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Hereditary Thrombocytopenia with Excessively Prolonged Bleeding Time

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A report is given of a hereditary bleeding disorder characterized by thrombocytopenia and excessively prolonged bleeding time.
The disorder was inherited as an autosomal dominant trait, and segregated independently of the ABO, Rh, MNSs and Duffy blood group systems, and probably of the ABH secretor genes.
The patients' own platelets had a shortened survival in the patients' own circulation, indicating an increased destruction. The increased destruction was not due to an intrinsic defect of the patients' platelets, because the platelets survived normally when transfused to a normal recipient. The patients must therefore have some factor or mechanism in their blood or vascular system which shortens the life-span of their own platelets as well as that of transfused normal platelets.
Another striking finding was the unproportionate increase of the bleeding time. The moderately reduced platelet count and normal AHG exclude von Willebrand's disease. The presently reported bleeding disorder did not show the characteristics of the thrombasthenic or the thrombopathic group of disorders.
The presently reported haemorrhagic disorder does not fit into any of the previously described ones.

Platelet disorders are classified according to platelet number, morphology, life span and various platelet function tests. They are usually acquired, but some are hereditary. Patients with hereditary platelet disorders usually have a normal platelet count, e. g., Glanzmann's thrombasthenia. In some groups of hereditary platelet disorders, however, there is a slight to moderate thrombocytopenia and, in addition, various qualitative platelet defects.

We have studied a platelet disorder with bleeding tendency afflicting several male and female members in 4 generations of a family originating from the Lofoten Islands, Norway. There was no instance of intermarriage.

The afflicted members have suffered severe nosebleeds in childhood, prolonged bleeding after tooth extractions, and the female members have a tendency to menorrhagia but not to increased postpartum bleeding.

MATERIAL AND METHOD

All accessible members of the 1st and 2nd generation were studied, but of the 3rd and 4th generation only accessible children of afflicted members were studied. The study consisted of a personal interview, determination of Duke's bleeding time from the ear lobe, platelet count, and blood grouping in several systems.

The interview. The persons were asked about bleeding tendencies in the form of severe nose bleeds, menorrhagia and post partum bleeding, severe bleeding after accidental cuts, tooth extractions, and surgical operations.

Duke's bleeding time from the ear lobe. When not otherwise stated an about 2 mm. deep cut was made in the ear lobe using a new surgical blade with the cutting edge held parallel to the skin surface. The normal range of the bleeding time from cuts made in this way depends very much on the depth of the cut. From 2 mm. deep cuts the normal range in men is 5–12 min., in women 5–16 min. (Stavem 1967).

Platelet count. Hellem's modification (1960) of Nygaard's method (1933) has been used, with a normal range of 150,000–350,000 per μl.

Blood grouping. For blood grouping the following antisera were used: anti-B, A, A_1, M, N, S, s, Ny^a, Vw, Wr^a, P, K, Lu^a, C, C^w, D, E, c, e, Fy^a, Le^a, Le^b.

Two afflicted members were submitted to the below mentioned additional studies. The two patients studied were Mrs. A.D. 44 years old (Figure 1, II 4), and her daughter Mrs. A.R.H. 20 years old (Figure 1, III 1). Both had severe nose bleeding in childhood, prolonged bleeding from small cuts and after tooth extractions, menorrhagia but *not* severe post partum bleeding, and easy bruising. Mrs. A.D. had been appendicectomized, and afterwards required a single blood transfusion because of oozing from the wound. She had also at one time received one pint of blood because of severe menorrhagia.

Platelets were counted by the method of Nygaard (1933) as modified by Hellem (1960). Normal values 150,000–350,000 per μl. blood.

Platelet survival studies were done with platelets labelled in vitro with ^{51}Cr by the method of Foss Abrahamsen (1965).

Platelet diameter was measured in May-Grünwald-Giemsa stained blood smears with an ocular micrometer.

Platelet morphology was evaluated by light microscopy of May-Grünwald-Giemsa stained blood smears and by electron microscopy as described by Hovig et al. (1968).

Megakaryocyte morphology was evaulated by light microscopy of May-Grünwald-Giemsa stained smears of bone marrow aspirate. Electron microscopic evaluation was done as described by Hovig et al. (1968).

Platelet electrophoretic mobility in plasma was measured by Gröttum's modification (1968) of Fuhrmann & Ruhenstroth-Bauer's method (1965).

Bleeding time was measured with Duke's method from cuts in the ear lobe, and with Ivy's method from cuts in the forearm. Cuts of different depths were made with new surgical blades. We did not make a stab with the tip of the knife blade, but made a cut holding the blade nearly parallel to the skin surface (Stavem 1967).

Capillary fragility was evaluated by a positive pressure method (Stavem 1965).

Clot retraction test was done in diluted plasma coagulated by thrombin, according to the method of Benthaus (1959).

Whole blood platelet adhesiveness test was done in citrated blood with Hellem's method (1960).

Collagen induced platelet aggregation test. The rate of collagen-induced aggregation of platelets in citrated platelet-rich plasma was measured at 25° C. by the fall in light absorption in an EEL titrator.

TABLE I

Mean platelet count, range for platelet counts, number of platelet counts, Duke bleeding time, and history of bleeding tendency for all persons studied

	Init.		Platelet count: Mean × 10^3	Platelet count: Range × 10^3	Platelet count: No. of counts	Duke bleeding time (min.)	History of bleeding tendency
I	1	■ TA	58	36–127	40	(>30 Ivy)	+ (Numerous transfusions)
II	1	□ LA	468		1	3½	−
	2	□ TA	249		1	11	−
	3	⊠ AA					
	4	● AD	48	25–91	8	>30	+ (Transfused twice)
	6	○ AsA	200		1	8	−
	7	○ PD	288		1	(1¾ microlance)	−
	8	■ OA	90	76–104	2	>30	+
	10	□ BA	225		1	5	−
	11	■ MA	38	30–45	2	>30	+
	12	■ NA	25		1	23	+
III	1	● ARH	36	24–59	6	>30	+
	3	● TD	72	45–98	2	>30	+ (3 transfusions)
	4	○ ED	238		1	8	−
	5	○ MD	255		1	6½	−
	6	■ DD	81	47–120	5	>30	+
	7	■ TD	60	41–90	4	>23 (too shallow cut)	+ (Several transfusions)
	8	○ BA	194		1	4½	−
	9	□ KA	263		1	9	−
IV	1	■ JH	82	68–90	3	>30	+

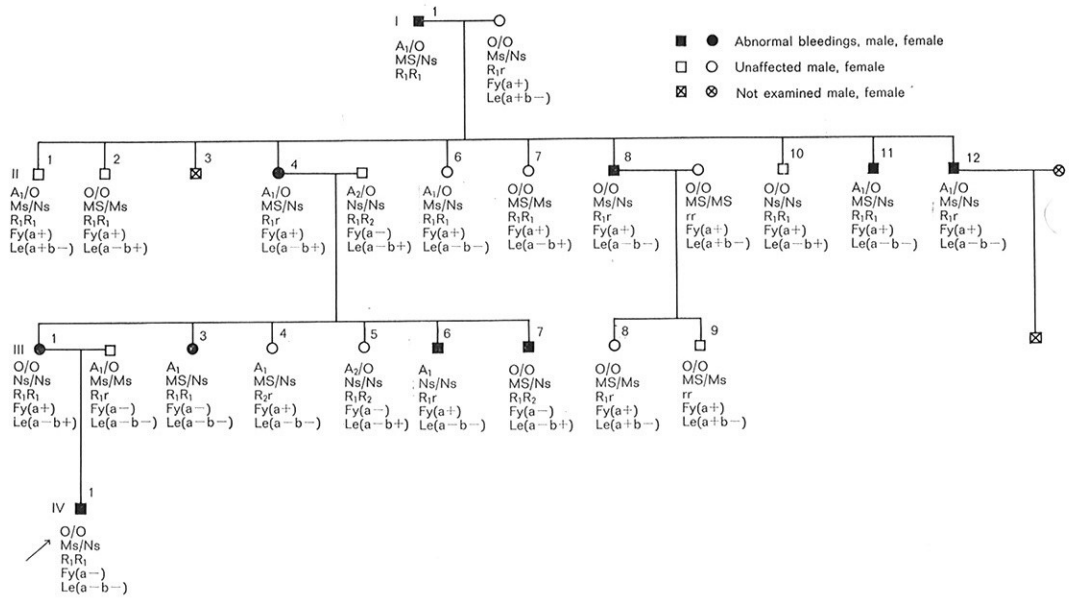

Figure 1. Pedigree of the family, with the blood types of each member.

Thromboplastin generation test was done as described by Dacie & Lewis (1963). The patient's platelets or normal platelets adjusted to the same number, were washed, resuspended and frozen before use.

Prothrombin consumption test was done as described by Dacie & Lewis (1963).

Total platelet factor 3 assay. Platelet-rich citrated plasma from the patients and normal control, was prepared, frozen and thawed twice, and then diluted as described by Hjort et al. (1955). 0.2 ml. diluted platelet-rich plasma, 0.2 ml. diluted Russel Viper Venom (Stypven, Burroughs Wellcome & Co.), and 0.2 ml. platelet-poor human plasma reagent were incubated for 3 minutes at 37° C. and then recalcified with 0.2 ml. calcium chloride (Hjort et al. 1966).

Platelet factor 3 availability was assayed with the same method as used for total platelet factor 3, except that the platelet-rich plasma was incubated with kaolin suspension instead of frozen and thawed. 1.4 ml. of platelet-rich plasma was incubated in plastic tubes at 37° C. with 0.2 ml. kaolin suspension (final concentration 2.5 mg. kaolin/ml. – see Hardisty & Hutton 1965). The mixture was thoroughly shaken every 5 minutes during the incubation. After 0, 5, 10, 20, and 30 minutes of incubation with kaolin, the available platelet factor 3 was determined.

RESULTS

Pedigree of the family, and the *blood groups* of each member are shown in Figure 1. One (II, 3) of the 10 members had succumbed. Results of *interview*, *bleeding time test* and *platelet count* for all the persons studied are given in Table I.

Platelet survival studies

The results are given in Figures 2 and 3. The radioactivity 15 min. after injection of the labelled platelets was taken as 100 %. The patients' platelets had a shortened life span in the patients' own circulation, and so did normal platelets transfused to the patient A.D. The patients' platelets, on the other hand, survived normally when transfused to healthy recipients.

Platelet diameter in blood smears

The larger diameter of platelets in stained blood smears, was recorded for 200 platelets. The platelet diameter showed considerable variation. Table II shows that the plate-

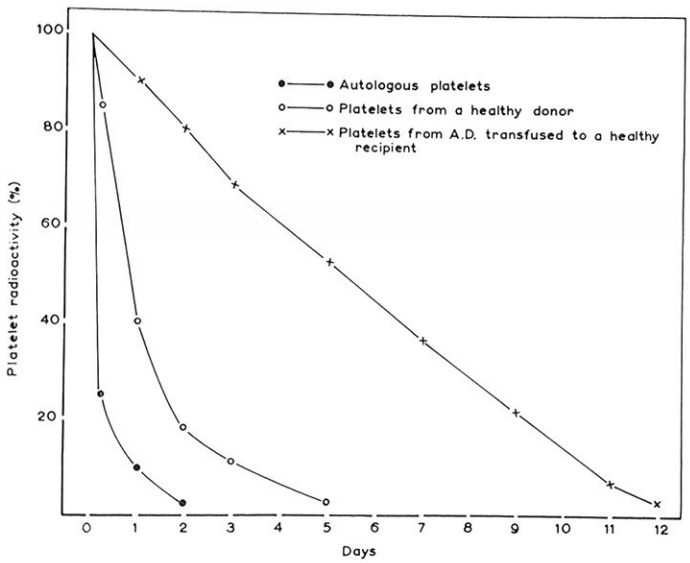

Figure 2. Survival of A.D.'s platelets, and survival of cross-transfused platelets.

TABLE II

Platelet diameter in stained blood smear

	No. of platelets measured	Mean (μ)	Range (μ)	% $\geqq 5$ μ
AD	200	3.01	1.3–6.3	8
ARH	200	3.09	1.3–6.9	7
Normal control	200	2.24	1.3–7.5	1

let diameter was somewhat larger than normal, but only 7–8 % of the platelets had a diameter of 5 μ or more.

Platelet morphology

By light microscopy the platelets of A.D. and A.R.H. appeared quite similar. The platelet granulations appeared normal. Some platelets were slightly vacuolated.

The electron microscopic appearance of the platelets did not differ from that of normal platelets (electron microscopic examination was kindly done by Dr. T. Hovig, Section of Electron Microscopy, Rikshospitalet).

Megakaryocyte morphology

By light microscopy the megakaryocytes of A.D. and A.R.H. appeared similar. The bone marrow smears of both patients contained a slightly increased number of megakaryocytes. Some of the more mature megakaryocytes contained one or more vacuoles.

The electron microscopic appearance of the megakaryocytes did not differ from that of normal ones (electron microscopic examination was kindly done by Dr. T. Hovig).

Electrophoretic mobility of platelets

The measurements were kindly done by Dr. K. A. Gröttum, Section of Haematology, Rikshospitalet.

In plasma the electrophoretic mobility of A.D.'s platelets was 1.15 and that of

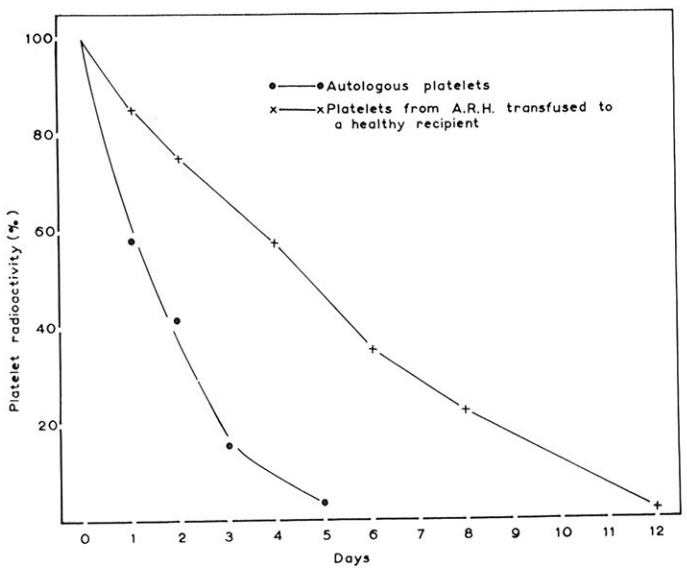

Figure 3. Survival of A.R.H.'s platelets in her own circulation, and cross-transfused to a healthy recipient.

TABLE III
Duke bleeding time (minutes)

	Platelet count × 1000	1 mm. deep cuts	2 mm. deep cuts
AD, ♀	35	14½	>30
ARH, ♀	30	23	>30
Leukaemia, ♂	12	1	9½
Leukaemia, ♂	15	8½	28½
Leukaemia, ♂	18	2½	>30
Leukaemia, ♂	41	2	9½
Leukaemia, ♀	20	6	27½
Mb. Gaucher, ♀	30	7½	14½

A.R.H.'s platelets was 1.12 μ/sec./volt/cm. (normal range 1.01–1.17).

Duke's bleeding time

Table III shows the Duke bleeding times from the ear lobe, and the platelet levels at the time of the tests. From the 2 mm. deep cuts the bleeding increased to a maximum of 7–8 drops per minute after a few minutes and continued at that rate for the full half hour. At that time, the bleeding was stopped in A.D. by applying a piece of cotton moistened with nor-adrenaline ¼ % solution against the cut for 3 minutes. In A.R.H., this was not enough, and a piece of Oxycel (oxydized cellulose – Park & Davis) had to be applied to stop the bleeding.

This was compared with the bleeding time of 6 other patients with thrombocytopenia with platelets between 12,000 and 41,000 per μl. Of these 6 patients only 1 had a Duke's bleeding time > 30 minutes from cuts 2 mm. deep.

It is evident that the bleeding in patients A.D. and A.R.H. was more severe and the bleeding time longer than corresponding to the platelet number.

The unproportionate increase of the bleeding time in our patients would probably have been even more striking if the comparison had been made with idiopathic thrombocytopenia and not leukaemia, as the latter not infrequently has a qualitative platelet defect in addition to the thrombocytopenia.

Ivy's bleeding time

Table IV shows the Ivy bleeding times and the platelet counts at the time of the tests. The bleeding continued from 1 mm. deep cuts also when the blood pressure cuff was deflated after ½ hour. A piece of cotton moistened with ¼ % nor-adrenaline was then pressed against the cuts for 3 minutes, and this stopped the bleeding.

This was compared with the bleeding time of 3 other patients with thrombocytopenia (due to idiopathic thrombocytopenic purpura) with platelet count between 12,000 and 35,000 per μl. All three had Ivy bleeding times > 30 minutes from cuts 1 mm. deep. However, only one of the 3 had bleeding time > 30 minutes from cuts ½ mm. deep.

It is evident that the bleeding time in the patients A.D. and A.R.H. was longer than corresponding to the platelet number.

Tourniquet test

The total number of petechiae in 8 square centimeters were 0 in A.D., 2 in A.R.H.; the normal range in 30 young women was 0–20, with a mean of 3.5.

TABLE IV
Ivy bleeding time (minutes)

	Platelet count × 1000	½ mm. deep cuts	1 mm. deep cuts
AD, ♀	35	>30	>30
ARH, ♀	30	>30	>30
ITP, ♀	12	>30	>30
ITP, ♀	35	25	>30
ITP, ♂	12	24½	>30

TABLE V

Clot retraction of the patients' plasma compared with normal plasma adjusted to the same platelet number
(The original length of clots is 100 scale units; longitudinal retraction is given in units)

Platelets per μl.	AD 90,000	ARH 65,000	Normal 90,000	Normal 61,000
1 hour	45	50	40	45
2 hours	50	60	45	53
3 hours	60	66	65	59
24 hours	78	82	82	78

Clot retraction

Table V shows that the clot retraction of the patients' plasmas was just as good as that of normal control plasma adjusted to the same platelet number.

Whole blood platelet adhesiveness

Table VI shows that the percentage of adhesive platelets was in the lower or subnormal part of the normal range. The measurements were kindly performed by Dr. A. Hellem, Medical Department A, Rikshospitalet.

Normal platelet aggregation was observed following the addition of collagen suspension. The assay was kindly performed by Mrs. Aa. Lund-Riise, Institute for Thrombosis Research, Rikshospitalet.

Thromboplastin generation test

Table VI gives the results of the test. Clearly the patient's platelets had the same effect as normal platelets.

Prothrombin consumption test

The results indicate (Table VI) that somewhat more prothrombin seems to have been consumed from the normal blood than from that of the patients. However, the difference is hardly greater than corresponding to the difference in platelet number.

Total platelet factor 3 assay

The Stypven clotting time for dilutions of frozen and thawed platelet-rich plasma from the patient A.D. corresponded well with frozen and thawed normal plasmas diluted to the same platelet number (Figure 4).

Platelet factor 3 availability assay

The Stypven clotting time for dilutions of kaolin-incubated platelet-rich plasma from A.D. was in the upper normal range. Considering the fact that her platelet count at the time of the test was reduced to $^1/_3$ to $^1/_5$ of the normal, her platelet factor 3 availability must be regarded as normal (Figure 5).

Other tests

Table VI shows that a series of other haemostatic tests were normal. Likewise, haemoglobin, RBC, WBC, eosinophils, and ESR were within normal limits.

DISCUSSION

From Figure 1 is seen that among the offspring from matings between affected and

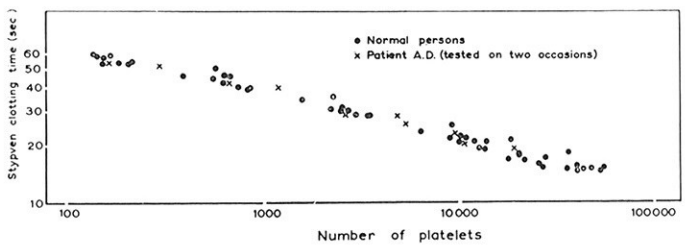

Figure 4. Total platelet factor 3 assay. Stypven clotting times plotted against platelet numbers for 9 normal persons (●) and for patient A.D. (+) (undiluted and diluted platelet-rich plasmas were used).

TABLE VI
Other haemostatic tests

	AD	ARH	Normal control	Normal range	Reference
Fibrinogen (mg. per 100 ml.)	325	375		150–400	Blombäck & Blombäck (1956)
Fibrinolysis	Normal	Normal			Astrup & Müllertz (1952)
Thrombin time (sec.)	20	23.2	22.5		
Cephalin time (sec.)	47.5	47.8	49	39–53	Schiffman et al. (1963)
Quick time (sec.)	15.2	14.1	14.5	13–16	
P&P test (sec.)	28.3	28.1	29.1	24–32	Owren & Aas (1951)
AHG (%)	110	82.5		60–150	Schiffman et al. (1963)
Adhesive platelets % of initial count	20	31		25–60	Hellem (1960)
Thromboplastin generation test	90,000 own plat.		90,000 norm. plat.		Dacie & Lewis (1963)
3 min. incub.	11.0 sec.		10.0 sec.		
6 min. incub.	10.8 sec.		11.0 sec.		
9 min. incub.	11.2 sec.		11.4 sec.		
12 min. incub.	11.6 sec.		12.0 sec.		
Thromboplastin generation test		65,000 own plat.	61,000 norm. plat.		
3 min. incub.		13.6 sec.	15.0 sec.		
6 min. incub.		13.8 sec.	14.2 sec.		
9 min. incub.		13.8 sec.	14.6 sec.		
12 min. incub.		15.0 sec.	15.0 sec.		
Prothrombin consumption test					Dacie & Lewis (1963)
Plat. × 1000 in blood	35	30	200		
Plasma time (sec.)	7.7	6.0	7.1		
Serum time (sec.)	62.5	35.4	95.0		
Prothr. cons. index	12 %	17 %	7.5 %		

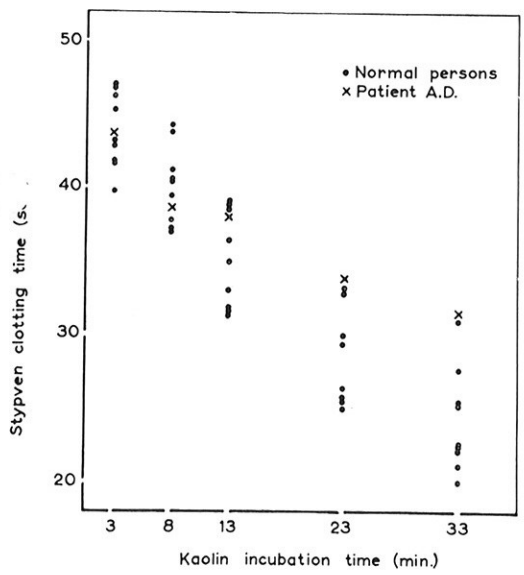

Figure 5. Platelet factor 3 availability assay. Stypven clotting times plotted against kaolin incubation time for 9 normal persons (●) and for patient A.D. (+) (undiluted platelet-rich plasmas were used).

normal persons 8 were affected and 9 not affected.

This indicates that the platelet disorder is inherited as a Mendelian dominant character.

The disorder is found to segregate independently of sex, of the ABO, Rh, MNSs and Duffy blood group systems. The findings in the Lewis system indicate that the disorder segregates independently of the ABH secretor genes.

No linkage information was obtained for the P, Kell, Lutheran, and Wright blood

group systems, as all the examined persons were found to be P_1+, K−, Lu(a−) and Wr(a−).

All the persons were also Ny(a−) and Vw−.

The patients' platelets had a shortened survival in their own circulation, indicating increased destruction. This was not due to an intrinsic defect in the patients' platelets, because they survived normally when transfused to normal recipients. Therefore, the patients must have some factor or mechanism in their blood or vascular system which shortens the life span of their own platelets as well as that of transfused normal platelets.

Another striking finding was the unproportionate increase of the bleeding time in these patients. The bleeding time in our patients was far longer than corresponding to the slight or moderate reduction in platelet number.

The 10 persons with a history of abnormal bleeding all had a greatly prolonged bleeding time and a moderately decreased number of platelets. The bleeding time exceeded 30 min. in 8 of the 10 afflicted persons, and in practically all instances the bleeding had to be stopped by compression for a few minutes with a piece of cotton wool soaked in a ½ % nor-adrenaline solution. The bleeding time was increased out

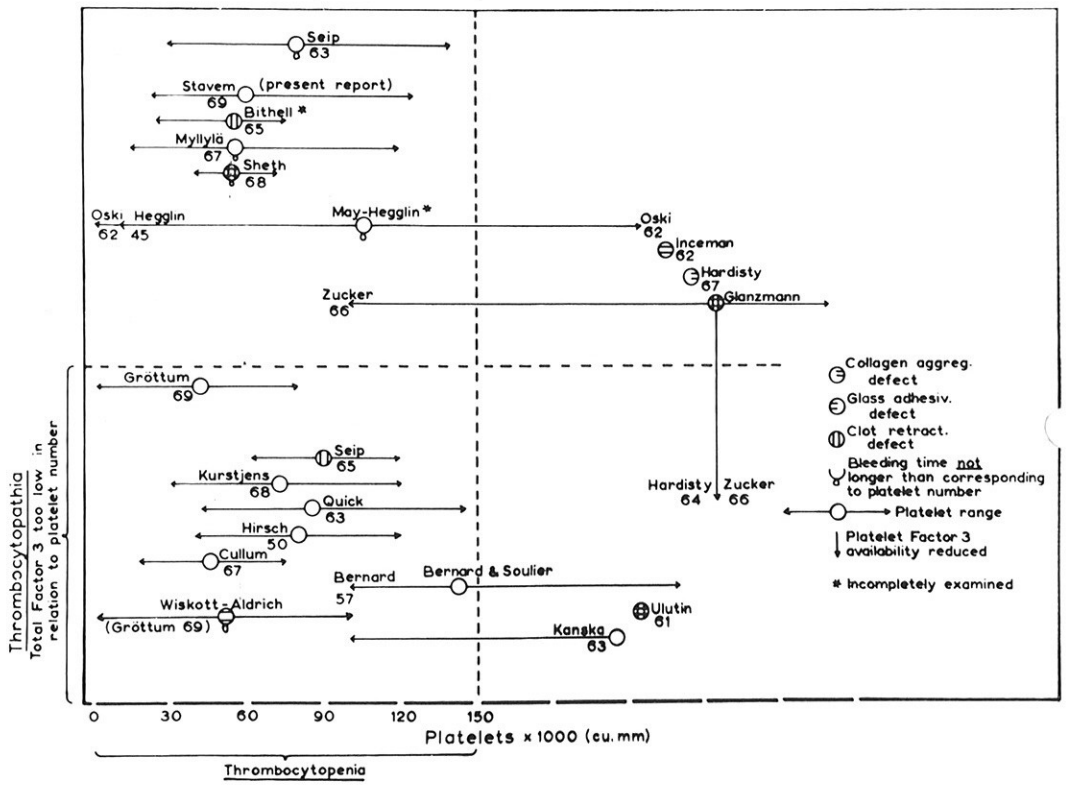

Figure 6. Hereditary thrombocytopenias and qualitative platelet disorders.
(All except 5 disorders have bleeding times prolonged more than corresponding to platelet number)

of proportion to the moderate reduction in platelets. This was most clearly demonstrated in D.D. (III 6), who had a bleeding time of more than 30 min. even when the platelet number was above 100,000 per μl.

The moderately reduced platelet count and normal AHG exclude von Willebrand's disease. The normal clot retraction, low normal whole blood platelet adhesiveness and normal collagen-induced platelet aggregation show that the presently reported bleeding disorder is not a form of thrombasthenia. The thromboplastin generation test, prothrombin consumption test, total platelet factor 3 assay and platelet factor 3 availability assay all gave results corresponding to the platelet count. In other words, the platelets' contribution to coagulation was quite normal when allowing for the reduction in platelet number, and the presently reported bleeding disorder is not a form of thrombopathia either.

Figure 6 illustrates some characteristics of different hereditary platelet disorders, including the presently reported. Although some recent studies suggest a platelet defect in von Willebrand's disease, we have not included it in the figure. A review of previously described thrombocyte disorders necessarily meets with difficulties. For obvious reasons, older reports do not contain results of modern tests, and such reports are rarely brought up to date. Another problem is that tests for platelet factor 3 and bleeding time are difficult to standardize. To decide whether the amount of factor 3 is reduced or the bleeding time is increased more than corresponding to the number of platelets may therefore be difficult.

Some of the disorders which have been separately drawn in Figure 6 might therefore ultimately prove to be a single entity. On the other hand, some of them will probably be subdivided into different entities by future tests.

Our patients' bleeding tendency could possibly be ascribed to some vascular defect. Such a vascular defect would explain the greatly prolonged bleeding time. A vascular defect also could explain a larger utilization of platelets and a shortened platelet survival. A vascular defect might be expected to cause a pathological tourniquet test. However, the tourniquet test was completely normal in our patients, rendering the vascular hypothesis less likely.

Another conceivable mechanism for the patients' bleeding tendency is lack of some serum enzyme necessary for the normal metabolism of platelets. This would explain the greatly shortened life span of the patients' own and of the transfused normal platelets. Lack of such an enzyme could also impair the quality of the platelets and explain the unproportionate prolongation of the bleeding time.

Autoantibodies directed against own as well as transfused platelets might be another mechanism. Autoantibodies directed against own intrinsic factor or gastric mucosa have been reported in families with pernicious anaemia. A similar inherited tendency to develop platelet antibodies is therefore conceivable in our patients.

The various techniques described for detection of platelet antibodies are not easy to standardize, and the results are difficult to interpret. Thus Baldini (1966) in a review article flatly states that in ITP, platelet antibodies have not been satisfactorily demonstrated *in vitro*, although *in vivo* studies have clearly shown that an anti-platelet factor with the characteristics of an antibody is present in the plasma of these patients.

These difficulties also make one some-

what hesitant to accept reports of such autoantibodies in familial thrombocytopenic purpura. Schaar (1963) reported a family in which 4 boys among 9 children had ITP. She found platelet agglutinins in 2 of 3 afflicted children, and in 1 of 4 healthy children. Schaar herself concluded that the platelet agglutinins did not appear to be the cause of the thrombocytopenia in the 4 boys. Harms & Sachs (1965) reported a family with chronic thrombocytopenia and platelet autoantibodies. Three sisters with slight to moderate thrombocytopenia all showed platelet antibodies with an antiglobulin consumption test. So did, however, their mother who had neither thrombocytopenia nor any bleeding tendency.

Nevertheless, it is conceivable that autoantibodies play a part in our patients. These autoantibodies would, however, have to differ from the autoantibodies in ITP, in order to explain the improportionate prolongation of the bleeding time.

The presently reported bleeding disorder is not identical with any of the previously described ones and probably represents a new type of hereditary bleeding disorder.

REFERENCES

Abrahamsen, A. F. (1965) 'The effect of EDTA and ACD on the recovery and survival of Cr^{51}-labelled blood platelets.' *Scand. J. Haemat.* **2**, 52–60.

Astrup, T. & Müllertz, S. (1952) 'The fibrin plate method for estimating fibrinolytic activity.' *Arch. Biochem.* **40**, 346–51.

Baldidni, M. (1966) 'Idiopathic thrombocytopenic purpura.' *New Engl. J. Med.* **274**, 1245–51, 1302–06, 1360–67.

Benthaus, J. (1959) 'Über die Retraktion des Blutgerinnsels.' *Thrombos. Diathes. haemorrh.* (Stuttg.) **3**, 311–52.

Bernard, J., Caen, J. & Maroteau, P. (1957) 'La dystrophie thrombocytaire hémorragipare congénitale.' *Rev. Hémat.* **12**, 222–49.

Bitchell, T. C., Didisheim, P., Cartwright, G. E. & Wintrobe, M. M. (1965) 'Thrombocytopenia inherited as an autosomal dominant trait.' *Blood* **25**, 231–40.

Blombäck, B. & Blombäck, M. (1956) 'Purification of human and bovine fibrinogen.' *Ark. Kemi* **10**, 415–43.

Cullum, C., Cooney, D. P. & Schrier, S. L. (1967) 'Familial thrombocytopenic thrombocytopathy.' *Brit. J. Haemat.* **13**, 147–59.

Dacie, J.V. & Lewis, S. M. (1963) *Practical Haematology*. J. & A. Churchill, London, 435 pp.

Fuhrmann, G. F. & Ruhenstroth-Bauer, G. (1965) 'Cell electrophoresis employing a rectangul measuring cuvette.' In Ambrose, E. J. (ed.) *Cell electrophoresis*, 204 pp. J. & A. Churchill, London.

Godal, H. C. (1961) 'Simple syneresis procedure for fibrinogen assay.' *Scand. J. clin. Lab. Invest.* **13**, 530.

Gröttum, K. A. (1968) 'Influence of aggregating agents on electrophoretic mobility of blood platelets from healthy individuals and from patients with cardiovascular disease.' *Lancet* **I**, 1406–08.

Gröttum, K. A. & Solum, N. O. (1969) 'Congenital thrombocytopenia with giant platelets: a defect in the platelet membrane.' *Brit. J. Haemat.* **16**, 277–90.

Hardisty, R. M., Dormandy, K. M. & Hutton, R. A. (1964) 'Thrombasthenia. Studies on three cases.' *Brit. J. Haemat.* **10**, 371–87.

Hardisty, R. M. & Hutton, R. A. (1965) 'The kaolin clotting time of platelet rich plasma: a test of factor-3 availability.' *Brit. J. Haemat.* **11**, 25 68.

Hardisty, R. M. & Hutton, R. A. (1967) 'Bleeding tendency associated with 'new' abnormality of platelet behaviour.' *Lancet* **I**, 983–85.

Harms, D. & Sachs, V. (1965) 'Familial chronic thrombocytopenia with platelet autoantibodies.' *Acta haemat.* **34**, 30–35.

Hegglin, R. (1945) 'Gleichzeitige konstitutionelle Veränderungen an Neutrophilen und Thrombozyten.' *Helv. med. Acta* **12**, 439–40.

Hellem, A. J. (1960) 'The adhesiveness of human blood platelets in vitro.' *Scand. J. clin. Lab. Invest.* **12** (Suppl. 51), 120 pp.

Hirsch, E. O., Favre-Gilly, J. & Dameshek, W.

(1950) 'Thrombopathic thrombocytopenia: successful transfusion of blood platelets.' *Blood* **5**, 568–80.

Hjort, P. F., McGehee, W. G. & Rapaport, S. I. (1966) 'Effects of thorium dioxide upon blood clotting and platelets. I. *In vitro* studies.' *Thrombos. Diathes. haemorrh.* (Stuttg.) **16**, 333–53.

Hjort, P. F., Rapaport, S. I. & Owren, P. A. (1955) 'A simple, specific one-stage prothrombin assay, using Russel's viper venom in cephalin suspension.' *J. Lab. clin. Med.* **46**, 89–97.

Hovig, T., Rowsell, H. C., Dodds, W. J., Jörgensen, L. & Mustard, J. F. (1968) 'Experimental hemostasis in normal dogs and in dogs with congenital disorders of blood coagulation.' *Blood* **30**, 636–68.

Inceman, S., Unügür, A. & Aran, M. (1962) 'Essential athrombia.' *Thrombos. Diathes. haemorrh.* (Stuttg.) **8**, 502–10.

Kańska, Barbara, Niewiarowski, S., Ostrowski, L., Poplawski, A. & Prokopowicz, J. (1963) 'Macrothrombocytic thrombopathia. Clinical, coagulation and hereditary aspects.' *Thrombos. Diathes. haemorrh.* (Stuttg.) **10**, 88–100.

Kurstjens, R., Bolt, C., Vossen, M. & Haanen, C. (1968) 'Familial thrombopathic thrombocytopenia.' *Brit. J. Haemat.* **15**, 305–17.

Myllylä, G., Pelkonen, R., Ikkala, E. & Apajalahti, J. (1967) 'Hereditary thrombocytopenia. Report of three families.' *Scand. J. Haemat.* **4**, 441–52.

Nygaard, K. K. (1933) 'A direct method of counting platelets in oxalated plasma.' *Proc. Mayo Clin.* **8**, 365–70.

Oski, F. A., Naiman, J. L., Allen, D. M. & Diamond, L. K. (1962) 'Leukocytic inclusions – Döhle bodies – associated with platelet abnormality (the May-Hegglin anormaly).' *Blood* **20**, 657–67.

Owren, P. A. & Aas, K. (1951) 'The control of dicumarol therapy and the quantitative determination of prothrombin and proconvertin.' *Scand. J. clin. Lab. Invest.* **3**, 201–08.

Quick, A. J. & Hussey, C. V. (1963) 'Hereditary thrombopathic thrombocytopenia.' *Amer. J. med. Sci.* **245**, 643–52.

Schaar, Frances E. (1963) 'Familial idiopathic thrombocytopenic purpura.' *J. Pediat.* **62**, 546–51.

Schiffman, S., Rapaport, S. I. & Patch, M. J. (1963) 'The identification and synthesis of activated plasma thromboplastin component (PTC').' *Blood* **22**, 733–49.

Seip, M. (1963) 'Hereditary hypoplastic thrombocytopenia.' *Acta paediat.* (Uppsala) **52**, 370–76.

Seip, M. & Kjærheim, Å. (1965) 'A familial platelet disease – hereditary thrombasthenic – thrombopathic thrombocytopenia.' *Scand. J. clin. Lab. Invest.* **17** (Suppl. 84), 159–69.

Sheth, N. K. & Prankerd, T. A. J. (1968) 'Inherited thrombocytopenia with thrombasthenia.' *J. Clin. Path.* **21**, 154–56.

Stavem, P. (1965) 'The tourniquet test.' *Scand. J. clin. Lab. Invest.* **17**, 607–13.

Stavem, P. (1967) 'The influence of depth of the cut on the bleeding time.' *Acta med. scand.* **182**, 389–96.

Ulutin, O. N. (1961) 'The qualitative platelet diseases.' In Henry Ford Hospital International Symposium *Blood Platelets*, 553 pp. J. & A. Churchill, London.

Zucker, Marjorie B., Pert, J. H. & Hilgartner, M. W. (1966) 'Platelet function in a patient with thrombasthenia.' *Blood* **28**, 524–34.

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