Plasma Thromboplastin Antecedent (PTA) Deficiency: Clinical, Coagulation, Therapeutic and Hereditary Aspects of a New Hemophilia-like Disease

By Robert L. Rosenthal, O. Herman Dreskin and Nathan Rosenthal

Plasma thromboplastin antecedent (PTA) deficiency was discovered in two sisters and their maternal uncle, all of whom had a moderately severe hemorrhagic disease with a blood coagulation disturbance resembling hemophilia. Further studies revealed that these patients had normal amounts of anti-hemophilic globulin (AHG) and plasma thromboplastin component (PTC) or Christmas factor in their blood. These findings have established that there are at least 3 factors: AHG, PTC and PTA, which react with platelets to form thromboplastin.

This paper presents observations on the clinical, laboratory, hereditary, and therapeutic aspects of PTA deficiency, based upon the study of thirteen members, comprising four generations, of the original PTA-deficient family.

Methods

This report presents clinical and laboratory studies performed over a 4-year period upon the three original cases of PTA deficiency (table 1). Studies performed upon other members of the family are described (table 2). These proved to be of great value in the elucidation of the hereditary factors as well as of certain other features of PTA deficiency. Figure 1 presents the genealogy of the PTA-deficient family and is used to identify members of the family.

Case Reports

A. A. (Case III, 1, fig. 1), a 54 year old male, had an uneventful circumcision as an infant. During childhood, he noted intermittent epistaxis. Swelling of his left knee occurred at age 12 and again at age 42, but no discolorization or x-ray changes were noted. At age 16, the patient bled profusely following a tooth extraction. A hemorrhage into the right thigh occurred at age 30. At the age of 48, the patient sustained a skull fracture in an automobile accident but made an uneventful recovery. Bleeding from small cuts was probably prolonged, but there had been no purpura.

M. W. (Case IV, 5, fig. 1), a 29 year old female, bled profusely following tonsillectomy at age 2. At age 19, more bleeding occurred, following the removal of 4 impacted wisdom teeth. At age 26, the patient developed shock following an appendectomy and removal of an ovarian cyst. She responded favorably to plasma and blood transfusions. This episode was thought to result from intra-abdominal hemorrhage. However, two years ago, there was no abnormal bleeding when a facial cyst was removed. Ecchymoses, especially of the legs, were noted intermittently, and there was occasional bleeding of the gums with brushing the teeth. The menstrual periods were normal.

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Submitted April 27, 1954; accepted for publication July 6, 1954.

Supported in part by a grant (H-1107) from the National Heart Institute, National Institutes of Health, Public Health Service. The authors wish to thank Esther Gendelman for her technical assistance and Dr. Seymour Fogel for his aid in the genetic analysis.
TABLE 1.—Coagulation Studies on Original PTA Deficient Cases

<table>
<thead>
<tr>
<th>Test and reference to method</th>
<th>Control range</th>
<th>A. A. (III 1)</th>
<th>B. Y. (IV 6)</th>
<th>M. W. (IV 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting time, min.</td>
<td>5-11</td>
<td>15, 17, 17, 19, 20, 27</td>
<td>17, 17, 20, 24, 25, 25, 29</td>
<td>13, 17, 20, 24, 24, 29</td>
</tr>
<tr>
<td>Heparin clotting time, min.</td>
<td>20-35</td>
<td>Over 180</td>
<td>Over 180</td>
<td>Over 180</td>
</tr>
<tr>
<td>Clot retraction</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time, sec.</td>
<td>Subj/control</td>
<td>$\frac{12}{15}$, $\frac{15}{13}$</td>
<td>$\frac{12}{15}$, $\frac{13}{13}$</td>
<td>$\frac{12}{12}$, $\frac{13}{13}$</td>
</tr>
<tr>
<td>Serum prothrombin time, sec.</td>
<td>Above 24</td>
<td>12, 13, 13, 17, 17</td>
<td>8, 12, 15, 15</td>
<td>11, 14, 16</td>
</tr>
<tr>
<td>Fibrinogen, mg/100cc</td>
<td>200-500</td>
<td>400</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Recalcified plasma clotting time, min.</td>
<td>Slow centrifuged</td>
<td>$2\frac{1}{2}$</td>
<td>5</td>
<td>$7\frac{1}{2}$</td>
</tr>
<tr>
<td></td>
<td>Rapid centrifuged</td>
<td>4$2\frac{1}{2}$</td>
<td>10-15</td>
<td>11-17</td>
</tr>
<tr>
<td></td>
<td>3 tube dilution clotting time, min.</td>
<td>9-9-15 (100%)</td>
<td>16-17-72</td>
<td>17-19-no clot</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-50% -25% blood</td>
<td>24-27-210</td>
<td>13-13-55</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td>150,000-350,000</td>
<td>230,000</td>
<td>210,000</td>
<td>200,000</td>
</tr>
</tbody>
</table>

Table 2.—Clinical and Coagulation Data on Other Members of the Original PTA Deficient Family

<table>
<thead>
<tr>
<th>Subject*</th>
<th>Sex</th>
<th>Age, yr</th>
<th>History of bleeding</th>
<th>Clotting time, min.</th>
<th>Heparin clotting time, min.</th>
<th>Prothrombin time, sec.</th>
<th>Serum prothrombin time, sec.</th>
<th>Plasma clotting time, min.</th>
<th>Slow cent.</th>
<th>Rapid cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II 1</td>
<td>F</td>
<td>39</td>
<td>None</td>
<td>8</td>
<td>15</td>
<td>18</td>
<td>24</td>
<td>25</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>III 2</td>
<td>M</td>
<td>47</td>
<td>Slight</td>
<td>7</td>
<td>36</td>
<td>15</td>
<td>18</td>
<td>5</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>III 3</td>
<td>F</td>
<td>53</td>
<td>None</td>
<td>10</td>
<td>28</td>
<td>15</td>
<td>18</td>
<td>3</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>III 4</td>
<td>F</td>
<td>52</td>
<td>Slight</td>
<td>9</td>
<td>36</td>
<td>15</td>
<td>18</td>
<td>3</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>III 7</td>
<td>F</td>
<td>45</td>
<td>Mod.</td>
<td>7</td>
<td>36</td>
<td>17</td>
<td>30</td>
<td>2</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>IV 1</td>
<td>F</td>
<td>31</td>
<td>None</td>
<td>7</td>
<td>16</td>
<td>16</td>
<td>44</td>
<td>4</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>IV 2</td>
<td>F</td>
<td>25</td>
<td>None</td>
<td>8</td>
<td>29</td>
<td>16</td>
<td>36</td>
<td>4</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>IV 3</td>
<td>F</td>
<td>14</td>
<td>None</td>
<td>7</td>
<td>16</td>
<td>16</td>
<td>35</td>
<td>3</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>IV 4</td>
<td>M</td>
<td>18</td>
<td>None</td>
<td>6</td>
<td>25</td>
<td>15</td>
<td>31</td>
<td>3</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
<tr>
<td>V 2</td>
<td>M</td>
<td>3</td>
<td>None</td>
<td>6</td>
<td>15</td>
<td>15</td>
<td>38</td>
<td>3</td>
<td>$2\frac{1}{2}$</td>
<td>$4\frac{1}{2}$-5</td>
</tr>
</tbody>
</table>

* Refer to figure 1 in order to identify relationships.

B. Y. (Case IV, 6, fig. 1) is a 25 year old female who had abnormal bleeding following a tonsillectomy 4 years ago. She experienced moderate bleeding after the extraction of 4 impacted wisdom teeth. Her menstrual periods have been normal.

Case I, 1

Male (deceased). Scanty history available. He bled from the mouth and died at the age of 57.

Case I, 2

Female (deceased). No known history of bleeding.
Case II, 1

Female. No history of abnormal bleeding after dental extractions, dilatation and curettage and finger operation. Coagulation studies were normal (table 2).

Case II, 2

Male (deceased). Scanty history. Bled frequently from the nose and, on a few occasions, from the gastrointestinal tract. There was no known abnormal bleeding after tooth extractions.

Case II, 3

Male (deceased). Scanty history of "questionable bleeding": no details authenticated.

Case III, 1

Original case, A. A.

Case III, 2

Male. No bleeding episodes except after tonsillectomy, many years ago. He has had numerous tooth extractions without any abnormal bleeding. Coagulation studies revealed a normal clotting time but impaired utilization of prothrombin and a slightly prolonged heparin clotting time. The recalcified clotting time of rapidly centrifuged plasma was slightly prolonged to 5 minutes (table 2).

Case III, 3

Female. No history of abnormal bleeding, not even after tonsillectomy, hysterectomy and tooth extractions. Coagulation studies revealed normal clotting time and heparin clotting time. Prothrombin utilization was moderately impaired, and the recalcified plasma clotting times of platelet-poor and platelet-rich plasma were prolonged (table 2).
TABLE 3.—Matching Studies Performed Upon Members of the PTA Deficient Family

<table>
<thead>
<tr>
<th></th>
<th>April 21, 1953</th>
<th>Own plasma clotting time (rapidly centrifuged), min.</th>
<th>Plasma clotting time of mixture .1 cc. own plasma + .1 cc. B.Y. plasma, min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.Y. (IV 6)</td>
<td>101/2-17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III 3</td>
<td>7-71/4</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>III 4</td>
<td>43/4</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

June 16, 1953; .1 cc. plus 1 cc. B.Y. freshly drawn blood

<table>
<thead>
<tr>
<th>Nothing added</th>
<th>Clotting time (min.)</th>
<th>Serum prothrombin time (sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>III 3 stored plasma</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>III 4 stored plasma</td>
<td>8</td>
<td>41</td>
</tr>
<tr>
<td>Control stored plasma</td>
<td>8</td>
<td>40</td>
</tr>
</tbody>
</table>

Case III, 4

Female. She bled profusely following tonsillectomy and on several occasions after tooth extraction. On a few occasions, however, the patient did not bleed abnormally after tooth extractions. Clotting time was normal but prothrombin utilization was impaired (table 2). Mixture studies on cases III, 3 and 4 with IV, 6 are shown in table 3. The fresh plasmas of cases III, 3 and 4 did not correct the defect in IV, 6 as judged by the recalcified plasma clotting time (April 21, 1953). However, after storage at −15 C. for 2 months, plasma from cases III, 3 and 4 corrected the defect in Case IV, 6 blood on June 16, 1953.

Cases III, 5 and 6

No history of any abnormal bleeding. Children (IV, 8, 9, 10, 11) also have no history of abnormal bleeding.

Case III, 7

Female. The patient gives a history of profuse bleeding after tooth extractions on 4 or 5 separate occasions. The bleeding sometimes persisted for several days. An appendectomy at age 21 was complicated by a peritoneal abscess, but no known abnormal bleeding. A submucous nasal resection at age 28 was followed by the seepage of blood for a period of a few weeks. Within the past year, the patient sprained her ankle and developed a large, painful hematoma. She has always had an intermittent tendency towards easy bruising and, occasionally, has developed subcutaneous hematomas. The bruising tendency was reported to be more marked just before the onset of menstrual periods. Coagulation studies performed during a quiescent period revealed normal values (table 2).

Case III, 8

Male (deceased). This subject, said to have been a mild bleeder, died at an early age with a diagnosis of rheumatic heart disease.

Case IV, 1

Female. No history of abnormal bleeding. Two normal, full-term deliveries. Blood coagulation studies were normal.

Case IV, 2

Female. No history of abnormal bleeding, even after tonsillectomy and appendectomy. Blood coagulation studies were normal (table 2).
PLASMA THROMBOPLASTIN ANTECEDENT DEFICIENCY

Case V, 1
Female. History negative for abnormal bleeding.

Case V, 2
Male. History negative for abnormal bleeding, including an uneventful circumcision. Blood coagulation tests were normal.

Case IV, 3
Female. No abnormal bleeding followed tonsillectomy or tooth extractions. Blood coagulation tests were normal.

Case IV, 4
Male. No history of abnormal bleeding. Blood coagulation tests were normal.

Case IV, 5 and 6
Original cases M. W. and B. Y.

Case IV, 7
Female. No abnormal bleeding.

COAGULATION STUDIES

Representative clotting results obtained on these patients over a 4 year period are listed in table 1. The platelet count, tourniquet test, bleeding time, clot retraction and fibrinogen were normal. Normal values were found for the one-stage prothrombin time. Additional tests also revealed that the two-stage prothrombin time, labile factor (Factor V, Pro-accelerin) and stable factor (Factor VII, SPCA Precursor, Pro-convertin) were within normal limits. Abnormal values were found for the coagulation time, heparin clotting time, serum prothrombin time, recalcified clotting times of slowly and rapidly centrifuged plasma and dilution clotting time. These studies suggested a clotting defect similar to that of classical hemophilia, marked by a prolonged clotting time, impaired prothrombin utilization and a normal prothrombin time. A circulating anticoagulant was ruled out by the methods of Conley et al. and Dreskin and Rosenthal. Mixture of normal blood with PTA deficient blood resulted in a correction of the clotting defect (table 4). The possibility of thrombasthenia or an inherent platelet defect was ruled out by the failure of washed platelets to

<table>
<thead>
<tr>
<th>Normal blood cc.</th>
<th>Subject blood cc.</th>
<th>Subject</th>
<th>Subject</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A. A. (III 1)</td>
<td>B. Y. (IV 6)</td>
<td>M. W. (IV 5)</td>
</tr>
<tr>
<td>0</td>
<td>2.0</td>
<td>19</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>.5</td>
<td>1.5</td>
<td>6</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>1.0</td>
<td>1.0</td>
<td>6</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>1.5</td>
<td>.5</td>
<td>6</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>2.0</td>
<td>0</td>
<td>6</td>
<td>33</td>
<td>7</td>
</tr>
</tbody>
</table>

C.T.—Clotting time, min. S.P.T.—Serum prothrombin time, min.
TABLE 5.—Matching Studies Performed on Bloods from PTA Deficient, AHG Deficient and Thrombocytopenic Subjects

<table>
<thead>
<tr>
<th>Cc. of blood</th>
<th>PTA def.</th>
<th>AHG def.</th>
<th>I.T.P.</th>
<th>Clotting time, min.</th>
<th>Serum prothrombin time, sec.</th>
<th>Clot retraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. W. (IV 5)</td>
<td>B. Y. (IV 6)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>24</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>19</td>
<td>62</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

* Patient with idiopathic thrombocytopenic purpura, platelet count 10,000.

TABLE 6.—Mutual Correction of the Clotting Defects of AHG, PTC and PTA Deficient Plasma Samples

<table>
<thead>
<tr>
<th>Subject A cc.</th>
<th>Subject B cc.</th>
<th>CaCl₂ .025 M cc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject A cc.</td>
<td>Subject B cc.</td>
<td>CaCl₂ .025 M cc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject A</th>
<th>Subject B</th>
<th>Plasma clotting time (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHG deficiency</td>
<td>PTC deficiency</td>
<td>27</td>
</tr>
<tr>
<td>PTA deficiency (A.A.)</td>
<td>PTC deficiency</td>
<td>10</td>
</tr>
<tr>
<td>PTA deficiency (A.A.)</td>
<td>AHG deficiency</td>
<td>12</td>
</tr>
<tr>
<td>PTA deficiency (A.A.)</td>
<td>PTC deficiency (Aggeler's case)</td>
<td>9</td>
</tr>
</tbody>
</table>

correct the clotting defect, and by the ability of the patients' blood to correct mutually the defect of thrombocytopenic blood.17, 18 (table 5). Matching studies also revealed that the 3 patients had a similar clotting deficiency. (Mixture of B.Y. and M.W. in table 5).

Other studies which are outlined in our initial report1 of PTA deficiency revealed that our patients' bloods mutually corrected the clotting defect in antihemophilic globulin (AGH) deficiency and plasma thromboplastin component (PTC) deficiency. These findings have been demonstrated by various technics of mixing experiments: (1) Mixtures of freshly drawn whole bloods and effects on clotting time and prothrombin utilization;1 (2) Mixtures of equally centrifuged plasma and performance of the recalcified plasma clotting time (table 6); (3) Addition of .05 or .1 cc. of a test material to freshly drawn blood and evaluation of effect on the clotting time and prothrombin utilization.9 This method has been useful in studies on the properties of the various plasma thromboplastin factors, which are summarized in table 7. While PTA differs in properties from both AHG and PTC, in general it bears a closer resemblance to PTC. Both are unconsumed during coagulation, are present in serum, and are stable on storage. Treatment of either normal plasma or serum with BaSO₄ or by Seitz filtration.
### Table 7.—Properties of AHG, PTC and PTA

<table>
<thead>
<tr>
<th>Fraction</th>
<th>AHG activity</th>
<th>PTC activity</th>
<th>PTA activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal plasma</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>BaSO₄-treated normal plasma</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Normal serum</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>BaSO₄-treated normal serum</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Citrate eluate of BaSO₄ after adsorption of either normal serum or plasma</td>
<td>Absent</td>
<td>Marked</td>
<td>Slight to moderate</td>
</tr>
<tr>
<td>Ammonium sulfate fraction of normal plasma (maximal activity)</td>
<td>0-25% present</td>
<td>33-50%</td>
<td>25-33% moderate</td>
</tr>
<tr>
<td>Seitz filtered normal plasma</td>
<td>Present</td>
<td>Absent</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cohn fractions (maximal activity)</td>
<td>I</td>
<td>III and IV-1</td>
<td>III and IV-1</td>
</tr>
<tr>
<td>AHG deficient plasma</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>PTC deficient plasma</td>
<td>Present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>PTA deficient plasma</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Stored normal plasma</td>
<td>Disappears</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Heated rabbit brain thromboplastin</td>
<td>Slight</td>
<td>Slight</td>
<td>Slight</td>
</tr>
<tr>
<td>Electrophoresis, filter paper technique</td>
<td>β₂ glob. (between β, and γ glob.)</td>
<td>β₂ glob. (between β₁ and γ glob.)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 8.—PTA Activity in BaSO₄-Treated Normal Serum and in Various Ammonium Sulfate Precipitates from Normal Plasma

<table>
<thead>
<tr>
<th>AHG deficiency</th>
<th>PTC deficiency</th>
<th>PTA deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT*</td>
<td>SPT1</td>
</tr>
<tr>
<td>.85% NaCl</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>BaSO₄-treated normal serum</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>.85% NaCl</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>0-25% Sat. ammonium sulfate precipitate</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>0-33% Sat. ammonium sulfate precipitate</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>0-50% Sat. ammonium sulfate precipitate</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>.85% NaCl</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>25-33% Sat. ammonium sulfate precipitate</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>33-50% Sat. ammonium sulfate precipitate</td>
<td>13</td>
<td>21</td>
</tr>
</tbody>
</table>

* CT—clotting time, min.
† SPT—serum prothrombin time, sec.
‡ Precipitates obtained by the indicated saturations of normal plasma with ammonium sulfate were redissolved in .85% NaCl, one-half the original plasma volume and dialysed against distilled water until the sulfate ion was completely removed.

Effects the complete removal of PTC, whereas only slight to moderate amounts of PTA are removed. AHG is not removed by these measures. Our studies have indicated that PTA is partially adsorbed in varying degree by BaSO₄ or Seitz filtration. As shown in table 8, however, BaSO₄-treated normal serum was capa-
ble of correcting the clotting defect of PTA deficient blood but did not correct that of either AHG or PTC deficient samples. Table 8 shows the corrective effect of various ammonium sulfate fractions of normal plasma on PTA deficiency. Maximal PTA activity is contained in the 25 to 33 per cent fraction, whereas AHG activity is chiefly in the 0-25 per cent fraction, and PTC activity is in the 33 to 50 per cent fraction.

Treatment of PTA Deficiency

In vivo studies were carried out in patient A. A., as shown in figure 2. In the initial study, 280 cc. of normal plasma, obtained from routine A.C.D. bank blood stored in the refrigerator for 2 days, brought the clotting time from 19 minutes to a normal value of 7 minutes. The clotting time gradually increased to the pre-treatment level after 1 week. There was no apparent effect upon prothrombin utilization. The heparin clotting time responded in a manner similar to the clotting time. On another occasion, the patient was given 450 cc. of plasma which had been refrigerated for about 7 days and was then kept frozen for 7 days more. Immediately following this infusion, which restored the clotting time, the heparin clotting time and the serum prothrombin time to

Fig. 2.—The effect of plasma infusions on the clotting time, heparin clotting time, and serum prothrombin time of a patient with PTA deficiency (Case III, 1, fig. 1). Immediately following the infusion of 450 cc. of plasma, a hernioplasty was performed with an uneventful post-operative course.
Plasma Thromboplastin Antecedent Deficiency

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Discussion

PTA is a newly described clotting factor which appears to react during coagulation with other plasma thromboplastin factors, AHG, and PTC, and platelets, to form thromboplastin. The properties of PTA have revealed definite differences from those of AHG and PTC. Clinically, PTA deficiency presents a relatively mild hemophilia-like disease, which can be differentiated from AHG and PTC deficiency. In the following discussion, the clinical nature of PTA deficiency will be emphasized, including its mode of transmission.

These studies have revealed that PTA deficiency can occur in varying degrees, with the clotting time ranging from a normal value to 30 minutes. In the severe degree of deficiency, as exemplified by cases III, 1, IV, 5 and 6, there were marked abnormalities in other clotting tests which reflect a deficiency in the formation of thromboplastin. These tests included the heparin clotting time, utilization of prothrombin, and the recalcified plasma clotting time of both slowly and rapidly centrifuged plasma. On the other hand, in the milder degree of PTA deficiency, as exemplified by cases III, 2, 3 and 4, the clotting time was normal, the heparin clotting time either normal or slightly prolonged, prothrombin utilization moderately impaired, as reflected in a serum prothrombin time of about 18 seconds, and the recalcified plasma clotting time of slowly and rapidly centrifuged plasma was either normal or slightly prolonged. The fresh plasma of these subjects did not correct the severe form of PTA deficiency. The plasma from subjects with mild PTA deficiency, however, following storage for more than a few days in a frozen state at about −15°C, developed an increased potency of PTA and was then capable of correcting PTA deficiency in matching experiments. We have now identified 12 other cases of mild PTA deficiency in which the PTA activity has seemed to increase during storage. This change in PTA activity on storage has made it difficult to evaluate studies using stored, frozen plasma samples sent great distances from other laboratories.

It is important to emphasize that the occurrence of hemorrhage in subjects with PTA deficiency, as well as in patients with other types of hemorrhagic disease, is subject to considerable variation. This variation depends both upon opportunities for abnormal bleeding and the interpretation of the degree of bleeding, as seen by the patient. Patients with PTA deficiency have rarely developed spontaneous bleeding. Their bleeding has usually followed trauma or a surgical procedure, whether a major operation or a tooth extraction. Hemarthrosis and purpura have been seen only rarely. The present study indicates, however, that there have been discrepancies between the bleeding tendency and the coagulation studies, and that chance has played an important part in the occurrence of hemorrhage. Subject III, 3 never had any abnormal bleeding, even after operative procedures, while her sister, III, 4, with a similarly mild PTA deficiency, has had marked bleeding following tonsillectomy and variable degrees of bleeding following tooth extractions. Subject III, 7 gave a history of

normal, a left inguinal hernioplasty was performed under general anesthesia. No unusual bleeding occurred during the procedure, and the patient had an uneventful post-operative course. No additional treatment was required. After one week, the clotting time had gradually returned to the pre-treatment level.
moderate bleeding but had normal coagulation values on the one occasion studied.

The treatment of PTA deficiency presents a problem somewhat similar to that of AHG and PTC deficiencies. It is advisable to avoid surgical procedures. If a surgical procedure must be carried out, the patient should receive adequate amounts of PTA factor prior to and, if indicated, following the procedure. Our studies have revealed that PTA is present in both stored plasma and serum. Therefore, plasma stored in a refrigerator is satisfactory for treatment. Following an infusion of 450 cc. of stored plasma, patient A.A., who had a marked degree of PTA deficiency, underwent surgery for a repair of an inguinal hernia and sustained no unusual bleeding during or after this procedure. It is of interest that a 280 cc. infusion of normal plasma, representing about a 9 per cent replacement, failed to correct prothrombin utilization, although the clotting time was lowered to normal. However, 450 cc., a 15 per cent replacement, corrected both the clotting time and prothrombin utilization.

The inheritance of PTA deficiency is of great interest. PTA deficiency is transmitted as an autosomal, dominant trait with an apparently high degree of penetrance and variable expression. It can be transmitted by either male or female to either male or female progeny. Thus there is a 50 per cent chance that the carrier, who also has the disease, will transmit it to offspring. It is not yet known whether the defect can be transmitted by an asymptomatic carrier who has no laboratory evidence of PTA deficiency.

Analysis on the basis of coagulation studies of 11 of the descendants of subjects II, 1 and 2 has revealed that 6 subjects (III, 1, 2, 3, 4; IV, 5, 6) had either a mild or marked PTA deficiency, while 5 subjects (IV, 1, 2, 3, 4; V, 2) were normal. The incidence of PTA deficiency in 55 per cent of the descendants falls very close to the theoretical incidence of 50 per cent, which would be expected in the case of a simple dominant mode of inheritance. The hereditary pattern for PTA deficiency differs from that of the sex-linked, recessive transmission of both AHG and PTC deficiencies. The inheritance of PTA deficiency as an autosomal, dominant trait, plus the mild degree of its hemorrhagic syndrome, indicates that it may well become a frequently encountered clotting defect.

**SUMMARY**

1. An analysis of the original PTA deficient family, including coagulation studies performed upon 13 members comprising 4 generations, has been presented.
2. PTA deficiency is transmitted as an autosomal dominant trait with a probable high degree of penetrance and variable expression of the gene.
3. PTA deficiency can occur in varying degrees ranging from a severe form with prolonged clotting time and markedly abnormal heparin clotting time and prothrombin utilization to a mild form manifesting a normal clotting time and slightly impaired prothrombin utilization.
4. Studies on the treatment of PTA deficiency reveal that the defect is corrected by the administration of stored plasma with the effect gradually disappearing over the period of one week.
5. Various properties of PTA are discussed and compared with AHG and PTC.
PLASMA THROMBOPLASTIN ANTECEDENT DEFICIENCY

Summary in Interlingua

(1) Es presentate un analyse del familia in qu "deficiencia del antecedente de thromboplastina plasmatic (ATP)" esseva originalmente observate. Le analyse coperi 13 individuos qui representa 4 generationes. Studios de coagulatio es includite.

(2) Deficiencia de ATP es transmittite como tracto dominante autosomal con probablemente un alte grado de penetration e un variabile expression del gen.

(3) Deficiencia de ATP pote occurrer in varie grados de severitate. Su formas sever es characterisate per un prolongate tempore de coagulation e un marcate abnormalitate del tempore de coagulation a heparina e del utilisation de prothrombina. In su formas leve illo se manifesta per un normal tempore de coagulation in combination con un parve defecto del utilisation de prothrombina.

(4) Studios therapeutic de deficiencia de ATP revela que iste condition pote esser corrigite per le administration de plasma immagazinate. Le effecto es un progressive disparition del symptomas in le curso de un septimana.

(5) Es discutite varie characteristicas de ATP. Iste factor es comparate con duo alteres: globulina anti-hemophilic (GAH) e le componente de thromboplastina plasmatic (CTP).

REFERENCES

It. L. ROSENTHAL, O. H. DRESKIN AND N. ROSENTHAL


24 Unpublished observations.


Plasma Thromboplastin Antecedent (PTA) Deficiency: Clinical, Coagulation, Therapeutic and Hereditary Aspects of a New Hemophilia-like Disease

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