Plasma Thromboplastin Component (PTC)
A Hitherto Unrecognized Blood Coagulation Factor
Case Report of PTC Deficiency
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In preliminary reports we described a new hemorrhagic disease caused by the deficiency of a previously unrecognized plasma thromboplastin component (PTC) and outlined a method for the partial purification and concentration of the PTC factor. It is the purpose of the present report to amplify the description of the hemorrhagic diathesis in our patient and to present the details of experimental procedures used in the investigation of his coagulation defect.

Case Report

The patient, K. K., an only child, is a 16 year old boy who first entered the University of California Hospital in October, 1936, at the age of 8 months with moderately severe purpura. Because of ecchymoses about the head and a low hemoglobin concentration, a blood transfusion was given during the first week of life. He was admitted to the hospital on six occasions during the ensuing twenty-six months because of recurrent attacks of purpura and intractable bleeding from skin and tongue lacerations. During this period platelet counts varied between 40,000 and 450,000 per cu. mm. Clot retraction was poor and the bleeding time normal. The capillary blood clotting times were within normal limits. Venous blood clotting times were not done. A splenectomy was performed in April, 1938. There was slightly increased bleeding from the wound during and immediately after the operation. There was no improvement in the bleeding tendency following splenectomy. During the ensuing year it was found that the bleeding time, platelet count, capillary resistance, clot retraction and the fibrinogen, calcium and one-stage prothrombin concentrations were normal, but that the venous whole blood coagulation time was markedly pro-
longed. Although there was no definite family history of hemorrhagic disease, the patient was thought to suffer from hemophilia. From 1938 to 1948 he was admitted to the hospital on 107 occasions at intervals of approximately one month, because of major bleeding, which involved the large joints and deep subcutaneous tissues, the muscles, gastro-intestinal tract, pharynx and retroperitoneal region. In all instances the prolonged coagulation time was markedly shortened, and the hemorrhage was rapidly controlled by the transfusion of whole blood, fresh or frozen plasma, or freshly lyophilized plasma. Since early in 1949 the patient has received transfusions of 500 cc. of fresh or freshly lyophilized plasma in the Out-Patient Department at intervals of ten to fourteen days as a prophylactic measure, and during this time he has required hospitalization on only four occasions for episodes of major bleeding. On many occasions during this interval, however, beginning hemorrhages into joints have been controlled by out-patient transfusion. It is estimated that the occurrence of major hemorrhagic episodes has been somewhat less than half as frequent as the incidence before the prophylactic transfusion regimen was instituted.

The patient's growth and physical development have not been impaired. He is 68 inches tall and weighs 110 pounds. He is above average in intelligence and is cheerful and cooperative. Despite frequent absences, his progress in school has not been affected. The only major illness not due to hemorrhage from which he has suffered was varicella which occurred in March, 1949. Physical examination at the present time is entirely normal, except for the splenectomy scar and for limitation of extension of the left elbow to 170 degrees.

Investigation of the Coagulation Defect: Methods and Results

Venous Whole Blood Coagulation Time

All coagulation time determinations were done by a modified Lee-White method at 37 C. In order to obtain blood free of tissue juices, meticulous care was exercised in all venipunctures. The first 3 to 5 cc. of blood were collected in a separate syringe and discarded, and the blood collected in a second syringe was used for testing.

It is difficult to state what the coagulation time of this patient's blood would be if it were possible for him to go an indefinite time without transfusion. During the past four years while he has been under intensive investigation, he has rarely been allowed to go longer than two weeks without transfusion of normal plasma. In general, the coagulation time has ranged between 7 and 12 minutes immediately following transfusion and between 20 and 30 minutes two weeks later. When longer periods have been allowed to elapse between transfusions, coagulation times as long as 135 minutes have been obtained. It has been a characteristic reaction of this patient that the effect of transfused blood or plasma on the coagulation time is of longer duration than in the usual case of hemophilia (table 1).

Plasma Coagulation Time

Five cc. of venous blood were placed in a glass tube containing 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate. The blood was centrifuged at 2400 r.p.m. for 10 minutes, and the supernatant plasma was used for testing. One-tenth cc. of plasma was mixed with 0.1 cc. of 0.9 per cent sodium chloride in clean glass tubes measuring 12 by 100 mm. and placed in a water bath at 37 C.; 0.1 cc. of 0.025 M calcium chloride was then added, and the tube was dipped in and out of the water bath until a fibrin clot appeared. The tests were done in triplicate and the results averaged. The normal range for this method is 100 to 200 seconds.

The patient's plasma coagulation time immediately after transfusion was within the normal range. When the whole blood coagulation time ranged upward of 20 minutes, the plasma coagulation time varied between 400 and 600 seconds.

One-Stage Prothrombin Determination

Various adaptations of Quick's one-stage procedure were employed, using Russell viper venom and tissue thromboplastins from a variety of sources, including human brain, rabbit brain and beef lung. In more recent determinations a commercial thromboplastin
calcium preparation,* which has proved satisfactory and convenient in our laboratory, has been used.

In numerous tests by this variety of methods, the patient’s prothrombin activity has always been found to be between 80 and 100 per cent of normal.

Two-Stage Prothrombin Determination

The procedure of Ware and Seegers,4 using a lyophilized reaction mixture† and bovine fibrinogen,‡ was employed.

In numerous tests with or without an added source of prothrombin accelerators, the patient’s prothrombin concentration has ranged between 80 and 100 per cent of normal.

Prothrombin Utilization Tests§,8

Two-stage prothrombin tests were done on serum obtained from blood incubated for one hour in pyrex test tubes at 37 C. The blood was citrated with 1/10 volume of 3.2 per cent sodium citrate at the expiration of the incubation period. The tests were done on the pooled serum from duplicate specimens. In order to convert prothrombin units to per cent

<table>
<thead>
<tr>
<th>TABLE 1.—Effect of Transfusions of 500 cc. of Whole Blood in Hemophilia and in PTC Deficiency</th>
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<tbody>
<tr>
<td>Whole Blood Coagulation Time (minutes)</td>
</tr>
<tr>
<td>Hemophilia</td>
</tr>
<tr>
<td>Before transfusion 60</td>
</tr>
<tr>
<td>After transfusion</td>
</tr>
<tr>
<td>½ hour 7</td>
</tr>
<tr>
<td>1 day 17</td>
</tr>
<tr>
<td>2 days 22</td>
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<tr>
<td>3 days 24</td>
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<tr>
<td>4 days 65</td>
</tr>
<tr>
<td>5 days 103</td>
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<tr>
<td>6 days 91</td>
</tr>
<tr>
<td>7 days 13</td>
</tr>
<tr>
<td>8 days 15</td>
</tr>
<tr>
<td>10 days 17</td>
</tr>
<tr>
<td>12 days 17</td>
</tr>
<tr>
<td>17 days 19</td>
</tr>
</tbody>
</table>

the values obtained were compared to normal plasma values. In the normal subject the residual serum prothrombin is 10 to 30 per cent of the original plasma value.

The residual serum prothrombin in this patient has ranged between 20 and 30 per cent of his plasma prothrombin values immediately after transfusion and between 80 and 100 per cent two weeks after transfusion.

All of the results herein reported were done by the above two-stage method. Similar results were found using the one-stage method of Stefanini and Crosby.9

Prothrombin Conversion Accelerator I Tests

Tests for labile factor were done by a modification of Quick’s method.10 The test plasmas were adsorbed with barium sulfate,§ and 0.1 cc. of test plasma was mixed with 0.4 cc. of

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* Simplastin, Chilcott Laboratories, Morris Plains, N. J. A lyophilized rabbit brain-lung preparation kindly supplied by the manufacturer.
† Baeto Prothrombin Two-Stage Reaction Mixture, Difco Labs. Inc., Detroit, Mich.
‡ Armour Laboratories, Chicago, Ill.
§ Fifty mg. barium sulfate per cc. of oxalated plasma.
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Aged plasma. The one-stage prothrombin time of the aged plasma was reduced from 32.1 seconds to 24.6 seconds by the patient's plasma and to 23.3 seconds by the normal control plasma.

The results of tests for plasma Ac-globulin, done by the method of Ware and Seegers, are shown in figure 1. The results obtained with the patient's plasma and with that of a normal control were almost identical.

Prothrombin Conversion Accelerator II Tests

SPCA was determined by a method based upon the effect of the admixture of serum on the prothrombin time of normal plasma. The activity of SPCA is expressed as the enhancement, in per cent, of the prothrombin activity of a serum-plasma mixture over and above the algebraic sum of the prothrombin activities of each component. The normal range is given by Alexander as 43 per cent to 271 per cent, with an average of 99.4 per cent.

It has been found necessary to supplement hemophilic and thrombocytopenic bloods with thromboplastin in order to induce normal serum SPCA. This is believed not to be due to the possibility of unconsumed thromboplastin in the serum. When this was done with the blood of our patient, the SPCA content of his serum was found to be 168 per cent, which is well above the average normal value. Without the addition of tissue thromboplastin to our patient's blood, the SPCA content of his serum was found to be 60 per cent, which is slightly low but within the normal range.

In the two-stage co-thromboplastin assay method of Mann, the ability of a 1:100 dilution of test plasma or serum, preincubated with thromboplastin and calcium, to accelerate the early formation of thrombin in normal plasma is determined. With this test the plasma of our patient was found to have 133 per cent co-thromboplastin activity.

In the proconvertin test of Owren and Aas and the Factor VII test of Koller et al., the accelerating effect of a test plasma or serum on the production of thrombin from prothrombin in oxalated, Seitz-filtered bovine plasma is determined. Using the proconvertin test, it was found that the patient's plasma and serum was 62 per cent to 85 per cent of the normal control.

Fig. 1.—Plasma and platelet Ac-globulin concentrations of normal and PTC-deficient patients.
Addition of 0.1 cc. of plasma, containing 10 per cent prothrombin and less than 10 per cent proconvertin, from a patient under treatment with Dicumarol to 2.0 cc. of our patient's blood resulted in reduction of his residual serum prothrombin from 100 per cent to 41 per cent. Addition of 0.1 cc. of serum from the same dicumarolized patient, containing less than 10 per cent proconvertin and prothrombin, added to 2.0 cc. of our patient's blood resulted in reduction of his residual serum prothrombin from 100 per cent to 18 per cent.

Exclusion of Anticoagulants

The characteristic reaction of the patient's coagulation time to transfused blood or plasma effectively demonstrated the absence of anticoagulants. Further in vitro tests confirmed this observation (table 2).

Exclusion of Anti-Hemophilic Factor Deficiency

The coagulation time of mixtures of the patient's plasma with each of three hemophilic plasmas (fig. 2) clearly demonstrated the ability of 3/10 volume of the patient's plasma to correct the hemophilic defect and of 3/10 volume of hemophilic plasma to correct the patient's defect. Mixtures of the three hemophilic plasmas with each other failed to result in any significant shortening of the coagulation time (fig. 3). It was also found that the addition of 1/10 volume of the patient's plasma to hemophilic blood not only resulted in a normal whole blood coagulation time but also in normal prothrombin utilization.

There was no shortening of the whole blood coagulation time following the intravenous administration of 1.2 Gm. (2 ampules)* of Fraction I of Cohn (fig. 4) nor following its addition to the patient's blood in various concentrations in vitro (fig. 5). The same preparations were found to be potent when tested in vivo and in vitro in hemophilic patients.

Effect of Tissue Thromboplastins

Plasma coagulation times were done on the patient's and on hemophilic plasma by the method described above, substituting diluted accelerator-free beef-lung thromboplastin for 0.9 per cent sodium chloride in the test. In both plasmas the coagulation time was significantly shortened by the addition of the 1 X $10^{-4}$ dilution of thromboplastin, and in both the coagulation time was shortened to the same degree, as was the normal, by the addition of the stock thromboplastin diluted to as much as $1 \times 10^{-3}$ (fig. 6). These results were comparable to those found by Biggs and Macfarlane in hemophilia.

The effect of heated rabbit brain thromboplastin on the prothrombin utilization in

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* Kindly supplied by the Cutter Laboratories, Berkeley, Calif. Each ampule contained 600 mg. of lyophilized material, of which 60 per cent was fibrinogen and 40 per cent anti-hemophilic globulin.
hemophilia, PTC deficiency and thrombocytopenic purpura is shown in table 3. In all three diseases prothrombin utilization was markedly enhanced by the addition of thrombo-
Fig. 4.—Coagulation times of hemophilic and PTC-deficient patients after administration of Cohn's Fraction I intravenously.

Fig. 5.—Reaction of PTC-deficient and hemophilic plasmas to Cohn's Fraction I in vitro.

plastin heated to 50 C. for 20 minutes. When the thromboplastin was heated to 60 C. for 20 minutes, prothrombin utilization remained poor in hemophilia and PTC deficiency but was still markedly enhanced in thrombocytopenia. Similar results were obtained with a
rabbit brain-lung preparation.* The results with respect to heated thromboplastins show that PTC deficiency behaves in a manner similar to that reported by Quick et al.\textsuperscript{22} for hemophilia. The supernate of thromboplastin centrifuged at 75,000 G. for 30 minutes was devoid of PTC activity, in contrast to the supernate of oxalated plasma which still retained all of its PTC activity after similar centrifugation (fig. 7).

![Graph of Dilution of Beef Lung-Ac. Free Thromboplastin](image)

Fig. 6.—Reaction of hemophilic, PTC-deficient and normal plasma to diluted Ac-free thromboplastin.

<table>
<thead>
<tr>
<th>Table 3. Effect of Heated Rabbit-Brain Thromboplastin on Prothrombin Utilization in Hemophilia, PTC Deficiency and Thrombocytopenic Purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Prothrombin in Per Cent*</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Without thromboplastin</td>
</tr>
<tr>
<td>Thromboplastin heated to 50 C. for 20 minutes</td>
</tr>
<tr>
<td>Thromboplastin heated to 60 C. for 20 minutes</td>
</tr>
</tbody>
</table>

* 0.05 cc. of heated thromboplastin (Difco) added to 2.0 cc. of patient’s blood.

It was also found that the serum prothrombin was reduced from 74 per cent to 5 per cent by the addition of 0.1 cc. (0.1 \(\mu\)g.) of Russell viper venom\textsuperscript{†} to 2.0 cc. of the patient’s blood. This result is similar to that found in hemophilia.

* CH-61 (Calcium-free Simplastin) kindly supplied by Chilcott Laboratories, Morris Plains, N. J.

† Stypven, Burroughs Wellcome Co., New York, N. Y.
The prothrombin utilization was not improved by the addition of 0.1 cc. amounts (containing 0.025 and 0.1 mg.) of beef brain cephalin-lecithin (prepared after the method of Milstone) to 2.0 cc. of the patient’s blood. This result is similar to that reported by Lang-dell et al., who found this fraction ineffective in hemophilia, and lends support to Mil-stone’s concept that “lipoid thromboplastins” are to be classified with platelets as “ac-cessory thromboplastins.”

Exclusion of Platelet-Factor Deficiencies

Ac-globulin tests by the method of Ware, Fahey and Seegers on various concentrations of washed platelet suspensions and their supernatants gave normal results (fig. 1). It was found that the addition of 0.1 cc. of either normal or hemophilic “platelet-poor” plasma, prepared by methods described below, to 2.0 cc. of the patient’s whole blood re-sulted in a marked shortening of the whole blood coagulation time and a marked increase in prothrombin utilization (fig. 7). Further evidence excluding platelet factor deficiencies was obtained by the finding that the patient’s washed platelets corrected the defective prothrombin utilization of normal platelet-poor native plasma (table 4).

Effect of Normal Serum

Human plasma was collected in sterile glass centrifuge tubes or bottles and allowed to stand at room temperature for 48 hours, by which time it was usually free of prothrombin as shown by the two-stage test. The addition of 0.1 cc. of such serum to 2 cc. of the pa-tient’s whole blood resulted in marked shortening of the coagulation time and a marked

* The term “platelet-poor” plasma as used in this paper refers to plasma which, after high speed centrifugation, showed no platelets by direct examination with the phase microscope. It is not meant to imply complete absence of platelets or platelet products.
increase in prothrombin utilization (fig. 8). Transfusion of 500 cc. of serum to the patient gave similar results; the whole blood coagulation time was reduced from 20 to 8 minutes, and the residual serum prothrombin decreased from 100 per cent to 38 per cent as shown by the two-stage test. These results further exclude a deficiency of the anti-hemophilic factor, since serum has little or no ability to correct the hemophilic defect.*

**Effect of Serum or Plasma Adsorbed with Barium Sulfate**

Adsorbed normal serum and oxalated platelet-poor plasma were prepared according to the method given below, using 50 mg. barium sulfate (C.P.) per cc. of plasma or serum.

**Table 4:** Effect of Washed Platelets from PTC-Deficient Patient on Prothrombin Utilization of Platelet-Poor Native Normal Plasma

<table>
<thead>
<tr>
<th>Substance Added to 1.0 cc. Platelet-poor Plasma</th>
<th>Serum Prothrombin in per cent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 cc. buffered saline</td>
<td>90</td>
</tr>
<tr>
<td>0.1 cc. platelet suspension from patient (4 × 10⁶ per cu. mm.)</td>
<td>10</td>
</tr>
</tbody>
</table>

* Two-stage method one hour after coagulation of plasma.

![Residual Serum Prothrombin (%)](image)

**Fig. 8.** Prothrombin utilization in hemophilia and PTC deficiency following the addition of various blood fractions (0.1 cc. of each fraction added to 2.0 cc. of blood).

The addition of 0.1 cc. of adsorbed plasma or serum to 2 cc. of the patient's blood resulted in little or no shortening of the coagulation time or in prothrombin utilization (figs. 7, 8). These results again served to differentiate the patient's coagulation defect from that in hemophilia and parahemophilia, since neither anti-hemophilic factor nor accelerator 1 is removed by barium sulfate adsorption.

**Comment**

It has been generally accepted that in the normal process of coagulation, prothrombin is converted to thrombin by the action of thromboplastin, cal-
calcium and two distinct prothrombin conversion accelerators (fig. 9 and table 5). Prior to the discovery of PTC the thromboplastin required for this reaction to occur in blood free of fixed tissue products was thought to be derived from the interaction of the blood platelets and a single plasma component, the anti-hemophilic factor. A normal one-stage prothrombin test associated with deficient prothrombin utilization has been shown to occur only when there is a defect in the production of thromboplastin from its precursors. Abundant proof was obtained in this patient that the anti-hemophilic and platelet factors were present in normal quantities, and it was therefore concluded that his coagulation defect was caused by the deficiency of a previously unrecognized element in the blood coagulation mechanism which we have designated as the plasma thromboplastin component (PTC).

The correction of the patient's coagulation defect by normal serum, its failure to be corrected by plasma which had been adsorbed with barium sulfate and the results of the SPCA test without added thromboplastin might suggest an ac-

**TABLE 5.—Synonyms for Some Factors in the Blood Coagulation Mechanism**

<table>
<thead>
<tr>
<th>Anti-hemophilic Factor</th>
<th>Prothrombin Conversion Accelerator I*</th>
<th>Prothrombin Conversion Accelerator II*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Globulin substance&quot;27</td>
<td>Labile factor29</td>
<td>Serum prothrombin conversion accelerator12</td>
</tr>
<tr>
<td>Anti-hemophilic globulin33</td>
<td>Factor V and VI32</td>
<td>Stable factor24</td>
</tr>
<tr>
<td>Thromboplastinogen29</td>
<td>Proaccelerin and accelerin18</td>
<td>Proconvertin16</td>
</tr>
<tr>
<td>Thromboctylosin30</td>
<td>Plasma and serum accelerator globulin33</td>
<td>Co-thromboplastin14</td>
</tr>
<tr>
<td>Thromboplastin Plasma component11</td>
<td></td>
<td>Factor VII13</td>
</tr>
</tbody>
</table>

* Accelerator I and II are not proposed as superior terms, but are used for convenience and clarity in the text.
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celerator II deficiency. However, the consistently normal one-stage prothrombin test and the finding of normal quantities of accelerator II in the patient's plasma and serum as shown by the proconvertin and co-thromboplastin tests and by the SPCA test with added thromboplastin completely excluded this diagnosis.

In the patient with congenital SPCA deficiency reported by Alexander et al., the principal abnormality was a prolonged one-stage prothrombin time. The venous whole blood coagulation time and the two-stage prothrombin utilization tests were normal. Tissue thromboplastin added to the patient's whole blood in vitro failed to produce normal quantities of SPCA in the serum. These findings are in direct contrast to those in our case, in which the whole blood coagulation time was prolonged, the one-stage prothrombin time was normal, the prothrombin utilization, as shown by the two-stage test, was deficient, and normal quantities of SPCA were found in the serum when the same amount and type of tissue thromboplastin as used by Alexander was added to the patient's blood.

With the two-stage co-thromboplastin assay method of Mann and the proconvertin test of Owren and Aas, normal quantities of accelerator II were found in the patient's plasma and serum, even though the latter contained large quantities of unconsumed prothrombin. We prefer these methods to the SPCA test for the determination of accelerator II because plasma, as well as serum, may be tested and because large quantities of unconsumed prothrombin in the serum from patients with thromboplastin deficiency diseases (hemophilia, thrombocytopenia, and PTC deficiency) do not alter the results of the tests. The proconvertin test has the added advantage in the stability of the frozen, Seitz-filtered, oxalated bovine plasma which is employed in the test.

In addition to the single case of SPCA deficiency reported by Alexander et al., there is an abundant source of accelerator II deficient plasma and serum in patients under treatment with Dicumarol. A roughly proportional decrease in prothrombin and accelerator II has been found following Dicumarol administration. It was found that accelerator II deficient plasma and serum from patients under treatment with Dicumarol corrected our patient's defective prothrombin utilization when added to his blood in vitro.

It has been clearly demonstrated by several groups of investigators that accelerator II hastens the early rate of thrombin formation as measured in a two-stage system. We have repeatedly found a normal rate of maximum thrombin formation in our patient, using a standard two-stage prothrombin determination method.

Additional data presented below shows that normal plasma heated to 56 C. for 3 minutes, normal plasma adjusted to pH 4.1 for 2 hours and then brought back to neutrality, the euglobulin fraction of normal serum, and the 45 to 50 per cent saturated ammonium sulfate fraction of normal plasma correct the patient's coagulation defect, despite the fact that they contain only small quantities of accelerator II. Finally, a purified PTC preparation made from normal serum, which is totally free of accelerator II, also completely corrects the patient's coagulation defect when added to his blood in vitro.

It must be concluded, therefore, that despite some superficial similarities between SPCA and PTC deficiency, the two diseases are distinct entities.

Parahemophilia (accelerator I deficiency), first reported by Owren, can be
easily distinguished from PTC deficiency, since in the former the one-stage prothrombin test is prolonged, the two-stage prothrombin test without an added source of accelerator I, such as beef serum, shows a deficient rate of thrombin formation, tests for labile factor and Ac-globulin give abnormal results, and the coagulation defect can be corrected by the addition of normal plasma which has been adsorbed with barium sulfate. These findings are all in direct contrast to those which were found in our patient with PTC deficiency. The principal points of similarity between the two diseases are the prolonged whole blood coagulation time, defective prothrombin utilization and correction of the coagulation defect by normal plasma.

PARTIAL CONCENTRATION, PURIFICATION AND CHARACTERIZATION OF PTC: METHODS

PTC Assay

No arbitrary units of PTC activity have been assigned, since it has been impossible yet to study PTC in a "purified" system of coagulation factors. However, it has been found convenient to express the PTC activity of various plasma and serum fractions by the percentage they enhance the patient's defective prothrombin utilization according to the following formula:

\[
\text{Per cent enhancement} = \frac{\text{Patient's serum prothrombin per cent after fraction added} - \text{Patient's serum prothrombin per cent}}{\text{Patient's serum prothrombin per cent}} \times 100
\]

For example, if the patient's serum prothrombin is 80 per cent and is reduced to 20 per cent after a corrective fraction is added:

\[
\text{Per cent enhancement} = \frac{80 - 20}{20} \times 100 = 300 \text{ per cent}
\]

The range of prothrombin enhancement for effective fractions was 130 to 700 per cent.

Oxalated Plasma

One volume of 0.1 M potassium oxalate per 9 volumes of blood.

Preparation of "Platelet-Poor" Plasma

Platelet-poor plasmas were prepared by several technics. The blood was collected as for venous whole blood coagulation time, except that the syringes were lined with silicone oil. The blood was centrifuged at 5000 r.p.m. for 30 minutes in lusteroid tubes in a small angle centrifuge placed in a refrigerator at 4°C. The supernatant plasma was placed in lusteroid tubes and centrifuged in a refrigerated ultracentrifuge at 30,000 r.p.m. (75,000 G.) for 30 minutes. The upper half of the plasma was carefully pipetted off and used for testing. This method was adopted in order to insure the sedimentation of "platelet fragments" and/or the plasma thromboplastin described by Chargaff et al. The efficiency of platelet removal was determined by prothrombin utilization tests done on recaclified oxalated plasma or on native plasma (containing no anticoagulant) allowed to clot in pyrex tubes. Only those specimens showing poor utilization of prothrombin were used.

* G. E. Silicone Oil #9996-300.
Adsorption of Plasma or Serum with Barium Sulfate

Varying amounts of barium sulfate (C.P.) were added to serum or oxalated platelet-poor plasma in thin-walled glass tubes and stirred continuously for 10 minutes at 37 C. The specimen was centrifuged at 3000 r.p.m. for 30 minutes and the supernatant plasma or serum was used for testing.

Preparation of Plasma Fractions by Ammonium Sulfate Precipitation

Of several methods investigated, the following proved most reliable. Saturated ammonium sulfate solution at pH 7.5 and at room temperature was added dropwise to a constantly stirred 1:3 dilution of platelet-poor oxalated plasma in distilled water kept at 2 C. in an alcohol-water-ice bath. When the desired salt concentration was reached, the plasma was allowed to stand for 1 hour at 4 C. The precipitates were collected by centrifugation and washed twice in ammonium sulfate of the same concentration as that from which they were precipitated. They were then dissolved and reconstituted with 0.32 per cent sodium citrate in 0.9 per cent sodium chloride to one-half the original volume of plasma from which they were obtained. Each specimen was placed in cellophane dialysis tubing which was suspended from a slowly rotating motor and immersed in 3 liters of 0.32 per cent sodium citrate in 0.9 per cent sodium chloride at 4 C. The dialysis solution was usually changed after 4 hours, and the dialysis was continued overnight. A negative test for sulfate ion with barium chloride was usually obtained with the dialysis solution after the above procedure. The dialyzed protein fraction was then reconstituted with the citrate-saline solution to the same volume of plasma from which it was derived and either frozen at minus 30 C. or lyophilized. The fractions so obtained were thrombin free.

Preparation of Euglobulin and Pseudoglobulin-Albumin Fractions

Serum was diluted 10 times in distilled water and 1 per cent acetic acid was added at room temperature until the pH was reduced to 5.1 as measured with a glass electrode. The euglobulin precipitate was allowed to settle at 4 C. for 1 to 2 hours and was then recovered by centrifugation. The supernate which contained the pseudoglobulin-albumin fraction was lyophilized, after which it was reconstituted to its original plasma volume with 0.32 per cent sodium citrate in 0.9 per cent sodium chloride and stored at minus 20 C. The euglobulin precipitate was washed twice in pH 5.1 distilled water and then dissolved and reconstituted to its original plasma volume with citrate-saline solution and stored at minus 30 C.

Preparation of PTC from Plasma

Five cc. aliquots of platelet-poor oxalated plasma were heated in thin-walled glass test tubes at 56 C. for 5 minutes and immediately cooled to room temperature in an ice bath. The coagulated fibrinogen was removed by centrifugation and the supernate adsorbed with barium sulfate. The button of barium sulfate with its adsorbed PTC was washed twice by dispersion with 5 cc. of 0.02 M acetate buffer (pH 5.2) and was centrifuged at 3000 r.p.m. for 30 minutes. The PTC was then eluted two times from the barium sulfate button with 5 per cent sodium citrate in 0.9 per cent sodium chloride, so that the final volume of eluate equaled the original volume of plasma processed. The citrate eluate was then dialyzed against 0.9 per cent sodium chloride at 4 C. for 24 hours. The dialyzed eluate may be either frozen at minus 30 C. or lyophilized. Such PTC preparations are free of platelet factors, thrombin, fibrinogen, and accelerator I, but usually contain traces of prothrombin and accelerator II, which, however, do not appear to affect the results of tests for PTC activity.

Preparation of PTC from Serum

Since the publication of our preliminary report,1 we have developed an improved method for the preparation of PTC from serum. Nine volumes of serum obtained from blood

* Fifty mg. barium sulfate (C.P.) per cc. of plasma.
allowed to clot for 24 hours in glass test tubes at room temperature are mixed with one volume of 3.2 per cent sodium citrate and allowed to stand at 37 C. for 30 minutes to assure neutralization of any remaining thrombin. The pH of the serum is then reduced to 2.9 by the dropwise addition of 1 N hydrochloric acid and is allowed to stand for 2 hours at 37 C. The pH is then readjusted to neutrality by the dropwise addition of 1 N sodium hydroxide. The pH determinations are made with a glass electrode. The complete inactivation of any remaining prothrombin and accelerator II by this procedure is shown by the proconvertin and two-stage prothrombin tests on the serum. The PTC fraction is then separated from the majority of the solids in the serum by adsorbing it on barium sulfate (50 mg. per cc. of serum) at 37 C. for 15 minutes. The preparation is then centrifuged at 3000 r.p.m. for 30 minutes and the supernate discarded. The PTC is then eluted from the barium sulfate button with a sufficient quantity of 5 per cent sodium citrate in 0.9 per cent sodium chloride at 37 C. for 15 minutes so that the volume of the eluate is equal to one-half that of the original volume of serum processed. The barium sulfate is removed by centrifugation at 3000 r.p.m. for 30 minutes and the supernatant eluate is dialysed against 0.9 per cent sodium chloride for 24 hours. The dialysed eluate is then reconstituted to the original volume of serum processed and either frozen at minus 30 C. or lyophilized. The preparations so obtained have been totally free of prothrombin and accelerator II and all other known coagulation factors. When our patient's serum was used as the starting material, an inert PTC preparation resulted.

RESULTS

PTC Content of Adsorbed Normal Plasma

All of the adsorbants® commonly employed to remove prothrombin from oxalated plasma also remove PTC. Neither factor is removed by Berkfeld V filtration, but both are removed by Seitz filtration. "Supereel,"® which removes Milstone's accessory thromboplastin,® does not adsorb prothrombin or PTC.

Barium sulfate was chosen as a satisfactory agent for the adsorption of PTC from plasma or serum, despite its known ability to also adsorb prothrombin, accelerator II®, and cholesterol and hexoses® from plasma and large amounts of thromboplastin from suspensions of tissue extract.® We have also found that it adsorbs platelet factors, unless platelet-poor plasma is employed.

In table 6 the effect of varying degrees of barium sulfate adsorption of normal oxalated

* Supplied by the Johns Manville Co., San Francisco, Calif.

<table>
<thead>
<tr>
<th>BaSO4 in mg. per cc. oxalated normal platelet-poor human plasma adsorbed for 10 minutes at 37 C.</th>
<th>Prothrombin concentration of adsorbed plasma in per cent*</th>
<th>Prothrombin conversion accelerator II concentration of adsorbed plasma in per cent†</th>
<th>Enhancement of patient's prothrombin utilization by adsorbed plasma in per cent‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>900</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>48</td>
<td>340</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>16</td>
<td>143</td>
</tr>
<tr>
<td>15</td>
<td>&lt;1</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

* Two-stage method of Ware and Seegers.†
† Method of Owren.‡
‡ 0.1 cc. adsorbed normal plasma added to 2.0 cc. patient's blood. On the day of this test, the patient's plasma prothrombin was 100% and the serum prothrombin without addition of adsorbed plasma was 100%. (No utilization of prothrombin.)
PLASMA THROMBOPLASTIN COMPONENT

platelet-poor plasma on the patient's defective prothrombin utilization is shown. The use of 50 mg. of barium sulfate per cc. of plasma resulted in complete removal of prothrombin, prothrombin conversion accelerator II and PTC. Lesser quantities of barium sulfate resulted in similar degrees of incomplete removal of all three factors. In other experiments, it was found that no clear-cut separation of these factors could be made with barium sulfate from citrated plasma or serum.

PTC Content of Plasma Fractions Obtained by Ammonium Sulfate Precipitation

Table 7 shows the effect of various plasma fractions obtained by ammonium sulfate precipitation. The PTC appears to be concentrated in the fraction which precipitates

<table>
<thead>
<tr>
<th>Ammonium sulfate fraction (per cent ammonium sulfate saturation)</th>
<th>Prothrombin concentration of ammonium sulfate fractions in per cent</th>
<th>Prothrombin conversion accelerator II concentration of ammonium sulfate fractions in per cent</th>
<th>Enhancement of patient's prothrombin utilization by ammonium sulfate fractions in per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 25</td>
<td>15</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>0 to 33</td>
<td>7</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>0 to 40</td>
<td>13</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>0 to 45</td>
<td>14</td>
<td>—</td>
<td>35</td>
</tr>
<tr>
<td>0 to 50</td>
<td>17</td>
<td>72</td>
<td>760</td>
</tr>
<tr>
<td>40 to 50</td>
<td>21</td>
<td>12</td>
<td>600</td>
</tr>
<tr>
<td>45 to 50</td>
<td>—</td>
<td>—</td>
<td>660</td>
</tr>
<tr>
<td>50 to 100</td>
<td>—</td>
<td>—</td>
<td>430</td>
</tr>
</tbody>
</table>

* Two-stage method of Ware and Seegers.4
† Method of Owren.5
‡ 0.1 cc. of ammonium sulfate fraction added to 2.0 cc. of patient's blood. On the day of this test the patient's plasma prothrombin was 100% and the serum prothrombin without the addition of the ammonium sulfate fractions was 50%.
§ Fraction heated to 56 C. for 5 minutes to inactivate accelerator I and II.6

PTC Activity of Normal Serum Euglobulin and Pseudoglobulin Fractions

Table 8.—PTC Activity of Normal Serum Euglobulin and Pseudoglobulin Fractions

<table>
<thead>
<tr>
<th>Fraction added</th>
<th>Prothrombin conversion accelerator II concentration of fraction in per cent</th>
<th>Enhancement of patient's prothrombin utilization by fraction added in per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglobulin</td>
<td>23</td>
<td>620</td>
</tr>
<tr>
<td>Pseudoglobulin-albumin</td>
<td>83</td>
<td>760</td>
</tr>
</tbody>
</table>

* Method of Owren.5
† 0.1 cc. fraction from 0.1 cc. normal serum added to 2.0 cc. of patient's blood. On the day of this test, patient's plasma prothrombin was 100% and the serum prothrombin without addition of serum fractions was 86%.

between 45 and 50 per cent saturation with ammonium sulfate. Our experience and that of others41, 42 has shown that the anti-hemophilic factor is precipitated by the 33 per cent saturated ammonium sulfate. As noted above, Cohn's Fraction I (obtained by ethanol fractionation) was ineffective in vivo and in vitro in this case.

PTC Content of Serum Euglobulin and Pseudoglobulin Fractions

It has been reported that prothrombin conversion accelerator II, which is also adsorbed by barium sulfate, is associated with the serum pseudoglobulins.41- 45 It was hoped
that the accelerator might be prepared free of PTC, if the latter proved to be confined to the euglobulin fraction. Unfortunately, the PTC activity was found to be divided about equally between the two fractions (table 8), but with most of the accelerator II in the pseudoglobulin fraction.

Effect of Heating on PTC Activity

Table 9 shows the effect of heating on the PTC activity of normal plasma. A considerable degree of PTC activity remained in the plasma after most of the prothrombin and

<table>
<thead>
<tr>
<th>Duration of heating at 56 C. in minutes</th>
<th>Prothrombin concentration of heated plasma in per cent</th>
<th>Prothrombin conversion accelerator II concentration of heated plasma in per cent</th>
<th>Enhancement of patient's prothrombin utilization by heated plasma in per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
<td>900</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>13</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>&lt;5</td>
<td>194</td>
</tr>
<tr>
<td>7</td>
<td>&lt;1</td>
<td>—</td>
<td>47</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
</tbody>
</table>

* Two-stage method of Ware and Seegers.4
† Method of Owren.18
‡ 0.1 cc. of heated plasma added to 2.0 cc. of patient's blood. On the day of this test, the patient's plasma prothrombin was 100% and the serum prothrombin without the addition of heated plasma was 76%.

Effect of pH on PTC Activity

The pH of platelet-poor aliquots of oxalated normal plasma was adjusted with 1 per cent acetic acid (v/v) and with 0.5 M sodium hydroxide, using a glass electrode for pH measurement. The plasma aliquots were allowed to stand for 2 hours at room temperature prothrombin conversion accelerator II was inactivated by heating for 3 minutes at 56 C. More prolonged heating resulted in marked loss of PTC activity. The fibrinogen was coagulated after 2 to 3 minutes at 56 C. and was removed by centrifugation before testing the plasmas.
and then were readjusted back to pH 7.5. All final volumes were adjusted with 0.9 per cent sodium chloride solution, so that each plasma had the same final dilution. It can be seen from table 10 that there was no significant reduction in PTC activity except at pH 11.2. The PTC activity of the various aliquots appeared to be unrelated to their prothrombin content.

**Potency of Partially Purified PTC Preparations Obtained from Normal Plasma and Serum**

Partially purified PTC preparations, made from normal plasma by the method of barium sulfate adsorption of heated plasma described above, retain approximately 15 to 20 per cent of the PTC activity of the original plasma (table 11). Analysis of one of the products showed that the amount of protein contained in 2.2 mg. of solids obtained from 1.0 cc. of normal plasma was equivalent to 8.1 µg. of tyrosine. The prothrombin and accelerator II contained in these preparations, as well as in the 45 to 50 per cent ammonium sulfate fraction, do not appear to exert any significant nonspecific effect in enhancing the patient's prothrombin utilization, since the same preparations do not enhance prothrombin utilization in hemophilic blood.

We have recently succeeded in preparing a more potent PTC concentrate from normal serum by the method of barium sulfate adsorption of acid inactivated serum described above. Such preparations are totally free of prothrombin and accelerator II and appear to retain the full PTC activity of the original serum from which they were derived (table 11).

**TABLE 11.—Potency of Partially Purified PTC Preparations from Normal Plasma and Serum**

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Prothrombin Conversion</th>
<th>Accelerator II</th>
<th>Enhancement of Patient's Prothrombin Utilization After Addition of PTC Preparation in Original Plasma Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilized plasma PTC preparation reconstituted to original plasma volume</td>
<td>6</td>
<td>10</td>
<td>80‡</td>
</tr>
<tr>
<td>Lyophilized plasma PTC preparation reconstituted to 1/2 original plasma volume</td>
<td>30</td>
<td>50</td>
<td>400‡</td>
</tr>
<tr>
<td>Frozen serum PTC preparation reconstituted to original serum volume</td>
<td>0</td>
<td>0</td>
<td>1000§</td>
</tr>
<tr>
<td>Frozen serum PTC preparation reconstituted to 10 times the original serum volume</td>
<td>0</td>
<td>0</td>
<td>460§</td>
</tr>
</tbody>
</table>

* Per unit volume of reconstituted preparation in terms of original plasma value. Two-stage method of Ware and Seegers.† Per unit volume of reconstituted preparation in terms of original plasma value. Method of Owren.¶ 0.1 cc. of PTC preparation added to 2.0 cc. of patient’s blood. On the day of this test, the patient’s plasma prothrombin was 80% and the serum prothrombin before addition of the PTC preparation was 70%. § 0.1 cc. of PTC preparation added to 1.0 cc. of patient’s blood. On the day of this test, the patient’s plasma prothrombin was 100% and his serum prothrombin before the addition of the PTC preparation was 50%.

**DISCUSSION**

The ultimate goal in the study of the blood coagulation mechanism is to prepare all elements concerned in the reaction in pure form, and with these reagents...
to reproduce the reaction under controlled conditions. Unfortunately, this goal has been difficult to achieve because most of the elements concerned in the reaction are labile, complex proteins, highly active in trace concentrations and difficult to separate from each other. Furthermore, one is never quite certain that all elements in the reaction are known. The discovery of some of these elements has come about through a study of the coagulation mechanism in normal blood. Several elements, including the anti-hemophilic factor and prothrombin conversion accelerator I and II, have been identified through studies of the defective coagulation mechanism in patients suffering from hemorrhagic disorders or under treatment with dicumarol. Through investigation of the coagulation defect in the subject of this report, we have been able to identify another heretofore unrecognized element in the reaction.

The deficient factor (PTC) in this case appears to be concerned with the production of thromboplastin in the plasma. Since PTC is associated with the globulin fraction of plasma and serum and is readily adsorbed from plasma or serum, particularly by barium sulfate, it is apparent that other elements in the blood coagulation mechanism which are prepared by adsorption or fractionation from these sources, especially prothrombin and the prothrombin conversion accelerator II group of factors, must be re-evaluated for purity. Approximately one-half of the protein adsorbed by barium sulfate is not of prothrombin or accelerator II origin. Furthermore, an inhibitor to the first stage of coagulation has recently been reported to be adsorbed by barium sulfate from normal plasma. It is therefore not surprising that an additional factor such as PTC is also adsorbed by this nonspecific agent.

The relationship between the thromboplastin components of the blood and those in fixed tissue has not been fully elucidated. The exact nature of fixed tissue thromboplastin has escaped precise chemical characterization and standardization. This has led to serious obstacles in research, as well as in clinical laboratory practice. Chargaff et al. have outlined some physico-chemical properties of a macromolecular lipoprotein obtained from lung extracts which has potent thromboplastic properties. However, certain investigators believe that Chargaff's materials are not definitely characterized. Ferguson, in a report on the thromboplastic activity of brain cephalin, concluded that it is a potent thromboplastic phospholipid. However, Milstone stated that as the prothrombin fraction becomes more purified, it also becomes more insensitive to the thromboplastic action of lipid thromboplastins (cephalin-lecithin). In a recent report he classified thromboplastins as either direct activators of prothrombin or as accessory thromboplastins. Trypsin (pancreas), crude saline extracts of fixed-tissue, and Milstone's thrombokinase (obtained from bovine plasma euglobulin) were classified as direct activators. Platelets, ether-soluble brain lipoids (cephalin-lecithin), and Milstone's Fraction A (obtained from bovine euglobulin), were classified as accessory thromboplastins. The subject of proteolytic enzymes and platelets in relation to blood coagulation has been studied by Travis and Ferguson. They concluded that trypsin is a potent thromboplastin, while platelets alone are a relatively weak source of thrombo-

* Fixed-tissue thromboplastin, such as crude extracts of brain and lung, as used for the one-stage prothrombin determination.
plastin. Biggs and Macfarlane recently reviewed the relationship between a proteolytic enzyme (Russell viper venom) and lecithin and concluded that the combination of these substances cannot be used to replace brain thromboplastin in a one-stage prothrombin determination. The subject of thromboplastins has recently become more complicated by the "characterization" of a lipid anti-thromboplastin obtained from ether-soluble brain lipids.

In a recent report by Quick et al., the heat lability of the anti-hemophilic factor was shown to contrast with the heat stability of platelet factors in rabbit brain thromboplastin heated to 60 C. We have found results similar to hemophilia in PTC deficiency.

The correction of the coagulation defect in our patient by Russell viper venom and by dilute tissue thromboplastin and the failure of its correction by lipid thromboplastins indicates that the PTC factor is not to be classified with Mistletoe's accessory thromboplastins and that, in accordance with other findings, it is probably a globulin.

Shinowara produced a good rate and yield of thrombin by using Cohn's Fraction I and platelets in place of tissue thromboplastin; however, this result was undoubtedly due to the presence of PTC in the "prothrombin fraction" which he obtained from the plasma euglobulin fraction.

The demonstration of PTC activity in a "purified" system of coagulation factors must await the development of new procedures which will allow preparation of prothrombin and prothrombin conversion accelerator II free of PTC. We have already succeeded in preparing PTC free of these factors.

Although it is not known whether PTC deficiency is hereditary, the similarity of the clinical and laboratory findings in this condition and those in hemophilia is striking. However, the two diseases can be easily distinguished in several ways (table 12). The simplest method is to observe the effect of the addition of volume of barium sulfate adsorbed normal plasma to the patient's blood. The prolonged coagulation time and deficient prothrombin utilization will be corrected in hemophilia but not in PTC deficiency.

There are remarkably few instances in the literature of hemophilia-like coagulation defects which can be corrected by both normal and hemophilic plasma. In the cases reported by Joules and Macfarlane and by Hewlett and Hayden, the defect was corrected by normal plasma but not by hemophilic plasma. It is possible that the results reported by Pavlovsky, which demonstrated that the blood from some cases of hemophilia apparently corrected the coagulation defect in other cases of hemophilia, may have been caused by mixtures of PTC-deficient and true hemophilic blood. A case investigated by Smith and Schulman appears to fulfill many of the diagnostic criteria for PTC deficiency. "Moena's anomaly," reported by Koller, Krüsi and Luchsinger, may possibly be caused by PTC deficiency, since it is claimed that individuals with this disease show deficient prothrombin utilization although the anti-hemophilic factor is present in normal quantities. However, these patients are also stated to have normal or

* Smith and Schulman's investigations were conducted independently of ours. We were informed of the existence of their case in a personal communication after the publication of our preliminary report, but had not had the opportunity to examine the data in their case at the time this report was submitted for publication.
only slightly prolonged whole blood coagulation times, while the clinically normal female conductors of the trait are said to show impaired prothrombin utilization. Prothrombin utilization is normal in the mother of our patient, and the patient's coagulation time, as noted above, is markedly prolonged. It is also of interest that the patient's parents, who have compatible blood types, served as donors, with immediate therapeutic response by the patient during periods of hemorrhage. Quick stated that he has observed patients with hemophilia in whom coagulation times were normal, yet prothrombin utilization was impaired. It is possible that patients with Moëna's anomaly may stand in relation to our

### Table 12—Differential Diagnostic Procedures in PTC Deficiency and Hemophilia

<table>
<thead>
<tr>
<th>Similarities</th>
<th>PTC Deficiency and Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood coagulation time</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Plasma coagulation time</td>
<td>Prolonged</td>
</tr>
<tr>
<td>One-stage prothrombin test</td>
<td>Normal</td>
</tr>
<tr>
<td>Two-stage prothrombin test</td>
<td>Normal</td>
</tr>
<tr>
<td>Prothrombin utilization</td>
<td>Deficient</td>
</tr>
<tr>
<td>Prothrombin conversion accelerators</td>
<td>Normal</td>
</tr>
<tr>
<td>Platelet factors</td>
<td>Normal</td>
</tr>
<tr>
<td>Calcium concentration</td>
<td>Normal</td>
</tr>
<tr>
<td>Fibrinogen concentration</td>
<td>Normal</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Absent</td>
</tr>
<tr>
<td>Effect of normal plasma</td>
<td>Corrective</td>
</tr>
<tr>
<td>Effect of platelet-poor normal plasma</td>
<td>Corrective</td>
</tr>
<tr>
<td>Effect of euglobulin fraction of normal plasma</td>
<td>Corrective</td>
</tr>
<tr>
<td>Enhancement of prothrombin utilization by heated (60°C) thromboplastin</td>
<td>Slight</td>
</tr>
<tr>
<td>Enhancement of prothrombin utilization by brain cephalin-lecithin</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissimilarities</th>
<th>PTC Deficiency</th>
<th>Hemophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of normal serum</td>
<td>Corrective</td>
<td>None</td>
</tr>
<tr>
<td>Effect of 45-50% (NH₄)₂SO₄ fraction of normal plasma</td>
<td>Corrective</td>
<td>None</td>
</tr>
<tr>
<td>Effect of eluate from BaSO₄ which was mixed with plasma or serum</td>
<td>Corrective</td>
<td>None</td>
</tr>
<tr>
<td>Effect of hemophilic plasma</td>
<td>Corrective</td>
<td>None</td>
</tr>
<tr>
<td>Effect of 0-33% (NH₄)₂SO₄ fraction of normal plasma</td>
<td>Corrective</td>
<td>None</td>
</tr>
<tr>
<td>Effect of BaSO₄ adsorbed normal plasma</td>
<td>None</td>
<td>Corrective</td>
</tr>
<tr>
<td>Effect of Cohn's Fraction I</td>
<td>None</td>
<td>Corrective</td>
</tr>
<tr>
<td>Effect of PTC-deficient plasma</td>
<td>None</td>
<td>Corrective</td>
</tr>
</tbody>
</table>

patient as Quick's atypical cases do to classic hemophilia. On the other hand, Moëna's anomaly may be caused by the deficiency of still another plasma thromboplastin component.

### Summary and Conclusions

1. A new hemorrhagic disease characterized by a prolonged whole blood coagulation time caused by the delayed formation of thrombin is described.
2. The patient suffering from this disease was found to have normal concentrations of all previously described coagulation factors.
3. Because the coagulation defect could be completely corrected by the addition of tissue thromboplastin or platelet-poor hemophilic plasma and because tests for prothrombin and prothrombin conversion accelerators gave normal results and prothrombin utilization was impaired, it was concluded that the missing factor was concerned with the production of thromboplastin in the plasma. Accordingly it was named the plasma thromboplastin component (PTC).

4. The clinical and laboratory resemblance of PTC deficiency and hemophilia is striking. However, the two diseases can be distinguished by the fact that normal serum, the 45 to 50 per cent saturated ammonium sulfate fraction of normal plasma, the citrate eluate from barium sulfate, which has been mixed with normal plasma or serum, and hemophilic plasma correct PTC deficiency but are ineffective in hemophilia. On the other hand, while the 33 per cent saturated ammonium sulfate fraction of normal plasma, barium sulfate adsorbed normal plasma, Cohn's Fraction I and PTC-deficient plasma correct the hemophilic defect, they are ineffective in PTC deficiency.

5. A method for the partial purification and concentration of the PTC factor is described.

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PLASMA THROMBOPLASTIN COMPONENT


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21 LANGDELL, R. D.: Personal communication.

22 ALEXANDER, B.: Personal communication.


35 QUICK, A. J.: Personal communication.
Plasma Thromboplastin Component (PTC) A Hitherto Unrecognized Blood Coagulation Factor Case Report of PTC Deficiency

SIDNEY G. WHITE, MAJOR, PAUL M. AGGELER and MARY BETH GLENDENING