulation and more complete clinical and experimental data on patients suffering from this type of hemorrhagic diathesis.

**SUMMARY AND CONCLUSIONS**

1. A case is reported of hemorrhagic diathesis in a woman in which the presence of an anticoagulant in the patient's blood and plasma could be demonstrated.

2. The anticoagulant was shown to be active in dilutions up to 1:350. It retained its potency after heating to 61 C. for 10 minutes and after storage, either in a refrigerator or at room temperature, for twenty-four hours.

3. The anticoagulant was not neutralized by protamine sulfate or by toluidine blue. Placental plasma corrected the clotting defect in vitro but was ineffective when administered intravenously to the patient.

4. Evidence is presented suggesting that the second and third stages of coagulation in this case are normal, that the patient's plasma has antithromboplastic activity, and that the anticoagulant may be antithromboplatin.

**REFERENCES**


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