

# DEFICIENCIES IN STUART (PROWER) FACTOR, PLASMA THROMBOPLASTIN COMPONENT, PROTHROMBIN, AND FACTOR VII, DUE TO MALABSORPTION OF VITAMIN K

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**H**EMORRHAGIC phenomena occur in the malabsorption syndromes as an infrequent complication,<sup>1-5</sup> and are due to the "hypoprothrombinemia" that results from the impaired absorption of fat and the fat-soluble vitamin K from the bowel. More specifically, it has been demonstrated<sup>6</sup> that in vitamin K deficiency, regardless of its pathogenesis, not only is the amount of prothrombin decreased, but also the amounts of factor VII (stable factor, serum prothrombin conversion accelerator, proconvertin) and plasma thromboplastin component (PTC, Christmas factor).

This paper describes the blood coagulation defect in a patient<sup>7</sup> with idiopathic steatorrhea; in addition to deficiencies of prothrombin, factor VII, and PTC, there was also a deficiency of the Stuart<sup>8</sup> (Prower<sup>9</sup>) clotting factor.

## Case History<sup>1</sup>

The patient, a 24-year-old white woman, was first examined on March 31, 1958, because of diarrhea and pedal edema of two years' duration, and severe anorexia of one month's duration. In June, 1956, and again in June and September, 1957, she received two units of whole blood because of anemia. After severe bleeding from the uterus and the urinary tract in December, 1957, she received six units of whole blood. For three weeks prior to examination she had persistent, frank, hematuria. Epistaxis and hemoptysis occurred occasionally, and she bruised easily. Excessive bleeding had not occurred in other members of the family.

On physical examination she weighed 115 pounds and appeared to be extremely malnourished. The tongue was red and atrophic. Numerous ecchymoses were present on both arms, and there were splinter hemorrhages beneath the fingernails. Moderate bilateral edema of the legs extended up to the thighs. Trousseau's sign was present. A tourniquet test was negative. The remainder of the physical examination gave normal findings.

Laboratory studies disclosed: blood hemoglobin content, 15.2 gm. per 100 ml.; hematocrit reading, 46 cc. per 100 cc.; white-cell count, 3,900 per cubic millimeter, with a normal differential count. There was macroscopic hematuria. Several stools contained occult blood (guaiac test) and large amounts of fat. A culture of the stool yielded no pathogens. The total serum protein content was 2.77 gm. per 100 ml.; serum

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albumin 0.43 gm., and serum globulin 2.34 gm. The serum potassium value was 3.4 mEq. per liter; serum calcium 5.0 mg. and serum phosphorus 2.9 mg. per 100 ml. The cephalin-cholesterol flocculation test was 2 plus in 24 hours. The results of an oral glucose tolerance test were consistent with malabsorption.

Roentgen examinations, of the chest, kidneys, ureters, bladder, and the upper and lower gastrointestinal tracts showed no abnormality. On roentgen examination of the small bowel there was evidence of fragmentation of the barium column consistent with a disordered motor pattern. The absorption curves of radioiodinated triolein and oleic acid indicated minimal absorption of both of these substances. A cystoscopic examination revealed blood emanating from the left ureteral orifice.

Preliminary coagulation studies disclosed a bleeding time (Ivy method) of three minutes, a platelet count (Rees-Ecker method) of 380,000 per cubic millimeter, a coagulation time (four-tube method) of 50 minutes (normal 10 to 20 minutes), and a normal clot retraction. The Quick one-stage prothrombin time ranged between 110 and 184 seconds. Circulating anticoagulants were not demonstrated by either the Conley<sup>10</sup> method or the Biggs and Macfarlane<sup>11</sup> method. There was 190 mg. per 100 ml. of fibrinogen (Fowell<sup>12</sup> method).

#### Material and Methods

All blood was drawn from antecubital veins by means of silicone-coated 20-gauge needles and silicone-coated glass syringes. Oxalated plasma was collected in plain glass tubes, and citrated plasma in silicone-coated tubes. Serum was obtained by allowing the blood to clot at 37° C. in uncoated glass tubes. Some specimens were immediately stored at -20° C. and were used, after thawing, as long as two months later.

Barium sulfate ( $\text{BaSO}_4$ ) adsorbed plasma was prepared by adding 100 mg. of powdered  $\text{BaSO}_4$  to each milliliter of plasma; the resulting mixture was incubated for 15 minutes at room temperature, and then was centrifuged. This  $\text{BaSO}_4$  adsorbed plasma was used within a few hours. An eluate was prepared from the  $\text{BaSO}_4$  used to adsorb normal plasma, by allowing the  $\text{BaSO}_4$  to stand in a 5 per cent solution of trisodium citrate in 0.89 per cent saline solution for 15 minutes at 37° C. and then centrifuging the mixture. The supernatant solution represented a volume equal to that of the plasma adsorbed.

Plasma and serum from a patient deficient in factor VII were stored for two months at -20° C. The factor VII deficiency had been diagnosed according to the following criteria: (1) a prolonged one-stage prothrombin time that could be corrected by normal serum but not by  $\text{BaSO}_4$  adsorbed normal plasma; (2) a normal thromboplastin generation test and Stypven time; (3) mutual correction with plasma deficient in Stuart factor; (4) a factor VII content of 8 per cent of normal. The PTC deficient serum used in the correction studies had been stored for four months at -20° C. Plasma from a patient with a deficiency of Stuart factor was obtained through the courtesy of John B. Graham, M.D., of Chapel Hill, North Carolina. The plasma had been lyophilized in a glass container and was reconstituted to its original volume by the addition of distilled water immediately before use.

In the Quick one-stage prothrombin test a commercial preparation of brain thromboplastin\* was used. For correction studies the various combinations were mixed immediately prior to performing the test. Prothrombin was assayed by the two-stage method of Ware and Seegers,<sup>13</sup> using commercial preparations of factor V and the incubation mixture.† The thromboplastin generation test was carried out according to the method of Biggs and Douglas,<sup>14</sup> but with a platelet suspension that was two or three times more concentrated than they recommend. Factor V was assayed by the method of Alexander, Goldstein, and Landwehr,<sup>15</sup> modified by the addition of oxalated normal serum to the test mixture. Factor VII was assayed by the method of Owren and Aas.<sup>16</sup> Circulating anticoagulant activity was estimated, both in the one-stage prothrombin test and in the thromboplastin generation test, by using equal mixtures of normal and abnormal fractions preincubated for 15 minutes at 37° C. Table 1 lists the relevant coagulation factors present in the various fractions of normal and of abnormal blood used.

Table 1.—*The relevant coagulation factors in the various fractions used in the correction studies. ‡*

	Normal plasma	BaSO <sub>4</sub> adsorbed normal plasma	Eluate from BaSO <sub>4</sub>	Normal serum	Factor VII deficient plasma	Factor VII deficient serum	Stuart factor deficient plasma	Stuart factor deficient serum	PTC deficient serum
Prothrombin	+	—	+	—	+	—	+	—	—
Factor VII	+	—	+	+	—	—	+	+	+
Stuart factor	+	—	+	+	+	+	—	—	+
Factor V	+	+	—	—	+	—	+	—	—
Plasma thromboplastin component (PTC)	+	—	+	+	+	+	+	+	—
Antihemophilic globulin	+	+	—	—	+	—	+	—	—

‡ + = present; — = absent.

### Results

The clinical history and the preliminary coagulation studies, which included prolonged coagulation time and one-stage prothrombin time, suggested the presence of a coagulation defect of considerable severity. More detailed investigation of the individual clotting factors showed that a multiplicity of defects existed.

The results of the one-stage prothrombin tests are presented in Table 2, and those of the thromboplastin generation tests in Table 3.

\*Bacto thromboplastin, manufactured by Difco Laboratories.

†Manufactured by Difco Laboratories.

**Table 2.**—*Correction studies using the one-stage prothrombin test before and after the administration of 72 mg. of menadione sodium bisulfite*

From the patient		Normal				Plasma deficient in		Prothrombin time (Quick), sec.
		Plasma, ml.	Serum, ml.	BaSO <sub>4</sub> adsorbed plasma, ml.	BaSO <sub>4</sub> eluate, ml.	Factor VII, ml.	Stuart factor, ml.	
Blood drawn before vitamin K therapy								
0.1	—	—	—	—	—	—	—	184
—	—	0.1	—	—	—	—	—	14
0.09	—	0.01	—	—	—	—	—	21
0.08	—	0.02	—	—	—	—	—	19
0.05	—	0.05	—	—	—	—	—	14
0.05*	—	0.05*	—	—	—	—	—	15*
0.09	—	—	0.01	—	—	—	—	37
0.08	—	—	0.02	—	—	—	—	35
0.09	—	—	—	0.01	—	—	—	115
0.09	—	—	—	—	0.01	—	—	25
—	—	—	—	—	—	0.1	—	49
0.01	—	—	—	—	—	0.09	—	47
0.09	—	—	—	—	—	0.01†	—	40
0.05	—	—	—	—	—	0.05	—	31
—	—	0.1	—	—	—	0.09	—	20
—	—	—	—	—	—	—	0.1	130
—	0.1	—	—	—	—	—	0.09	130
—	—	—	0.1	—	—	—	0.09	20
—	—	0.1	—	—	—	—	0.09	30
Blood drawn after vitamin K therapy								
8 hours								
0.1	—	—	—	—	—	—	—	16
0.01	—	—	—	—	—	—	0.09	44
0.01	—	—	—	—	—	0.09	—	22
36 hours								
0.1	—	—	—	—	—	—	—	15
0.01	—	—	—	—	—	—	0.09	37
0.01	—	—	—	—	—	0.09	—	20
5 days								
0.1	—	—	—	—	—	—	—	14
0.01	—	—	—	—	—	—	0.09	27
0.01	—	—	—	—	—	0.09	—	20

\* Mixture incubated at 37° C. for 15 minutes prior to performing the test.

† Serum.

**Table 3.**—*Correction studies using the thromboplastin generation test before and after the administration of 72 mg. of menadione sodium bisulfite*

Variables in the incubation mixture	Incubation time, minutes					
	1	2	3	4	5	6
	Substrate clotting time, seconds					
Normal	55	14	8	8	9	9
Patient's BaSO <sub>4</sub> adsorbed plasma	55	20	10	8	8	9
Patient's serum	150	135	110	60	30	25
Patient's serum 90% + normal serum 10%	—	35	12	11	11	10
50% + 50%	32	11	10	9	9	9
50%* + 50%*	40	16	12	9	9	9
PTC deficient serum	60	25	25	28	30	31
Patient's serum 10% + PTC serum† 90%	60	25	25	25	25	25
50% + 50%	—	30	22	18	16	14
90% + 10%	90	60	20	18	16	15
Stuart factor deficient serum	105	98	80	60	40	26
Patient's serum 10% + Stuart serum‡ 90%	69	60	53	50	28	27
50% + 50%	32	14	13	13	13	13
90% + 10%	57	20	18	15	13	13
50% + { Stuart serum‡ 25% } { PTC serum† 25% }	55	27	12	11	10	11
Patient's serum after injection of synthetic vitamin K—						
8 hours	72	16	12	11	13	13
5 days	42	8	7	8	10	10

\*Preincubated for 15 minutes at 37° C.

†PTC deficient serum.

‡Stuart factor deficient serum.

In the preliminary studies the abnormality observed was so great as to suggest the presence of a circulating anticoagulant. However, by conventional methods no such anticoagulant was demonstrated. It was further shown that the abnormality neither in the one-stage prothrombin test nor in the thromboplastin generation test was due to circulating anticoagulant. Repeated assays of factor V throughout the investigation always showed values to be 100 per cent of normal. The patient's BaSO<sub>4</sub> adsorbed plasma acted normally in the thromboplastin gen-

eration test, indicating that there was no deficiency of antihemophilic globulin; however, no specific assay of this factor was made.

When the amounts of fibrinogen and factor V are normal, and there is no circulating anticoagulant, a prolonged one-stage prothrombin time reflects a deficiency of prothrombin, factor VII, or Stuart factor.

It appeared that a deficiency of prothrombin existed when it was shown that the long one-stage prothrombin time was corrected to a greater extent by normal plasma, and by an eluate of BaSO<sub>4</sub> containing the factors adsorbed from normal plasma, than by normal serum and by BaSO<sub>4</sub> adsorbed plasma. Confirmation was obtained by the assay of prothrombin which was 8 per cent of normal.

The fact that normal serum partially corrected the patient's abnormal prothrombin time indicated that either factor VII or Stuart factor or both factors were reduced. A deficiency of factor VII was proved by the inability of the patient's plasma to correct the one-stage prothrombin time of plasma known to be deficient in factor VII. Specific assays of factor VII in the patient's plasma and serum were less than 5 per cent of normal.

Although the patient's plasma did not correct factor VII deficient plasma, factor VII deficient serum did partially correct the patient's abnormality in the one-stage prothrombin test. Thus, factor VII deficient serum appeared to contain some factor in which the patient was deficient. This factor proved to be Stuart factor when it was shown that the patient's serum was unable to correct a Stuart factor deficiency, either in the one-stage prothrombin test or in the thromboplastin generation test. Unfortunately, the quantity of plasma obtained from the patient prior to vitamin K therapy was insufficient to test whether or not the serum deficient in Stuart factor would correct the patient's abnormal one-stage prothrombin time by virtue of its factor VII content.

A deficiency of PTC, as well as of Stuart factor, existed in the patient's serum and was partly responsible for the abnormal results of the thromboplastin generation test. This was proved when the patient's serum failed to correct the abnormal thromboplastin generation of serum deficient in PTC. Both serum deficient in PTC (by virtue of its content of Stuart factor), and serum deficient in Stuart factor (by virtue of its PTC content) were able partially to correct the defect in the patient's serum. As one might expect, an equal mixture of sera deficient in PTC and in Stuart factor corrected the thromboplastin generation to a greater extent than did either alone, and to an extent comparable to the correction obtained with normal serum. These findings offered further confirmation of the dual deficiency of Stuart factor and of PTC.

#### Effect of the Injection of Vitamin K

All clinical evidence of hemorrhage rapidly disappeared after the patient

received a single intravenous injection of 72 mg. of menadione sodium bisulfite.\* In vitro coagulation studies (*Tables 2-4*) showed a correspondingly rapid improvement. Within 24 hours after the injection, the factors previously deficient had returned to nearly normal values, and within five days to normal values. Stuart factor reappeared at the same rate as did the other factors. The patient has continued to receive vitamin K parenterally and her coagulation mechanism has remained normal.

**Table 4.**—*Factor VII and prothrombin values, and the one-stage prothrombin times, before and after the administration of 72 mg. of menadione sodium bisulfite*

After injection of vitamin K, hr.	One-stage prothrombin time, sec.	Factor VII assay, %	Prothrombin assay, %
0	184	5	8
8	16	35	30
36	15	100	60
56	14	100	100

### Discussion

Douglas<sup>7</sup> has shown that PTC, as well as prothrombin and factor VII, is reduced in vitamin K deficiency. The results in our case confirm his findings and, in addition, show a significant reduction in Stuart factor. Since the concentration of this factor is low in the plasma of patients who have received coumarin drugs,<sup>8</sup> one would expect it to be reduced in vitamin K deficiency. However, there is no previous report of deficiency of Stuart factor as the result of the malabsorption of vitamin K.

It is possible that yet other factors were deficient in our patient. Thus, plasma thromboplastin antecedent (PTA) was not specifically investigated; however, the findings do not suggest that a deficiency of this factor existed. In investigating multiple coagulation defects, one is largely limited by the available number of known abnormal plasmas and methods of specific assay. Despite these limitations, a deficiency often can be inferred by cross-correction studies. In this case, for instance, whereas the patient's serum did not correct the long one-stage prothrombin time of plasma deficient in factor VII, serum deficient in factor VII did partially correct the patient's prolonged one-stage prothrombin time. These findings suggested that besides factor VII, the patient's serum was deficient in another factor—subsequently shown to be Stuart factor.

\*Hykinone (menadione sodium bisulfite), Abbott Laboratories.

There is little doubt that the various coagulation deficiencies present in our patient were due to the malabsorption of vitamin K. The principal evidence for this conclusion is the existence of a disease, idiopathic steatorrhea, in which poor absorption of vitamin K might be expected, and the rapid favorable response to the administration of synthetic vitamin K. Such rapid improvement following administration of vitamin K is well documented. As was expected, Stuart factor and the other factors returned to normal almost simultaneously. The four factors involved, namely, Stuart factor, PTC, prothrombin, and factor VII, have several properties in common: they are dependent on vitamin K for their production, depressed by coumarin drugs,<sup>8, 17, 18</sup> and adsorbed from plasma by inorganic precipitates such as BaSO<sub>4</sub>. Single deficiencies of these factors do occur, mainly as hereditary defects. However, these factors appear to be more closely related than might be suggested by their actions in different stages of blood coagulation.

### Summary

A case of idiopathic steatorrhea with severe hemorrhagic manifestations due to malabsorption of vitamin K is described. Detailed coagulation studies disclosed a deficiency of Stuart factor, in addition to deficiencies of plasma thromboplastin component, prothrombin and factor VII. The coagulation mechanism was rapidly restored to normal by the intravenous administration of synthetic vitamin K.

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### Addendum

Since submitting this paper for publication, the paper by T. H. Spaet and Mona Kropatkin entitled, *Studies on "Prothrombin Derivatives" in Vitamin K Deficiency*, has been published in the *A.M.A. Archives of Internal Medicine*, volume 102, pages 558-561, October, 1958. The authors report a case of intestinal malabsorption resulting in vitamin K deficiency, associated with deficiencies of Stuart factor, factor VII, and prothrombin.