Thrombocytopenia Inherited as an Autosomal Dominant Trait

By T. C. Bithell, P. Didisheim, G. E. Cartwright and M. M. Wintrobe

In contrast to the hereditary disorders of red cells and white cells, inherited disorders of the platelets appear to be rare. Among the few reports of hereditary thrombocytopenia, some lack essential history or supporting laboratory data. Those which present more convincing evidence display a remarkable variety of clinical features and genetic patterns. Only the so-called Aldrich syndrome emerges as a definite clinical and genetic entity. This report concerns a family of eight members of a kindred in which four generations have been afflicted with a hemorrhagic diathesis which appears to be the result of mild thrombocytopenia inherited as an autosomal dominant trait.

Family Report

The occurrence of bleeding symptoms and thrombocytopenia in this kindred is summarized in pedigree form in figure 1. Our first contact with this family was made in 1958, when V-31 was referred to this center for evaluation of thrombocytopenia which had not responded to splenectomy. In 1962, V-29 was referred for evaluation of abnormal bruising, and when she was found to be thrombocytopenic, a study of the entire family, which consists of eight members of generations IV and V, revealed thrombocytopenia in her father (IV-23) and in two of her remaining four siblings (V-28, V-33).

Of the five family members found to be thrombocytopenic (IV-23, V-28, V-29, V-31, V-33), the date when abnormal bleeding began was apparent in only one instance (V-29); here it was first noted at age 14. The others recalled symptoms beginning in "childhood." These symptoms included increased bruising in all five, frequent spontaneous epistaxes in two of five, and prolonged bleeding and "slow" wound healing in two of five. In V-28, prolonged bleeding, sufficient to require resuturing, followed a tonsillectomy, but circumcisions at birth in IV-23, V-28 and V-31, and an appendectomy and a tooth extraction in IV-23, were tolerated without complications. There is no other history of surgical procedures, and the only potentially serious bleeding manifestations related were two self-limited episodes of hematuria in V-28, which were presumed to be the result of a flank contusion. There is no history of petechial skin lesions, or of swollen, discolored, or painful joints. No one in the family has ever required hospitalization or received blood transfusions for hemorrhage, and the bleeding symptoms have caused concern sufficient to result in medical consultation in only one instance (V-29).

IV-24 and V-29 related a history of mild eczema, and V-28 and V-31 have suffered from recurrent generalized urticaria following contact with foliage and penicillin administration. The medical history of the family was otherwise essentially negative. None of the heretofore described causes of thrombocytopenia has affected the thrombocytopenic members of this family in common, except for epidemic parotitis or mumps. However, this infection developed after definite symptoms of abnormal bleeding had been noted by

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Fig. 1.—Condensed pedigree of thrombocytopenia and abnormal bleeding symptoms. The generations in this pedigree are numbered with roman numerals from I to VI and members of sibships are illustrated from left to right in order of age. The numbers which designate the family studied here are illustrated in bold-faced type. The symbols for all spouses of the descendants of II-2 are omitted. The family lines of the paternal side are solid (——) whereas those of the maternal side are interrupted (······). Numbered individuals designate those in whom adequate history has been obtained, whereas in those not numbered, the information was considered to be inadequate. The symbols of members without a significant history of abnormal bleeding symptoms are uncolored, whereas those judged to have a significant history of abnormal bleeding symptoms are half-colored. Those with normal platelet counts are cross-hatched, whereas those with thrombocytopenia (see also text and table 1) are solid colored.

IV-23, V-28 and V-31. A complete physical examination of all eight members was negative, and revealed none of the stigmata which are frequently associated with the Fanconi syndrome or the amegakaryocytic or hypoplastic variety of congenital thrombocytopenia.15

FAMILY HISTORY

Information concerning other members of the kindred was obtained by correspondence and from unusually complete and accurate family records. Platelet counts, blood smears, and more detailed histories were obtained, when possible, through the courtesy of local physicians. The results of tests performed in such cooperating laboratories are included within the text.
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Both parents in this family are of German extraction. The maternal side of the family originated in Stemmen, near Rinteln (Niedersachsen province), whereas the paternal side emigrated from Niedermœllrich, Kreis Melsungen (Nordrhein-Westfalen province). These areas are separated by approximately 100 miles. No history of consanguinity could be elicited in the five generations of the family that have lived in the United States.

There is no history of abnormal bleeding among members of the maternal side of the family. Platelet counts on two of the four siblings of IV-24 (IV-25, IV-26) were normal. In contrast, the history of abnormal bleeding in four generations of the paternal side of the family is impressive.

**Generation II**

The history of abnormal bleeding on the paternal side of the family can be traced as far back as II-2. He suffered from a relatively severe hemorrhagic diathesis, judging from incidents related in family records and confirmed by his surviving children. These included frequent and severe spontaneous epistaxes which lasted for several days and frequently required hospitalization. Large bruises and alarming hemorrhage from trivial injuries completely incapacitated him for manual labor and a diagnosis of hemophilia was made by one physician. He nevertheless lived to age 79, when he died of apoplexy. His sister (II-7) and her descendants (III-14, V-49) apparently were also afflicted with some form of abnormal bleeding, but little definite history is available concerning this branch of the family.

**Generation III**

Among the 12 children of II-2 the platelet counts were normal and the bleeding histories were negative in two (III-7, III-12), and two (III-8, III-11) were thrombocytopenic but had otherwise normal blood counts. III-8 (platelet count 50,000/mm³) has suffered from increased bruisability, prolonged epistaxes, and hemorrhages following dental surgery since childhood which have, on occasion, required hospitalization and blood transfusions. III-11 (platelet count 72,000/mm³) has similar but somewhat less severe symptoms.

**Generation IV**

Of the 41 grandchildren of II-2, the platelet counts were normal in 18, who related no symptoms of abnormal bleeding. Four were thrombocytopenic (IV-1, IV-3, IV-9, IV-23). IV-9 has chronic thrombocytopenia (platelet count 25,000/mm³), first discovered in adult life, which has not responded to either cortico-steroid hormone therapy or splenectomy. Except for the presence of moderate hypersegmentation of the neutrophils and Howell-Jolly bodies in the blood smear, his blood counts are normal. Two others (IV-1, IV-3) have low platelet counts (77,000/mm³ and 61,000/mm³, respectively) but no symptoms of abnormal bleeding. Of the remaining 19 grandchildren, a history of increased bruisability was related by IV-5, and seven members have no symptoms of abnormal bleeding. No information is available concerning the remaining 11 members, six of whom are deceased.

**Generation V**

Among the 64 great-grandchildren of II-2, four (the children of IV-23) have thrombocytopenia and one other (V-21) has equivocal thrombocytopenia (platelet count 109,000/mm³) but no symptoms of abnormal bleeding. The platelet counts were normal in 23 members. Eighteen others have no symptoms of abnormal bleeding. No information is available concerning the remaining 18.

**Generation VI**

To date, 25 children have been born in this generation. The platelet counts were normal in two members (VI-8, VI-9). No symptoms of abnormal bleeding were related by seven others, and no information is available regarding the remaining 16.
LABORATORY DATA

The following laboratory data were obtained on the eight members of the family studied here. The results of the platelet counts, hemostatic studies, eosinophil counts, and neutrophil lobe counts are found in table 1. Platelet counts were performed by the method of Brecher and Cronkite, and were confirmed by examination of the peripheral blood smear. The values tabulated are the observed range of several independent counts on separate samples. Clot retraction was determined quantitatively. The tourniquet test was carried out by a standard method. The bleeding times recorded are the mean of three separate determinations at three separate sites. Lobe counts of 500 neutrophils were made from four different coded smears by four independent observers. Hypersegmentation of neutrophils of normal size was present in all thrombocytopenic members of the family, and normally segmented cells were found in normal members, except for V-32, whose neutrophils evidenced slight hypersegmentation.

Differential white cell counts were made by counting 500 white cells on four different smears. Four of the five thrombocytopenic members of the family (IV-23, V-28, V-29, V-33) evidenced eosinophilia statistically significant for their age (p = .05). Significant eosinophilia had been found in the remaining thrombocytopenic member (V-31) on several occasions. Eosinophil counts in unaffected members of the family were normal. IV-23 had significant basophilia (p = .05), and the blood smear of V-31 demonstrated poikilocytosis of the red cells and the presence of Howell-Jolly bodies.

The platelets in both unaffected and thrombocytopenic members of the family were morphologically normal in stained preparations and under the phase contrast microscope. Marrow aspirates were obtained from affected members and revealed megakaryocytes normal in number and appearance but with few surrounding platelets. The bone marrow preparations were otherwise normal. The spleen removed at surgery in V-31 demonstrated no specific histologic abnormalities. No agglutinins for normal isologous platelets were demonstrable in the serum of either the thrombocytopenic or the unaffected members by the technic of Harrington, Minnich, and Arimura. The chromosomes of IV-23 were normal in number and appearance.

Utilizing standard methods, the following coagulation studies were carried out with normal results: glass tube clotting time, qualitative whole blood clot lysis, thromboplastin generation test utilizing normal isologous platelets, and the one-stage prothrombin time. Supplementary studies on the five thrombocytopenic members included quantitative assay of the levels of Factor I (fibrinogen), Factor V (accelerator globulin), Factor VIII (antihemophilic factor), plasma recalcification time, plasma thrombin time, and siliconed tube clotting time. The results of these tests were normal.

Normal values were obtained for the following additional tests: volume of packed red cells, red cell count, hemoglobin, red cell indices, peripheral blood smear, complete urinalysis, stool for occult blood (guaiac method), serologic test for syphilis (V.D.R.L.), total serum protein and albumin and globulin, serum acid and alkaline phosphatases, fasting blood sugar, blood
INHERITED THROMBOCYTOPENIA

Table 1.—Pertinent Laboratory Data on the Reported Family

<table>
<thead>
<tr>
<th>Patient (Pedigree Number)</th>
<th>Platelets (per mm³ x 10⁹)</th>
<th>Clot Retraction (Per cent*)</th>
<th>Tourniquet Test</th>
<th>Bleeding Time (Minutes)</th>
<th>Percentage of Neutrophils with More than 4 Lobes</th>
<th>Eosinophils (per mm³ x 10⁹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV-23</td>
<td>26-74</td>
<td>0</td>
<td>0</td>
<td>&gt;15</td>
<td>10.4</td>
<td>4451</td>
</tr>
<tr>
<td>IV-24</td>
<td>200-250</td>
<td>3</td>
<td>55</td>
<td>1+</td>
<td>5</td>
<td>2.2</td>
</tr>
<tr>
<td>V-28</td>
<td>22-50</td>
<td>4†</td>
<td>0</td>
<td>&gt;15</td>
<td>15.8</td>
<td>4171</td>
</tr>
<tr>
<td>V-29</td>
<td>32-40</td>
<td>3</td>
<td>55</td>
<td>&gt;15</td>
<td>10.3</td>
<td>4201</td>
</tr>
<tr>
<td>V-30</td>
<td>300-320</td>
<td>3</td>
<td>58</td>
<td>0</td>
<td>6</td>
<td>2.4</td>
</tr>
<tr>
<td>V-31</td>
<td>47-58</td>
<td>6†</td>
<td>0</td>
<td>1+</td>
<td>20</td>
<td>8.9</td>
</tr>
<tr>
<td>V-32</td>
<td>265-318</td>
<td>3</td>
<td>55</td>
<td>0</td>
<td>6</td>
<td>5.9</td>
</tr>
<tr>
<td>V-33</td>
<td>52-76</td>
<td>3</td>
<td>36</td>
<td>1+</td>
<td>&gt;15</td>
<td>936§</td>
</tr>
</tbody>
</table>

Normal Range
(95% Confidence Limits)

*Clot retraction is expressed as a percentage of the theoretical maximum volume of serum expressed in 4 hours.
†Includes counts obtained over a period of 4 years.
‡Ages 15—adulthood.
§Ages 8—14.

urea nitrogen, serum bilirubin, fecal urobilinogen (random stool specimen), urine urobilinogen (2-4 p.m. excretion), Coombs test (direct and indirect), reticulocyte count, preparation for lupus erythematosus cells, paper electrophoresis of serum proteins, nuclear binding antibodies, immuno-electrophoresis of serum globulins for antibodies to common foods, stool examination for ova and parasites, and roentgenograms of the chest and skeleton. A complete blood phenotype revealed no apparent correlation between any factor and the presence or absence of thrombocytopenia, and in all instances the major blood groups of V-28-33 were compatible with legitimacy.

DISCUSSION

Many of the problems encountered in the study of genetic disorders in humans are illustrated in the literature on inherited thrombocytopenia. Most reports have, of necessity, relied on a study of one family supplemented by a history of bleeding symptoms in their kindred, an approach which is most fruitful in those varieties which are sublethal, i.e., invariably result in death in childhood. The disorder in the present family, however, can exist as a virtually asymptomatic condition, which limits the value of the family history and imposes a reliance on externally supplied laboratory data. Furthermore, thrombocytopenia may be the result of a large variety of diseases and etiologic factors which may affect more than one member of a sibship, or more than one generation of a kindred. As a result, it is not surprising that some reports of hereditary thrombocytopenia, when critically examined, are more compatible with the presence of secondary or symptomatic thrombocytopenia, another hemostatic defect, or one of the congenital varieties of thrombocytopenia. In the present family, the bone marrow findings are inconsistent with the amegakaryocytic or hypoplastic variety of congenital thrombocytopenia. The more common "auto-immune" variety of congenital thrombocytopenia,
which occurs in infants born of mothers with thrombocytopenia or a history of purpura, cannot explain the disorder in this family, since the father is affected, whereas the mother is hemostatically normal and gives no history of thrombocytopenia or purpura. The normal life expectancy of affected members and the negative physical examination and laboratory studies, together exclude a secondary form of thrombocytopenia, as well as the Heggelin anomaly or an incomplete form of the Fanconi syndrome.15

Conversely, it is probable that cases of hereditary thrombocytopenia which are clinically mild have been confused with idiopathic thrombocytopenic purpura (ITP). Individually, the members of this family resemble cases of chronic ITP, a common disorder wherein affected individuals frequently volunteer a family history of abnormal bleeding.15,23,24 Few of these families have been carefully studied, and several reviews of ITP include families whose history suggests a hereditary basis for the thrombocytopenia.23,25-27 The possibility that the coincidental occurrence of ITP could explain the presence of thrombocytopenia in the present kindred can be excluded only on the basis of its statistical probability; this, although indefinable, is negligible.

Sufficient information concerning this kindred is available to support a simple single-factor genetic hypothesis. The reported family exhibits three affected males, and two affected females. Of the living individuals with documented thrombocytopenia in the kindred, including those for whom platelet counts were supplied by outside physicians, five are males and six are females. The conclusion that an autosomal trait is involved appears justified. It is further probable that a dominant mode of inheritance is responsible. In the two instances in which platelet counts were obtained on both parents and children, the thrombocytopenic members had an affected parent. Although deceased, II-2, the father of III-8 and III-11 and the apparent propositus of the trait in this pedigree, had an impressive history of abnormal bleeding. No counts are available on the parents of IV-1, IV-3, IV-9 and V-21, who are deceased.

The small numbers involved in this study render statistical treatment tenuous, but the number of persons who would be expected to be thrombocytopenic, assuming a dominant mode of inheritance, corresponds closely to that observed, whether computed only on sibships with a known thrombocytopenic parent (11 members, \(X^2 = .05, p = > .9\)) or on all sibships which contain a documented thrombocytopenic member (23 members, \(X^2 = .34, p = > .5\)).

The authors base their preliminary conclusion that the hemorrhagic diathesis in the reported family is the result of inherited thrombocytopenia on the following evidence: (a) the exclusion of other hemostatic defects or presently known causes of symptomatic or secondary thrombocytopenia; (b) the occurrence of thrombocytopenia in several members of three generations, a pattern that excludes the coincidental occurrence of idiopathic thrombocytopenia or congenital thrombocytopenia as an explanation; and (c) the fact that the numbers and sex of affected individuals and the pattern of occurrence of thrombocytopenia are predictable by a simple genetic hypothesis. Table 2
### Table 2.—Summary of Reports of Inherited Thrombocytopenia

<table>
<thead>
<tr>
<th>Author and Publication</th>
<th>Mode of Inheritance</th>
<th>Hypothesized Severity of Symptoms and Prognosis</th>
<th>Megakaryocytes</th>
<th>Ancillary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Varieties with Recessive Inheritance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roberts and Smith⁶</td>
<td>Autosomal</td>
<td>Severe; early death</td>
<td>Numbers decreased in 1 case, normal in 1 case. Not examined in 2 cases</td>
<td>Leukopenia, Anemia</td>
</tr>
<tr>
<td>Aldrich and others⁷</td>
<td>Sex-linked</td>
<td>Severe; early death</td>
<td>Normal</td>
<td>Allergies, Eosinophilia</td>
</tr>
<tr>
<td>Schaar⁸</td>
<td>Sex-linked</td>
<td>Mild; normal life expectancy</td>
<td>Normal numbers in 1 case. Not examined in 6 cases</td>
<td>Eosinophilia</td>
</tr>
<tr>
<td><strong>B. Varieties with Dominant Inheritance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Witts¹⁰</td>
<td>Autosomal</td>
<td>Mild; normal life expectancy</td>
<td>Not examined</td>
<td>None</td>
</tr>
<tr>
<td>Woolley¹¹</td>
<td>Autosomal</td>
<td>Mild; normal life expectancy</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>Quittner¹²</td>
<td>Autosomal</td>
<td>Mild; normal life expectancy</td>
<td>Not examined</td>
<td>None</td>
</tr>
<tr>
<td>Present report</td>
<td>Autosomal</td>
<td>Mild; normal life expectancy</td>
<td>Normal; few surrounding platelets</td>
<td>Eosinophilia, Hypersegmented Neutrophils</td>
</tr>
<tr>
<td>Quick and Hussey¹³</td>
<td>Autosomal</td>
<td>Moderate; ameliorated in adolescence</td>
<td>Not examined</td>
<td>Platelets morphologically and functionally abnormal</td>
</tr>
<tr>
<td>Larrain and Etcheverry¹⁴</td>
<td>Autosomal</td>
<td>Mild; ameliorated in adolescence</td>
<td>Numbers increased, but without surrounding platelets in 2 cases</td>
<td>Morphological abnormalities of platelets antedating thrombocytopenia</td>
</tr>
</tbody>
</table>

summarizes reports from the literature in which comparable evidence is presented. Two reports which have been presented in only preliminary form are not included.⁴,⁵

At least two varieties of thrombocytopenia inherited as a recessive trait have been described. In the family reported by Roberts and Smith,⁶ four of ten siblings of both sexes died in early childhood of hemorrhage, although only one generation was studied. The authors concluded that an inherited trait was responsible, but the ancillary blood findings are compatible with the possibility, albeit remote, that an underlying disorder, such as an incomplete form of the Fanconi syndrome, could explain the observed thrombocytopenia. In 1954, Aldrich⁷ described a syndrome characterized by thrombocytopenia, recurrent otitis media, bloody diarrhea, and an invariably fatal termination in early life, which was inherited from unaffected mothers by male children, and was frequently associated with allergic symptoms and eosinophilia. With the exception of the allergic symptoms and the eosinophilia, the presently described family bears no resemblance to this syndrome, wherein the sex-linked recessive mode of inheritance has been confirmed repeatedly. Schaar⁸ has recently reported a family in which four of seven male children
were affected with moderate thrombocytopenia since birth. The inheritance was compatible with a sex-linked recessive trait, and eosinophilia was noted in the affected members. Except for their benign clinical course, Schaar’s cases resemble the Aldrich syndrome, and it is possible that they represent a mild form of this disorder. Other patients with the Aldrich syndrome who survived beyond childhood have been described. With these exceptions, however, the genetic abnormality responsible for the recessive varieties of hereditary thrombocytopenia appears, without obvious explanation, to be sublethal.

Several examples of thrombocytopenia inherited as a dominant trait have been described, and in contrast to the severe hemorrhagic diathesis observed in the recessive varieties, these families evidenced a mild bleeding disorder which is apparently compatible with a normal life span. With the exception of the eosinophilia and the hypersegmented neutrophils, the family here reported resembles closely those reported by Witts, Wooley, and Quittner, and hence represents the fourth published example of the disorder. Two additional reports, although resembling the aforementioned cases with respect to the genetic mechanism and the benign clinical course, differ in that the platelets of affected individuals evidenced striking morphologic abnormalities. In the family studied by Quick and Hussey, the clot retraction was normal, but abnormalities in prothrombin consumption and thromboplastin generation were observed which were interpreted by the authors as indicating deficient platelet function. The second family, reported by Larrain and Etcheverry, although resembling Quick’s patients in most respects, evidenced no clear-cut abnormalities of platelet function. The morphologic abnormalities of the platelets apparently antedated the development of thrombocytopenia by several years, an interesting observation which suggests that a nosologic connection may exist between inherited thrombocytopenia and the various types of thrombocytopathy with morphologically abnormal platelets and autosomal dominant inheritance.

It is apparent that inherited thrombocytopenia may not be as rare as heretofore supposed, and it is probable that at least three and probably multiple genetic mechanisms are involved. With few exceptions, neither splenectomy nor cortico-steroid therapy appears to be of value in the treatment of inherited thrombocytopenia. Splenectomy produced a remission in one case reported by Wooley and in one member of the family reported by Schaar, but in two other members of the latter family, splenectomy, although alleviating the hemorrhagic symptoms, failed to restore a normal platelet count.

Little, beyond sheer speculation, can be said with regard to the etiology and pathogenesis of these disorders. A hereditary deficiency of a humoral substance which regulates platelet production is a tenable hypothesis, which is rendered even more attractive by a recently reported case in which chronic thrombocytopenia of obscure etiology could be predictably alleviated by infusions of normal plasma.

Conclusions

This report summarizes information obtained on four generations of a kindred afflicted with a mild hemorrhagic diathesis. Studies carried out on a
family of eight members and platelet counts obtained on fifty-one additional members demonstrated only mild thrombocytopenia in eleven members of three generations. The thrombocytopenia appears to be inherited as an autosomal dominant trait.

**Acknowledgments**

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