Congenital Vascular Defect Associated with Platelet Abnormality and Antihemophilic Factor Deficiency

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The congenital hemorrhagic diseases characterized by prolonged bleeding time are poorly classified and incompletely understood. The bleeding tendency in these diseases is usually attributed to (a) a "defect of the capillary wall," or (b) a "qualitative defect of platelets." Under the first heading are included those individuals in whom the prolonged bleeding time is the only demonstrable abnormality. Such individuals are often classified under the name of "hereditary capillary defect" or "pseudo-hemophilia." The second group includes those cases in which the prolonged bleeding time is associated with a morphologic, physical or chemical abnormality of platelets, for which reason the term "thrombocytopenic purpura" has been applied to these conditions. The simplicity of this classification is only apparent. Thus, with the continuous evolution of the technics used in the field of hemorrhagic diseases, "new" phenomena are constantly being discovered, and the number of subdivisions of these main groups, and their overlap with other groups, is proportionally increased.

The most remarkable example of this process is offered by the recognition of the conditions in which the prolonged bleeding time is associated with a deficiency of plasma factors. Alexander and Goldstein described in 1953 a case of this kind. Numerous other reports followed this communication and the possible identity of the deficient factor with antihemophilic factor (AHF) became apparent. Within the category "defect of the capillary wall" a new subdivision was created, and the terms "pseudo-hemophilia B" and "angiohemophilia" were introduced to include these cases. While these developments were unfolding Jürgens was conducting a new cycle of investigations on the Aland families previously studied, demonstrating a deficiency of AHF in those patients in whom a platelet qualitative defect had already been proved.
Three abnormalities, (a) prolonged bleeding time, (b) abnormality of platelets, and (c) plasma defect, seem then to be variously combined in a group of patients who otherwise exhibit a clinical picture often remarkably similar. The purpose of this paper is to present a study of a large kindred, many of whose members are affected by various combinations of these three defects. The kindred is composed of approximately 311 members, 216 of whom reside in southwestern Michigan. Dutch ancestry predominates. Since 1945 nine individuals in six different sibships have been referred to the University Hospital in Ann Arbor for an evaluation of their bleeding tendency. These original patients (propositi) are indicated by arrows on the pedigree comprising figure 1. The propositae, VI-2 and VI-7 were unaware of the bleeding difficulties of propositus VII-138, and vice versa. When a detailed family history obtained from both groups brought out the fact of common ancestry, it was at once apparent that the kindred presented unusual opportunities for the study of a poorly understood disease complex, and the present investigation was undertaken.

Materials and Methods

Blood morphology.—The morphology of the formed elements of the blood was studied on coverslip preparations stained by the Wright method and the cresyl blue-Wright method. In the assessment of platelet characteristics, blood films of the members of the family under observation were mixed with preparations obtained from normal subjects. Films were identified by numbers; each film was examined independently by three hematologists. Platelets were classified as normal, abnormal, doubtful, or no classification possible. The opinion on platelet morphology was based on size, shape, staining characteristics and clumping. In two patients, platelet morphology was also studied with electron microscopy by the method of Hutter.13

Platelet count.—Performed by phase microscopy using the method of Brecher and Cronkite.14 Normal: 200,000 to 350,000/cu.mm.

Capillary fragility.—Estimated by the method of Stefanini and Petrillo.15 Normal: less than 15 petechiae.

Bleeding time.—Estimated by the method of Ivy16 (normal: 3 to 5 minutes) or by the method of Duke.17 Normal: 3 to 7 minutes.

Clot retraction.—Estimated by the method of Macfarlane.18 The tubes were rinsed with normal saline solution. Normal: 40 to 60 per cent of serum expressed from the clot. Consistency of the clot was also considered. A final judgment on the condition of the clot was expressed by the words “normal,” “fair” or “poor” clot.

Thrombelastography.*—Performed with the Harter’s instrument19 following the technics of De Nicola.20 The venipuncture was performed with “hemorepellent” Fenwal needles #17† and 0.36 ml. of blood obtained with the two-syringe method was transferred immediately to the apparatus. Normal values: reaction time = 14.3’ (SD ± 2.54’), coagulation time = 6.1’ (SD ± 0.92’), and maximum amplitude = 48.2 mm. (SD ± 3.40 mm.).

Whole blood clotting time.—The technic of Lee and White21 was followed, with the use of 3 tubes whose inside diameter was 8 mm. The tubes were rinsed with normal saline solution and one ml. of blood was placed in each. The tubes were kept in a water bath at 37 C. and tilted sequentially every 1/2 minute. Normal: 8 to 13 minutes in the third tube (only value reported in the text).

“Silicone” clotting time.—Estimated by the same technics followed for the whole blood

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*The thrombelastograph was purchased with funds from the Michigan Alumni Fund, Faculty Research Equipment Project #36.
†Fenwal Laboratories, Inc., Framingham, Mass.
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clotting time but using silicone (Dri-Film 88)* coated tubes, not rinsed with saline solution. Normal: 15 to 35 minutes in the third tube (only value reported in the text).

Serum prothrombin activity.—Estimated by the method of Sussman et al.22 According to this method, the results were expressed as “normal” (above 30”),”doubtful” (between 20 and 30”), and “abnormal” (less than 20”).

Thromboplastin generation test (TGT).—The classical technic described by Biggs and Douglas21 was followed. The method was also used with the modifications previously described by this laboratory.24 According to this method, the results are reported in one figure, the prothrombin activation index (PAI). Normal values (complete, plasma or serum PAI): 9.8 ± 2.9. Platelet thromboplastic activity was estimated by the method described in the same paper.

Plasma antihemophilic factor concentration.—Estimated by means of a modification of the thromboplastin generation test previously described.24 In a number of patients the method of Biggs and Macfarlane23 and the “partial thromboplastin time” of Langdell et al.,26 employing both hemophilic human plasma and hemophilic dog plasma substrates, were also used as specified in the text. The “partial thromboplastin time” determinations were carried out in Dr. J. B. Graham’s laboratory. The plasma was frozen after collection and shipped by Air Express in vacuum bottles containing solid CO2.

One-stage “prothrombin time.”—Carried out by the method of Quick.27

Two-stage “prothrombin time.”—Carried out by the method of Ware and Seegers.28

Factor V.—Estimated by the method of Wolf.29

Stable factors.—Estimated by the method of Owren.30

Fibrinogen assay.—Carried out by the method of Ratnoff as adapted by Holburn.31

Normal: 200 to 400 mg./100 ml.

Heparin clotting time.—Performed by the method of Rosenthal.32 Normal: 25 to 35 minutes.

Prothrombin time.—Performed by the method of Allen et al.33 Clot forms, normally, in tubes containing 0.14 to 0.16 ml. of a solution of protamine sulfate containing 100 mg./100 ml. of water.

Anticoagulant in circulation.—Estimated using a modification of the TGT previously described by this laboratory.24

Rectification test.—The plasma of subjects with known diagnoses of hemophilia was used as basic material with which the plasma of patients under study was mixed in various proportions. The technical procedure has been reported previously.24

Life span of platelets.—Estimated by the method of Leeksma and Cohen34 with minor modifications. Diisopropylfluorophosphonate-P32 (DFP32)† with specific activity of 141 m.c./mg. was used. DFP32 was received in a propylene glycol solution of 1 mg./ml. One and one-half ml. were diluted to 10 ml. in normal saline solution and injected intravenously in 10 minutes. This represented a total of 211 m.c. of specific activity. Platelets were separated by differential centrifugation, washed three times, hydrolyzed with 30 per cent sodium hydroxide and the radioactivity of the material measured in a Geiger proportional counter using stainless steel planchets. An aliquot of DFP32 was hydrolyzed by the same method and used as a control.

Blood group determination.—Typings were performed using washed red blood cells and commercially available antisera.

Field work.—A number of patients who were unable to travel to Ann Arbor were studied in their home towns, to which equipment was transported for the occasion. The thromboplastin generation tests, the AHF estimations, the two-stage prothrombin time determination, and the estimation of thromboplastic activity of platelets were always performed on

*General Electric.
†With this test no distinction can be made between factor VII (SPCA) and the Stuart factor. No attempt to differentiate between them was made, since no abnormality of prothrombin complex was present in this group of patients.
‡Manning Research Laboratories, Waltham, Mass.
Fig. 1.—Pedigree of the family under study. The generations are indicated by Roman numerals and the individuals by Arabic numerals.
the day after the field trip. The materials were collected as follows: plasma and serum were separated in the movable laboratory, immediately transferred into vacuumized tubes and frozen in a vacuum bottle containing solid CO₂. Platelets were separated and washed immediately after the collection of the blood and kept at +4 C. until the next day in large vacuum bottles containing ice.

RESULTS

Clinical picture.—The large number of individuals studied and the wealth of laboratory data obtained prohibit reporting the full details of the present investigation. A typical case history (VI-2) and laboratory results are given at the end of this section. The full account of the case of patient VII-138 is also presented because of its importance in the comprehension of the condition described in this paper. The remainder of the case histories and detailed laboratory results are on file with the American Documentation Institute, Library of Congress, from which they can be obtained.

Table 1 summarizes the type of abnormal bleeding experienced by those members of the kindred who were personally interviewed and who either claimed, or were believed by the investigators, to have an abnormal bleeding tendency. An additional 8 patients had a history of “excessive bleeding” as reported by the relatives (V-2, V-5, VI-19, VI-25, VII-6, VII-78, VII-81, VII-124), but documentation in these cases is not felt to be sufficiently adequate to warrant tabulation of the findings. Even though it is unlikely that all the hemorrhages listed in this table are to be ascribed to the congenital disease present in the kindred, some observations can be made on the pattern of the manifestations. The most frequent complaints were oral bleeding, ecchymoses and hematomata, excessive bleeding after trauma, vaginal bleeding and epistaxis, in this order. It should be noted, however, that since 9 of the 26 patients listed in table 1 are males, vaginal bleeding in those anatomically predisposed is almost as common as oral or cutaneous hemorrhage. The relative mildness of hypermenorrhea and of obstetric hemorrhages is remarkable, even though this last complication was outstanding in one of the most seriously affected members (VI-2). This woman, however, never experienced hypermenorrhea. Interestingly, it seems that the definitely or probably affected mothers bled more in the parturition of an affected child than when the newborn was normal or only mildly affected. The only delivery when subject VI-2 experienced no hemorrhage was at the birth of her fourth child, who was either not affected or very mildly affected. An analogous observation was made in the case of subjects VI-7 and VI-47. Subject VI-58, on the other hand, never bled save when her fifth child, the only one gravely affected, was born. These observations provoke obvious speculations concerning the transplacental transfer of a humoral factor.

Other sites frequently involved in bleeding were superficial regions: gingivae, nasal mucosa and skin. To be emphasized is the constancy with which bleeding occurred from a site of deciduous tooth loss. Ecchymoses were more frequent than petechiae or hematomata. Internal bleeding was exceptional. Relative mildness, variable intensity, and improvement with age were the general characteristics of this condition. There were no deaths referable to the
Table 1.—Type of Hemorrhagic Manifestations Experienced by Members of the Kindred

<table>
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Section Totals | 3 | 10      | 21         | 3 | 13         | 19         | 1 | 14

hemorrhagic diathesis and VII-138 was the only member seriously and permanently incapacitated by the disease. From the case history of this patient it can be seen that his clinical picture differs significantly from the above general outline.

Laboratory results.—Fifty-nine individuals were personally interviewed by one or more physicians and/or a field worker. These individuals were also investigated in the laboratory (29 during field trips). Whenever possible, subjects of critical importance from the genetic standpoint or in whom the interpretation of the laboratory results were ambiguous were studied at least twice. The laboratory results of patients considered affected or possibly affected are summarized in table 2. The words “abnormal” (A) and “normal” (N) are used there to express the final conclusion of the investigators on the basis of re-
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peatedly confirmed laboratory results. The word "doubtful" (D) is used in reference to unconfirmed results or borderline values. From the table it can be seen that the TGT, the bleeding time, and the "silicone" clotting time most frequently gave abnormal results. The plasma was responsible for the defective thromboplastin generation since the serum always demonstrated normal activity. Prothrombin, factor V, stable factors (Stuart factor and factor VII) and fibrinogen were constantly within normal limits. The thromboplastic activity of platelets, investigated according to the technic described by Biggs and Macfarlane25 gave abnormal results in six patients (VI-2, VI-7, VI-47, VI-58, VII-34, and VII-110). When, however, the platelet activity was tested with a semi-volumetric method,24 no changes from the normal pattern of platelet activity could be demonstrated. The platelet count was found definitely decreased in only one patient (VI-2) and moderately decreased in two patients (VII-1, her son, and VII-29). Repeated platelet counts gave variable results in VI-2 and VII-1. The variability of the platelet count was noticed in VI-2 by other physicians during admission in another hospital. A blood film done simultaneously with the platelet count in VI-2 and VII-1 was estimated to exhibit a normal number of platelets, while the platelet count showed respectively 50,000 and 108,500 elements per cu.mm.

The blind test on platelet morphology gave surprising results: of the 85 blood films taken from normal subjects and from members of this kindred (table 2), the 7 slides on which there was unanimity concerning the occurrence of platelet abnormality were all from members of this kindred already classified as bleeders on the basis of the results of the other tests. The morphologic abnormalities described were: increase in size (some elements being as large as 7 to 8 μ), anisocytosis, and an increased amount of hyalomere (fig. 2). Electron microscopy in VII-138 revealed predominance of spread forms and decrease of dendritic forms (fig. 3b). His mother, VI-58, however, demonstrated normal distribution of platelet forms by the same technic (fig. 3a).

The estimation of the platelet life span attempted in four patients (VI-58, VII-1, VII-134 and VII-138) and in two normal volunteers by the DFP32 technic yielded values of between 7 and 10 days in the controls and in three patients. These figures are within the limits considered normal for this technic. In the fourth patient (VII-1) the test failed because of the impossibility of obtaining an adequate yield of platelets by differential centrifugation of the whole blood, in spite of the multiple attempts during the seven days of the test and the large amounts of blood withdrawn each time (up to 70 ml.).

The estimations of antihemophilic factor levels were considered reliable only when multiple determinations by four different methods carried out in two different laboratories gave comparable results. The values listed in table 2 are approximate averages of these various results. Multiple determinations were done in 16 selected subjects. When there was a discrepancy between the different methods, the results were considered doubtful. Six individuals consistently gave values of 50 per cent or less. Thrombelastography was obtained in 12 selected patients. Definite abnormalities, consisting of a prolongation of both the "reaction" and "coagulation" times, could be observed only in five. Decrease of the maximum amplitude was observed only in VII-138 under
<table>
<thead>
<tr>
<th>Patient</th>
<th>Platelet count</th>
<th>Thromboelastography</th>
<th>Hemostasis assessment</th>
<th>History of clotting abnormalities</th>
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Table 2—Summary of Laboratory Results and Clinical Impression on Reported Episodes of Bleeding in 45 Patients

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<th>Laboratory tests and summary of results</th>
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The results of the investigation of the second and third stages are not reported because they are consistently normal.
(N = normal; A = abnormal; D = doubtful. For the criteria of classification, see text and figure 1.)
Fig. 2.—Platelets of patient VII-1. Wright’s stain. 1200×.

Fig. 3.—Electron microscopy of platelets at 8 minutes from preparation of slide: a (at left), patient VI-58 showing a large number of dendritic forms (normal distribution); b (at right), patient VII-138 showing a large number of spread forms (abnormal distribution). 1500×.

the circumstances described in the case report. In this patient we were able to apply this technic in different stages of his clinical course (see case report). The post-maximal retraction was absent in five patients (VI-2, VI-7, VII-2, VII-5 and VII-34). These patterns are similar to those observable in mild hemophilia or other similar deficiency of the thromboplastin complex. The
identity with AHF of the plasma factor deficient in our patients was demonstrated by mixing experiments in which hemophilic plasma was used.

The association of a prolonged bleeding time with an abnormality of the coagulation mechanism was the outstanding characteristic of the laboratory results. Of the 9 individuals who demonstrated an abnormal thromboplastin generation test, 6 also had a definitely prolonged bleeding time (VI-2, VI-7, VII-1, VII-3, VII-5 and VII-118). In 5 of these 6 patients (VII-3 excluded) the platelet morphology was unanimously considered to be abnormal. In one patient (VII-134) the bleeding time was prolonged on one occasion and normal on another and thus the result of this test is indicated in table 2 as doubtful. In no instance in which the platelet defect was clearly present was the AHF titer normal. The propositus, VII-138, had a consistent plasma defect, but his bleeding time was never found to be abnormal in our laboratories. Correspondence with the family physician, however, brought out the fact that this test was prolonged on two occasions (December, 1943 and September, 1956), once above 40 minutes. This patient's platelets, furthermore, were considered abnormal by all three of the observers participating in the "blind" morphologic study, and the electron microscopy confirmed this observation. These observations were made in periods during which this patient was not bleeding. Conversely, the bleeding time was found prolonged without clear-cut evidence of plasmatic defect in two patients (VII-34 and VI-21). The fact that some of the tests used may be abnormal due either to a plasma or a platelet defect ("silicone" clotting time, clot retraction at one hour, heparin clotting time) makes it impossible to identify with certainty the type of defect and to attempt a larger analysis of the associations of abnormalities. A definite characteristic of the laboratory results was the variability in the same individual of the magnitude of a detectable defect.

The blood grouping results provided no parentage exclusions.

Classification.—In table 2 a general assessment of the patients considered affected or possibly affected is attempted. This is based upon the laboratory results and our clinical impression of the nature of the bleeding episodes reported by the various members of the kindred. The individuals listed in the table were grouped in three classes according to the following criteria:

Class I (10 persons): individuals with clinical evidence of bleeding tendency and one or more definitely abnormal laboratory findings. General assessment A-A. Definitely affected.

Class II (18 persons): individuals with either borderline or unconfirmable laboratory abnormalities and a history of bleeding episodes not, however, clearly related to a hemorrhagic diathesis; or more definite laboratory abnormalities without history of bleeding. General assessment A-N, A-D, D-D, N-A, D-A. Possibly affected: suggestive evidence but not clear-cut proof of a bleeding tendency.

Class III (17 persons): individuals with borderline laboratory tests and a negative history; or normal laboratory tests and a doubtful history of bleeding. General assessment N-D or D-N. Possibly affected: insufficient over-all evidence.
The remaining members of the kindred were grouped in the following additional classes not included in table 2:

Class IV (14 persons): individuals personally interviewed who gave no history of bleeding and whose laboratory results were consistently normal. Normal.

Class V (8 persons): individuals possibly affected on the basis of history.

Class VI (205 persons): individuals on whom reliable information was obtained and who had no history of abnormal bleeding. Probably normal.

Class VII (39 persons): individuals on whom no adequate information or laboratory studies could be obtained.

The above classification is summarized in table 3. According to these criteria, any subject who had episodes of bleeding or laboratory abnormalities was considered a possibly affected individual, but only the combined evidence of clinical manifestation and multiple significant findings in the laboratory was considered definite proof of the presence of a hemorrhagic diathesis. Individuals with strong laboratory evidence without clinical manifestations were considered probable bleeders and included in class II.

This type of classification certainly resulted in inclusion of normal subjects in the class of possibly affected individuals (class III) on the basis of feeble laboratory or clinical evidence (for instance, subject VI-1 had only a doubtfully abnormal clot retraction), and also in the exclusion from the class of affected individuals of subjects with fairly good laboratory evidence of an abnormal hemostatic mechanism but no clinical manifestations (e.g., VI-18, VI-21, VI-43, VII-84 and VII-109). However, it is felt that this system accurately reflects some of the uncertainties that pervade this type of research; the alternative, of forcing each individual into one or the other of two clear-cut categories, scarcely seems appropriate.

**Genetics.**—The pedigree of this family is presented in figure 1. The symbols used there are based upon the classification just described.

**Case Reports**

VI-2: Female, born 1913, first seen at University Hospital on 1/29/52. She has been known to be a bleeder since infancy. The hemorrhagic manifestations included ecchymoses, profuse bleeding from small cuts, oral, ocular, gastrointestinal, vaginal and renal bleeding as well as hemorrhagic complications following surgical interventions. The bleeding from minor cuts could be interrupted only by applying a dry dressing with pressure. Bleeding from sockets after loss of deciduous teeth or extractions was grave, lasting from many hours

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**Table 3.—Incidence of Hemorrhagic Diathesis in the Members of the Described Kindred on the Basis of Collected Information**

<table>
<thead>
<tr>
<th>Class</th>
<th>Affected Class I</th>
<th>Indicative evidence Class II</th>
<th>Insufficient evidence Class III</th>
<th>Probably nonaffected Class IV</th>
<th>Reliable indirect evidence No lab. study</th>
<th>History of bleeding Class V</th>
<th>History negative Class VI</th>
<th>No information or lab. study Class VII</th>
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<tr>
<td></td>
<td>10</td>
<td>18</td>
<td>17</td>
<td>14</td>
<td>8</td>
<td>205</td>
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</table>

**TOTALS**

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<td></td>
<td></td>
<td></td>
<td>Total: 311</td>
</tr>
</tbody>
</table>

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CONGENITAL VASCULAR DEFECT

819
to several days. Epistaxes were numerous and severe to the point that the patient was “almost exsanguinated” on several occasions. Following one episode the patient had to stop school for one year. Her menstruation has always been irregular (2 to 3 months apart), but the flow was never excessive. The patient had six pregnancies. One week after the delivery of the first child, the patient had severe bleeding per vaginam. Transfusions were administered to control the anemia. The patient experienced moderate bleeding after the birth of her second, third and fifth children but not with the fourth. About three weeks postpartum, after her sixth pregnancy, she experienced severe vaginal bleeding, which could be controlled only with transfusions and surgical intervention. Castration by x-ray was carried out thereafter. On April 9, 1952 the patient underwent an emergency appendectomy. The postoperative course was complicated by an episode of intra-abdominal bleeding followed by shock. The patient was discharged after 45 days of hospitalization and has remained well since. She states that the ecchymoses were less frequent in recent years. The physical examination was within normal limits except for the presence of scattered ecchymoses throughout the body.

Laboratory results (1/29/52): bleeding time (Duke), interrupted at 20'; blood clotting time, 18'; clot retraction, poor at one hour; platelets estimated moderately decreased in number on blood film. Laboratory results (8/12/52): blood clotting time, 35'. Patient was re-examined 11/25/57. Interval history: she was transfused once following an episode of vaginal bleeding. Laboratory results: platelet count, 50,000/cu.mm., clumping of elements noticed; capillary fragility test, 25 petechiae; bleeding time, interrupted at 30'; clot retraction, poor at 1 hour; blood clotting time, 10'; silicon clotting time, 65'; serum prothrombin activity, 13.6", abnormal; TGT, plasma PAI 50.0, serum PAI, 8.2, complete PAI 23.0; AHF estimation, 25 per cent (method of Biggs and Macfarlane), 18 per cent (method of Raccuglia et al.); rectification test: patient’s plasma failed to correct the abnormality of the plasma of a known hemophilic; heparin clotting time, 60-4". Seen again on 4/7/58. Interval history: negative. Physical examination: negative except for presence of large ecchymoses. Laboratory results: bleeding time, interrupted at 20'; clot retraction, poor at one hour and at 24 hours; many RBC in the serum; serum prothrombin activity, 14.8", abnormal; TGT, plasma PAI 11.6, serum PAI 9.7, complete PAI 11.2; AHF estimation 80 per cent (method of Raccuglia et al.). Seen again 6/12/58. Interval history: negative. Physical examination: negative except for ecchymoses. Laboratory results: TGT, complete PAI 11.2; AHF estimation: 83 per cent (method of Raccuglia et al.), 71 per cent (partial thromboplastin time with hemophilic dog substrate), 70 per cent (partial thromboplastin time with human hemophilic substrate); thrombelastography: reaction time = 17', coagulation time = 8', maximum amplitude = 51 mm.

VII-138: Male, born 1941. First seen at University Hospital in 1945. The child was circumcised at the age of 7 days without difficulty but subsequently had severe bleeding following minor traumata. At the ages of 15 months and 2 years the patient experienced hemarthrosis involving, respectively, an ankle and a knee joint. Subcutaneous hematomata have been frequent. There has been no spontaneous bleeding from mucous membranes and no petechiae have been noticed. Physical examination: presence of many ecchymoses on lower extremities. Laboratory results (1/5/45): Hg., 13.7 Gm./100 ml.; ht., 41.5 volumes per cent; RBC, 4.7 million/cu.mm.; WBC, 15,200/cu.mm.; differential, normal; platelets estimated on blood film as "slightly increased;" bleeding time (Duke), 7 1/2'; clot retraction, good in one hour; blood clotting time, 14'. The patient was referred again and admitted to University Hospital in May, 1950. Interval history: had been seen by the family doctor an average of "twice or more per month because of subcutaneous or internal bleeding." A tooth extraction two months prior to admission provoked profuse bleeding requiring cauterization. Physical examination, negative. Laboratory results (May, 1950): capillary fragility, negative; bleeding time (Duke), 2 1/2'; clotting time, 18'; platelets estimated on blood film as "adequate."

The patient was first interviewed and examined in connection with the present study in October, 1957. Interval history: he has been almost constantly under medical care because of episodes of bleeding. The mother started daily notes in August, 1956. Since that day,
patient had 77 episodes of bleeding (subcutaneous, intra-articular, hematuria) requiring 9 hospitalizations. He received a total of 11 units of whole blood, 9 units of plasma, and 15 units of purified AHF (Michigan Dept. Health). There was no specific pattern of frequency or gravity of bleeding episodes. Cautious physical therapy had been given by the mother. Patient has always been able to restore normal range of motion of joints with exception of the right ankle and foot following bleeding in the calf in 1955. Following this episode, patient has been confined to a wheel chair. Physical examination: severe heel cord shortening and varus foot deformity. The fingers could easily be hyperextended. Otherwise he is a healthy-appearing, cheerful 16 year old boy. X-ray: marked generalized demineralization of knees and right foot. Equinovarus deformity of the right foot. Laboratory results (10/10/57): platelet count, 407,500/cu.mm.; capillary fragility test, 3 petechiae; bleeding time, 2 1/2'; clot retraction, poor at one hour; blood clotting time, 10 1/2'; silicone clotting time, no clot after 60'; serum prothrombin activity, 14.7n, abnormal; TGT, plasma PAI 32, serum PAI 9.0, complete PAI 36; AHF estimation: 40 per cent (Biggs and Marfarlane); rectification test using known hemophilic plasma as substrate: patient's plasma fails to correct the defect. Anticoagulant in circulation: patient's plasma fails to reveal presence of anticoagulant. Total proteins 7.2 Gm./100 ml. Serum electrophoresis: albumin 41.7 per cent; α1 globulins 7.0 per cent; α2 globulins 11.9 per cent; β globulins 20.0 per cent; γ globulins 19.6 per cent. The blood film revealed normal morphology of RBC and normal WBC. The platelets were large. Electron microscopy: distribution of platelet forms was as follows: round, O; dendritic, 14; intermediate, 10; spread, 76 (average of three counts).

The patient was admitted to University Hospital on 6/9/58 for a period of observation. Interval history: there have been 19 episodes of minor bleeding in subcutaneous tissue but no transfusions were required. Patient has no complaints at present and feels particularly well after a long vacation in Florida. Physical examination: essentially unchanged. Laboratory results during hospital admission: Hg., 16.2 Gm./100 ml.; ht., 50 volumes per cent; RBC, 5.9 million/cu.mm.; WBC, 6,650/cu.mm.; differential, normal; sedimentation rate, 5; platelet count, 315,000/cu.mm.; platelet morphology on blood film: elements are large and isolated; bleeding time (Duke), 5'; bleeding time (Ivy), 2'; TGT, plasma PAI 22.7, serum PAI 9, complete PAI 20.5; AHF estimation: 50 per cent (Biggs and Macfarlane); thrombelastography: reaction time = 37 1/2', coagulation time = 21 1/2', maximum amplitude = 48 mm. (fig. 4A); platelet life span, 9 days. While in the hospital (June 18th) the formation of a small hematoma in the right buttock, not related to trauma, was noticed. The AHF estimation that day was less than 5 per cent by two methods. Thrombelastography revealed the following values: reaction time = 56', coagulation time = 151', maximum amplitude = 26 mm. (fig. 4B). One vial of purified AHF (Michigan Dept. Health), equivalent of 200 mg. of proteins, dissolved in distilled water, was injected intravenously. Two hours later the estimation of AHF in the patient's plasma was 15 per cent. After 4 hours it was 13 per cent, and after 24 hours 6 per cent. The thrombelastogram at 2 hours from the infusion showed the following values: reaction time = 33 1/2', coagulation time = 11 1/2', maximum amplitude = 53 mm. (fig. 4C). At the fourth hour, reaction time = 30 1/2', coagulation time = 16', maximum amplitude 51 mm. At the twenty-fourth hour, reaction time = 30', clotting time = 13 1/2', maximum amplitude = 46 mm. On June 19, 200 ml of fresh plasma were administered. The patient's AHF estimation was 6 per cent before the infusion rose to 52 per cent 3 hours later.

**DISCUSSION**

**Terminology.**—No attempt will be made to review thoroughly the voluminous literature on the subject of congenital hemorrhagic diatheses characterized by vascular defects, much of which has been covered in the recent paper of Valberg and Brown. Nevertheless, some discussion of terminology seems unavoidable if we are to relate the present findings to those of others.

In the past, the following terms have been applied to the same condition,
studied in different cycles, in the same group of patients: (a) pseudohemophilia, (b) von Willebrand’s disease, (c) constitutional thrombopathy, and (d) von Willebrand-Jürgens’ disease. The first name was given by von Willebrand to a condition described in 1926 in a number of inhabitants of the Aland Islands. In this description, a prolonged bleeding time was the main laboratory abnormality reported. The eponym “von Willebrand’s disease” was thereafter used by many authors dissatisfied with the term “pseudohemophilia.” In a second cycle of studies on the same patients, a “new” phenomenon, a functional abnormality of platelets, was thought to be responsible for the described hemorrhagic diathesis and the name of the disease was changed to “constitutional thrombopathy.” The eponym “von Willebrand-Jürgens’ disease” has been used subsequently to describe congenital hemorrhagic diatheses characterized by prolonged bleeding time and a “platelet qualitative” defect. Subsequently, in a third cycle of studies of the Aland Islanders, prothrombin consumption was found abnormal, and abnormal thromboplastin generation tests when patients’ platelets were used was also said to be characteristic of the von Willebrand-Jürgens’ disease. The last addition to the Aland Islander syndrome is the deficiency of antihemophilic factor recently reported by Jürgens.

The eponym “Glanzmann’s disease” refers to a purpuric condition described in 1918 in which the poor retraction of the clot was the main abnormality observed. Since it is impossible to know what the complete picture of this
disease was, attempts should not be made to apply the same name to conditions observed today. The terms “thrombasthenia,” “thrombopathy” or “thrombocytopathy,” sometimes used as synonyms of “Glanzmann’s disease,” are applied to conditions characterized by defective agglutinability and adhesiveness as well as an abnormal morphology of the platelets,37 abnormal clot retraction and poor prothrombin consumption,46 abnormal activity of the platelet factor 323 or defective release of this factor from the platelets.41 These terms are often used by European authors interchangeably with “von Willebrand-Jürgens’ disease.”38

The differentiation between “pseudo-hemophilia” and “thrombocytopathy” is not clear. Stefanini and Dameshek12 and Soulier37 base the differentiation on the morphologic aspect of the platelets and the results of the prothrombin consumption test, which are by definition normal in “pseudo-hemophilia” and abnormal in thrombocytopathy. However, a morphologic abnormality of the platelets has not uncommonly been described in cases classified as “pseudo-hemophilia.”8'43'44'45 Jürgens himself describes morphologic changes in the disease of the Aland Islanders,46 while Glanzmann47 mentions the occurrence of mixed forms of “thrombasthenia” and “pseudo-hemophilia.” On the other hand, the “prothrombin consumption” in thrombocytopathies has been reported as normal.48'51

In conclusion, it seems to us that the separation of the congenital diseases characterized by prolonged bleeding time into two distinct classes, one in which a pure vascular factor is recognizable and one in which a primary platelet abnormality is the basic abnormality, has no clear-cut justification. The attempt to separate a new group of conditions under the names of “pseudohemophilia B”8 or “angiohemophilia”9 is also not justified, since the plasmatic defect was certainly present in the original cases of “pseudohemophilia” and many others described later.

It would be of great advantage for the sake of clarity to consider all the congenital hemorrhagic diatheses characterized by prolonged bleeding time under a single nosologic heading with the name of “hereditary vascular defect,” as proposed by the Committee on Nomenclature.1 The complete laboratory triad would be: (1) prolonged bleeding time, (2) platelet morphologic abnormality and (3) plasmatic defect, and should always be sought for. The prolonged bleeding time is the obligatory feature. In the event that the complete triad could not be demonstrated, the special features of the observed case could qualify the first definition according to the following table:

<table>
<thead>
<tr>
<th>Congenital Vascular Defect</th>
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<tbody>
<tr>
<td>a. with platelet abnormality</td>
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<tr>
<td>b. with plasma abnormality</td>
</tr>
<tr>
<td>c. with both plasma and platelet abnormality</td>
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<tr>
<td>d. without plasma or platelet abnormality</td>
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</table>

Pathophysiology.—The pathophysiology of the hemostatic mechanism in this class of conditions is obscure. Various hypotheses and theories have been proposed to elucidate both the vascular and the plasma abnormality. With respect to the former, at least five different explanations have been advanced, as follows:
CONGENITAL VASCULAR DEFECT

1. There is present a congenital anatomic alteration of the blood vessels. This theory has been based on capillaroscopic findings. Such an explanation does not exclude that the vascular abnormality may be secondary to a platelet defect.

2. There is a functional abnormality of the platelets, as shown by an absence of the movements normally demonstrated by these elements, by their abnormal behavior in clot retraction, and by their lack of adhesiveness. This may be reflected in the morphologic abnormality of these elements.

3. There is a deficiency of platelet thromboplastic factor (platelet factor 3). This hypothesis has mainly been based on two types of evidence: (a) prothrombin consumption may be impaired in these conditions, and (b) the TGT may be abnormal when a patient's platelets are used. In regard to the first fact it should be said that there is satisfactory proof that a numerical platelet defect is associated with abnormal prothrombin consumption but that a qualitative abnormality of the platelets responsible for this change is more often assumed than proved. Convincing experiments on the influence of platelets on prothrombin consumption have been performed in isolated cases. These, however, were reported before the demonstration, especially by the school of Roskam, that platelets carry adsorbed plasma factors and the proof that these factors are essential for the normal function of the platelets.

4. Platelet factor 3 is present, but its release from platelets is abnormal.

5. There is a deficiency of still another plasma factor in addition to AHF. This subject is still controversial since the administration of fresh or old plasma did not correct the bleeding time in several of the reported cases.

Turning now to the explanation of the AHF deficiency, this presents even more difficulties. Biggs advanced the hypothesis that the capillary defect
is the primary change and that AHF is decreased because it is used in excess during the continuous process of repair of the vascular lesions. Graham discusses the possibility that two separate and independent factors are deficient in these patients. The report of a disorder characterized by prolonged bleeding time and factor IX (plasma thromboplastin component) deficiency is thought to corroborate such a possibility.

The study of the kindred described in this paper demonstrates that the same genetic predisposition (see below) may manifest itself with the complete picture in some patients, while in others the objective manifestations may be limited and variously combined (table 2).

The exact nature of the relationships between the different manifestations of this disease have not been satisfactorily elucidated by the present investigation. It seems most probable that an abnormality of platelets is responsible for the prolonged bleeding time of our patients, as demonstrated by the almost constant association of the microscopic finding of giant thrombocytes with prolonged bleeding time. The possibility that the platelet abnormality is also responsible for the plasma defect has been our working hypothesis. This has been that the platelets of affected individuals were abnormally fragile and that the resulting release of excessive thromboplastic substance in the blood stream provoked an excessive utilization of antihemophilic factor or established an inhibition in the formation of thromboplastin which would mimic AHF deficiency. The hypothesis of excessive fragility was suggested by the observation that in at least two patients (VI-2 and VII-1) platelets were abundant in the blood film, moderately reduced by count, and extremely scarce or absent in the sediment after differential centrifugation. This suggestion seemed to find support in the fact that platelets possess inhibitory activity demonstrable in vitro. The platelet life span, however, was normal in the most seriously affected of our patients (VII-138), his mother (VI-58) and his sister (VII-134). An investigation of this type could not be extended and confirmed, and therefore our hypothesis could not be presently substantiated.

**Genetics.—**The genetic problems raised by this kindred are no less complex and perplexing than the questions regarding the mechanisms of hemostasis which the kindred poses. We may start with the fact that 10 individuals with a clear-cut, definite hemorrhagic tendency have been encountered in 6 different sibships in this kindred. With a few exceptions, each of these individuals presents acceptable evidence for abnormality at two different points in the coagulation mechanism. Thus, there is evidence, either in the form of microscopic abnormality of the platelets or a prolonged bleeding time, of abnormality on the platelet-capillary side, and there is evidence, in the form of an AHF defect, of abnormality on the plasma side.

The first question which should be considered is whether the genetic basis for the bleeding tendency is the same in all affected individuals. We see the defect in the sisters VI-2 and VI-7 and one or more of their children. Few would doubt that the genetic basis of the defect is the same in these 7 individuals. The father of these sisters has an equivocal bleeding tendency—the mother appears to be normal. VI-58 and VII-138 are an affected mother and son. A niece of the mother (VII-118) is also affected; the niece’s father, VI-53
CONGENITAL VASCULAR DEFECT

(mother’s brother) shows equivocal changes. Unfortunately, the parents of the affected mother were both deceased, but in view of the distribution of the trait in their descendants, one or the other of them certainly carried the responsible gene or genes. It would seem to be stretching the long arm of coincidence to postulate that such an uncommon combination of defects appears in related individuals other than through a common origin of the responsible gene or genes. One way of accounting for a common origin is to postulate that the defect was transmitted to their descendants by the siblings V-1 and V-10. Since V-1 was found to be normal, the implication is that the defect may be transmitted by a normal individual. This in turn requires that the responsible gene or genes exhibit a variability in their manifestation which is truly remarkable. An alternative to the assumption of failure of the genotype to express itself in V-1 is provided by the fact that she married a second cousin once removed (IV-1). This individual shows borderline abnormality, and it may be that he transmits the predisposition. This avoids the conclusion that one who transmits the defect can be entirely normal, but still is consistent with the postulate of a common origin of the predisposition. While the possibility cannot be excluded that this rare defect was introduced into the family from two different sources, this seems very unlikely.

We turn now to consider the genetic relationship of the AHF and the platelet-capillary defect to one another. Both defects are obviously of genetic origin. We have, then, two alternatives: (1) their association is purely by chance, the traits being due to independently segregating genes, the two genes presumably introduced by IV-2 and/or IV-3, or (2) the traits are due to closely linked genes or a single gene with pleiotropic effects. Were the former possibility the case, and were the genes segregating independently, the traits should be encountered apart more often than together. Only one of the 10 certainly affected individuals (VI-58) may show one of the defects in the absence of the other. We conclude, then, that this association is most likely to be explained either on the basis of closely linked genes or else due to a single gene which appears to have effects at two points in the clotting mechanism. Solely on the basis of the probabilities involved, i.e., the unliikelihood in this and other possibly similar families of encountering 2 genes as uncommon as these in the coupling phase, we incline to the single gene hypothesis, the gene being a dominant of variable expression. Since there are no proved instances of male to male transmission, sex-linkage cannot be excluded. The obvious question of whether the two apparently separate effects of the postulated gene represent true pleiotropy, or whether one is somehow precursor to the other, cannot be answered. In an earlier section we have attempted to indicate how a platelet defect might result in a deficiency of AHF; further speculation on this point seems fruitless. It should be pointed out at this juncture that this genetic interpretation rests only on persons with a clear hemorrhagic tendency; any subsequent developments as regards the individuals not readily classifiable as to hemorrhagic tendency are not apt to alter the genetic interpretation.

The extreme variability in the manifestations of this diathesis prevents any more precise genetic analysis. We think this to be real rather than a laboratory artifact. It should, however, be pointed out that from the standpoint of the
mechanism of gene action this variability in expression is not necessarily characteristic of the primary gene-controlled reaction involved. Rather, the basic defect may be relatively constant but influenced in its manifestations by genetic modifiers and fluctuating environmental variables influencing a delicately poised system. For instance, in the hereditary hemoglobinopathies two individuals with the same proportion of abnormal hemoglobin may exhibit very different symptoms. Exploration of this possibility is rendered difficult by the “trace protein” nature of so many of the components of the blood coagulation system.

**Summary**

1. A kindred of 311 individuals, many members of which are affected by a hemorrhagic diathesis, has been described.

2. The variability in the manifestations of this diathesis is extreme. In its fullest expression the disease is characterized by a prolonged bleeding time with evidence of a morphologic defect in the platelets, and a deficiency in antihemophilic globulin. Some possibly affected individuals exhibit only a prolonged bleeding time, while, on the other hand, the clinically most severely affected individual, with AHF levels on several occasions of 5 to 10 per cent, has not been observed by us to have a prolonged bleeding time, although his platelets are morphologically abnormal.

3. Genetic analysis suggests that the hemorrhagic tendency is determined by a single dominant gene of variable penetrance and expressivity.

4. No satisfactory explanation can be developed on the basis of these studies for the association between platelet abnormality and AHF deficiency. More specifically, it is impossible to conclude whether the platelet defect is precursor to the AHF deficiency, or whether—as on *a priori* grounds seems less likely—this is an example of true genetic pleiotropy.

5. The terminologic chaos which afflicts the literature on hemorrhagic diatheses characterized by a prolonged bleeding time is discussed in the light of the findings in this one large kindred, and suggestions are advanced for minimizing confusion based on terminology alone.
CONGENITAL VASCULAR DEFECT

determinate per un sol gen dominante de penetrantia e expressivitate variable.

4. Super le base del presente studios, il non es possibile disveloppar un satisfascente explication pro le association de anormalitate plachettal con carentia de factor antihemophilic. Plus specificamente, il es impossibile determinar si le defecto plachettal es un precursor del carentia de factor antihemolytic o si—un possibilitate que es minus probable super le base de consideraciones a priori—isto es un exemplo de ver pleiotropia genetic.

5. Le chaos terminologic que afflige le litteratura relative al diathese hemorrhagic characterisate de prolongation del tempore sanguinatori es discutite in le lumine del constatationes in le presente grande phratria. Es presentate suggestiones serviente a reducer Ic confusion in tanto que jib es purmente terminologic.

ACKNOWLEDGMENTS

We wish to express our gratitude to the subjects studied in this paper for their continuous cooperation; to the family physicians, Drs. Richard De Mol, William Haeck and F. M. Burroughs, who cooperated in this study of their patients; to Dr. J. W. Rebuck for the study of platelets by electron microscopy; to Dr. J. B. Graham for the antihemophilic factor assays in the numerous plasma specimens; to Dr. D. R. Korst and Miss M. H. Rennie for their assistance in the assessment of radioactivity of labeled platelets; to Drs. M. C. Meyers and R. C. Bishop for their help in the assessment of platelet morphology; and to Dr. H. Gershowitz for the blood group determination.

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GIOVANNI RACCUGLIA, JAMES V. NEEL, Ruth T. Davidson and Mary Jane Ussery

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