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Blood coagulation changes at high altitude predisposing to pulmonary hypertension

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Blood coagulation studies were carried out in 38 Indian soldiers who were resident at altitudes between 12,000 and 18,000 feet for 2 years. Compared with 16 sea-level controls, 6 of these 38 subjects who had developed pulmonary hypertension during their stay at high altitude showed a significant increase of plasma fibrinogen, fibrinolytic activity, platelet adhesiveness, platelet factor 3, factor V, and factor VIII. In the remaining 32 subjects who did not develop pulmonary hypertension there was a significant increase of plasma fibrinogen and fibrinolytic activity only. The above differences between subjects who develop pulmonary hypertension at high altitude and those who do not develop pulmonary hypertension suggest that high altitude pulmonary hypertension is of occlusive origin and is dependent on changes in blood coagulation at high altitude.

The pathogenesis of high altitude pulmonary hypertension is far from clear. Rotta *et al.* (1956) found a striking inverse correlation between the degree of arterial oxygen saturation and the level of the mean pulmonary arterial pressure. However, with acetylcholine and oxygen therapy, pulmonary hypertension decreased only to the extent of 15 to 20 per cent. Evidently, hypoxia does not affect the pulmonary arterial pressure directly to any conspicuous extent.

Campos and Iglesias (1957) observed an obvious dilatation of the vascular bed of the lungs. There is also thickening of the muscular layer of the small pulmonary arteries and muscularization of the pulmonary arterioles (Arias-Stella and Saldaña, 1962). Peñaloza *et al.* (1963) attributed high altitude pulmonary hypertension to increased pulmonary vascular resistance resulting from widespread narrowing of the lumen of the pulmonary blood vessels on account of these changes. However, in our experience with soldiers temporarily posted at high altitudes, who develop pulmonary hypertension and die of it, these changes are not prominent (see below). It seems more likely that these changes are not causal but secondary to long-standing hypertension. The pulmonary blood flow, as indicated by a normal cardiac output, is not increased in pulmonary hypertension. In itself, therefore, an increased pulmonary vascular bed is not contributory. In the absence of these changes, dilatation of the vascular bed may be found in association with an increased pulmonary blood volume, but without pulmonary hypertension.

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Polycythaemia *per se* does not seem to predispose to pulmonary hypertension. Pulmonary hypertension may be present without polycythaemia, or it may persist after the red blood cell count has returned to normal when the individual has returned to sea-level.

In our soldiers who are temporarily posted from sea-level to altitudes in the Himalayas, the symptoms of pulmonary hypertension begin after a stay of 5 to 42 months at high altitude. After the initial onset of the disease, periodic returns to sea-level on leave for 2 to 3 months once a year do not alter the picture. The hypertension either persists at sea-level or, if it abates, it reappears within 2 to 3 weeks after the individual returns to high altitude. Though pulmonary vasoconstriction, increased pulmonary blood volume, and polycythaemia may have some role in the pathogenesis of high altitude pulmonary hypertension, these bases do not explain its slow disappearance or persistence when the subjects return to sea-level.

In a previous study (Singh *et al.*, 1965), based on necropsy findings in high altitude pulmonary hypertension, we reported the presence of numerous occluding fibrin thrombi in the smaller branches of the pulmonary artery. Several segments of the pulmonary artery and its larger branches showed small but patchy atherosclerotic changes and evidence of repeated episodes of thrombosis. A

terminal occluding thrombosis in the main vessel led to death. In addition, some portions of the vessels showed evidence of inflammatory arteritis with patchy destruction of the medial coat. The intima showed diffuse fibrous thickening. The wall of the right ventricle and the muscle coat of the smaller branches of the pulmonary artery were thickened, but this was not a prominent feature. Comparative blood coagulation studies now carried out at sea-level and at high altitude reveal a significant increase of plasma fibrinogen, platelet adhesiveness, platelet factor 3, factor V, and factor VIII in subjects who develop high-altitude pulmonary hypertension, and an increase in plasma fibrinogen alone in those who do not develop pulmonary hypertension. On return to sea-level these abnormalities decrease *pari passu* with pulmonary hypertension. The above differences between subjects who develop pulmonary hypertension at high altitude and those who do not develop pulmonary hypertension suggest that high altitude pulmonary hypertension is of occlusive origin and is dependent on changes in blood coagulation at high altitude. The findings are presented and discussed.

Subjects and methods

The study was carried out in 38 Indian soldiers, normally residents of plains, but stationed at altitudes between 12,000 and 18,000 feet for 2 years. By the end of 2 years' stay at high altitudes, 6 of the 38 subjects developed high altitude pulmonary hypertension whereas the remaining 32 showed no clinical, radiological, or electrocardiographic evidence of pulmonary hypertension. On the basis of an equal duration of stay at high altitude, the 32 subjects who did not develop pulmonary hypertension served as comparable high altitude controls for the 6 patients who developed pulmonary hypertension. For the purpose of comparison, 16 soldiers stationed throughout at sea-level served as sea-level controls.

The diagnosis of pulmonary hypertension was based on clinical, radiological, and electrocardiographic abnormalities, i.e. dyspnoea with encroachment on effort to which the individual was previously accustomed; chest pain of the anginal type, a split pulmonary sound, especially if associated with a pulmonary systolic murmur;

TABLE I *Means, standard deviation of means, differences of means, standard deviation of differences of means, and results of 't' test for clot lysis time and blood coagulation studies in 16 sea-level controls, 32 high altitude controls, and 6 patients who developed pulmonary hypertension at high altitude*

Serial No.	*Factors*	*Sea-level controls*		*High altitude controls*		*Patients*		*Differences of means*		
		Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Sea-level controls versus high altitude controls*	*Sea-level controls versus patients*	*High altitude controls versus patients*
1	Haematocrit (%)	45·30	1·97	51·59	2·96	51·83	2·03	−6·29	−6·53	−0·24
2	Platelet count (thousands/mm³)	271·30	43·67	309·81	67·61	286·50	34·82	−38·51	−15·20	23·31
3	Platelet adhesiveness (%)	35·63	5·01	34·31	7·58	47·35	5·63	1·32	−11·72	−13·04
4	Platelet factor 3 (%)	86·69	13·14	75·48	23·08	117·00	21·04	11·21	−30·31	−41·52
5	Clot retraction (%)	55·30	0·36	54·88	7·10	56·33	4·96	0·42	−1·03	−1·45
6	Plasma fibrinogen (mg/100 ml)	335·00	68·74	551·28	143·71	470·17	121·95	−216·28	−135·17	81·11
7	Clot lysis time (hr)	5·54	2·33	2·52	0·97	2·04	0·73	3·02	3·50	0·48
8	Factor V (%)	108·00	8·67	111·42	24·06	134·17	9·08	−3·42	−26·17	−22·75
9	Factor VIII (%)	96·64	15·24	100·68	36·38	139·67	15·98	−4·04	−43·03	−38·99
10	Factor XII (%)	92·69	15·63	78·81	30·00	89·33	22·79	13·88	3·36	−10·52
11	Thrombotest activity (%)	74·70	2·26	40·62	19·48	56·33	27·60	34·08	18·37	−15·71
12	Bleeding time (min)	2·94	0·65	3·52	0·95	2·90	0·44	−0·58	0·04	0·62
13	Clotting time in glass tube (min)	4·85	1·00	5·13	1·24	4·53	1·05	−0·28	0·32	0·60
14	Clotting time in silicon tube (min)	8·35	1·02	9·37	1·62	8·25	1·35	−1·02	0·10	1·12
15	Prothrombin time (sec)	13·53	0·78	16·18	1·87	17·25	2·12	−2·65	−3·72	−1·07
16	Stypven time (sec)	13·48	0·66	15·82	2·36	15·50	2·16	−2·35	−2·02	0·32
17	Calcium time (sec)	103·00	8·50	146·60	53·05	125·00	29·44	−43·60	−22·00	21·60
18	Thrombin clotting time (sec)	9·70	0·73	13·78	2·11	13·83	0·69	−4·08	−4·13	−0·05

	Table value at 5%	*Table value at 1%*
* Degree of freedom 46	2·02	2·69
† Degree of freedom 20	2·09	2·84
‡ Degree of freedom 36	2·03	2·72

§ Significant at 5% level.
‖ Significant at 1% level.

a prominent pulmonary artery on *x*-ray examination, and electrocardiographic abnormalities of grade 1 right ventricular hypertrophy (dominant R in lead V4R or dominant S in lead V5), right ventricular strain (T inversions in leads V1–V4), right bundle-branch block (slurred R in leads V1–V3 and V3R–V4R), and QRS interval above 0·10 sec. The pulmonary arterial pressure was not measured.

The diagnosis of pulmonary hypertension based on these criteria had proved reliable when correlated with pressure studies previously.

Blood coagulation studies were done at sea-level in the 16 sea-level controls and at high altitude in the 32 high altitude controls and 6 patients. Five out of the 6 patients were further studied after 1, 3, and 5 weeks of evacuation to sea-level; one patient was not available for this purpose.

Fibrinolytic activity, as indicated by dilute clot lysis time, was determined by Fearnley's technique (Fearnley, Balmforth, and Fearnley, 1957; Fearnley and Chakrabarti, 1962) within 5 minutes of blood collection from the antecubital vein. Plasma fibrinogen was estimated by the biuret technique, as defined by Wootton (1964), from blood samples to which Trasylol 500 K.I. units for every 5 ml blood were added during collection to prevent fibrinolytic activity.

Blood coagulation studies involved bleeding time (Duke, 1912), coagulation time (Lee and White, 1913), one-stage prothrombin time (Quick, 1942), stypven time (Miale, 1967), thrombotest activity (Owren, 1959), thrombin clotting time (Fletcher, Alkjaersig, and Sherry, 1959), calcium time (Dacie and Lewis, 1963), clot retraction (Macfarlane, 1939), platelet count and platelet adhesiveness (Pegrum, Shaw, and Wolff, 1967), platelet factor 3 (Weiss and Eichelberger, 1962), factor V and factor XII (Stefanini and Dameshek, 1962), factor VIII (Bergna, 1960), and thromboplastin generation test (Biggs and Douglas, 1953) using platelet substitute (Bell and Alton, 1954). Alterations in factor VII and factor X were obtained from the results of the thromboplastin generation test (Dacie and Lewis, 1963). The presence of circulating anticoagulants was also inferred from the thromboplastin generation test (Dacie and Lewis, 1963). Haematocrit values were determined by the method of Wintrobe (1933).

Results

The means, the standard deviation of the means, differences of means, standard deviation of the differences of means, the results of 't' test for clot lysis time and blood coagula-

SD of differences of means			*'t' value*		
Sea-level controls versus high altitude controls	*Sea-level controls versus patients*	*High altitude controls versus patients*	*Sea-level controls versus high altitude controls**	*Sea-level controls versus patients†*	*High altitude controls versus patients‡*
0·84	1·00	1·30	7·53‖	6·54‖	0·19
18·98	20·81	29·05	2·03§	0·73	0·80
2·14	2·60	3·34	0·62	4·50‖	3·90‖
6·35	7·88	10·41	1·76	3·85‖	3·99‖
1·81	1·31	3·11	0·23	0·79	0·47
38·74	43·46	20·31	5·58	3·11‖	3·99‖
0·49	1·02	0·43	6·18‖	3·44‖	1·12
6·34	4·41	10·23	0·54	5·93‖	2·22§
9·69	7·76	15·53	0·42	5·55‖	2·51§
8·16	8·97	13·25	1·70	0·37	0·79
4·99	7·30	9·59	6·83‖	2·52§	1·64
0·27	0·30	0·41	2·15§	0·13	1·53
−0·36	0·51	0·55	0·77	0·63	1·08
0·45	0·56	0·72	2·25§	0·18	1·55
0·50	0·65	0·87	5·32‖	5·74‖	1·23
0·61	0·63	1·06	3·81‖	3·19‖	0·30
13·63	26·99	22·88	3·20‖	0·82	0·94
0·55	0·36	0·89	7·35‖	11·45‖	0·06

tion studies in 16 sea-level controls, 32 high altitude controls, and 6 patients who developed pulmonary hypertension at high altitude are given in Table 1. For ready reference, these results are summarized in Table 2.

The differences of means, standard deviation of differences of means, and the results of 't' tests for clot lysis time and blood coagulation studies in 6 patients who developed pulmonary hypertension at high altitude, before evacuation, and after 1, 3, and 5 weeks of evacuation to sea-level are given in Table 3.

Findings at high altitude (a) *Thirty-two high altitude controls* In comparison with sea-level controls, the haematocrit, platelet count, plasma fibrinogen, bleeding time, clotting time in silicon tube, prothrombin time, stypven time, calcium time, and thrombin clotting time were significantly increased. Factor V, factor VIII, and clotting time in glass tube were also increased but the increase was not significant. Clot lysis time and thrombotest activity were significantly decreased. Platelet adhesiveness, platelet factor 3, clot retraction, and factor XII were also decreased, but the decrease was not significant.

TABLE 2 *Changes in clot lysis time and blood coagulation factors at high altitude in 32 high-altitude controls and 6 patients as compared with sea-level controls*

Serial No.	*Factors*	*Changes at high altitude*	
		32 high altitude controls	*6 patients*
1	Haematocrit	Increased*	Increased*
2	Platelet count	Increased†	Increased NS
3	Platelet adhesiveness	Decreased NS	Increased*
4	Platelet factor 3	Decreased NS	Increased*
5	Clot retraction	Decreased NS	Decreased NS
6	Plasma fibrinogen	Increased*	Increased*
7	Clot lysis time	Decreased*	Decreased*
8	Factor V	Increased NS	Increased*
9	Factor VIII	Increased NS	Increased*
10	Factor XII	Decreased NS	Decreased NS
11	Thrombotest activity	Decreased*	Decreased†
12	Bleeding time	Increased†	Decreased NS
13	Clotting time in glass tube	Increased NS	Decreased NS
14	Clotting time in silicon tube	Increased†	Decreased NS
15	Prothrombin time	Increased*	Increased*
16	Stypven time	Increased*	Increased*
17	Calcium time	Increased*	Increased NS
18	Thrombin clotting time	Increased*	Increased*

* Significant at 1 per cent level.
† Significant at 5 per cent level.
NS Not significant.

TABLE 3 *Differences of means, standard deviation of differences of means, and results of 't' test for clot lysis time and blood coagulation studies in respect of 6 patients who developed pulmonary hypertension at high altitude, before evacuation and after 1, 3, and 5 weeks of evacuation to sea-level*

Serial No.	*Factors*	*Differences of means*			*SD of difference of means*		
		At high altitude versus after 1 wk of evacuation to sea-level	*After 1 wk of evacuation versus after 3 wk of evacuation to sea-level*	*After 3 wk of evacuation versus after 5 wk of evacuation to sea-level*	*At high altitude versus after 1 wk of evacuation to sea-level*	*After 1 wk of evacuation versus after 3 wk of evacuation to sea-level*	*After 3 wk of evacuation versus after 5 wk of evacuation to sea-level*
1	Haematocrit (%)	5·20	1·60	0·40	1·94	1·62	0·80
2	Platelet count (thousands/mm³)	18·20	−74·00	−42·00	54·77	98·20	114·96
3	Platelet adhesiveness (%)	9·22	2·04	2·08	3·62	5·18	4·77
4	Platelet factor 3 (%)	4·40	−1·20	13·80	19·53	13·45	12·04
5	Clot retraction (%)	2·44	−4·00	0·96	6·39	5·22	6·49
6	Plasma fibrinogen (mg/100 ml)	−113·20	145·20	−21·20	155·63	47·37	57·08
7	Clot lysis time (hr)	−2·91	−0·56	0·83	1·50	1·21	0·89
8	Factor V (%)	12·00	15·60	0·50	15·01	21·77	7·85
9	Factor VIII (%)	16·90	37·50	3·70	44·42	36·40	12·81
10	Factor XII (%)	15·40	−30·40	12·40	32·71	13·99	12·03
11	Thrombotest activity (%)	5·00	−26·40	—	36·25	21·28	—
12	Bleeding time (min)	−0·47	0·38	0·28	1·15	1·38	0·63
13	Clotting time in glass tube (min)	−1·09	0·18	0·66	1·97	1·36	0·52
14	Clotting time in silicon tube (min)	−1·13	0·72	0·47	1·34	1·23	1·59
15	Prothrombin time (sec)	1·30	1·20	0·60	2·20	0·81	1·11
16	Stypven time (sec)	0·90	0·10	0·20	1·11	1·02	0·60
17	Calcium time (sec)	−19·60	40·20	12·00	42·85	25·60	11·83
18	Thrombin clotting time (sec)	3·86	−0·26	0·90	1·43	1·13	0·73

* Significant at 1% level (t 4 = 4·60) Table value.
† Significant at 5% level (t 4 = 2·78) Table value.

(b) *Six patients* In comparison with sea-level controls, the haematocrit, platelet adhesiveness, platelet factor 3, plasma fibrinogen, factor V, factor VIII, prothrombin time, stypven time, and thrombin clotting time were significantly increased. The platelet count and calcium time were also increased, but the increase was not significant. Clot lysis time and thrombotest activity were significantly decreased. Clot retraction, bleeding time, clotting time in glass tube, clotting time in silicon tube, and factor XII were also decreased, but the decrease was not significant.

(c) *Difference between high altitude controls and patients* Platelet adhesiveness and platelet factor 3 were decreased in controls but the decrease was not significant; both platelet adhesiveness and platelet factor 3 were significantly increased in patients. Factor V and factor VIII were increased in controls but the increase was not significant; both factor V and factor VIII were significantly increased in patients. Plasma fibrinogen was significantly increased in patients. Plasma fibrinogen was significantly increased in controls as well as in patients; it was however significantly lower in patients than in controls. Thrombotest activity was significantly decreased in both controls and patients, but the decrease was less significant in patients. The bleeding time and clotting time in silicon tube were significantly increased in controls but decreased in patients, though the decrease was not significant. The clotting time in glass tube was increased in controls and decreased in patients but these changes were not significant. The calcium time was significantly increased in controls but not significantly increased in patients.

Non-specific changes were observed in the thromboplastin generation test in 5 out of 32 high altitude controls. In 2, the abnormality was in plasma and in the remaining 3 the abnormality was in platelets. By comparison, only 1 out of 6 patients showed abnormality in platelets only.

As assessed by the thromboplastin generation test, factor X was deficient in 17 out of 32 high altitude controls and in 3 out of 6 patients.

Factor VII was deficient in 7 of 32 controls as compared to 3 of 6 patients.

Circulating anticoagulants were present in only 9 out of 32 controls but in all the 6 patients.

Findings after evacuation of patients to sea-level The haematocrit, platelet adhesiveness, clot lysis time, factor V, factor VIII, stypven time, thrombin clotting time, and thromboplastin generation test returned to normal within the first week, and platelet factor 3, plasma fibrinogen, thrombotest activity, prothrombin time, and calcium time returned to normal within one to three weeks of arrival at sea-level. Factor XII, however, showed an increase within one to three weeks of arrival and the difference in the means at high altitude and after arrival at sea-level is significant at the 5 per cent level. One out of 3 patients who had deficiency of factor VII at high altitude continued to show the deficiency after 5 weeks of arrival at sea-level. Circulating anticoagulants disappeared within the first week of arrival at sea-level in 5 out of 6 patients. In the remaining patient the circulating anticoagulants disappeared within one to three weeks.

't' value		
At high altitude versus after 1 wk of evacuation to sea-level	*After 1 wk of evacuation versus after 3 wk of evacuation to sea-level*	*After 3 wk of evacuation versus after 5 wk of evacuation to sea-level*
5·36*	1·97	1·00
0·66	1·51	0·73
5·10*	0·79	0·87
0·45	0·18	2·29
0·76	1·53	0·30
1·45	6·13*	0·74
3·89†	0·93	1·87
1·60	1·43	0·13
0·76	2·06	0·58
0·94	4·34†	2·06
0·28	2·48	—
0·82	0·55	0·89
1·11	0·26	2·55
1·69	1·18	0·59
1·18	2·95†	1·08
1·62	0·20	0·67
0·91	3·14†	2·03
5·38*	0·46	2·45

Discussion

In Table 1 it will be seen that increased plasma fibrinogen levels associated with decreased clot lysis time at high altitude are common to residents with pulmonary hypertension and without pulmonary hypertension. Apparently

both changes are induced by hypoxic stress. The relative inadequacy of factor XII at high altitude, as indicated by its rise on return to sea-level, suggests that though blood fibrinolytic activity is increased at high altitude, it is short of requirement. However, in residents without pulmonary hypertension, the plasma fibrinogen levels are higher than in residents with pulmonary hypertension. In the absence of a significant difference in the blood fibrinolytic activity both in residents with pulmonary hypertension and without pulmonary hypertension, it appears that the higher plasma fibrinogen levels in residents without pulmonary hypertension may result from fibrinogen sparing, whereas in residents with pulmonary hypertension fibrinogen is constantly being depleted by its conversion into fibrin, as is evident in necropsy findings.

The comparatively higher plasma fibrinogen levels in residents without pulmonary hypertension suggest that increased plasma fibrinogen levels at high altitude *per se* do not predispose to the formation of pulmonary thrombi which result in pulmonary hypertension. The conversion of fibrinogen into fibrin in high altitude residents with pulmonary hypertension appears to be facilitated by increased platelet adhesiveness in the presence of factor V and factor VIII. The coincidental increase of platelet factor 3 with increased platelet adhesiveness suggests that increased platelet adhesiveness is associated with increased platelet aggregation. Since platelet factor 3 is a property of the platelet membrane (Marcus *et al.*, 1966), the membrane change associated with platelet aggregation seems to provide an active catalytic surface for the interaction of plasma coagulation factors which lead to thrombin formation followed by consolidation of the platelet plug, degranulation of the platelets, further release of platelet factor 3, and more fibrin formation (Hardisty and Hutton, 1966). The coagulation process is therefore self-perpetuating. However, what initiates an increase of platelet adhesiveness, factor V and factor VIII, and more so, the local defibrination of blood in high altitude residents with pulmonary hypertension, is not clear. Platelet adhesiveness may be based on rapid lipid mobilization at high altitude. Whitten and Janoski (1969) reported an increase in the serum free fatty acid on the day of arrival at 14,100 feet, which remained high throughout 9 days of exposure. Serum triglycerides were significantly higher on days 6, 7, 8, and 9 though the total cholesterol and serum phosphorus remained unchanged. The percentage of linoleic acid was decreased and the percentage of plamitic and oleic acids was increased in the serum free fatty acid fraction as well as the triglyceride fraction. The possibility that local defibrination may be associated with decreased inactivation of serotonin and increased release of catecholamines locally in the lungs on exposure to high altitude hypoxia needs consideration. It is interesting, however, that thrombus formation and inflammatory arteritis seen in necropsy specimens from cases of high altitude pulmonary hypertension (Singh *et al.*, 1965) can also be produced in calves aged 2 to 4 months living at 11,000 feet by daily intravenous injections of 100 μg ADP for 1 to 4 weeks (Reeves *et al.*, 1968). Whether ADP plays any part in the development of high altitude pulmonary hypertension is uncertain. As erythrocytes and platelets are increased at high altitude, there is a possibility that in the presence of a turbulent right heart blood flow, ADP is continuously released in the pulmonary circulation and causes pulmonary hypertension. To verify to what extent this may actually be the case, we have done preliminary estimations of ADP in the right ventricular blood and in the femoral blood in 12 high altitude controls and in 5 patients with high altitude pulmonary hypertension. The results are equivocal. High altitude controls have higher ADP concentration in femoral blood than in right ventricular blood, whereas in patients with pulmonary hypertension the ADP concentration in femoral blood is either the same as in the right ventricular blood or lower. However, the ADP concentration in the right ventricular blood is higher in high altitude controls than in patients with pulmonary hypertension. It thus seems probable that in high altitude controls blood from the right ventricle is replenished with, but not deprived of, ADP, whereas in patients with pulmonary hypertension blood from the right ventricle is replenished with, but deprived of, its ADP content during its passage through the lungs.

The prolongation of one-stage prothrombin time and thrombin clotting time which occurred in high altitude residents with pulmonary hypertension and without pulmonary hypertension is known to be associated with fibrinogen breakdown products (Fletcher *et al.*, 1959). It is presumptive that platelet adhesiveness (Wilson, McNicol, and Douglas, 1968), the effect of circulating anticoagulants, reduction of thrombotest activity, and increased stypven time which also occurred in high altitude residents with pulmonary hypertension and without pulmonary hypertension *pari passu* with increased blood fibrinolytic activity may also have been the result of release of fibrinogen breakdown products in

the systemic circulation. However, the reduction of thrombotest activity and increased stypven time probably had relevance to a deficiency of factor VII and factor X, and factor X, respectively.

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