At least 22 members of a large kindred have a bleeding tendency resulting from a dominantly transmitted platelet disorder in at least 22 members of a family that appears to differ from other well-defined platelet disorders and may represent a new genetic disease. Six family members reportedly developed hematologic neoplasms: acute monocytic leukemia nine years after treatment for congenital neuroblastoma; lymphosarcoma at age 10 years; myeloid leukemia at age 23 years; acute myelocytic leukemia at age 62 years; leukemia of unknown type at age 48 years; and lymphocytic lymphoma at age 52 years.

**Materials and Methods**

The proband presented with pancytopenia and a family history of thrombocytopenia. A genealogic survey identified 192 members of the family in seven generations (Fig 1). History of bleeding tendencies and cancer in family members was sought by interview of living individuals and by review of death certificates, hospital records, and pathology slides.

Fifty family members were evaluated in connection with the present study. With informed consent of 32 family members who resided nearby, we performed physical examinations and the following laboratory studies: complete blood count by Coulter Counter (Coulter, Hialeah, Fla); bleeding time by a modification of the Ivy method using the General Diagnostic Simplate device; and prothrombin time/partial thromboplastin time (PT/PTT) performed by standard techniques. These studies were also performed at local hospitals on 18 other patients who resided at a distance. For some patients evaluated at other centers, bleeding time was performed by alternate techniques with different reference ranges (Table 1). In addition, the serum level of factor VIII (von Willebrand factor) was measured in three patients and platelet aggregation studies were performed in 13 patients, using an aggregometer and the method of Born and Cross. The reagents used were 3 μmol/L and 30 μmol/L epinephrine, 2.9 μmol/L and 29 μmol/L ADP, 116 μg/mL collagen, and 1.5 mg/mL ristocetin. Aggregometry was repeated 12 months later in three patients. Results of bone marrow examinations were available for four patients, and transmission electron microscopy of platelets was performed in two patients. One patient had an autologous platelet survival study. Indirect antiplatelet antibodies were sought in four patients, using the platelet opsonization technique of Handin and Stossel.

Platelet surface proteins were labeled with 125I-NaI using the lactoperoxidase method. Major surface glycoproteins were identified by their electrophoretic mobilities under reduced and nonreduced conditions using two-dimensional sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE).

Peripheral blood chromosome analysis was performed by G-banding at Biotech Research Lab, Inc. A genetic linkage study was performed by M.A. Spence and M.L. Marazita at the University of California, Los Angeles by means of 32 typeable plasma proteins, red cell antigens, and enzymes. Defined definitely affected members had clinical symptoms of a hemostatic disorder associated with thrombocytopenia and/or bleeding time prolongation. Individuals who were probably affected had clinical symptoms alone or a single laboratory abnormality in the absence of clinical symptoms. Aggregation studies were not considered in this classification system.

Pathology slides in two patients who developed childhood cancer were reviewed. For adults with cancer, pathology slides were not obtainable, and the diagnoses were based upon hospital and mortality records.

**Results**

Among 192 family members, clinical information was available for 71 persons in generations III to VII, and 50 of them underwent laboratory studies. Twenty-two family members definitely had a hemostatic disorder, and seven others were probably affected (Fig 1). The bleeding tendency usually appeared in the first decade of life. Common signs and symptoms included purpura, menorrhagia, epistaxes, and ecchymoses occurring spontaneously or with slight trauma. Severe hemorrhage requiring blood transfusion occurred after surgery, dental extractions, or childbirth in some cases.

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Hemorrhage had not been the cause of death among members of this family. Females were often more severely affected than males, some of whom denied excessive bleeding despite abnormal laboratory findings. Clinical severity appeared to fluctuate with time and was not altered by puberty. No environmental precipitating factors were identified.

The major laboratory manifestation of the bleeding disorder in this family was thrombocytopenia (platelet counts 30,000 to 150,000/μL) without qualitative or quantitative abnormalities of red or white blood cells in 23 persons (Table 1). Sixteen of 22 definitely affected members had prolonged bleeding times and six had normal bleeding times at the time of study. However, the normal bleeding times were not repeated and disease severity may fluctuate. Among affected individuals, poor aggregation was documented with collagen in six of 12 individuals, and with epinephrine in 11 of 13 (Table 2). Aggregometry with ristocetin and ADP were normal on at least one occasion in all 13 family members tested.

PT and PTT were normal in all patients evaluated. Factor VIII (von Willebrand factor) assay was normal in three thrombocytopenic patients (V,19; V,22; V,7) (91% to 105%; reference range: 60% to 180%). Three other affected patients (V,18; V,30; V,40) had normal megakaryocyte numbers on microscopic examination of bone marrow obtained by aspiration, but two members (V,28; V,40) were reported to have had a slight reduction in the number of megakaryocytes in at least one bone marrow examination each. Electron microscopy of platelets in two patients (V,26; V,18) revealed normal thrombocyte size and presence of all organelles in adequate quantity and configuration. Platelet-directed antibodies were not detected in the four patients studied (IV,9; V,26; V,7; V,18). Auto- logical platelet survival was normal in one patient (V,26) (platelet half-life = 4.6 days). Peripheral blood chromosomes were normal in two affected patients (V,23; V,11). Blood urea nitrogen and serum IgA concentrations were normal in six affected patients studied.

Radiograms of two-dimensional SDS-PAGE of platelet proteins labeled with 125I from four affected individuals revealed the presence of glycoproteins Iб, IIα, IIb, IIIα, and IV, confirming that the thrombopathy is different from Glanzmann’s thrombasthenia and Bernard-Soulier disease.

Using only sibships with coagulopathic members and including all probably affected individuals, the ratio of affected to unaffected members in this pedigree is 29:23. The male to female ratio of affected members is 12:17. Father-to-son transmission is evident from affected persons V,19 and VI,7. These features suggest autosomal dominant inheritance. No significant linkage was demonstrated between the hemostatic disorder and the 32 markers examined in 66 family members and spouses who participated in the linkage study.

Leukemia or lymphoma developed in two children, a young adult and three older adults, all but one of whom reportedly had an antecedent bleeding disorder.

**Case 1**

(VI,18) (proposita): This girl was born four weeks prematurely and a 2 x 3-cm mass was noted between the sacrum and anus at birth. Excisional biopsy revealed normal thrombocyte size and presence of all organelles in adequate quantity and configuration. Platelet-directed antibodies were not detected in the four patients studied (IV,9; V,26; V,7; V,18). Autologous platelet survival was normal in one patient (V,26) (platelet half-life = 4.6 days). Peripheral blood chromosomes were normal in two affected patients (V,23; V,11). Blood urea nitrogen and serum IgA concentrations were normal in six affected patients studied.

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**Case 1**

(VI,18) (proposita): This girl was born four weeks prematurely and a 2 x 3-cm mass was noted between the sacrum and anus at birth. Excisional biopsy revealed neuroblastoma. Cyclophosphamide was given for 15 months. Minor bruising occurred in the first six years of life with platelet counts varying 30 to 160,000/μL, but WBC and hematocrit were normal. At age 7 years, she developed pancytopenia and an increased bleeding tendency. Decreased megakaryocytes and an excess of myeloid blasts were detected in a bone marrow examination. Bone marrow cytogenetic studies were initially normal. Fourteen months later, a clonal 46 XX, –7, +mar bone marrow karyotype appeared shortly before overt acute monocytic leukemia. The patient died at age 9 years.

**Case 2**

(VI,40): this patient had a history of spontaneous purpura and epistaxes since age 8 months without clinical evidence of pseudoalbinism. She had prolonged bleeding time at age 9 years, when her platelet count
was 390,000/μL. At age 10 years, lymphoblastic lymphosarcoma was diagnosed by submandibular node biopsy. Examination of bone marrow revealed no tumor, but decreased megakaryocyte numbers before initiation of therapy. Despite cyclophosphamide and irradiation, followed by vincristine and prednisone, she died three months after diagnosis.

Case 3

(IV,13): this woman died in 1944 at age 29 years, six years after the initial diagnosis of chronic leukemia. Family members report multiple episodes of severe menorrhagia and cutaneous ecchymoses before the onset of leukemia. The death certificate indicated chronic myeloid leukemia, but additional clinical data are not available.

Case 4

(V,4): the death certificate revealed that this woman died in 1977 at age 52 years from lymphocytic lymphoma. There are no data indicating she was ever evaluated for thrombopathy.

Case 5

(IV,15): the medical records of a hematologist questioned whether this man, who died at age 48 years from valvular heart disease, had leukemia. Further details of this evaluation are unavailable. Family members report multiple episodes of severe bruising and hemorrhage throughout life.

Case 6

(IV,9): this woman had cutaneous bruising and petechiae since the first decade of life. When she was...
43 years old, a hysterectomy was performed after she had had severe menometrorrhagia for three years. Thrombocytopenia (80,000 to 100,000/μL) and bleeding-time prolongation were documented on multiple occasions for at least the last 15 years. Studies of the patient by us in November 1982 and August 1983 revealed no hematologic abnormalities other than those of the bleeding disorder. However, four months later, she developed a myelodysplastic syndrome characterized by splenomegaly and fever and died within five months at age 62 years of acute myelocytic leukemia. Lifelong bleeding tendency and absence of findings of preleukemia nine months preceding her death from acute leukemia indicate that the patient probably had two hematologic diseases.

Ten family members developed diverse cancers other than leukemia and lymphoma (Table 2). In one of them (VI,62), unilateral left adrenal neuroblastoma was diagnosed at 6 weeks of age. He is free from recurrent neuroblastoma and has no clinical or laboratory evidence of deficient hemostasis at age 14 years.

**DISCUSSION**

The familial disorders of platelet production are characterized by abnormalities of platelet number or function, or both (Table 3). Thrombocytopenia in such disorders may result from reduced platelet production or diminished platelet survival. Despite occasional phenotypic overlap, clinical features help distinguish some hereditary platelet abnormalities, eg, pseudo-albinism with Chediak-Higashi disease, radial aplasia in the TAR syndrome, and predisposition to infection and eczema in the Wiskott-Aldrich syndrome. Other thrombocytopenias may be distinguished in part by structural platelet aberrations, such as large platelets in the syndromes of Bernard-Soulier, the macrothrombocytopenia/deafness/nephritis association and the May-Hegglin anomaly, and agranular platelets in the gray platelet syndrome. Specific platelet surface glycoproteins are deficient in Glanzmann’s thrombasthenia and Bernard-Soulier disease. Bernard-Soulier platelets are lacking glycoprotein Ib, the receptor for von Willebrand’s factor. These platelets will not agglutinate in the presence of ristocetin. In Glanzmann’s thrombasthenia, the numerically adequate platelets lack glycoproteins IIb and IIIa, are severely dysfunctional, and do not aggregate in response to ADP, epinephrine, or collagen.

The hemostatic disorder in the family in our study, characterized by mild thrombocytopenia, bleeding-time prolongation, and platelet aggregation abnormalities, can not readily be ascribed to any of the well-defined quantitative or qualitative hereditary platelet disorders. Among dominantly inherited thrombocytopenic diseases, this family appears to differ from other families whose findings include: shortened platelet lifespan, unusually large platelets, increased number of bone marrow megakaryocytes, predilection for expression of the disorder in males, morphologically abnormal platelets, neutrophil nuclear hypersegmentation and eosinophilia, and absence of spontaneous purpura or ecchymoses (Table 3). In families reported by Seip and Myllyla et al, which hematologically resemble affected members in our kindred, aggregation abnormalities were not

<table>
<thead>
<tr>
<th>Pedigree No.</th>
<th>Age* (years)</th>
<th>Sex</th>
<th>Type of Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>VI, 18</td>
<td>8; birth</td>
<td>F</td>
<td>Acute monocytic leukemia; neuroblastoma</td>
</tr>
<tr>
<td>VI, 40</td>
<td>10</td>
<td>F</td>
<td>Lymphosarcoma</td>
</tr>
<tr>
<td>IV, 13</td>
<td>24</td>
<td>F</td>
<td>Myeloid leukemia</td>
</tr>
<tr>
<td>V, 4</td>
<td>52</td>
<td>F</td>
<td>Lymphocytic lymphoma</td>
</tr>
<tr>
<td>IV, 15</td>
<td>48</td>
<td>M</td>
<td>Leukemia</td>
</tr>
<tr>
<td>IV, 9</td>
<td>62</td>
<td>F</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>III, 10</td>
<td>75</td>
<td>M</td>
<td>Prostatic carcinoma</td>
</tr>
<tr>
<td>III, 11</td>
<td>78</td>
<td>F</td>
<td>Gastric carcinoma</td>
</tr>
<tr>
<td>IV, 3</td>
<td>d.67</td>
<td>M</td>
<td>Laryngeal carcinoma</td>
</tr>
<tr>
<td>IV, 4</td>
<td>?</td>
<td>F</td>
<td>Metastatic carcinoma—primary unknown</td>
</tr>
<tr>
<td>IV, 7</td>
<td>d.69</td>
<td>M</td>
<td>Colon carcinoma</td>
</tr>
<tr>
<td>IV, 16</td>
<td>58</td>
<td>F</td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td>IV, 30</td>
<td>70</td>
<td>M</td>
<td>Cerebral metastasis of mucin-producing carcinoma</td>
</tr>
<tr>
<td>IV, 31</td>
<td>20</td>
<td>F</td>
<td>Mixed tumor of lacrimal gland</td>
</tr>
<tr>
<td>V, 5</td>
<td>d.55</td>
<td>M</td>
<td>Lung carcinoma</td>
</tr>
<tr>
<td>VI, 62</td>
<td>&lt;1</td>
<td>M</td>
<td>Neuroblastoma</td>
</tr>
</tbody>
</table>

*Age at diagnosis or death (d).
†Diagnosis confirmed by medical or death record.

**Table 2. Malignancies in Family Members**
Table 3. Familial Platelet Diseases

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Platelet Count</th>
<th>Platelet Size</th>
<th>Platelet Microscopy</th>
<th>Bleeding Time</th>
<th>Aggregation</th>
<th>Inheritance Pattern</th>
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</thead>
<tbody>
<tr>
<td>Glanzmann’s Thrombasthenia10–12</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>Recessive</td>
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<tr>
<td>Bernard Soulier Disease11–15</td>
<td>D(N)</td>
<td>I</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>Recessive</td>
</tr>
<tr>
<td>May Hegglin Anomaly16–18</td>
<td>D(N)</td>
<td>I</td>
<td>N/A</td>
<td>N/A</td>
<td>N</td>
<td>Dominant</td>
</tr>
<tr>
<td>Wiskott-Aldrich Syndrome19,20</td>
<td>D</td>
<td>D</td>
<td>N/A</td>
<td>A</td>
<td>A</td>
<td>X-Linked</td>
</tr>
<tr>
<td>Thrombocytopenia-Radial Aplasia21–23</td>
<td>D(D)</td>
<td>N/D</td>
<td>A</td>
<td>A/N</td>
<td>Recessive</td>
<td></td>
</tr>
<tr>
<td>Chediak Higashi Disease24–25</td>
<td>N/D</td>
<td>A</td>
<td>A</td>
<td>A/N</td>
<td>Recessive</td>
<td></td>
</tr>
<tr>
<td>Gray Platelet Syndrome26</td>
<td>D</td>
<td>N/I</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>?</td>
</tr>
<tr>
<td>Hermansky Pudlak Syndrome27,28</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Recessive</td>
<td></td>
</tr>
<tr>
<td>Idiopathic Storage Pool Disease1</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>Primary Release Disorder29</td>
<td>N</td>
<td>N</td>
<td>nd</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
</tr>
<tr>
<td>Isolated Families [Reference]</td>
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<td></td>
<td></td>
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<tr>
<td>30–33</td>
<td>D(I)</td>
<td>I</td>
<td>A</td>
<td>N</td>
<td>A</td>
<td>Dominant</td>
</tr>
<tr>
<td>34</td>
<td>D(N)</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>D(N)</td>
<td>V</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
<td></td>
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<tr>
<td>36</td>
<td>D(N/I)</td>
<td>I</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>Dominant</td>
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<tr>
<td>37</td>
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<td>A</td>
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<tr>
<td>38</td>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>D(N/I)</td>
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<td>A</td>
<td>A</td>
<td>Dominant</td>
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</tr>
<tr>
<td>40</td>
<td>D</td>
<td>V</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
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<tr>
<td>41</td>
<td>D(N)</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
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<tr>
<td>42</td>
<td>D(N)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
<td></td>
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<tr>
<td>43</td>
<td>D(N/I)</td>
<td>A</td>
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<tr>
<td>44</td>
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<td>45</td>
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<tr>
<td>46</td>
<td>D(D)</td>
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<td>N</td>
<td>Recessive</td>
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<tr>
<td>47</td>
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<td>A</td>
<td>Recessive</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>D(V)</td>
<td>A</td>
<td>X-Linked</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>D(N)</td>
<td>N</td>
<td>N</td>
<td>A</td>
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<td>X-Linked</td>
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<tr>
<td>Current family</td>
<td>D(N/D)</td>
<td>N</td>
<td>N</td>
<td>A</td>
<td>A</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

N, normal; D, decreased; A, abnormal; I, increased; nd, nondiagnostic; V, variable.

*Bone marrow megakaryocyte number is indicated in parentheses.

reported. In addition, affected male sibs in one family had hematuria and urinary tract infections, associated with hydronephrosis and bilateral absence of the 12th ribs in one.43 The platelet disorder in the current family could be a variant form of the primary release disorder. In contrast with storage pool disorders, which are characterized by reduced amounts of nonmetabolic storage pool adenosine diphosphate (ADP), the storage pool ADP concentration is normal in primary release disorders. The release reaction of storage granule contents in response to stimulation is defective in primary release disorders.1 A single family with a primary release disorder has been reported (Table 3). Thrombocytopenia was not found in that family.

The etiologic relationship between the hereditary platelet defect, which may be a manifestation of a bone marrow stem cell defect, and the occurrence of hematologic malignancy in this family is unknown. Luddy et al.16 described a family in which three siblings died of nonlymphocytic leukemia before 10 years of age, and five had thrombocytopenia since the first year of life. Thrombocytopenia developed in other members of the pedigree who did not develop leukemia. However, mental retardation was also present in four siblings, and one sibling with normal platelet aggregation had elevation of serum vitamin B12 level.

Our proband had an interesting and potentially related array of diseases: congenital neuroblastoma, childhood thrombocytopenia, and preleukemia followed by acute monocytic leukemia with clonal 7-monosomy. Her neuroblastoma was treated with cyclophosphamide for 15 months, but persistent thrombocytopenia during childhood is uncommon after this therapy. However, cyclophosphamide, an alkylating agent, can induce acute monochytic or myelomonocytic leukemia, often following a preleukemic phase, as in our patient.57 The six-year interval between cyclophosphamide therapy and leukemia with 7-monosomy has been described in other patients, but the hereditary platelet disorder in our patient may have enhanced the leukemogenic effect of cyclophosphamide. However, the relation of the platelet disorder to her neuroblastoma is unclear. One other member of this family had congenital neuroblastoma but no
hematologic abnormalities. Familial neuroblastoma has been reported in approximately 50 cases in 20 families. The two cases of neuroblastoma in our family may represent chance association or a second familial condition (familial neuroblastoma) in the kindred.

The present study has identified a potentially new familial platelet disorder that may be associated with the development of hematologic neoplasms. The clinical observation of variation in severity of the bleeding tendency over time merits follow-up study, and may be useful in scheduling elective procedures.

ACKNOWLEDGMENT

The cooperation of family members, their physicians and hematologists during collection of data for this study is appreciated. Nancy Upp Potter, RN, contributed greatly to the collection of epidemiologic data.

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SB Dowton, D Beardsley, D Jamison, S Blattner and FP Li

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