A "New" Family with Stuart-Prower Deficiency

J. Roos, C. van Arkel, M. C. Verloop and F. L. J. Jordan,
Utrecht/Netherlands

In 1952, van Belle (4) in our clinic described a family (Fig. 1) with consanguineous parents (first cousins), six of whose twelve children had shown a haemorrhagic diathesis since birth. This was manifested by nasal and gingival haemorrhages, after-haemorrhages from wounds, blue skin discoloration following slight blows, haematuria, haemarthrosis (?) and severe menorrhagia. There were no physical anomalies except sometimes a more or less marked anaemia. Liver function tests yielded normal results. Administration of vitamin K was ineffective. The remaining membres of this family showed no haemorrhagic tendencies.

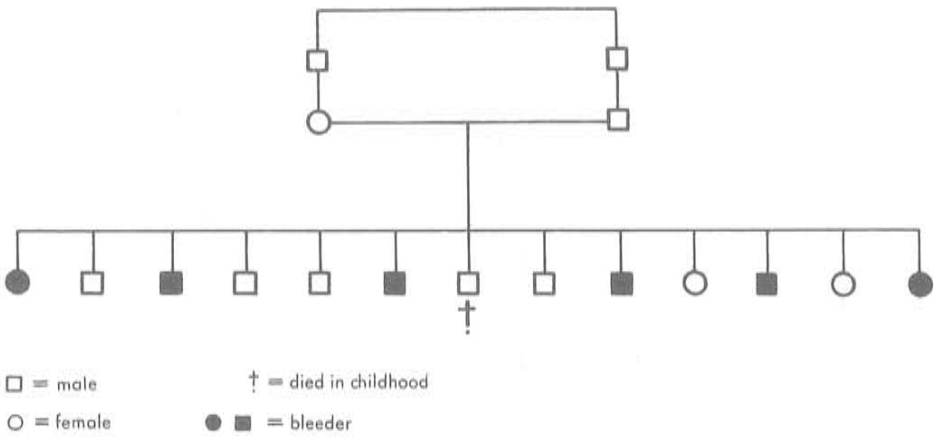

Fig. 1: Family K.

v. Belle — using the techniques available at the time — found the following disorders (table 1):

Tab. 1: Data on these bleeders in 1950:

1. slightly prolonged clotting time.
2. prolonged one stage "prothrombin" time (Quick [19]).
3. prolonged two stage "prothrombin" time (Warner, Brinkhous and Smith [22]).
4. diminished prothrombin consumption.
5. correction of 2 and 3 by normal serum.

This activator from normal serum was destroyed by heating at 56 ° C for 15 minutes but withstood storage at room temperature. It could be removed by means of $Ca_3(PO_4)_2$. These findings led to the diagnosis of factor VII-deficiency.

Our understanding of the mechanism of blood coagulation has greatly improved since 1952, particularly with regard to the mechanism of thromboplastin formation. By means of the thromboplastin generation test and techniques derived from it, it was possible to divide "factor VII" deficiencies into two groups, viz.: a group associated with normal thromboplastin formation, whose clotting defect is not corrected by the case of hypoproconvertinaemia described by Alexander (1) in 1951, and another group which is corrected but shows a disturbance in the thromboplastin generation test. The latter group of cases is referred to as Stuart-Prower deficiency, after the first patients found to have this deficiency (Hougie et al. [14], Telfer et al. [21]).

Some confusion arose from initial registration of these patients as cases of factor VII deficiency — an error due to the fact that the factor VII value was determined with the aid of a substrate consisting of a Seitz-filtered plasma, from which not only factor VII but also the Stuart-Prower factor proved to have been removed.

As to the members of the family under discussion a few modifications were seen in the course of their disease since 1952. For example, hospitalization of the children because of haemorrhagic episodes was less frequently required. The question remains as to whether spontaneous haemorrhages occur in episodes in bleeders with a constant low concentration of some clotting factor. Haemorrhages resulting from traumatic discontinuity of the vascular wall have probably decreased in frequency with increasing age. Treatment was required on only two occasions, both involving an accident with a motor-aided bicycle. Hysterectomy was necessary in the case of the oldest girl. Three children have married, including one bleeder, but the two grandchildren originate from two non-bleeders.

We had occasion to repeat coagulation tests in the bleeders described here and a number of their siblings. None of the subjects examined showed a haemorrhagic diathesis at the time of examination.

Materials and Methods

Human Brain Thromboplastin (HBT) was prepared according to Quick (19).

Russell's viper venom-cephalin reagent: according to Hjort et al. (12). The final concentration of R.V.V. ("Stypven", Burroughs and Wellcome) was 1 : 80 000, that of cephalin 0.05 g per cent.

Veronal buffer (Michaelis) was our diluent.

$CaCl_2$ solution was 1/40 n.

Plasma was prepared from 9 parts of blood and 1 part of sodium citrate 3.8% by centrifugation (2000 R.P.M., 5 minutes).

Serum was obtained from blood clotted in uncoated glass tubes and incubated therein during 3—4 hours at 37° C.

$BaSO_4$ — serum refers to serum which was adsorbed onto $BaSO_4$ (B.D.H.; analar) for 5 minutes at room temperature by stirring with a glass rod and centrifugated (2000 R.P.M., 5 minutes).

Chloroform brain extract was prepared according to Bell and Alton (3).

Coagulation time according to Lee and White (16).

One stage "prothrombin" time according to Quick (19).

One stage "prothrombin" time with R. V.V.-cephalin was performed by substituting 0.1 ml of Human Brain Thromboplastin in Quick's method by 0.1 ml R.V.V.-cephalin reagent.

Prothrombin consumption according to Merskey (17).

Thromboplastin Generation Test according to Biggs and Douglas (5). The results are expressed in the shortest coagulation time as well as in the largest percent of thromboplastic activity which were obtained. The plasma was adsorbed onto $BaSO_4$ (25 mg/ml). The dilution of plasma was 1/5, the dilution of serum 1/10.

"Factor VII", prothrombin and factor V according to Owren (18).

Stuart-Prower factor assay was performed according to method 3 (with R.V.V.) of Bachmann et al. (2).

Antihaemophilic factor according to Bounameaux (6).

Christmas factor (factor IX) according to Geiger et al. (9).

Fibrinogen according to Clauss (8).

Antithrombin test according to Greep (11).

Results

The data pertaining to the eldest daughter in the family (VI—29 in fig. 3) are presented here as an example of the findings obtained in the bleeders (table 2).

A circulating anticoagulant was excluded by determination of the antithrombin time and by the recalcification time, the "factor VII" determination and the thromboplastin generation test from a normal control, in all of which the sample was incubated up to one hour with patient's serum in a 50 : 50 ratio.

The most important disturbances seen included prolongation of the one-stage "prothrombin" time, both with human brain thromboplastin and with Russell's viper venom-cephalin, a disturbance in prothrombin consumption and thromboplastin generation, and a marked decrease in the concentration of the Stuart-Prower factor and of "factor VII".

One stage prothrombin time with Human Brain Thromboplastin (table 3). The one-stage "prothrombin" determination using brain thromboplastin was corrected by 20% normal plasma, 20% normal serum, 20% serum from a patient given large doses of tromexan 24 and 12 hours previously, 20%

Tab. 2: Data on a bleeder.

	Patient	Normal
Platelets (Fonio)	286 000	130 000—400 000
Platelets morphology	normal	normal
Bleeding time (Duke)	2 min.	1—4 min.
Clot retraction (Macfarlane)	58%	38—64%
Rumpel Leede	negative	negative
Coagulation time	10, 10, 10, 11 min.	5—8½ min.
Recalcification time	180 sec.	90—180 sec.
Prothrombin consumption index	44%	< 20%
Thromboplastin Generation test	abnormal	normal
One stage "prothrombin" time		
with Human Brain Thromboplastin	51.2 sec.	15.0 sec. S.D.*) ± 6.0 sec.
with R.V.V.-cephalin	24.0 sec.	9.7 sec. S.D.*) ± 0.6 sec.
Fibrinogen	310 mg%	200—300 mg%
Prothrombin	80%	88% S.D. ± 14%
Factor V	100%	100% S.D. ± 15.7%
"Factor VII"	4.2%	110% S.D. ± 20%
Antihaemophilic factor	105%	61% S.D. ± 28%
Factor IX (Christmas factor)	44%	93% S.D. ± 28%
Stuart-Prower factor	5%	104% S.D. ± 12%

*) S.D. = standard deviation = $\sqrt{\frac{\Sigma (x_i - \bar{x})^2}{(n-1)}}$

Tab. 3: Correction of the one stage "prothrombin" time (Quick) with HBT by different plasmas or sera.

	0.1 ml	0.02 ml to 0.08 ml plasma of patient K.
	in seconds	
Patient K.	51.2	
Normal plasma	14.6	18.6
Normal serum		14.8
Normal serum after $BaSO_4$ adsorption		52.4
Normal serum after heating (30 min., 56° C)		53.0
Serum from a patient after 24 hours tromexan treatment		19.4
Plasma from a patient after long term dicoumarol treatment	88	36.0
Congenital VII-deficient plasma (lyophilized)	82	23.5
Congenital IX-deficient serum		16.0
Congenital Stuart-Prower deficient plasma	86	65

plasma from a patient with congenital hypoproconvertinaemia*) and 20% serum from a patient with haemophilia-B. No correction was effected by plasma from a patient given dicoumarol for some considerable time or by plasma from the patient with congenital Stuart-Prower deficiency described by Bachmann*) et al. (2). Normal serum heated at 56° C for 30 minutes or adsorbed onto $BaSO_4$ was likewise incapable of correction.

Prothrombin consumption (table 4). The prothrombin consumption according to Merskey (17) was corrected by addition of 0.1 ml normal serum to 1 ml blood reserved for the coagulation time according to Lee and White. Concentrations below 0.1 ml normal serum failed to improve the prothrombin consumption.

Tab. 4: Correction of the prothrombin consumption (Merskey) by normal serum.

Blood patient Normal serum	1 ml	1 ml 0.1 ml	1 ml 0.01 ml	1 ml 0.001 ml
Lee White (minutes)	9	6	7.5	8.5
Plasma time (secs)	26.8			
Serum time (secs)	61	180	80	68
Index (%)	45	15	34	39

Thromboplastin generation test (fig. 2). The thromboplastin generation test according to Biggs and Douglas (5) was normal if in the incubation mixture plasma and/or platelets from the patient were used. There was a severe disturbance when normal plasma and normal platelets were incubated with patient's serum (fig. 2).

This defect of the patient's serum in the thromboplastin generation test was corrected by 50% normal serum and 50% serum from a patient given large doses of tromexan 24 hours previously. No correction occurred if the normal serum had previously been adsorbed onto $BaSO_4$ or had been heated at 56° C for 30 minutes. Nor was any correction effected by serum from a patient given dicoumarol for some considerable time (one-stage "prothrombin" time 88 seconds). Serum from a patient with congenital factor VII deficiency gave a good correction, whereas serum from Bachmann's female patient with Stuart-Prower deficiency gave no correction. The correction tests with serum

*) Acknowledgements are due to Drs. Waaler and Voss (Oslo) and Dr. Bachmann (Zürich) for their kindness in making samples available.

from subjects suffering from haemophilia-B will be discussed later (fig. 6). The bleeders from our family did not correct each other's thromboplastin generation test (fig. 4, group c.).

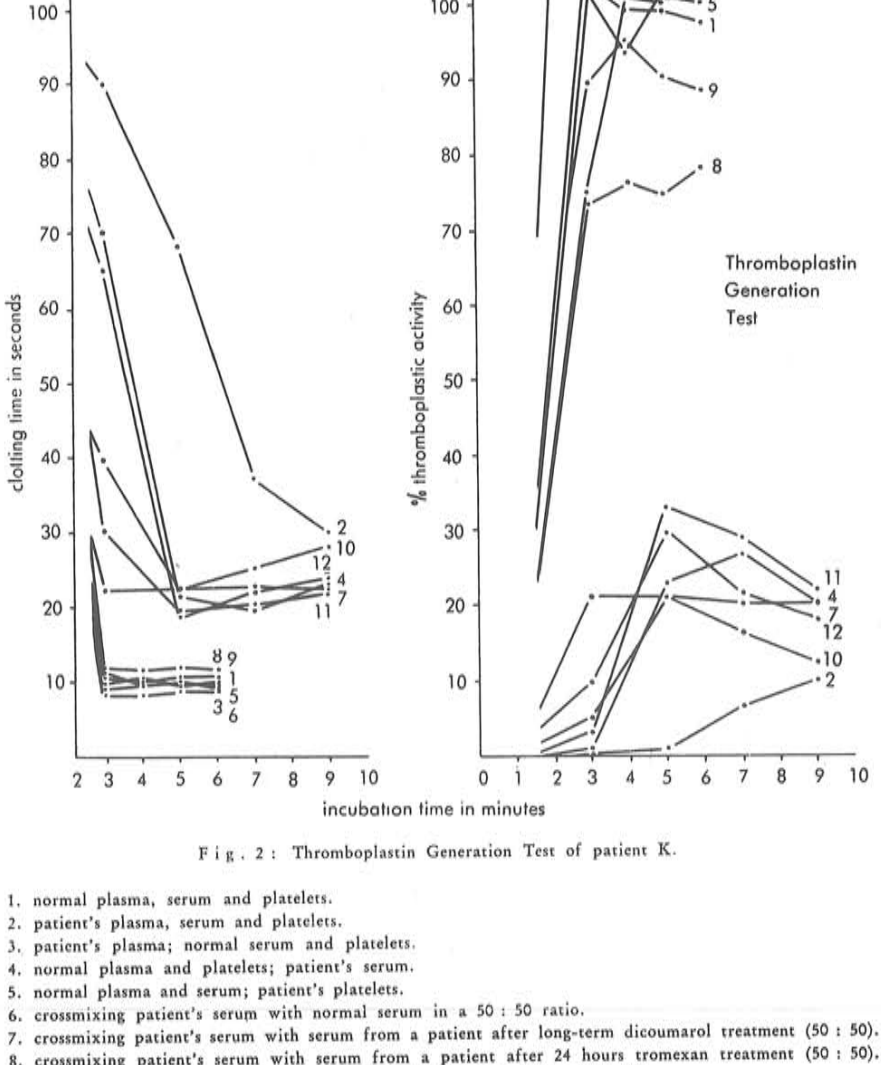

Fig. 2: Thromboplastin Generation Test of patient K.

1. normal plasma, serum and platelets.
2. patient's plasma, serum and platelets.
3. patient's plasma; normal serum and platelets.
4. normal plasma and platelets; patient's serum.
5. normal plasma and serum; patient's platelets.
6. crossmixing patient's serum with normal serum in a 50 : 50 ratio.
7. crossmixing patient's serum with serum from a patient after long-term dicoumarol treatment (50 : 50).
8. crossmixing patient's serum with serum from a patient after 24 hours tromexan treatment (50 : 50).
9. crossmixing patient's serum with congenital VII-deficient serum (50 : 50).
10. crossmixing patient's serum with congenital Stuart-Prower-deficient serum (50 : 50).
11. crossmixing patient's serum with normal $BaSO_4$-serum (50 : 50).
12. crossmixing patient's serum with normal serum heated at 56° C. for 30 minutes.

6—12 are performed with normal plasma and platelets.

This patient's plasma concentration of Stuart-Prower factor was 5% as determined by the Bachmann (2) method. The concentration was 62—70% if five parts of the patient's plasma were mixed with five parts of normal plasma; admixture of five parts of plasma from another bleeder in this family or from Bachmann's patient effected no correction (5.8%).

On the basis of these findings the condition was diagnosed as Stuart-Prower deficiency. Up to this moment we know of four cases described as such in the literature (2, 10, 14, 21). A survey of possible cases can be found in papers by Hougie et al. (14) and Bachmann et al. (2); the case of Hörder (13) probably also belongs to this group.

The data on our six subjects with Stuart-Prower clotting deficiency are summarized in Table 5. In this table, patients are indicated by the numbers from the pedigree (fig. 3).

Tab. 5: Pathological data on our 6 bleeders.

	Sex	Age	Coagulation time (min.)	Recalcification time (secs)	One stage "prothrombin" time with HBT (secs)	One stage "prothrombin" time with RVV-cephalin (secs)	"Factor VII" (%)	Stuart-Prower Factor (%)	Factor IX (%)	Prothrombin consumption index (%)	Thromboplastin Generation Test (Minimum clotting time in secs)	Correction TGT by normal serum (50 : 50) (secs)	Correction TGT from a patient with cong. IX-deficiency (50 : 50) (secs)
Normal			5 to 8½	120 to 180	15.0	9.7	110	104	93	<20	8.0 to 9.6		9.2
S.D. ±					0.6	0.6	20	12	28				
Number													
VI – 29	♀	29	10	180	51	24	4.2	5.0	44	44	29.8	9.2	11.5
—31	♂	25	9	210	48	25	6	6.2	52	56	21.8	9.2	9.4
– 34	♂	21	9.5	230	45	24	4.6	5.1	46	56	22	9.8	12.3
—37	♂	18	9	220	59	24	4.2	5.2	94	45	21.5	9.2	8.0
—39	♂	15	11.5	195	47	28	4	6	80	32	19.2	10.2	12.5
—41	♀	10	8	180	52	25	3.2	5	35	64	21.5	9.0	8.0

Tab. 6: Data on relatives.

	Sex	Age	Relation to probandi	One stage "prothrombin" time with HBT (secs)	One stage "prothrombin" time with RVV-cephalin (secs)	"Factor VII" (%)	Stuart-Prower Factor (%)	Factor IX (%)	Prothrombin consumption index (%)	Thromboplastin Generation Test (secs)	Correction TGT from a bleeder (50 : 50) (secs)	Correction TGT from a patient with cong. IX-deficiency (50 : 50) (secs)
Normal				15.0	9.7	110	104	93	< 20	8.0—9.6	9.0—10.2	9.2
S.D. ±				0.6	0.6	20	12	28				
Number												
IV—15a	♀	82	grandmother	15	9	95	95	40	—	8.4	9.3	8.2
IV—32	♀	81	great-aunt	15	9	75	95	110	—	8.0	8.5	8.7
V —34	♀♂	61	maternal uncle	10	9	200	100	110	—	9.5	9.8	9.6
V —43	♀♂	50	mother*)	17	11	54	68	52	40	9.2	11.6	10.5
V —44	♀♂	50	father*)	16	11	48	62	34	9	13.0	14.8	11.9
V —45	♀♂	54	paternal aunt*)	18	11	75	82	17	78	9.8	11.9	12.0
V —46	♀♂	54	uncle by marriage	15	9	100	100	90	—	9.8	10.8	10.9
V —50	♀♂	27	grand-niece	15	9	107	97	—	19	8.2	10.4	11.8
V —52	♀♂	36	grand-nephew	16	10	105	90	—	< 10	9.4	10.5	10.2
VI—30	♂	27	brother*)	15	11	80	50	85	< 10	10.2	14.2	12.3
VI—32	♂	24	brother*)	15	10	68	62	32	11	8.4	11.8	14.1
VI—33	♂	23	brother*)	16	10	58	58	105	< 10	9.4	11.6	10.2
VI—36	♂	19	brother	15	9	90	100	100	10	9.0	9.4	9.5
VI—38	♀	16	sister*)	17	12	58	68	104	< 10	10.0	11.2	10.5
VI—40	♀	12	sister	17	11	52	75	50	< 10	8.6	10.8	11.2
VI—42	♀	27	cousin	15	9	90	82	54	25	8.8	9.6	9.3
VI—43	♀♂	24	cousin	16	11	100	100	75	< 10	8.2		
VI—44	♀♂	15	cousin	16	9	110	120	54	10	7.8	8.3	9.4
VI—45	♂	13	cousin*)	18	13	58	61	28	10	9.8	13.0	11.0
VI—46	♀	23	cousin*)	11	10	180	80	62	—	8.0	12.0	13.5

*) = carriers

Pedigree. The pedigree of these subjects with Stuart-Prower deficiency is extensive (fig. 3).

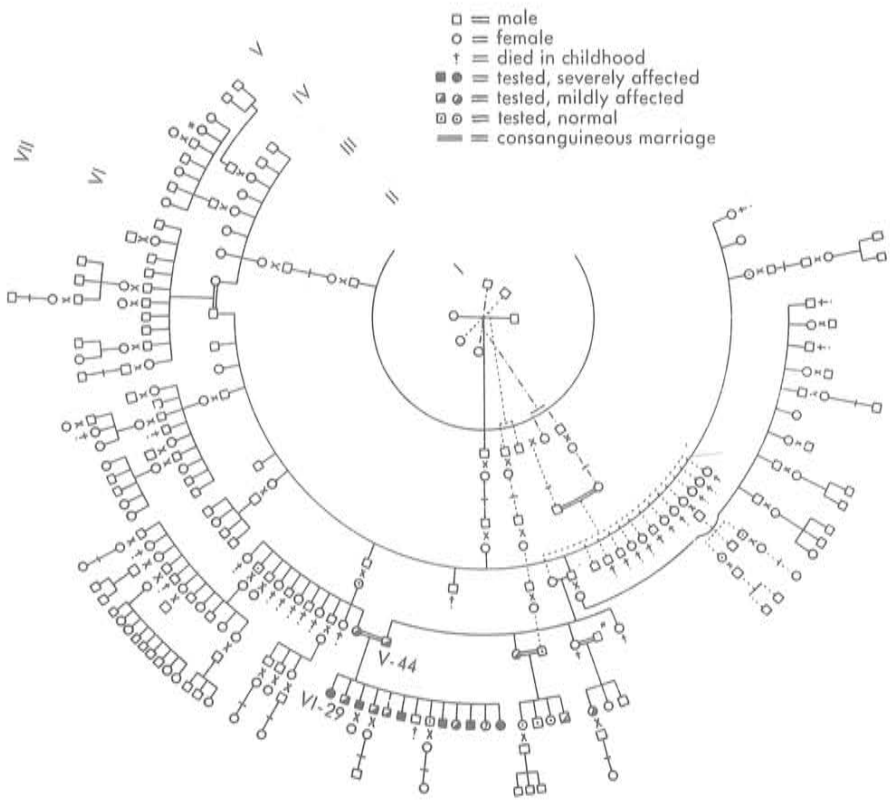

Fig. 3: The K. pedigree*)

The five consanguinities in this pedigree are: III_4 x III_5; IV_8 x IV_9; V_5 x V_{47}; V_{45} x V_{46} and V_{43} x V_{44}. Among these, only the first and the last one can have exerted any influence on the family including the bleeders under discussion. Particulars from the histories include nosebleeds and haematuria in IV_{15}, alcaptonuria in V_{45} and nosebleeds in VI_{45}.

We had occasion to examine a number of these siblings with regard to the data which showed an abnormality in their haemorrhagic relatives (table 6).

A review of these data leads to the conclusion that ten of these relatives were undoubtedly normal in the terms of this investigation; they were: IV_{15a}, $_{32}$, V_{34}, $_{46}$, $_{50}$, $_{52}$, VI_{36}, $_{42}$, $_{43}$, $_{44}$. The Stuart-Prower factor in these subjects was

*) (V_5 = V_{48}); VI_{29} = III_1 in Fig. 1.

found in concentrations between 120% and 82% (fig. 5). It was found that they (fig. 4, group a) were capable of correcting the thromboplastin generation test in their bleeder relatives in a ratio of 50 : 50 as did normal serum.

A group of nine subjects ($V_{43, 44, 45}$ and $VI_{30, 32, 33, 38, 45, 46}$) should be included among those referred to by Graham et al. (14) as heterozygotes. They had Stuart-Prower factor concentrations between 50 and 82% (fig. 5). Since the mean value of Stuart-Prower determinations made in our laboratory is 104%, with a standard deviation of ± 12%, values under 80% indicate a probability of abnormality exceeding 95%. Hence our hesitation to include V_{45} in this group of heterozygotes. However, since her son VI_{45} is a heterozygote without a doubt, we believe that V_{45} must also be a heterozygote, as her husband V_{46} is normal. Since we had no occasion to examine the children of VI_{42}, we feel that we cannot consider her a heterozygote.

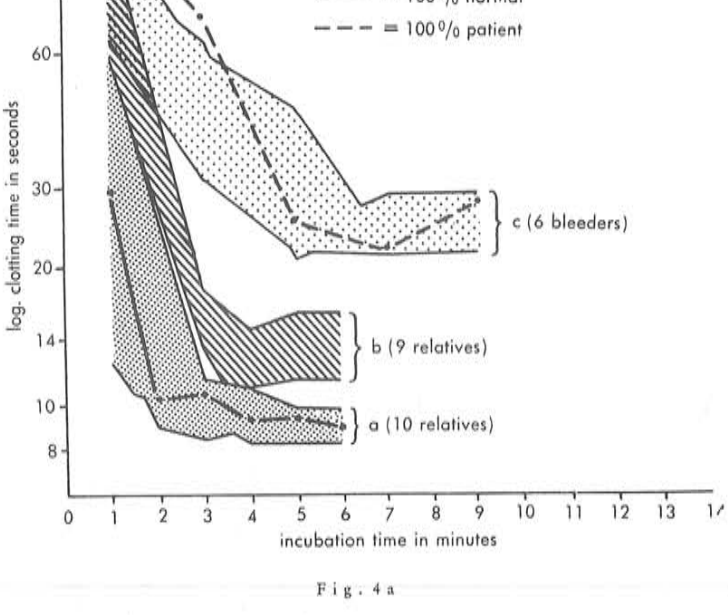

Fig. 4a

Fig. 4: *Thromboplastin Generation Test* with normal plasma and platelets. Serum of patient VI-34 was mixed in a 50 : 50 ratio and incubated for some minutes with serum from a normal control and from each of 25 relatives. 10 Relatives behaved like normal serum; their curves all fell between the limits of group a. None of the bleeders gave any correction: group c. Between groups a and c fell the correction-curves with serum of 9 relatives; their outside values gave the limits of group b.

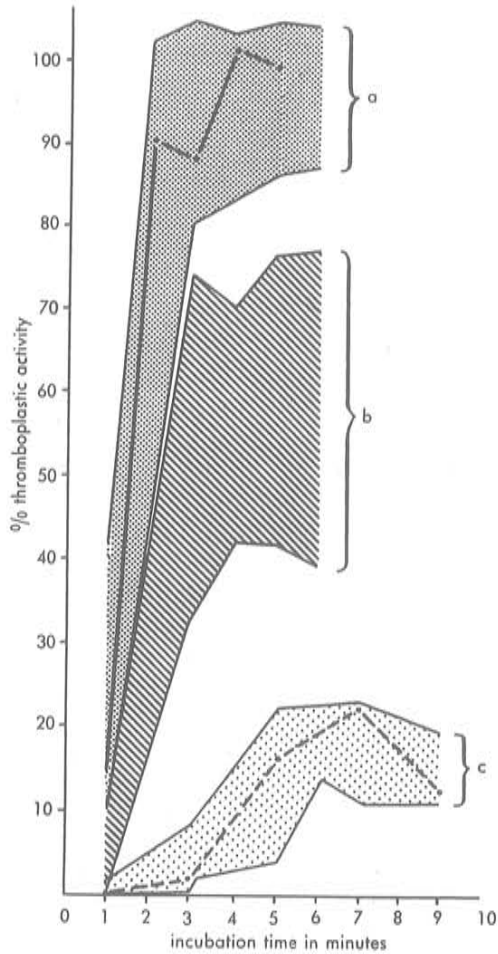

Fig. 4b

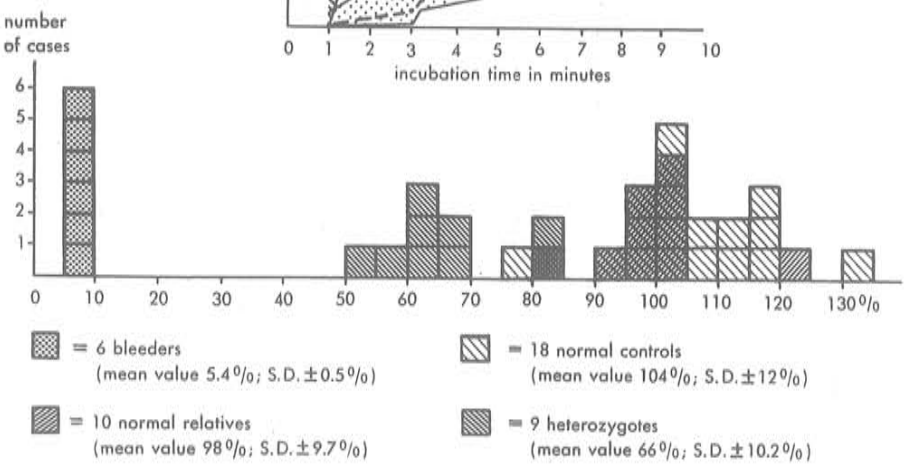

Fig. 5: Stuart-Prower concentration in bleeders, their relatives and normal controls.

The established heterozygotes sometimes show a slight prolongation in the one-stage "prothrombin" time, both with human brain thromboplastin and with Russell's viper venom-cephalin. The "factor VII" concentration as a rule shows a significant decrease. The thromboplastin generation test is as a rule normal, but the serum, mixed in a 50 : 50 ratio, never corrected the thromboplastin generation test of their bleeder relatives to a clotting time shorter than 11 seconds (75% thromboplastic activity); this we consider insufficient (fig. 4, group b). One sister (VI_{40}) could not be classified with certainty: she had a Stuart-Prower concentration of 75%, with a slightly prolonged one-stage "prothrombin" time and a decreased "factor VII" concentration; yet she was well capable of correcting her bleeder relatives.

Relation to factor IX (Christmas factor). The results of crossmatching experiments in the thromboplastin generation test of the serum from our homozygotes and heterozygotes suffering from Stuart-Prower deficiency with serum from a case of congenital deficiency in factor IX (Christmas factor) were obscure. Although the heterozygotes and homozygotes included 15 subjects with serum capable of correction of the thromboplastin generation test in a

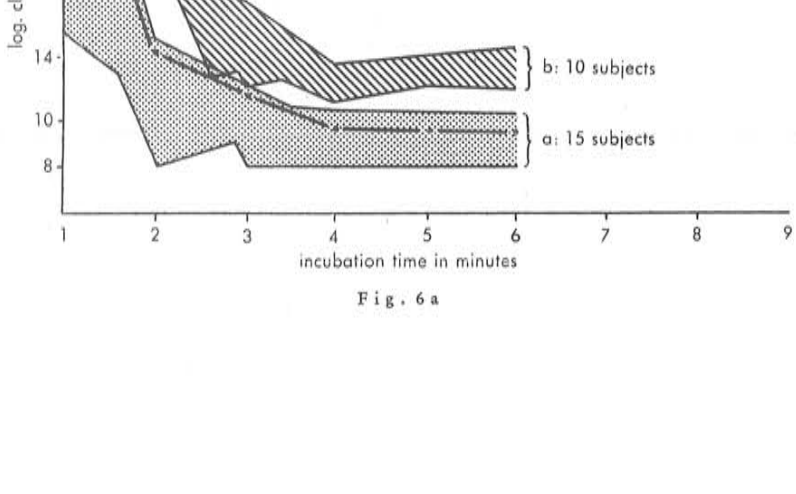

Fig. 6a

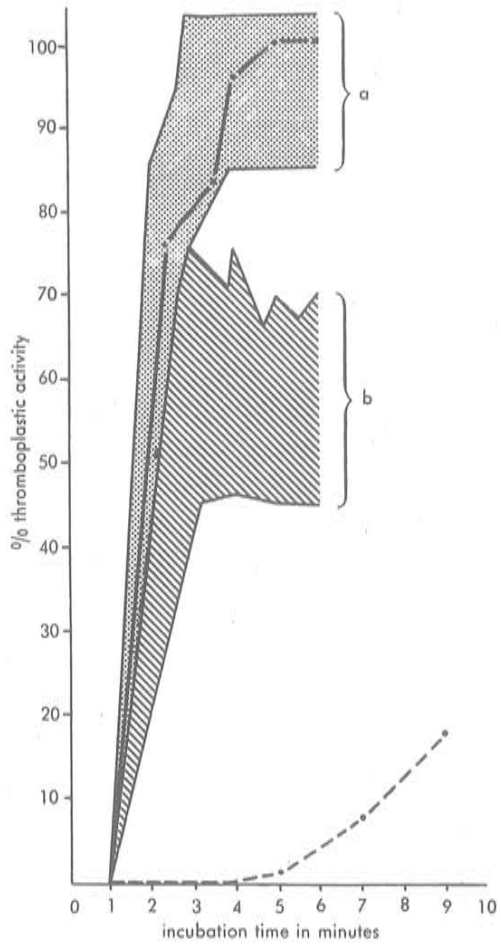

Fig. 6b

Fig. 6: *Thromboplastin Generation Test* with normal plasma and platelets. Serum from a patient with congenital factor-IX-deficiency (Stuart-Prower content 104%) was mixed in a 50 : 50 ratio with serum from a normal control and from each of our 6 bleeders and their 19 relatives and incubated for some minutes. The curves could be distinguished into 2 groups; the outside values gave the limits of groups a and b. Group a behaved like normal serum, group b gave insufficient correction.

subject with haemophilia — B (with a Stuart-Prower concentration of 104%) as complete as normal serum (fig. 6, group a: $IV_{15a, 32}$, $V_{34, 43, 46, 52}$, $VI_{31, 33, 36, 37, 38, 41, 42, 44, 45}$), yet there were ten others who effected a considerably less striking correction, varying from 11.2 seconds (76% thromboplastic activity) to 14.1 seconds (46%) in a ratio of 50 : 50 (fig. 6, group b: $V_{44, 45, 50}$, $VI_{29, 30, 32, 34, 39, 40, 46}$). Among the latter, three appeared to be homozygotically

deficient in the Stuart-Prower factor (VI29, 34, 39); one certainly was homozygotically normal, five were heterozygotes and one was not classifiable. Among those effecting satisfactory correction there were three homozygotically abnormal, eight homozygotically normal and four heterozygous as to Stuart-Prower deficiency.

Nor was an unmistakable correlation found with the values of the one-stage determination of the Christmas factor according to Geiger (9): values in those capable of good correction ranged from 28 to 110% (average 80%), and values in those effecting less excellent correction from 17 to 85% (average 50%); however, we dare not attach value to these differences, as we found an average value of 93% with a standard deviation of ± 28% in 19 normal subjects.

For the moment we cannot go further than saying that the term "concomitant haemophilia — B" (Koller [15]) cannot be applied to this family. However, we cannot exclude either the possibility of a relationship between Stuart-Prower deficiency and the Christmas factor with certainty.

Combination with alcaptonuria. A more detailed investigation was made because of concomitance of heterozygotism for Stuart-Prower deficiency and alcaptonuria in one female patient (V45) of this family. The essential phenomenon of alcaptonuria is the absence of an enzyme which — during tyrosine breakdown — governs the further breakdown of homogentisic acid (7). The urine of this particular patient showed an unmistakable increase in tyrosine in the two-dimensional chromatogram : T = 2.5 (normal value : 0.04)*).

Coagulation determinations made in this case are summarized in Table 7.

Apart from signs of heterozygotism for Stuart-Prower deficiency (established with certainty on the basis of heterozygotism in the patient's son), therefore, no anomalies were found besides a marked disturbance in prothrombin consumption, insufficiently corrected by normal serum. In view of the chemical similarity between homogentisic acid and vitamin K (fig. 7), a search was made for a circulating anticoagulant. No disturbances were found, however, in the recalcification time, the antithrombin test, anti-VII-complex value (Bachmann et al. [2]) and in the serum fraction of the thromboplastin generation test in a normal control following incubation with 50% patient's serum for 30 minutes. The patient's son — also heterozygous for Stuart-Prower deficiency — showed no anomalies in the urinary chromatogram. No other case of alcaptonuria was found in the familial history.

*) Acknowledgement is due to Dr. Meulemans (Wilhelmina Children's Hospital, Utrecht) for preparing the chromatograms.

Tab. 7 : Data on a carrier (V—45) with alcaptonuria.

	Patient	Normal
Coagulation time	7.5, 8.5, 9.5, 10	5—8.5 min.
with 0.1 ml normal serum	6.5	
with 0.01 ml normal serum	7	
with 0.001 ml normal serum	7	
Recalcification time	160 sec.	90—180 sec.
Prothrombin consumption index	78%	< 20%
with 0.1 ml normal serum	44%	
with 0.01 ml normal serum	64%	
with 0.001 ml normal serum	59%	
Thromboplastin Generation Test	9 8 sec.	8.0—9.6 sec.
Correction T.G.T. from a bleeder (VI—34), ratio 50 : 50	12.0 sec.	9.0 sec.
One Stage "prothrombin time"		
with Human Brain Thromboplastin	17.9 sec.	15.0 sec. S.D. ± 0.6 sec.
with R.V.V.-cephalin	11.3 sec.	9.7 sec. S.D. ± 0.6 sec.
Fibrinogen	490 mgr%	200—300 mgr%
Prothrombin	130%	88%; S.D. ± 14%
Factor V	104%	100%; S.D. ± 15.7%
"Factor VII"	75%	110%; S.D. ± 20%
Antihaemophilic factor	108%	61%; S.D. ± 28%
Factor IX (Christmas factor)	17%	93%; S.D. ± 28%
Stuart-Prower factor	82%	104%; S.D. ± 12%

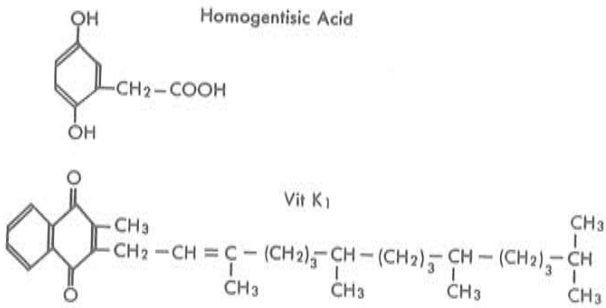

Fig. 7

Although alcaptonuria and a clotting deficiency as described both can be regarded as inborn errors of metabolism, yet we have not succeeded in demonstrating any other correlation between these two anomalies than their concomitance in one patient.

*Heredity**). As was already mentioned above, Graham et al. (14) supposed the serious form of the Stuart-Prower deficit to depend on the presence of a gene in homozygous condition (a_1a_1). The heterozygotes (a_1a_2) were found to be distinguishable by means of the described criteria.

The evidence obtained pointed out that both parents of the family discussed here (V_{43} and V_{44}) should be regarded as being heterozygous. The fact that both parents carry the rare gene is readily explained by their genetic relation (cousin marriage). It may be expected that the distribution of the genotypes a_1a_1, a_1a_2 and a_2a_2 among the offspring of this type of mating resembles the ratio 1 : 2 : 1. In the present case (in which the number of children totals 12) the actual distribution of genotypes as judged from the phenotypes appears to be 6 homozygous abnormals against 4 (possibly 5) heterozygotes and 2 (or 1 ?) genetic normals.

The statistical analysis of the data (Roos and Huizinga [20]) revealed that this discrepancy between observed and expected numbers of genotypes easily may be due to chance ($\cdot 10 < P < \cdot 15$). Therefore there is no reason to reject the hypothesis that the occurrence of the Stuart-Prower deficit depends on the presence of a mutated gene which, when represented once in the genetic make-up (heterozygous state) is responsible for a deficit detectable by laboratory methods, but, when represented twice (homozygous condition) leads to the clinically serious form of deficiency.

Summary

A description is given of the coagulation disturbances in six patients with a haemorrhagic diathesis due to Stuart-Prower deficiency. Relatives of these patients, if heterozygous for this deficiency, showed no significant haemorrhagic diathesis; in the laboratory, their one-stage "prothrombin" times showed only a slight prolongation. Thromboplastin formation in these relatives was sufficient, but determination of the Stuart-Prower factor revealed lower values. The relatives in question were incapable of giving the same correction of the thromboplastin generation test in their bleeder relatives as normal serum does.

The relation between Stuart-Prower deficiency and Christmas factor is discussed.

One patient is described who combined heterozygotism for Stuart-Prower deficiency with alcaptonuria.

The mode of inheritance of the Stuart-Prower deficiency is discussed.

*) We are greatly indebted to Prof. Mijsberg and Dr. Huizinga (Utrecht) for their vivid interest and contribution in the preparation of this section.

Résumé

Description des défauts de la coagulation chez six malades atteints d'une diathèse hémorragique causée par une déficience du facteur Stuart. Les membres de la famille qui sont hétérozygotes pour le facteur en question n'ont pas de manifestations cliniques d'une diathèse hémorragique. Au laboratoire on leur découvre une légère prolongation du temps de "prothrombine". La formation de la thromboplastine est adéquate bien que le taux du facteur Stuart-Prower est abaissé. Ces membres de la famille sont incapables de corriger les résultats du "Thromboplastin Generation Test" des malades au même dregré que le sérum normal.

Un des malades présente une alcaptonurie et est en même temps hétérozygote pour la déficience en facteur Stuart-Prower.

La transmission de la déficience en facteur Stuart-Prower est discutée.

Zusammenfassung

Die Gerinnungsstörung bei 6 Patienten mit einer durch Mangel an Stuart-Prower-Faktor bedingten hämorrhagischen Diathese wird beschrieben. Verwandte der Patienten, die bezüglich des Stuart-Prower-Faktors heterozygot waren, zeigten keine hämorrhagische Diathese; ihre Einstufen-Prothrombinzeit war nur wenig verlängert. Die Thrombokinasebildung war bei diesen Verwandten ausreichend, aber die Bestimmung des Stuart-Prower-Faktors zeigte niedrigere Werte. Das Serum dieser Verwandten vermochte die Thrombokinasebildung ihrer blutenden Verwandten nicht im gleichen Ausmaß zu normalisieren wie Normalserum.

Die Beziehung zwischen Stuart-Prower-Faktor und Christmas-Faktor wird diskutiert.

Eine Patientin wies neben einem heterozygoten Stuart-Prower-Faktor-Mangel eine Alcaptonurie auf.

Der Erbgang des Stuart-Prower-Defektes wird diskutiert.

Addendum: Since Denson (Brit. J. Haematol. 4: 313 [1958]) published his more detailed studies of his patient Prower, the term "Stuart-Prower deficiency" no longer seems to be up to date and has to be replaced by "Stuart deficiency".

References

(1) Alexander, B., Goldstein, R., Landwehr, G. and Cook, C. D.: Congenital SPCA-deficiency. J. clin. Invest. 30: 596 (1951).

(2) Bachmann, F., Duckert, F., Geiger, M., Baer, P. and Koller, F.: Differentiation of the Factor VII Complex. Thromb. Diath. haem. 1: 169 (1957).

(3) Bell, W. N. and Alton, H. G.: A brain extract as a substitute for platelet suspensions in the thromboplastin generation test. Nature (Lond.) 174: 880 (1954).
(4) Belle, C. J. van: Parahaemophilie. Thesis. Utrecht 1952.
(5) Biggs, R. and Douglas, A. S.: The thromboplastin generation test. J. clin. Path. 6: 23 (1953).
(6) Bounameaux, Y.: Dosage du facteur VIII en un temps. Acta haemat. (Basel) 17: 355 (1957).
(7) Bunim, J. J.: Alcaptonuria. Ann. intern. Med. 47: 1210 (1957).
(8) Clauss, A.: Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta haemat. (Basel) 17: 237 (1957).
(9) Geiger, M., Duckert, F. und Koller, F.: Quantitative Bestimmungen von Faktor VIII und IX bei Blutersippen. 5th Congr. Eur. Soc. Haemat., Freiburg 1955, p. 413.
(10) Gonyea, L. M. and Krivit, W.: Congenital coagulation deficiency of Stuart factor activity. J. Lab. clin. Med. 51: 398 (1958).
(11) Greep, C.: to be published.
(12) Hjort, P., Rapaport, S. I. and Owren, P. A.: A simple specific one-stage prothrombin assay using Russell's viper venom in cephalin suspension. J. Lab. clin. Med. 46: 89 (1955).
(13) Hörder, M. H.: Kongenitaler familiärer Faktor-VII-Mangel mit zusätzlichem Defekt in der Thromboplastinbildung. Acta haemat. (Basel) 19: 30 (1958).
(14) Hougie, C., Barrow, E. and Graham, J. B.: Stuart clotting defect. J. clin. Invest. 36: 485 (1957).
(15) Koller, F.: Is hemophilia a nosologic entity? Blood 9: 286 (1954).
(16) Lee, R. I. and White, P. D.: A clinical study of the coagulation time of blood. Amer. J. med. Sci. 145: 495 (1913).
(17) Merskey, C.: The consumption of prothrombin during coagulation. J. clin. Path. 3: 130 (1950).
(18) Owren, P. A. and Aas, K.: The control of dicoumarol therapy and the quantitative determination of prothrombin and proconvertin. Scand. J. clin. Lab. Invest. 3: 201 (1951).
(19) Quick, A. J.: The physiology and pathology of hemostasis. London 1951.
(20) Roos, J. and Huizinga, J.: To be published.
(21) Telfer, T. P., Denson, K. W. and Wright, D. R.: A "new" coagulation defect. Brit. J. Haematol. 2: 308 (1956).
(22) Warner, E. D., Brinkhous, K. M. and Smith, H. P.: A quantitative study on blood clotting. Prothrombin fluctuations under experimental conditions. Amer. J. Physiol. 114: 667 (1936).