Differentiation of the Factor VII Complex
Studies on the Stuart-Prower factor

From the coagulation laboratory (Prof. F. Koller) of the Department of Medicine (Prof. W. Löffler), University of Zurich, Switzerland

F. Bachmann, F. Duckert, M. Geiger, P. Baer and F. Koller

Many discrepancies in the results of clotting studies of the so-called 'Factor VII deficiencies' have been cleared up with the segregation of new clotting factors similar to F. VII, as far as prothrombin conversion in the presence of thromboplastin is concerned, but clearly distinguishable from F. VII by means of the thromboplastin generation test (TGT).

F. VII is not neccessary for blood thromboplastin formation (1, 4, 10, 14, 16—18, 24, 32, 37, 40, 45), whereas these newly found factors are indispensable for thromboplastin formation.

1953/54, Duckert, Flückiger and Koller (17, 18, 39a, 40a) described a factor, deficient in sera of Marcoumar*)-treated patients, which is different from F. VII and F. IX. Decrease of this factor produces an abnormal thromboplastin formation in the TGT (Factor X).

Telfer, Denson and Wright (56) studied a patient with a Factor VII-like deficiency whose serum and plasma were able to correct the prolonged one-stage 'prothrombin time' of Dindevan-treated patients (Prower defect).

Graham, Hougie and Barrow (23, 24, 30—32) re-studied a case originally reported as SPCA-deficiency (42) and found correction of the clotting defect when adding plasma or serum of Alexander's patient (2, 3) to the blood of their patient (Stuart factor deficiency).

In a study of the serum factors necessary for thromboplastin formation, Biggs (10) distinguishes three serum factors in addition to F. VII: Thromboplastin B (F. IX), Thromboplastin C (probably F. X) and Thromboplastin D (Prower factor).

Bachmann, Duckert, Flückiger, Hitzig and Koller reported on a case (4) identical to the Stuart factor deficiency.

The following study tries to characterise the physicochemical properties of the Stuart-Prower factor and its role in blood coagulation. Exhaustive reports on this subject have already been presented by Graham et al. (24) and Hougie et al. (32) while our studies were going on.

Materials and Methods:

Human Brainthromboplastin (BTP), prepared according to Quick (49) was used.

Russell's Viper Venom (RVV): The Burroughs Wellcome product 'Stypven'**) was used. A stock solution of 0,5 mgr. in 5 ml of distilled water was stored at + 4° C. without loss of activity for at least 8 days. From this stock solution dilutions in veronal buffer were prepared immediately before use.

*) Marcoumar is a Dicoumarol derivative.

**) Obtained by courtesy of Burroughs and Wellcome, London.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Lecithin: a commercial crude lecithin was suspended in veronal buffer to a concentration of 1 : 100 and stored in small quantities at — 20° C. It proved stable for 2—4 weeks. Before use it was diluted to a final concentration of 1 : 500.

Russell's Viper Venom-Cephalin Reagent: was prepared according to the technique of Hjort, Rapaport and Owren (29). The final concentration of RVV was 1 : 100 000, that of cephalin about 0,05 Gm. per cent.

Veronal buffer prepared by the method of Michaelis was used throughout in all experiments, as diluent.

Stock solution: 9.714 gr $CH_3COONa \cdot 3 H_2O$ and 14.714 gr Veronal Na in 500 ml H_2O.

Buffer solution: 250 ml stock solution, 200 ml NaCl 4,25%, 217 ml HCl 0,1 n, 683 ml H_2O.

$CaCl_2$-solution was used in a concentration of 0,025 m, unless otherwise indicated.

Commercial Thrombin (Roche) with 45 NIH/mgr was used for the construction of a calibration curve in the thrombin generation test.

Fibrinogen was prepared by use of repeated ammonium sulfate precipitations.

Plasma refers to plasma prepared from oxalated blood (9 parts blood, 1 part sodium oxalate 0,1 M) by centrifugation (2500 RPM × 10 min.).

Sedimented plasma for recalcification times and thrombin generation tests was allowed to sediment at room temperature.

$BaSO_4$-plasma or *serum* refers to oxalated plasma or serum which has been adsorbed with $BaSO_4$ (for X-rays examination, Merck, Germany) for 5 minutes at room temperature, by stirring with a glass rod, followed by centrifugation (2500 RPM for 5 minutes).

Serum was obtained by incubating blood in uncoated glass tubes for 3—4 hours at 37° C.

Chloroform brain extract was prepared according to the method of Bell and Alton (7).

Eluate of $BaSO_4$ adsorbed serum was obtained by washing the $BaSO_4$ twice with NaCl 0,9%. The elution is done with one third of the original volume of 0,14 M trisodium citrate, pH 7.8, by stirring with a glass rod for 5 minutes. Centrifugation. The supernatant is stored at — 20° C.

The one-stage 'prothrombin time' was performed after the method of Quick (49).

Specific one-stage prothrombin times were performed according to Koller, Loeliger and Duckert (39).

A modified one-stage 'prothrombin time assay' with RVV was performed by substituting 0,1 ml of BTP in Quick's method by 0,1 ml of Stypven and 0,1 ml of lecithin.

Unless otherwise indicated the concentration of the Stypven was 1 : 80 000 and of lecithin 1 : 500.

This test is not affected by changes in the concentration of F. VII, but is influenced by different levels of fibrinogen, prothrombin, F. V and Stuart-Prower factor.

Fibrinogen was determined by the method of Clauss (13).

F. IX assays were done on serum, according to Geiger, Duckert and Koller (20).

Thrombin generation test was performed by the technique of Pitney and Dacie (48). Sedimented oxalated plasma was used instead of citrated plasma.

Thromboplastin generation test (TGT) was performed after the modified method of Duckert et al. (16). $BaSO_4$-adsorbed normal plasma was used in a 1 : 10 dilution in buffer unless otherwise indicated. Chloroform brain extract prepared according to Bell and Alton was substituted for normal platelets.

All normal reagents for the TGT were stored at — 20° C.

F. VII-complex, Stuart-Prower factor assays and F. VII assays were done with the following techniques:

Method 1. F. VII-complex: 0,1 ml of Seitzfiltered ox plasma, 0,1 ml of plasma or serum dilution 1 : 10, 0,1 ml of brain thromboplastin are incubated at 37° C. 0,1 ml of $CaCl_2$ is added and the clotting times recorded. This method is sensitive to changes of the F. VII *and* Stuart-Prower factor concentration. Prothrombin concentration of Seitzfiltered plasma: 30%. Substitution of 1 : 10 diluted plasma or serum by buffer gives clotting times of 240—300 seconds.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Method 2. Stuart-Prower factor assay: For economical reasons Stuart-Prower factor deficient plasma was mixed 1 : 1 with Seitzfiltered plasma, and used as substrate as indicated above. This reagent contains sufficient amounts of F. VII, but no Stuart-Prower factor.

Method 3. Stuart-Prower factor assay with RVV. Since the clotting action of RVV in the presence of lipoid is equivalent to activated F. VII (Thromboplastin + F. VII), all clotting systems using RVV are independant of the F. VII content (1, 24, 28, 29, 32, 34, 35, 51).

0,1 ml of Seitzfiltered plasma + 0,1 ml of 1 : 10 diluted plasma or serum + 0,1 ml of lecithin + 0,1 ml of RVV (1 : 80 000) are incubated at 37° C. for 30 seconds. 0,1 ml of $CaCl_2$ is added and the clotting times recorded. A very flat calibration curve is obtained if small amounts of Stuart-Prower factor are present in the Seitzfiltered plasma. It is therefore very important to collect during filtration small portions of filtered plasma and to determine in each fraction the prothrombin level and the clotting time adding RVV + lecithin. Filtration of oxalated ox plasma through 30% and then through 50% asbestos filter pads (diameter 14 cm) gives for the first 200 ml of filtered plasma insufficient prothrombin concentrations. A fraction of about 50—100 ml may then supply sufficient amounts of prothrombin, but no F. VII and no Stuart-Prower factor. Continuing the filtration, F. VII and Stuart-Prower factor reappear in the filtrate. Plasmas of different oxes show large variations concerning prothrombin and Stuart-Prower factor concentration.

A good reagent should have at least 30% prothrombin and a clotting time of over 70 seconds when adding buffer instead of 1 : 10 diluted plasma to the assay system. Instead of RVV + lecithin a RVV-cephalin reagent according to the technique of Hjort, Rapaport and Owren may be used, which has the advantage that it can be frozen in a deepfreeze without loss of activity. For obtaining good calibration curves the RVV concentration should not exceed 1 : 100 000.

Method 4. F. VII assay: F. VII deficient plasma is mixed 1 : 1 with Seitzfiltered plasma. This mixture contains sufficient amounts of Stuart-Prower factor and of prothrombin. This reagent is substituted for simple Seitzfiltered plasma in method 1.

Method 2 and 3 give similar but not always identical results. In plasma and serum stored for some days, method 2 gives higher concentrations than method 3, which is probably due to changes in the F. X concentration.

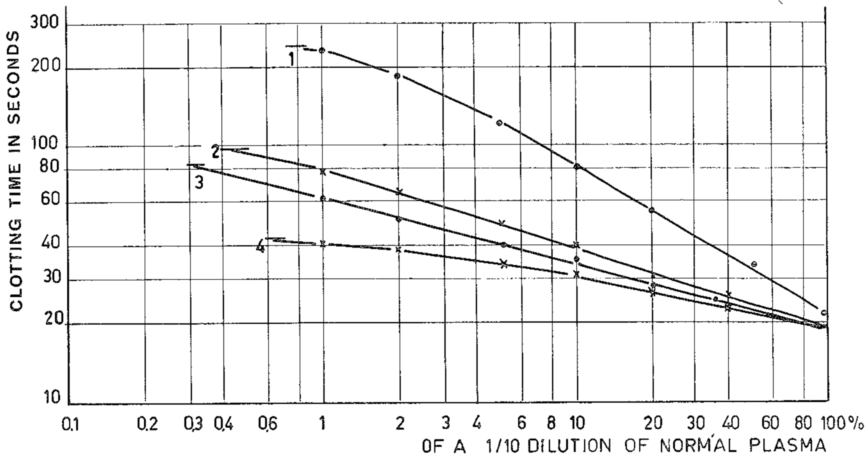

Fig. 1: *calibration curves, obtained with various plasma dilutions in different assay systems* (see text)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Calibration curves for method 1—4 are obtained plotting clotting times against factor concentrations obtained by various dilutions of normal plasma or serum. The 100% value is given by determining the clotting times of several normal 1 : 10 diluted plasmas. The clotting times and concentrations, when plotted on double logarithmic paper give straight lines, except at concentrations below 1—2%.

Results

Fibrinogen, prothrombin, F. V, F. VIII, F. IX, antithrombin and platelet count were all normal. A circulating anticoagulant could be excluded (4).

Crossmixing experiments with plasma and serum of a patient with congenital F. VII deficiency (Owren))*

It can be seen from Table 1 that the prolonged 'prothrombin times', recalcification times and clotting times in the F. VII-complex assay of both plasmas are mutually corrected by mixing these two plasmas. In clotting systems which

Table 1: The effect of a F. VII deficient plasma*) (Owren) on the clotting defect of ow patient Delia B. plasma in different clotting systems.

Plasma of	Amounts in ml.				
Patient Delia B.**)	0,1	0,08	0,05	0,02	0
F. VII deficiency	0	0,02	0,05	0,08	0,1
Recalcification time:	750"	190"	125"	130"	260"
Patient Delia B.	0,1	0,08	0,05	0,02	0
F. VII deficiency	0	0,02	0,05	0,08	0,1
One stage 'prothrombin time' (Quick) with BTP.	175" (1%)	19,5" (42%)	18" (50%)	19" (45%)	97" (3%)
Patient Delia B.	0,1	0,08	0,05	0,02	0
F. VII deficiency	0	0,02	0,05	0,08	0,1
Modified one stage prothrombin time with RVV + lecithin	91" (<1%)	13" (40%)	10,5" (95%)	9,5" (>100%)	10,2" (100%)
Patient Delia B.	0,1	0,08	0,05	0,02	0
F. VII deficiency	0	0,02	0,05	0,08	0,1
F. VII complex assay with BTP (method 1)	123" (3%)	35" (45%)	35" (45%)	37" (42%)	61" (14%)***
Patient Delia B.	0,1	0,08	0,05	0,02	0
F. VII deficiency	0	0,02	0,05	0,08	0,1
Stuart-Prower factor assay (method 3)	63" (>1%)	30" (17%)	24" (40%)	20" (75%)	19" (85%)

*) lyophilized platelet poor plasma.

**) sedimented platelet rich plasma.

***) Real F. VII content of this plasma probably 1—2%. A mixture of 98% F. VII deficient plasma and 2% D. B. Plasma gives still a significantly shorter clotting time than F. VII deficient plasma alone.

*) we are greatly thankful to Prof. Owren, who provided us with samples of lyophilized F. VII deficient plasma and serum.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

use RVV + lecithin, F. VII deficient plasma behaves like normal plasma, whereas the plasma of patient Delia B. shows greatly prolonged clotting times. There is an evident parallelism of clotting times and Stuart-Prower factor concentration in the Stuart-Prower factor assay, which shows that this method is insensitive to changes of the F. VII concentration.

The factor lacking in the blood of our patient Delia B. is therefore distinct from the factor lacking in the blood of Owren's patient. The concentration of F. VII, assayed by method 4, in the plasma of our patient was 80%, compared with a normal test plasma.

The concentration of Stuart-Prower factor in the plasma of Owren's patient was assayed by method 2 and 3 and we found values of 85 and 90% respectively.

It may be seen from the results obtained in a modified one-stage 'prothrombin time' with RVV + lecithin, that this method does not reflect very well the real concentration of Stuart-Prower factor. It will be very difficult, if not impossible to distinguish by this method persons with slightly reduced Stuart-Prower factor levels (for example heterozygotes [24]) from normal individuals.

The thromboplastin generation test with F. VII deficient serum is normal, with Stuart-Prower factor deficient serum highly pathological (Fig. 2A). A mixture of these two sera containing 9 tenth of the normal Stuart-Prower factor concentration supplied by F. VII deficient serum produces normal thrombo-

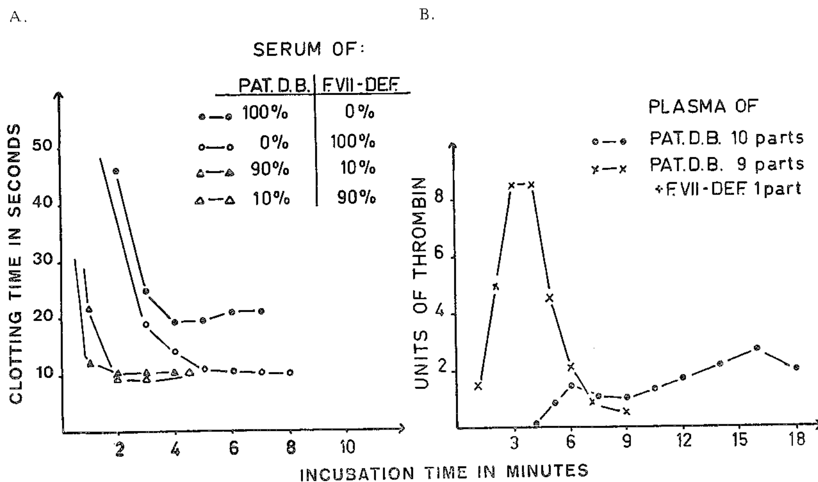

Fig. 2: *Results of matching experiments with Stuart-Prower factor deficient (Patient Delia B.) and F. VII deficient (Owrens' Patient) plasma and serum.*

A: Thromboplastin generation test. Serum mixtures were performed on 1:10 diluted serum of patient Delia B. and Owren's patient. — $BaSO_4$ adsorbed normal plasma and chloroform brainextract were used in all mixtures.

B: Thrombingeneration test. 0,4 ml of plasma or plasmamixture + 0,4 ml of veronalbuffer + 0,4 ml of $CaCl_2$ were incubated at 37° C. At intervals of 1 min. 0,025 ml of the incubationmixture were added to 0,1 ml of fibrinogen (100 mgr.%) and the clotting times recorded.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

plastin generation, whereas one tenth Stuart-Prower factor concentration gives slightly prolonged clotting times. The significant shortening of the incubation times in the mixture is due to the high prothrombin concentration in Stuart-Prower deficient serum.

The highly abnormal thrombin generation test of patient Delia B.'s plasma is completely normalized by addition of 1 part F. VII deficient plasma to 9 parts of Delia B.'s plasma (Fig. 2B).

The effect of plasma and serum of Graham and Hougie's (23, 24, 30—32) (Stuart), Telfer, Denson and Wright's (56) (Prower) and Beaumont et Bernard's (6) (M. M.) patients on the clotting defect of our patient (Delia).

The same matching experiments as with the blood of Owren's patient were performed. *There is no corrective effect in all experiments,* except in the recalcification test with plasma of the patient Prower, which may be explained by the fact that Prower plasma was lyophilized platelet poor plasma, whereas Delia B.'s plasma was sedimented platelet rich plasma (Table 2).

Table 2: The non-corrective effect of different plasmas of patients with congenital lack of the Stuart-Prower factor on patient Delia B.'s clotting defect in different clotting systems.

Amounts in ml.		Assay system				
		Recalcification time	one stage prothrombin time BTP (Quick)	one stage prothrombin time with RVV + lec.	F. VII complex assay with BTP	Stuart-Prower factor assay (method 3)
Patient Delia B.	Stuart +					
0,1	0	300"	150" (3%)	49" (4%)	159" (3%)	not perf.
0	0,1	660"	140" (4%)	not perf.	64" (13%)	not perf.
0,05	0,05	510"	112" (4,5%)	not perf.	72" (10%)	not perf.
Patient Delia B.	Prower ++					
0,1	0	480"*	113" (2%)	51" (3%)	153" (3,5%)	63" (<1%)
0	0,1	450"**)	29" (20%)	21" (14%)	59" (17%)	38" (7%)
0,05	0,05	270"	38" (12%)	26" (9%)	76" (11%)	49" (3%)
Patient Delia B.	M. M.+++					
0,1	0	1440"	270" (<1%)	63" (2%)	165" (1,2%)	63" (<1%)
0	0,1	450"	52" (11%)	31" (7%)	88" (5%)	54" (1%)
0,05	0,05	480"	61" (9%)	37" (4,5%)	101" (3,5%)	57" (1%)

+ We are indebted to Dr. Graham who sent us samples of his patient Stuart, to ++ Dr. Telfer and Denson for supplying us with plasma and serum of their patient Prower and to +++ Dr. Caen and Dr. Beaumont for samples of their patient M. M.

*) Sedimented platelet rich plasma.
**) lyophilized platelet poor plasma.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

The values obtained with the F. VII complex assay are in all plasmas higher than the values obtained with the Stuart-Prower factor assay, fact which is easily explained by the normal values of the real F. VII in all these plasmas. Matching experiments with the plasma of patient Prower and Owren's patient were mutually corrective:

F. VII-complex assay: Prower plasma (17%) + Owren's patient plasma (14%) mixed 1 : 1 gave: 50%. (Real concentration of F. VII of Prower's plasma: 90%).

Serum mixtures in the TGT, which was abnormal in all four patients gave no correction (Figure 3).

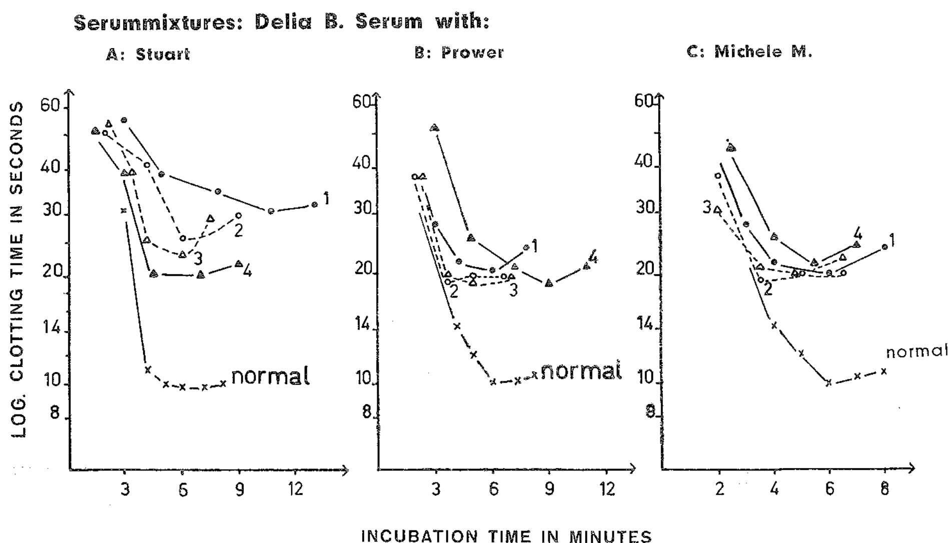

Fig. 3: Thromboplastin generation tests. Serum mixtures were performed with 1:10 diluted serum of patient Delia B. and:

A. patient Stuart (Hougie and Graham)
B. patient Prower (Telfer et al.)
C. patient M. M. (Beaumont and Bernard)

1. serum of D. B. 5 parts
2. serum of D. B. 4 parts + serum of A, B or C 1 part
3. serum of D. B. 1 part + serum of A, B or C 4 parts
4. serum of A, B or C 5 parts.

$BaSO_4$ adsorbed normal plasma and chloroform brainextract were used in all mixtures.

It may be concluded therefore that all four patients lack the same factor.

The role of the Stuart-Prower factor in the one-stage 'prothrombin time' with brain thromboplastin. Effect of different concentrations.

It may be seen from Table 3 that already a small reduction of the Stuart-Prower factor concentration in a clotting system in which all other necessary factors are kept constant (Fibrinogen, prothrombin, F. V and F. VII) produces

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

a slight increase of the clotting times. However, a significant prolongation from the normal variations (0,5 — 1,5 sec.) is only produced if the Stuart-Prower factor concentration is lower than 50%. It is very striking that a concentration of only 1% of Stuart-Prower factor gives still values of 11% in the Quick test, a result which was confirmed by the experiments with Beaumont and Bernard's patient's plasma which produced clotting times corresponding to 11% in the Quick test with a Stuart-Prower factor level of 1% (see Table 2).

Table 3: The effect of the Stuart-Prower factor concentration on the one stage 'prothrombin time' (Quick) with BTP.

Stuart-Prower factor concentration in %	Prothrombin time (Quick) in sec.	expressed in %
100%	15,2	100%
80%	15,5	95%
60%	16,0	85%
40%	17,0	75%
20%	19,5	56%
10%	27,0	35%
5%	37,0	22%
2,5%	43,0	18%
1%	54,0	11%
Delia B.'s plasma alone (0—1%)	270,0	1%

For the mixtures of 10—100% Stuart-Prower factor concentration undiluted normal and Stuart-Prower factor deficient plasma were mixed in corresponding amounts.
For the mixtures of 1—5% one tenth of a 1:2, 1:4 and 1:10 dilution of normal plasma in buffer was given to nine tenth of Stuart-Prower factor deficient plasma.
Fibrinogen, prothrombin, F. V. and F. VII are kept constant.

The effect of various dilutions of brain thromboplastin on the clotting defect of patient Delia B.'s plasma.

Jürgens (37) found in his case of F. VII deficiency shorter clotting times in a one-stage 'prothrombin time' test when diluting the BTP. The same was observed in our case (Fig. 4). Dilution of 1 : 16 BTP in buffer produced shorter clotting times in the Quick test than indiluted BTP. It may be concluded therefore, that undiluted BTP has an inhibitory effect on our patient's clotting time. It is possible that Stuart-Prower factor acts in a stoichiometric relation with BTP. When Stuart-Prower factor is deficient, only a small quantity of the undiluted BTP may be utilized, the rest being at least useless, if not inhibitory. This phenomenon with Delia B.'s plasma may be produced by non-optimal concentration, or by an excess of normally present inhibitors in BTP.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Effect of different dilutions of BTP. on the one stage 'prothrombin time'

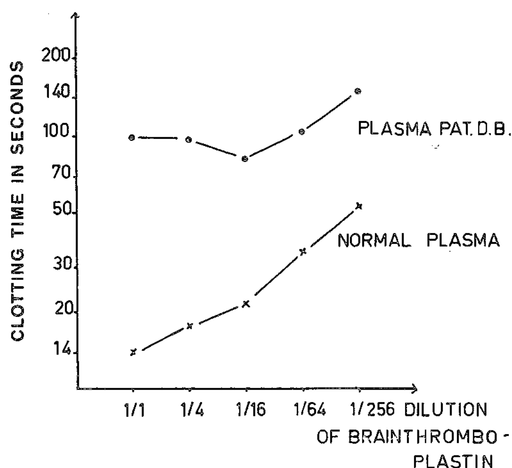

Fig. 4: Clotting times of 0,1 ml of Stuart-Prower factor deficient, resp. normal plasma + 0,1 ml of various dilutions of BTP + 0,1 ml of $CaCl_2$.

The effect of various dilutions of RVV (Stypven) on the modified one-stage 'prothrombin time'

The graphics in Figure 5 show, that increasing dilutions (higher than 1 : 20 000) of RVV (plasma and lecithin concentration being kept constant) increase the clotting times in both, normal and Stuart-Prower factor deficient plasma.

Effect of different dilutions of stypven in a one-stage 'prothrombin-time' assay system

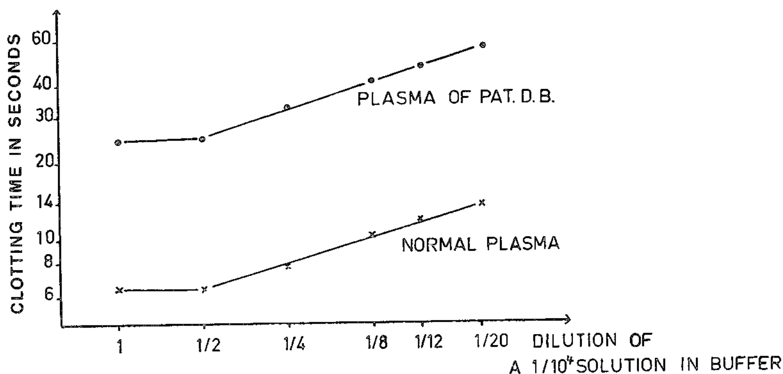

Fig. 5: Various dilutions of a stock solution (Conc. 1:10'000) of RVV were made in buffer. Clotting system: 0,1 ml of Stuart-Prower factor deficient of normal plasma, undiluted + 0,1 ml of Lecithin 1:500 + 0,1 ml of various dilutions of RVV (Stypven) + 0,1 ml of $CaCl_2$.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Similar curves are obtained by diluting RVV in the Stuart-Prower factor assay system (method 3); the curve for Stuart-Prower factor deficient plasma however being steeper than the curve obtained with normal 1 : 10 diluted plasma or serum. This fact was used in our method for producing a steeper calibration curve, working with a non-optimal concentration of 1 : 80 000 diluted RVV.

Absence of specific inhibitors against the F. VII-complex in the plasma of Delia B.

In a previous report we showed already that addition of small quantities of Delia B.'s plasma to normal plasma did not lengthen the recalcification times of normal plasma. A circulating anticoagulant could therefore be excluded (4).

Normal plasma and serum were mixed with Stuart-Prower factor deficient plasma or serum and incubated at 37° C. At different intervals 0,1 ml of a 1 : 10 dilution of each mixture was assayed in a F. VII-complex system. Unlike Chevallier et al. (11) we found no deterioration of the F. VII-complex content in the mixtures (Table 4).

Table 4: Absence of a specific inhibitor against the F. VII complex.

	Clotting time in sec.		Clotting time in sec.
Patient Delia B. plasma	178	Patient Delia B. serum	134
Normal plasma (100%)	22	Normal serum (200%)	15"
N-plasma + buffer 1 : 1	35	N-serum + buffer 1 : 1	24
N-plasma + D. B. plasma 1 : 1	33	N-serum + D. B. serum 1 : 1	24
after 10' incub. at 37° C	34	after 15' incub. at 37° C	23,5
after 30' incub. at 37° C	34,5	after 30' incub. at 37° C	23
after 60' incub. at 37° C	34	after 60' incub. at 37° C	24
after 2h incub. at 37° C	35	after 4h incub. at 37° C	24
after 6h incub. at 37° C	31		

Normal plasma or serum were mixed with Stuart-Prower factor deficient plasma or serum and incubated at 37° C. At different intervals 0,1 ml. of each mixture (1:10 dil.) was assayed in a F. VII complex system (method 1).

The role and effect of various concentrations of Stuart-Prower factor in the thromboplastin generation test.

It has already been shown that Stuart-Prower factor deficient serum produces a highly abnormal TGT (Fig. 2 and 3), whereas in the substrate Stuart-Prower factor is not needed (Fig. 6), which confirms the findings of Duckert et al. (16) and Newcomb (45), that an active blood thromboplastin acts directly on prothrombin, without interference of any other coagulation factors.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

The curves relating clotting times and percentages of various concentrations of Stuart-Prower factor (obtained by mixing normal with Stuart-Prower factor deficient serum in corresponding amounts) are given in Fig. 7. Mixtures containing 25—50% Stuart-Prower factor produce still normal TGT, which reach the maximum level of thromboplastic activity even faster than normal serum. For comparison we show the TGT-results with the sera of heterozygous (24) family members, whose Stuart-Prower factor levels were 28—50%, measured by the one-stage method 3 (Figure 8).

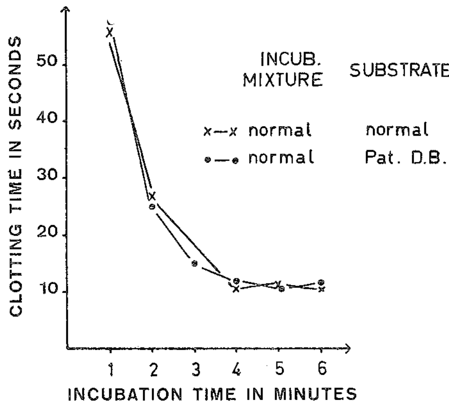

Fig. 6: *Thromboplastin generation test. Delia B.'s plasma taken as substrate in the TGT.* The incubation mixture consisting of normal $BaSO_4$ adsorbed plasma, normal serum and chloroform brain extract and $CaCl_2$ was added at regular intervals (together with additional $CaCl_2$) to the following substrates:

1. normal oxalated plasma
2. oxalated plasma of our patient Delia B.

Effect of Stuart-Prowerfactor concentration on the Thromboplastin generation

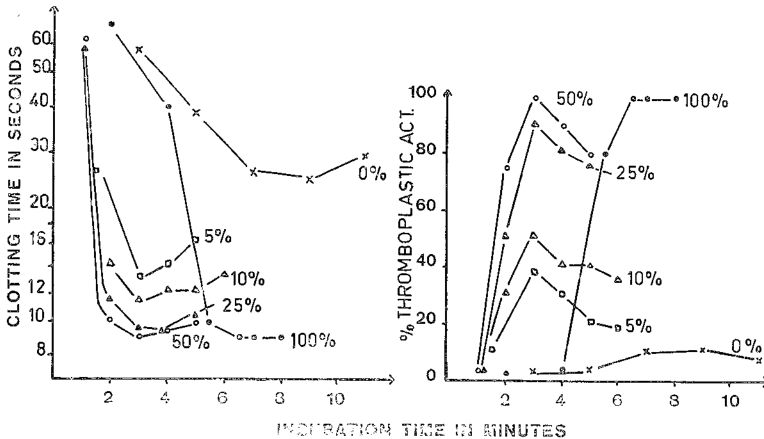

Fig. 7: *Thromboplastin generation test.* 1:10 diluted serum of patient Delia B. and a normal control were mixed in corresponding amounts. The concentration of Stuart-Prower factor of the normal control was considered as 100%, of patient Delia B. as 0%.
Prothrombinconcentration in serum of: Delia B: 60%, control: 2%
$BaSO_4$ adsorbed normal plasma and chloroform brainextract were used in all mixtures.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

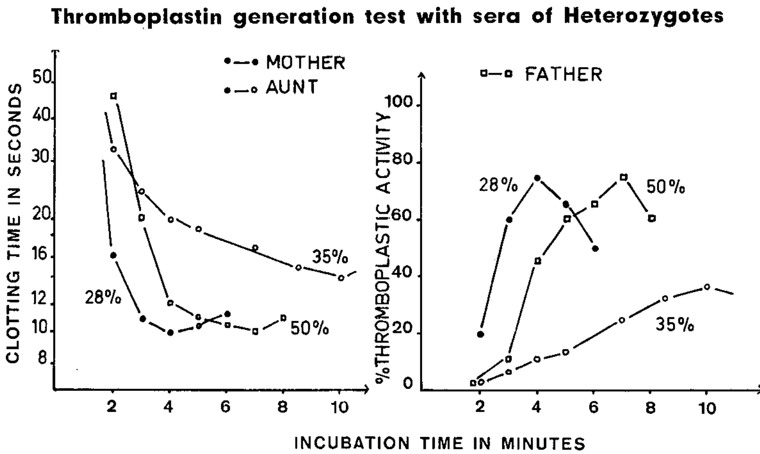

Fig. 8: *Thromboplastin generation test.* Results of the TGT, performed with the sera of family members of our patient Delia B. The percentages given on the curves are concentrations of Stuart-Prower factor in the sera, obtained by assay with one-stage method 3.

Prothrombin concentration in the sera was: Mother 3%, Aunt 1,5%, Father 4%. F. IX level of all these sera was found normal with the one-stage method of Geiger et al. (20)

Although there is a certain correlation between Stuart-Prower factor concentration and TGT activity, it can not be concluded directly from the TGT activity on the Stuart-Prower factor level in the serum, other serum factors being involved, such as prothrombin, F. IX and F. X.

The high prothrombin concentration in Delia B.'s serum accounts partly for the very fast thromboplastin formation in the mixtures of normal and Stuart-Prower factor deficient serum.

We showed already that the abnormal TGT is not due to a lack of F IX, crossmixing experiments with F. IX deficient plasma and serum, and one-stage F. IX determinations being normal (4).

Physicochemical properties of the Stuart-Prower factor

The previous results have shown that Stuart-Prower factor is adsorbed by Seitzfiltration, by $BaSO_4$, $Al(OH)_3$ (32, 56) and $Ca_3(PO_4)_2$ (56). The Stuart-Prower factor can be easily eluted from the $BaSO_4$ by means of 0,14 M sodium citrate. Figure 9 shows the results of mixing $BaSO_4$ adsorbed F. IX deficient serum or its eluate with Stuart-Prower factor deficient serum in the proportion 1 : 1 in the TGT. A 1 : 40 dilution of the F. IX deficient eluate normalizes the pathological TGT of Stuart-Prower factor deficient serum. The factor is present in plasma and serum and relatively storage stable (Table 5). Heating at 56° C. destroys the Stuart-Prower factor, whereas at 50° C. the loss in activity is less pronounced.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

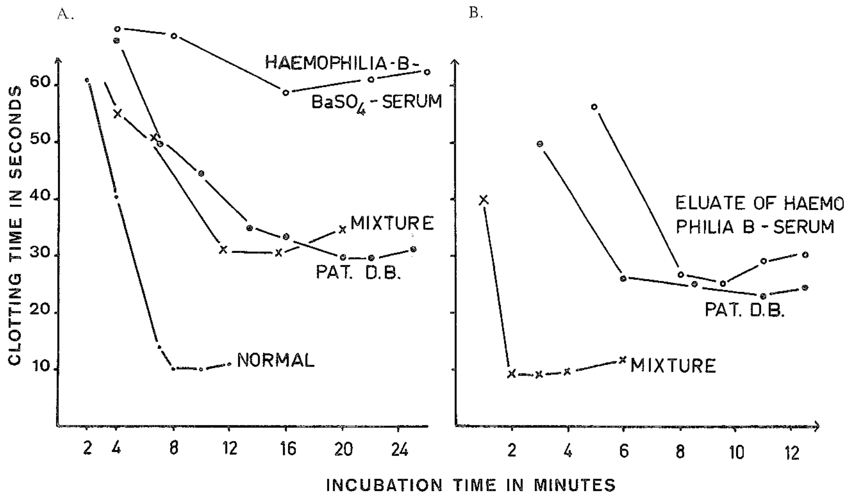

Fig. 9: *Thromboplastin generation test.*
A: Serum of a patient with F. IX (Haemophilia B) deficiency was adsorbed with $BaSO_4$ and mixed in the proportion 1:1 with Delia B.'s serum.
B: A 1:40 diluted eluate of $BaSO_4$ adsorbed F. IX deficient serum was mixed 1:1 with 1:10 diluted serum of Delia B. — $BaSO_4$ normal adsorbed plasma and chloroform brainextract were used in all experiments.

Table 5: Storage stability and heat resistance of the Stuart-Prower factor

Material treated	Temperature	Length of exposure	Residual Stuart-Prower factor in %
Plasma and Serum*)	roomtemperature	1 day	110
	roomtemperature	3 days	90
	roomtemperature	8 days	60
Plasma and Serum*)	refrigerator 4° C	3 days	115
	refrigerator 4° C	8 days	100
Serum	refrigerator 4° C	4 weeks	85
Plasma	refrigerator 4° C	4 weeks	75
Serum	refrigerator 4° C	8 weeks	80
Plasma	refrigerator 4° C	8 weeks	50
Plasma and Serum*)	deepfreeze — 20° C	no significant decrease after 2 months of storage. A plasmasample stored for 5 years in the deepfreeze showed still 120% of Stuart-Prower factor activity.	
Serum	50° C	10 min.	65
	50° C	30 min.	55
	50° C	60 min.	20
	56° C	10 min.	2
	56° C	30 min.	1
	56° C	60 min.	0

*) Mean values of 10 normal plasmas and 10 normal sera. Separate values of sera and plasmas are only given when a significant difference of at least 10% Stuart-Prower factor activity occurs.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 6: Effect of Brainthromboplastin on the Stuart-Prower factor content in recalcified plasma.

Stuart-Prower factor content of the original plasma: 100%

	before centrifugation	% Stuart-Prower factor concentration in the obtained sera — centrifugation for 30' at 25 000 G	20' at 10^5 G
Plasma + undiluted BTP	15	4,5	3,5
Plasma + 1 : 10 dil. BTP	50	55	40
Plasma + 1 : 100 dil. BTP	90	95	100
Controls:			
Serum without BTP	95	95	100
Serum with 1 : 10 dil. BTP	› 100	› 100	70

Normal Plasma was mixed with the same amount of a dilution of BTP, recalcified with an optimal amount of calcium and incubated for 3 hrs. in a waterbath at 37° C. In the controls ordinary serum of the original plasma was incubated with and without BTP for 3 hrs. at 37° C. Before recalcification all mixtures and the serum without any addition of BTP were diluted with buffer, so that the final concentration of plasma or serum was 1/10 the original concentration.

The so obtained sera were divided into three lots. One sample of each preparation was spun in an international refrigerated centrifuge at 25'000 G for 30 minutes, the second sample in a Spinco centrifuge at 100'000 G for 20' (temp. 0 ° C), the third sample was stored at room temperature until centrifugation was finished.

Stuart-Prower factor assays were done on all preparations according to method 3 all at the same time.

During clotting in a system with an excess of BTP Stuart-Prower factor seems to be consumed or adsorbed on BTP. Artificial sera prepared from plasma with addition of BTP with the intention to improve the prothrombin consumption in haemophilic states, showed beside a low prothrombin consumption reduced levels of Stuart-Prower factor. In a study using different concentrations of BTP, we observed that addition of a great excess of BTP to diluted plasma could reduce the concentration of Stuart-Prower factor in a considerable degree (Table 6). When the so prepared sera were centrifuged with 25 000 or 100 000 G we found even less residual Stuart-Prower factor. Addition of a 1 : 100 dilution of BTP to plasma and controls with normal serum without any addition showed no significant variation in the Stuart-Prower factor level in these experiments, whereas addition of 1 : 10 diluted BTP to serum followed by incubation at 37° produced even an activation measured by the Stuart-Prower factor assay system (method 3), removed by centrifugation.

The sediment obtained by centrifugation of the serum prepared with undiluted BTP was grinded in a potter and buffer (1 tenth the original volume of the incubation mixture) was added. The Stuart-Prower factor assay of this suspension gave a 100% value, i. e. 10% in relation to the original volume.

It is not clear from the foregoing experiments whether Stuart-Prower factor is consumed in the presence of BTP or is adsorbed on BTP. The F. VII-complex

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

values of these artificially prepared sera are always much higher than the values for the Stuart-Prower factor, what presumes that the real F. VII concentration is probably high.

F. IX levels in sera prepared by this method are higher than in the ordinary sera, measured by the one-stage determination of Geiger et al. (20).

Physiological properties of the Stuart-Prower factor

In vivo the Stuart-Prower factor is destroyed in some days, taking into consideration the effect of a transfusion of fresh plasma to our patient, Delia B.

Figure 10 shows the values of the F. VII-complex assay and of the Stuart-Prower factor assay before and after transfusion. Fresh blood, about one tenth of the child's total blood volume was given by intraveneous transfusion. The Stuart-Prower factor level raised to about 10%, the level of the F. VII-complex much higher. Five days after transfusion there was hardly any more effect, which matches well with the clinical experience that new spontaneous haemorrhages happened only at least 6—8 days after a transfusion of fresh blood or plasma.

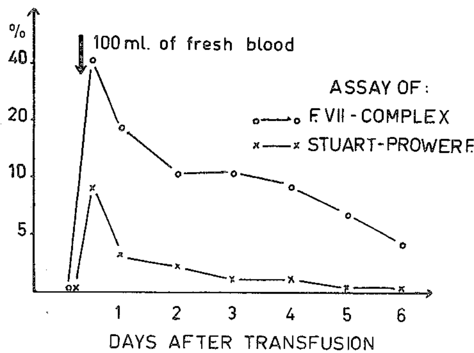

Fig. 10: *Effect of Transfusion of 100 ml of fresh blood on patient Delia B.'s clotting defect.* Weight of D. B.: 12 kgs. Oxalated plasma was stored at 4° C and assays of the F. VII complex and Stuart-Prower factor were performed of all samples collected at the same time with the same reagents, the 6th day after transfusion.

Liver diseases as hepatitis and grave hepatic cirrhosis, and Vitamin-K deficiencies result all in a variable decrease of the Stuart-Prower factor level. In

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

this respect as during therapy with dicoumarol derivatives the behaviour of the Stuart-Prower factor is similar to this of F. VII, prothrombin, F. IX and F. X. In the beginning of Marcoumar-therapy the Stuart-Prower factor concentration is still high (4, 32), even if F. VII is already very low. With Marcoumar we observed however, that the Stuart-Prower factor is reduced faster than F. IX, nearly parallel to prothrombin.

Figure 11 shows the non corrective effect of serum of a patient under longterm Marcoumar-treatment on the abnormal TGT of our patient Delia B. There is no normalisation of the defective clotting time, but the incubation time is greatly shortened by the high prothrombin concentration in Delia B.'s serum.

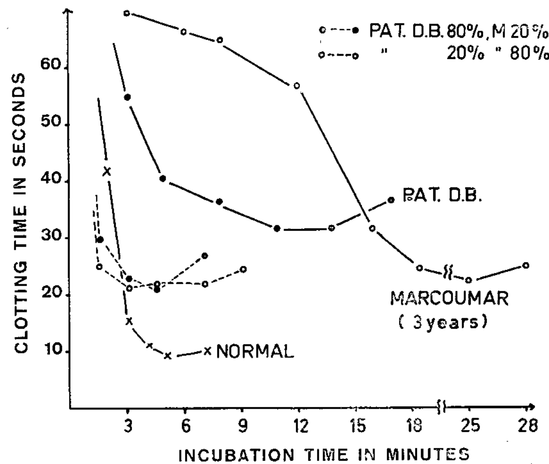

Fig. 11: *Thromboplastin generation test. Effect of the serum of a patient with a longterm Marcoumar treatment on the thromboplastin generation of Delia B.'s serum.*
Prothrombin concentration: of Marcoumar serum 1,5%, of Delia B.'s serum 55%
1:25 diluted $BaSO_4$ adsorbed normal plasma and chloroform brainextract were used in all mixtures.

Discussion

Graham and Hougie's, Telfer, Denson and Wright's and our findings leave no doubt that we are dealing with a new clotting factor, the lack of which is reflected in the classical F. VII assay with Seitz filtered plasma. This new factor, which might be called Stuart-Prower factor after the name of the first two patients described, is necessary for blood thromboplastin formation, in contrast to F. VII. Stuart-Prower factor can easily be distinguished from F. VII with the present routine examinations, but not from a combined deficiency of F. VII + F. IX, unless special experiments with Russell's viper venom or F. IX deficient plasma are performed.

The following table indicates the characteristics of the above mentionned similar deficiencies:

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Table 7: Differentiation of F. VII, F. VII + IX and Stuart-Prower factor deficiencies by means of laboratory investigations.

	Deficiency of		
	F. VII	F. VII + IX	Stuart-Prower factor
One-stage 'prothrombin time' with BTP (Quick test)	abnormal	abnormal	abnormal
One-stage 'prothrombin time' with RVV + lecithin	normal	normal	abnormal
F. VII complex assay with BTP (method 1)	abnormal	abnormal	abnormal
Stuart-Prower factor assay with RVV + lecithin (method 3)	normal	normal	abnormal
Clotting time	normal*)	abnormal	abnormal
Recalcification time	normal*)	abnormal	abnormal
Prothrombin consumption	normal	abnormal	abnormal
TGT with Serum	normal	abnormal	abnormal
Matching experiments with F. IX deficient serum in TGT		abnormal	normal

*) In very severe cases of F. VII deficiency clotting time and recalcification time may be slightly prolonged.

Our case (Delia B.) has to be classified as a deficiency of the Stuart-Prower factor since it has all the characteristics of the already described cases, and matching experiments with both plasma and serum from the patients Stuart and Prower are not corrective, whereas cross-mixing experiments with plasma and serum from a pure F. VII deficiency were corrective.

Like Factor V, the Stuart-Prower factor acts in two clotting systems: in the formation of blood thromboplastin as well as in the presence of tissue thromboplastin.

Stuart-Prower factor and Factor X

Factor X was discovered by matching experiments of Marcoumar*) or hepatitis serum with haemophilia-B-serum. The normalisation produced by this mixture lead to the conclusion that normal serum contains besides Factor VII and IX (Christmas factor, PTC) a third factor, Factor X, which is indispensable for the blood thromboplastin formation, as we already pointed out in 1954, Factor VII plays an insignificant if any role in blood thromboplastin formation.

*) Marcoumar is a dicoumarol derivative.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

In table 8 the identical as well as the apparently dissimilar properties of Stuart-Prower factor and Factor X are summarized.

Table 8: *Factor X and Stuart-Prower factor*

Identical properties.

1. Present in normal serum
2. Present in Haemophilia-B-serum
3. Present in serum of congenital Factor VII deficiency
4. Necessary for blood thromboplastin formation
5. Adsorbed on $BaSO_4$
6. Decreased by Dicoumarol (more slowly than F. VII)
7. Increased by Vitamin K (more slowly than F. VII)
8. Decreased in liver diseases

Apparent dissimilarities.

	Factor X	Stuart-Prower factor
Prothrombin consumption (in the respective defic.)	normal	pathological
Effect on Quick's prothrombin time	?	marked
Resistance to storage	variable	marked
Effect on the rate of thromboplastin formation	marked	variable
Effect on the amount of thromboplastin formation	variable	marked

If we consider the reason of the dissimilarities, it has to be pointed out, that the existence of Factor X was postulated on the basis of acquired clotting defects but not of a congenital (hereditary) one. Acquired defects are characteristized by simultaneous deficiency of several clotting factors, whereas in hereditary defects usually only one factor is lacking. This may explain our finding of normal prothrombin consumption in Factor X-deficiency: during Marcoumar treatment prothrombin as well as other factors are lowered in plasma, therefore the prothrombin content of serum cannot be high. The fact that Marcoumar decreases at same time the concentration of prothrombin, Factor VII etc. has another consequence: An eventual effect of Factor X on Quick's prothrombin time can be hidden by the well known action of the above mentioned factors on tissue thromboplastin. Graham and Hougie claim that storage stability (and heat resistance) of the Stuart-Prower factor and of F. X appear to be different. We have repeated our previous experiments on F. X stability and could not regularly find a significant decrease in activity of this factor in normal sera stored at room temperature (or heated at 50° C for 30 minutes). On the other hand we observed that the Stuart-Prower factor activity in stored sera can decrease in some cases rather rapidly.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

We stated that F. X influences the rate and not the yield of thromboplastin formation but emphasized that the amount of thromboplastin formed may become insignificant if Factor X is very low. Newcomb (45) claimed that the low concentration of prothrombin in sera of Dicoumarol treated patients may account for the delayed thromboplastin generation of these sera. There is no doubt that the prothrombin content of serum has a certain influence on the rate of thromboplastin formation. In ar attempt to exclude this influence we prepared artificial Factor IX deficient sera with low prothrombin content (by adding $^1/_{20}$ diluted brain thromboplastin to diluted plasma, recalcifying and incubation for 4—6 hours at 37° C). These artificial sera were mixed with Factor X deficient sera showing a greatly prolonged incubation time in the thromboplastin generation test and having at least the same amount of prothrombin left. A definite though not complete compensation of the deficient thromboplastin generation was observed. These results demonstrate that the „Factor X-phenomenon" is not only due to the low prothrombin content of Marcoumar serum but to the deficiency of another clotting factor, Factor X.

Biggs described another congenital clotting defect named thromboplastin C-deficiency, different from the Prower defect. This case was not available and it was impossible to verify the hypothesis of Biggs, mentioning the possibility that Thromboplastin C and Factor X are identical (10). Also Greig and Tattersall found three different serum factors necessary for blood thromboplastin formation in a study of congenital haemorrhagic disorders (26).

The present situation is not entirely clear. Further work is necessary in order to elucidate definitively the relations between these different clotting factors.

Reviewing all cases published as F. VII (SPCA, Proconvertin) deficiencies, and taking into account the performed matching experiments, we can distinguish three groups of congenital defects:

A. Real F. VII deficiencies: normal TGT, normal or only slightly prolonged clotting time, normal prothrombin consumption, correction of the prolonged one stage prothrombin time when adding Russell's viper venom.

B. Stuart-Prower factor deficiencies: Since it is not yet possible to distinguish this group from group C by means of todays laboratory techniques, we classified in this group only cases on which matching experiments have been performed, partly by Hougie and Graham, partly in our laboratory.

C. Thromboplastin C deficiencies: abnormal TGT like in group B, but mutual correction with serum of Telfer's case (Stuart-Prower deficiency).

The remaining cases cannot yet be clearly classified. It would be very instructive to re-study the unclassified cases with regard to TGT and RVV „prothrombin time". It will be of great help to exchange samples of lyophilized plasma and serum, only matching experiments being able to indicate with certainty if we are dealing with the same factor or not.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Case	Year	Authors	Sex	Prothrombin time with BTP (sec) patient	Prothrombin time with BTP (sec) control	Prothrombin time with RVV pat.	TGT with serum	Clotting time	Recalc. time	Prothrombin-consumption
1. Cases of pure F. VII deficiency										
1	1951	Alexander et al (2, 3)	F	62—93	15—16		N (32)	slightly prolonged		N
2	1952	Owren (46, 47, 47a, 29, 45)	M	55—60	14	N	N	slightly prolonged		N
3	1953	Owren (47, 47a, 29, 45) case 1	F	55—60	14	N	N	N		N
4		case 2	F	1—3%		N	N			N
5	1953	Jürgens (36, 37)	M	6,2—9,5%			N		N	N
6	1954 1956	Jenkins (34) Ackroyd (1)	M	42—70	12—16	N	N	N		N
7	1954	Koch et al. (38) case 1 A. P.	F	50	21—23		N	slightly prolonged	N	N
8		case 2 Chr. K.	F	25	21—23		N	N	N	N
9	1955	Hicks (28)	F	25—105	11,5—14	N	N	N	N	N
10 11 12	1956	van Crefeld et al. (14) three sisters with similar results	F F F	60			N	N		N
2. Cases of Stuart-Prower factor deficiency										
1	1949	Crocket et al. (15)	F	50—92		abn.*)	abn.*)	abn.		
2	1953 1956	Lewis et al. (42) Hougie and Grah. (30—32)	M	48—55		abn.	abn.	abn.	abn.	abn.
3	1953	Beaumont et Bernard (6)	F	65—205	12—13	abn.**)	abn.**)	N		abn.
4	1956	Telfer et al. (56)	F	24—30	8,8—12	variable	abn.	N		abn.**)
5	1957	Bachmann et al. (4)	F	58—270	12—15	abn.	abn.	abn.	abn.	abn.
3. Cases of Thromboplastin C deficiency										
1 2	1956 1956	Biggs (10) identical twins	F F	29—42	17	abn.	abn.	N		abn.
4. Cases of F. VII complex-deficiency, not yet classified										
1	1943	Giordano (22)	M	210	25			N		
2	1950	Landwehr et al. (41)	M	40—76	12			N		N
3	1952	Van Belle (9) Case 1	F	41,2—50	15,3—20			N		
4		Case 3	M	60,2	18,4			N		abn.
5		Case 6	M	40,2—44,3	15,3—17,2			N		

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Case	Year	Authors	Sex	Prothrombin time with BTP (sec) patient	Prothrombin time with BTP (sec) control	Prothrombin time with RVV pat.	TGT with serum	Clotting time	Recalc. time	Prothrombin-consumption
6		Case 8	M	39,9—42,5	15,3—17			N		
7		Case 10	M	40,7—41,2	15,3—17			N		
8		Case 12	F	40,6—42,2	15,3—15,8			N		
9	1948 1953	Hagen & Watson (27) Frick & Hagen (19)	F	67,5	15—16			slightly prolonged	abn.	N
10	1953	Lewis et al. (42) (Case M. T.)	F	73—110	15—18			abn.		abn.
11	1953	Marciniakowna et al. (44)	F	35—153	14—17			N		N
12	1954	de Vries et al. (57, 58) case A	M	17—20	15,5		abn.	abn.	abn.	
13		case B	M	17	12,8		abn.	N		
14		case C****	M	19,8	14,7		abn.	abn.	abn.	abn.
15	1954	Wurzel et al. (59)	F	17,1	12—13			N		abn.
16	1954	Brinkhous et al. (10)	M	60	13			slightly prolonged		N
17	1955	Bell and Alton (8) case 1	F	65%			98%	N		N
18		case 2	F	75%			93%	N		N
19		case 3	F	72%			80%	N		N
20		case 5	M	50%			93%	N		N
21		case 6***	M	45%			12%	abn.		abn.
22		case 7***	M	46%			10%	abn.		abn.
23		case 8***	M	48%			11%	abn.		abn.
24	1955	Quick et al. (50) case 1 M. P.	F	35—72	12			N		N
25		case 2 H. S.	F	26—45	12			N		N
26	1955	Long et al. (43) case 1 P. G.	F	120	18			N	N	
27		case 2 Y. G.	F	160	18			N	N	
28	1955	Stefanovic (54) case 1 P. D.	M	26	10		abn.	N		N
29		et al. case 2 S. M.	M	27	13		abn.	±N		N
30	1955	Chevallier et al. (11) case 1 Cor. D.	M	45	12,5			N-abn.	abn.	N
31		case 2 Fer. J.	M	31—50	11			slight. abn.	abn.	slight. abn.
32	1955	Soulier et al. (53)	F	29—85	11		slight. abn.	N		N
33	1955	Hule et al. (33)	M	172—211	13—14			abn.		N after-transfusion
34	1956	Stein and Abrahams (55)***	M	53—70%			abn.	N	±N	abn.
35	1956	Choremis et al. (12)	M	70—80"	12—13			N		N
36	1956	Greig et al. (25)								
		Greig and Tattersall (26)	M	65—235	12		abn.	N	N	N?
37	1956	Gillot et al. (21)	F	30	17		abn.	N	N	±N
	1956	Serafini and Pericoli (52)								
38		Case 1 L. Enzo	M	27	18		slight. abn.	N	N	±N
39		Case 2 L. Sergio	M	33	17		slight. abn.	N	N	±N
40	1957	Barnett (5)	M	150—270				abn.	abn.	abn.

*) work of Hougie, Graham and Barrow (32)
**) work of present authors
***) published as combined F. VII + IX deficiency. No matching experiments with F. IX deficient blood were performed.
****) published as combined F. VII + IX deficiency. Matching experiments with F. IX deficient serum gave one time compensation, one time no compensation.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Literature reviews have already been published by Ackroyd in his instructive study about the function of Factor VII (1), by Koch (38) and by Hougie et al (32).

The determination of the Stuart-Prower factor during Dicoumarol therapy may be of great practical interest, since we observed in nearly all accidental haemorrhages due to overdosage a very low Stuart-Prower factor activity (2—4%).

Genetic studies of the family of Graham's patient revealed that the Stuart defect is inherited as a highly penetrant incompletely recessive autosomal characteristic. In our family the mode of inheritance of the Delia B.-defect seems to be an intermediate autosomal one. In both, Graham's and our family heterozygous members showed reduced Stuart-Prower levels: 20—52% (Graham) and 25—60% (our findings), with no manifest haemorrhagic diathesis.*)

Summary

A factor recently described and for which the designation Stuart-Prower Factor is proposed, was investigated. It is detected by the usual Factor VII assay but differs from this factor (Matching experiments with plasma and serum of Owren's Factor VII deficient patient). Stuart-Prower factor is necessary for the conversion prothrombin-thrombin with tissue thromboplastin as well as for the formation of blood thromboplastin. Therefore lack of Stuart-Prower factor produces abnormal Quick's prothrombin time (not normalized with Russell's viper venom [Stypven]), and also abnormal prothrombin consumption, abnormal recalcification time and abnormal thromboplastin generation with serum. Matching experiments with plasma and serum of the patients of Graham and Hougie, Telfer Denson and Wright, and Beaumont and Bernard show that we are dealing with the same defect. Physiological and physico-chemical properties are indicated. The possible relationship between Stuart-Prower factor and Factor X is discussed. A critical review with 59 cases of the so-called Factor VII deficiency is given. Investigation of the family of our patient Delia B. indicates that the mode of inheritance is an intermediate autosomal one.

Résumé

Un facteur, récemment décrit et pour lequel le nom de "Stuart-Prower factor" est proposé, est étudié. Il est mis en évidence par le test de dosage du Facteur VII mais diffère du Facteur VII (Essais en présence du plasma ou du

*) We are indebted to Prof. Rosin (Bern) for his interest and advice in our family investigations.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

sérum du patient d'Owren déficient en Facteur VII). Le "Stuart-Prower factor" est indispensable à la conversion prothrombine-thrombine en présence de thromboplastine tissulaire et également à la formation de la thromboplastine sanguine. Un déficit en "Stuart-Prower factor" provoque un temps de Quick anormal, non corrigé par le venin de la vipère de Russell (Stypven). La consommation de la prothrombine, le temps de recalcification et le test de formation de la thromboplastine avec le sérum sont pathologiques. Des essais croisés avec les plasmas et sérums des patients de Graham et Hougie, de Telfer, Denson et Wright, et de Beaumont et Bernard montrent qu'il s'agit de la même déficience. Les propriété physiologiques et physicochimiques sont indiquées. Les rapports entre le "Stuart-Prower factor" et le Facteur X sont discutés. Une revue critique de 59 cas de soi-disant déficience en Facteur VII est présentée. L'étude de la famille de notre malade Delia B. montre que le mode de transmission est à caractère intermédiaire autosomal.

Zusammenfassung

Ein neuer Gerinnungsfaktor, für den wir den Namen Stuart-Prower-Faktor vorschlagen, wird beschrieben. Er drückt sich in der üblichen Faktor-VII-Bestimmung aus, ist jedoch verschieden von Faktor VII (Mischversuche mit Plasma und Serum eines Falles von Faktor-VII-Mangel von Owren). Der Stuart-Prower-Faktor ist sowohl notwendig für die Überführung von Prothrombin in Thrombin in Gegenwart von Gewebsthrombokinase, als auch für die Bildung der bluteigenen Thrombokinase. Ein Mangel an Stuart-Prower-Faktor bewirkt deshalb eine verlängerte Quick-Zeit (die durch Russell's viper venom [Stypven] nicht korrigiert wird); der Prothrombinverbrauch, die Rekalzifizierungszeit und der Thrombokinasebildungstest mit Serum sind pathologisch. Mischversuche mit Plasma und Serum der Patienten von Graham und Hougie, von Telfer, Denson und Wright und von Beaumont und Bernard zeigen, daß es sich in allen diesen Fällen um den gleichen Mangel handelt. Die physiologischen und die physikochemischen Eigenschaften des Faktors werden beschrieben. Die Beziehungen zwischen Stuart-Prower-Faktor und Faktor X werden diskutiert. Es folgt eine kritische Übersicht von 59 sogenannten Faktor-VII-Mangel-Fällen. Die Familienuntersuchung bei unserer Patientin Delia B. ergibt einen intermediären autosomalen Vererbungsgang.

References

(1) Ackroyd, J. F.: The Function of F. VII. Brit. J. Haemat. 2: 397 (1956).
(2) Alexander, B., Goldstein, R., Landwehr, G. and Cook, C. D.: Congenital SPCA-Deficiency: A hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. J. clin. Invest. 30: 596 (1951).
(3) Alexander, B.: Discussion on Owren (46), p. 112 (1952).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(4) Bachmann, F., Duckert, F., Flückiger, P., Hitzig, W. and Koller, F.: Über einen neuartigen kongenitalen Gerinnungsdefekt (Mangel an Stuartfaktor). Thromb. Diath. haem. **1:** 87 (1957).
(5) Barnett, C. P.: Hemorrhagic Diathesis due to Factor VII deficiency. A. M. A. Arch. intern. Med. **99:** 280 (1957).
(6) Beaumont, J. L., et Bernard, J.: Syndrome hémorrhagique congénital dû au défaut du facteur de coagulation récemment isolé sous le nom de Facteur VII, Convertine, S. P. C. A. Acta med. scand. **145:** 200 (1953).
(7) 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).
(8) Bell, W. N. and Alton, H. G.: Christmas disease associated with Factor VII deficiency. Case report with family survey. Brit. med. J. **1:** 330 (1955).
(9) van Belle, C. J.: Parahaemophilie. Academisch Proefschrift. Utrecht (1952).
(10) Biggs, R.: Some observations on the blood of patients with 'Factor VII' deficiency. Brit. J. Haemat. **2:** 412 (1956).
(10a) Brinkhous, K. M., Langdell, R. D., Penick, G. D., Graham, J. B. and Wagner, R. H.: Newer approaches to the study of hemophilia and hemophiloid states. J. Amer. med. Ass. **154:** 481 (1954).
(11) Chevallier, P., Bernard, J., Fiehrer, A., Bilski-Pasquier, G., Samama, M. et Cerf, M.: Deux cas d'hypoconvertinémie familiale. Sang **26:** 650 (1955).
(12) Choremis, C., Padiatellis, C., Tsevrenis, I., Hadjidimitriou, E., Priovolos, I. et Mandalaki, T.: A propos d'un cas d'hypoproconvertinémie congénitale. Helv. paediat. Acta **11:** 301 (1956).
(13) Clauss, A.: Gerinnungsphysiologische Schnellmethode zur Bestimmung des Fibrinogens. Acta haemat. (Basel) **17:** 237 (1957).
(14) van Crefeld, S., Veder, H. and Blans, M.: Congenital hypoproconvertinemia. Ann. paediat. (Basel) **187:** 373 (1956).
(15) Crockett, C. L., Jr., Shotton, D., Craddock, C. G., Jr. and Leavell, S. S.: Hypoprothrombinemia: studies of a case of the idiopathic type and the effect of serum administration. Blood **4:** 1298 (1949).
(16) Duckert, F., Flückiger, P., Isenschmid, H., Matter, M., Vogel-Meng, J. and Koller, F.: A modification ot the thromboplastin generation test. Acta haemat. (Basel) **12:** 197 (1954).
(17) Duckert, F., Flückiger, P. and Koller, F.: Le rôle du facteur X dans la formation de la thromboplastine sanguine. Rev. Hémat. **9:** 489 (1954).
(18) Duckert, F., Flückiger, P., Matter, M. and Koller, F.: Clotting Factor X. Physiologic and physicochemical properties. Proc. Soc. exp. Biol. (N. Y.) **90:** 17 (1955).
(19) Frick, P. G. and Hagen, P. S.: Congenital familial deficiency of the stable prothrombin conversion factor. Restudy of a case originally reported as 'idiopathic hypoprothrombinemia'. J. Lab. clin. Med. **42:** 212 (1953).
(20) Geiger, M., Duckert, F. and Koller, F.: Quantitative Bestimmungen von Faktor VIII und IX bei Blutersippen. 5the Congr. Europ. Soc. Haemat. Freiburg. p. 413 (1956).
(21) Gillot, F., Venezia, R., Boineau, N. et Colonna, M.-C.: Un cas d'hypoconvertinémie congénitale chez le nourrisson. Pédiatrie **11:** 439 (1956).
(22) Giordano, A. S.: Idiopathic hypoprothrombinemia. Amer. J. clin. Path. **13:** 285 (1943).
(23) Graham, J. B. and Hougie, C.: The Stuartfactor (hypoproconvertinemia?). The clotting defect and mode of inheritance. 6the Congr. Int. Soc. Haemat. Boston. p. 327 (1956).
(24) Graham, J. B., Barrow, E. and Hougie, C.: Stuart clotting defect. II. Genetic aspects of a 'new' hemorrhagic state. J. clin. Invest. **36:** 497 (1957).
(25) Greig, H. B. W., Falcke, H. C., Simon, M. and Cohen, H.: Congenital Factor VII deficiency. Arch. Dis. Childh. **31:** 293 (1956).
(26) Greig, H. B. W. and Tattersall, J. C.: Evidence for the existence of a third serum clotting factor. Brit. J. Haemat. **2:** 421 (1956).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(27) Hagen, P. S. and Watson, C. J.: Idiopathic (familial) hypoprothrombinemia. J. Lab. clin. Med. **33**: 542 (1948).
(28) Hicks, N. D.: A coagulation disorder due to a Factor VII-like defect. Med. J. Austr. **2**: 331 (1955).
(29) 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).
(30) Hougie, C. and Graham, J. B.: The blood clotting role and mode of inheritance of the Stuart factor. 6the Congr. Int. Soc. Blood Transf. Boston. p. 80 (1956).
(31) Hougie, C.: The role of Russell's viper venom on the Stuart clotting defect. Proc. Soc. exp. Biol. **93**: 570 (1956).
(32) Hougie, C., Barrow, E. and Graham, J. B.: Stuart clotting defect. I. Segregation of an hereditary hemorrhagic state from the heterogeneous group heretofore called 'Stable Factor' (SPCA, proconvertin, Factor VII) deficiency. J. clin. Invest. **36**: 485 (1957).
(33) Hule, V., Šabacký, J. and Saxl, O.: Ein Fall von angeborenem Mangel von Faktor VII (SPCA-Mangel, Hypoproconvertinemia congenita). Helv. paediat. Acta **10**: 419 (1955).
(34) Jenkins, J. S.: Haemorrhagic diathesis due to a deficiency of Factor VII. J. clin. Path. **7**: 29 (1954).
(35) Jenkins, J. S.: The thromboplastic activity of Russell's viper venom and its relationship to Factor VII. J. clin. Path. **7**: 287 (1954).
(36) Jürgens, J.: Congenital Factor VII deficiency — a haemophilia-like haemorrhagic disease — and its response to a plasma fraction (Behring's accelerator 76). Abstract in 4th Congr. Europ. Soc. Haemat. Amsterdam. p, 54 (1953).
(37) Jürgens, J.: Kongenitaler Faktor VII (SPCA)-Mangel als Ursache einer hämophilieartigen hämorrhagischen Diathese. Acta haemat. (Basel) **16**: 181 (1956).
(38) Koch, Fr., Schultze, H. E., Schwick, G. and Beller, F. K.: Beobachtungen bei angeborenem Faktor VII-Mangel (Hypokonvertinämie). Zschr. f. Kinderh. **76**: 208 (1955).
(39) Koller, F., Loeliger, A. and Duckert, F.: Experiments on a new clotting factor (Factor VII). Acta Haemat. **6**: 1 (1951).
(39a) Koller, F.: Die Physiologie der Blutgerinnung. Arch. exper. Pathol. and Pharmak. **222**, 90 (1954).
(40) Koller, F.: Is hemophilia a nosologic entity? Blood **9**: 286 (1954).
(40a) Koller, F.: Le facteur X. Rev. Hémat. **10**: 362 (1955).
(41) Landwehr, G., Lang, H. and Alexander, B.: Congenital hypoprothrombinemia. A case study with particular reference to the role of non-prothrombin factors in the conversion of prothrombin. Amer. J. Med. **8**: 255 (1950).
(42) Lewis, J. H., Fresh, J. W. and Ferguson, J. H.: Congenital hypoproconvertinemia. Proc. Soc. exp. Biol. (N. Y.) **84**: 651 (1953).
(43) Long, L. A., Letendre, P. and Colpron, G.: Hypoproconvertinémie congénitale. Acta Haemat. **13**: 242 (1955).
(44) Marciniakówna, E., Krakowska, J., Bober, S. and Safarzynska, I.: Przypadek skazy krwotocznej wskutek niedoboru akcleratora konwersji protrombiny. Pol. Tyg. lek. **8**: 1601 (1953).
(45) Newcomb, T.: The role of known coagulation factors in the thromboplastin generation test. J. clin. Invest. in press.
(46) Owren, P. A.: New clotting factors. Trans. 5th Conf. Blood Clotting and Allied Problems, p. 92. Josiah Macy, Jr. Foundation, New York (1952).
(47) Owren, P. A.: Prothrombin and accessory factors: clinical significance. Amer. J. Med. **14**: 201 (1953).
(47a) Owren, P. A., Newcomb, T. and Hjort, P.: Personal communications to R. Biggs (10).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(48) Pitney, W. R. and Dacie, J. V.: A simple method of studying the generation of thrombin in recalcified plasma. Application in the investigation of haemophilia. J. clin. Path. **6:** 9 (1953).
(49) Quick, A. J.: The prothrombin in hemophilia and in obstructive jaundice. J. biol. Chem. **109:** 523 (1935).
(50) Quick, A. J., Pisciotta, A. V. and Hussey, C. V.: Congenital hypoprothrombinemic states. Arch. int. Med. **95:** 2 (1955).
(51) Rapaport, S. I., Aas, K. and Owren, P. A.: The clotting action of Russell's viper venom. Blood **9:** 1185 (1954).
(52) Serafini, U. M. and Pericoli, F.: Sindrome emorragica di tipo emofilio da difetto congenito di Fattore VII. Boll. Soc. Ital. Emat. **4:** 70 (1956).
(53) Soulier, J. P., Alagille, D., Martin, C. et Buhot, S.: Un cas d'hypoconvertinémie congénitale. Sang **26:** 660 (1955).
(54) Stefanovic, S., Milosavljevic, A. and Stefanovic, R.: Deux cas d'hypoconvertinémie congénitale. Sang **26:** 315 (1955).
(55) Stein, H. B. and Abrahams, O. L.: Combined mild PTC (Plasma thromboplastin component) and Factor VII deficiencies. S. Afr. J. med. Sci. **21:** 13 (1956).
(56) Telfer, T. P., Denson, K. W. and Wright, D. R.: A 'new' coagulation defect. Brit. J. Haemat. **2:** 308 (1956).
(57) de Vries, S. I., Kettenborg, H. K. and van der Pool, E. T.: Haemorrhagische diathese door tekort aan Factor VII (hypoproconvertinaemia). Ned. T. Geneesk. **98:** 2987 (1954.
(58) de Vries, S. I., Kettenborg, H. K. and van der Pool, E. T.: Haemorrhagic diathesis due to a deficiency of factor VII. (Hypoproconvertinaemia). Acta haemat. (Basel) **14:** 43 (1955).
(59) Wurzel, H. A., Roth, K. and Zubrow, S.: Mild familial hypoproconvertinemia J. Lab. clin. Med. **44:** 403 (1954).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.