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Adverse Changes in Fibrinolysis, Blood Coagulation and Platelet Function in High Altitude Pulmonary Oedema and their Role in its Pathogenesis

by

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INTRODUCTION

In high-altitude pulmonary oedema evidence has been previously brought forward (Nayak, Roy and Narayanan, 1964; Singh et al., 1965a) of widespread sludging of RBCs and formation of thrombi within the alveolar capillaries, venules and some branches of the pulmonary arteries in the lungs, the glomerular and the peritubular arteries in the kidneys, the sinusoids of the liver, and the intestinal blood vessels. Investigations involving fibrinolytic activity, blood coagulation factors and platelet function which were undertaken to elucidate the possible causal connections have shown that fibrinolytic activity is reduced, plasma fibrinogen and factors V, VIII and X are increased, factor XII is decreased, and platelet adhesiveness and platelet factor 3 are increased. It seems that intravascular sludging of RBCs and formation of thrombi possibly result from these changes. Details are described and discussed.

MATERIALS AND METHODS

The subjects were 32 Indian soldiers. All were normally residents of plains. Eight soldiers who developed high-altitude pulmonary oedema on the first day when airlifted to 3,692 m served as patients; another 8 who had not developed high-altitude pulmonary oedema when airlifted to the same location under similar circumstances served as high-altitude controls: 16 soldiers stationed throughout at sea level served as sea level controls. Blood coagulation studies were done in 16 sea level controls at sea level. Comparative studies were done in 8 high-altitude controls, who had not received oxygen or any other form of treatment, on days 1, 3, 7 and 14 of arrival at high altitude to allow the study to cover the period during which new arrivals are most likely to develop high-altitude pulmonary oedema, and in 8 patients on first day of arrival before any treatment was given and repeated on days 3, 7 and 14 after treatment with oxygen, morphine and Frusemide (Singh, 1967).

The methodology involved was as has been described previously (Singh and Chohan, 1972a).

RESULTS

Differences and their significance obtained from comparison of the means, standard deviation of means, and the results of t test for haematocrit, fibrinolytic activity, blood coagulation factors and platelet function in 16 sea level controls and 8 high-altitude controls on days 1, 3, 7 and 14 of arrival at high altitude are given in Table 1.

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TABLE 1. Numerical data and their significance obtained from comparison of the means, standard deviation of means and the results of t test for haematocrit, fibrinolytic activity, blood coagulation factors and platelet functions in 16 sea-level controls and 8 high-altitude controls on days 1, 3, 7 and 14 of arrival at high altitude

Systems/Factors	Sea level controls		High-altitude controls								t value* High-altitude controls versus sea level controls			
			Day 1		Day 3		Day 7		Day 14		Day 1	Day 3	Day 7	Day 14
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Haematocrit	45.3	2.03	45.2	3.45	47.7	5.12	46.9	3.83	48.9	2.10	0.05	1.68	1.34	4.02**
Fibrinolytic activity														
Clot lysis time (hr)	5.5	2.41	1.9	0.55	2.1	0.61	2.5	1.28	2.5	1.31	4.14**	3.91**	3.25**	3.29**
Plasma fibrinogen (mg %)	335.0	71.00	308.2	44.96	333.4	28.23	335.9	64.28	340.5	74.91	0.97	0.06	0.03	0.18
Thrombin clotting time (sec)	9.7	0.75	11.2	1.41	10.6	1.43	10.6	1.06	11.3	1.02	3.39**	2.14*	2.36*	4.34**
Blood coagulation factors														
Factor V (%)	108.0	8.95	110.6	19.22	87.1	14.67	115.7	28.99	108.1	15.51	0.45	4.34**	1.00	0.26
Factor VIII (%)	96.6	15.74	48.1	15.00	98.7	31.56	162.8	31.56	164.1	35.10	7.22**	0.22	6.94**	6.39**
Factor X (%)	101.0	4.50	112.9	13.34	97.6	12.95	111.2	15.41	97.4	10.86	3.29**	0.95	2.50*	0.37
Factor XII (%)	92.7	16.14	122.7	11.40	115.6	15.02	120.4	11.21	122.0	17.03	4.69**	3.35**	4.33**	4.19**
Thrombotest activity (%)	74.7	23.30	119.7	24.62	87.2	26.55	99.6	25.23	106.2	10.93	4.38**	1.19	2.41*	3.61**
Bleeding time (min)	2.9	0.67	2.6	1.07	2.3	0.53	2.5	0.67	2.5	0.72	0.89	2.27*	1.49	1.55
Clotting time in glass (min)	4.8	1.03	4.2	0.98	4.5	0.73	3.3	0.94	4.6	1.48	1.52	0.34	3.62**	0.54
Clotting time in silicone (min)	8.3	1.05	7.2	1.86	8.7	1.33	6.9	1.16	7.8	2.05	1.90	0.68	3.04**	0.90
Prothrombin time (sec)	13.5	0.81	12.2	1.89	13.1	1.47	12.0	0.63	13.6	1.82	2.32*	0.96	4.64**	0.19
Stypven time (sec)	13.5	0.68	12.9	3.56	12.2	1.88	11.5	1.98	12.2	1.92	0.63	2.42*	3.61**	2.49*
Calcium time (sec)	103.0	8.78	108.2	41.77	98.9	34.42	96.1	30.20	93.2	21.45	0.51	0.46	0.82	1.63
Platelet functions														
Platelet count ($10^3/mm^3$)	271.3	45.10	356.9	66.76	373.7	54.50	375.7	47.42	392.5	61.18	3.77**	5.76**	5.26**	5.51**
Platelet adhesiveness (%)	35.6	5.17	33.8	5.55	37.7	6.62	33.9	7.38	35.9	3.24	0.77	0.69	1.05	0.14
Platelet factor 3 (%)	86.7	13.57	93.1	9.86	90.9	16.51	118.5	13.23	107.9	19.11	1.19	0.66	5.04**	3.15**
Clot retraction (%)	55.3	0.37	48.9	3.34	53.3	6.12	53.3	3.49	55.5	6.87	7.73**	1.34	2.37*	0.10

t value at $p < 0.05$ t value at $p < 0.01$

* degree of freedom 22 2.074 2.819 *) $p < 0.05$ **) $p < 0.01$

TABLE 2. Numerical data and their significance obtained from comparison of the means, standard deviation of means, and the results of t test for haematocrit, fibrinolytic activity, blood coagulation factors and platelet functions in 8 high-altitude controls and 8 patients on days 1, 3, 7 and 14 of arrival at high altitude

Systems/Factors	High-altitude controls								Patients								t values* Patients versus high-altitude controls			
	Day 1		Day 3		Day 7		Day 14		Day 1		Day 3		Day 7		Day 14					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Day 1	Day 3	Day 7	Day 14
Haematocrit	45.2	3.45	47.7	5.12	46.9	3.83	48.9	2.10	48.5	3.02	48.5	5.13	48.6	4.08	45.4	3.24	1.84	0.27	0.83	2.56*
Fibrinolytic activity																				
Clot lysis time (hr)	1.9	0.55	2.1	0.61	2.5	1.28	2.5	1.31	6.5	1.07	2.4	0.97	3.2	1.35	2.8	1.26	10.58**	0.62	0.99	0.53
Plasma fibrinogen (mg %)	308.2	44.96	333.4	28.23	335.9	64.28	340.5	74.91	599.7	57.26	395.8	70.96	425.7	88.06	363.2	50.13	10.71**	2.28*	2.28*	2.26*
Thrombin clotting time (sec)	11.2	1.41	10.6	1.43	10.6	1.06	11.3	1.02	10.2	0.82	11.3	1.04	11.1	1.46	11.7	0.87	1.58	0.96	0.75	0.77
Blood coagulation factors																				
Factor V (%)	110.6	19.22	87.1	14.67	115.7	28.99	108.1	15.51	130.2	14.32	89.3	20.69	88.1	19.33	76.7	14.92	2.09	0.23	2.13	4.12**
Factor VIII (%)	48.1	15.00	98.7	31.56	162.8	31.56	164.1	35.10	211.9	58.74	165.8	49.34	160.7	49.45	109.4	44.47	7.66**	3.11**	0.10	2.72*
Factor X (%)	112.9	13.34	97.6	12.95	111.2	15.41	97.4	10.86	120.3	7.34	95.3	14.08	111.9	6.79	92.6	8.93	1.22	0.32	1.47	0.96
Factor XII (%)	122.7	11.40	115.6	15.02	120.4	11.21	122.0	12.03	94.4	11.83	108.7	12.16	96.9	30.44	109.6	14.74	4.53**	0.93	2.04	1.55
Thrombotest activity (%)	119.7	24.62	87.2	26.55	99.6	25.23	106.2	10.93	108.3	14.45	67.3	27.82	82.4	28.94	93.2	17.19	1.01	1.36	1.23	1.81
Bleeding time (min)	2.6	1.07	2.3	0.53	2.5	0.67	2.5	0.72	2.8	0.41	2.8	0.62	3.5	1.47	3.4	1.17	0.41	1.63	1.66	1.90
Clotting time in glass (min)	4.2	0.98	4.5	0.73	3.3	0.94	4.6	1.48	5.0	0.52	4.6	0.84	4.5	0.67	4.5	1.11	1.80	1.02	2.88*	0.05
Clotting time in silicone (min)	7.2	1.86	8.6	1.33	6.9	1.16	7.8	2.05	8.7	1.27	10.0	3.91	8.7	1.50	7.3	1.25	1.69	0.92	2.61*	0.51
Prothrombin time (sec)	12.2	1.89	13.1	1.47	12.0	0.63	13.6	1.82	13.0	0.93	14.2	1.45	14.4	1.35	15.0	2.28	0.93	1.37	4.45**	1.35
Stypven time (sec)	12.9	3.56	12.2	1.88	11.5	1.98	12.2	1.92	14.8	2.16	12.8	3.14	12.9	2.43	11.8	2.94	1.16	0.46	1.23	0.28
Calcium time (sec)	108.2	41.77	98.9	34.42	96.1	30.20	93.2	21.45	120.2	27.47	108.2	13.76	118.3	40.62	99.2	14.72	0.67	0.62	1.21	0.66
Platelet functions																				
Platelet count ($10^3/mm^3$)	356.9	66.76	373.7	54.50	375.7	47.42	393.5	61.18	318.2	54.38	415.8	115.21	299.6	89.40	346.7	99.68	1.15	0.91	2.10	1.11
Platelet adhesiveness (%)	33.8	5.55	37.7	6.62	33.9	7.38	35.9	3.24	51.9	4.76	33.2	4.84	33.8	6.37	31.6	6.79	6.40**	1.28	0.25	1.61
Platelet factor 3 (%)	93.1	9.86	90.9	16.51	118.5	13.23	107.9	19.11	114.2	10.69	90.8	5.04	80.3	10.93	84.0	17.61	3.81**	1.01	6.04**	2.64*
Clot retraction (%)	48.9	3.34	53.3	6.12	53.3	3.49	55.5	6.87	44.2	4.46	49.1	4.26	50.8	5.54	52.7	4.48	2.25*	1.44	0.94	0.92

t value at $p < 0.05$ t value at $p < 0.01$

* degree of freedom 14 2.145 2.977 *) $p < 0.05$ **) $p < 0.01$

TABLE 3. Numerical data and their significance obtained from comparison of the means, standard deviation of means and the results of t test for haematocrit, fibrinolytic activity, blood coagulation factors and platelet functions in 16 sea-level controls and 8 patients on days 1, 3, 7 and 14 of arrival at high altitude

Systems/Factors	Sea level controls		Patients								t values* Patients versus sea level controls			
			Day 1		Day 3		Day 7		Day 14		Day 1	Day 3	Day 7	Day 14
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD				
Haematocrit	45.3	2.03	48.5	3.02	48.5	5.13	48.6	4.08	45.4	3.25	2.88**	2.21*	8.38**	0.07
Fibrinolytic activity														
Clot lysis time (hr)	5.5	2.41	6.5	1.07	2.4	0.97	3.2	1.35	2.8	1.26	0.92	3.53**	2.52*	2.92**
Plasma fibrinogen (mg %)	335.0	71.00	599.7	57.26	395.8	70.96	425.7	88.06	363.2	50.13	6.92**	1.98	2.73*	1.00
Thrombin clotting time (sec)	9.7	0.75	10.2	0.82	11.3	1.04	11.1	1.46	11.7	0.87	1.24	4.35**	3.04**	5.76**
Blood coagulation factors														
Factor V (%)	108.0	8.95	130.2	14.32	89.3	20.69	88.1	19.33	76.7	14.92	4.39**	3.12**	3.48**	6.44**
Factor VIII (%)	96.6	15.74	211.9	58.74	165.8	49.34	160.7	49.45	109.4	44.47	7.43**	5.20**	4.81**	1.04
Factor X (%)	101.0	4.50	120.3	7.34	95.3	14.08	101.9	6.79	92.6	8.93	7.55**	1.49	0.40	3.09**
Factor XII (%)	92.7	16.14	94.4	11.83	108.7	12.16	96.9	30.44	109.6	14.74	0.24	2.46*	0.44	2.49*
Thrombotest activity (%)	74.7	23.30	108.3	14.45	67.3	27.82	82.4	28.94	93.2	17.19	3.28**	0.69	0.71	1.99
Bleeding time (min)	2.9	0.67	2.8	0.41	2.8	0.62	3.5	1.47	3.4	1.17	0.41	0.48	1.23	1.32
Clotting time in glass (min)	4.8	1.03	5.0	0.52	4.6	0.84	4.5	0.67	4.5	1.11	0.27	0.69	0.80	0.67
Clotting time in silicone (min)	8.3	1.05	8.7	1.27	10.0	3.91	8.7	1.50	7.3	1.25	0.72	1.68	0.71	2.08*
Prothrombin time (sec)	13.5	0.81	13.0	0.93	14.2	1.45	14.4	1.35	15.0	2.28	1.23	1.39	1.89	2.37*
Stypven time (sec)	13.5	0.68	14.8	2.16	12.8	3.14	12.9	2.43	11.8	2.94	2.32*	0.81	0.86	2.20*
Calcium time (sec)	103.0	8.78	120.2	27.47	108.2	13.76	118.3	40.62	99.2	14.72	2.29*	1.12	1.47	0.79
Platelet functions														
Platelet count ($10^3/mm^3$)	271.3	45.10	318.2	54.38	415.8	115.21	299.6	89.40	346.7	99.68	2.06	4.46**	1.04	2.58*
Platelet adhesiveness (%)	35.6	5.17	51.9	4.76	33.2	4.84	33.8	6.37	31.6	6.79	6.72**	1.10	0.74	1.61
Platelet factor 3 (%)	86.7	13.57	114.2	10.69	90.8	5.04	80.3	10.93	85.0	17.61	9.30**	0.83	1.16	0.42
Clot retraction (%)	55.3	0.37	44.2	4.46	44.1	4.26	50.8	5.54	52.7	4.48	10.28**	5.93**	3.29**	2.33*

t value at $p < 0.05$ t value at $p < 0.01$

* degree of freedom 22 2.074 2.819 *) $p < 0.05$ **) $p < 0.01$

Table 2 compares these differences in 8 high-altitude controls and 8 patients, and Table 3 in sea level controls and 8 patients.

On arrival at high altitude, in high-altitude controls, there was significant increase in Factor X, Factor XII and thrombotest activity, and significant decrease in prothrombin time. In support, the bleeding time, clotting time in glass and silicone and stypven time showed a trend towards decrease which however was not significant. These changes were associated with a significant decrease in clot lysis time with prolongation of thrombin clotting time and factor VIII, and somewhat belatedly in factor V on the third day. Subsequently, factor VIII started increasing on the third day and the increase was significant on the seventh and fourteenth days. Factor V also showed an increase on the seventh and fourteenth days but the increase was not significant. Factor X fluctuated with insignificant decrease on third and fourteenth days and significant increase on the seventh day. Factor XII remained significantly increased throughout. Thrombotest activity fluctuated with insignificant increase on the third day and significant increase persisting on the seventh and the fourteenth days. The decrease in bleeding time was significant on the third day, in clotting time in glass and silicone on the seventh day and in stypven time on the third, seventh and the fourteenth days. Prothrombin time fluctuated with insignificant decrease on the third day, significant decrease on the seventh day and insignificant increase on the fourteenth day. No significant change was found in calcium time throughout. No abnormality in factor VII was detected on day 1, 3, 7 and 14. Abnormality in plasma was detected in 3, 2 and 1 out of 8 high-altitude controls on first, third and seventh day respectively but not found in any of these on day 14. Circulating anticoagulants were present in 3 out of 8 high-altitude controls on first, third and seventh days but in none on the fourteenth day. Expressed on the basis of a numerical score, 0 for no change, 1 for an insignificant change, 2 for change significant at 5% level, and 3 for change significant at 1% level, the net coagulation state as obtained from the difference of the total score of factors indicating increase in coagulation minus the total score of factors indicating decrease in coagulation was +11 on the first day, +9 on the third day, +28 on day 7 and +17 on day 14.

The main differences in the coagulation state in patients and high-altitude controls on the first day were significant increase in clot lysis time, plasma fibrinogen and factor VIII, insignificant increase in factor V and factor X, and significant decrease in factor XII. Abnormality in factor VII, in plasma, and in circulating anticoagulants was conspicuous by its absence. On the basis of a similar numerical score as used in case of high-altitude controls (vide supra) the net coagulation state in patients was +10 on the first day (before treatment), and -2 on the third day, -15 on day 7 and -11 on day 14 (after treatment). While the plus score on day 1 indicates the severity of abnormality in the blood coagulation state in patients in comparison with the high-altitude controls, the negative scores in patients on days 3, 7 and 14 may be taken as a measure of recovery. Thus, between patients and sea-level controls the numerical scores were +25 on day 1, +3 on day 3, +2 on day 7 and -2 on day 14.

Hitherto there has been some evidence to suggest that altitude exposure may alter blood coagulation (Garvey, Dennis and Conrad, 1958; Grover and Alexander, 1970; Hurtado, 1932; Kemp, 1902; Kingma and De Langen, 1955). More convincing evidence of a hypercoagulable state developing in calves on exposure to high altitude has been recently brought forward by Genton et al. (1970) with turnover studies of platelets and fibrinogen in conjunction with coagulation tests. In our experience with troops stationed between 3,692 and 5,538 m in the Himalayas, clinical manifestations indicating that an abnormal state of blood coagulation may develop at high altitude have been venous thrombosis involving the peripheral and splenic veins, and arterial thrombosis involving the coronary, cerebral and mesenteric arteries. More obtrusive, but seen in necropsy studies, was evidence also of an abnormal state of blood coagulation in high-altitude pulmonary oedema

(Singh et al., 1965a) and in high-altitude pulmonary hypertension (Singh et al., 1965b). In high-altitude pulmonary oedema, the abnormal state of blood coagulation occurs within the first few days of arrival at high altitude. Manifestations of venous thrombosis, arterial thrombosis and pulmonary hypertension are usually delayed and may occur weeks or months after arrival at high altitude. In some cases of high-altitude pulmonary oedema the concurrent pulmonary hypertension may continue to persist without a break (Singh et al., 1965b). Abnormalities in blood coagulation found in high-altitude pulmonary hypertension have been described elsewhere (Singh and Chohan, 1972b).

What initiates the blood coagulation changes on arrival at high altitude is not clear. During the first few days of arrival the total blood volume and the haematocrit are not significantly altered (Singh et al., 1969) and the total protein concentration and the percentage distribution of albumin, alpha-1, beta and gamma globulins remains uninfluenced. Hence the increase in plasma fibrinogen and the coagulation factors is probably the result of abnormal synthesis. The differences between the high-altitude controls and patients are probably determined by the difference in severity of hypoxia in the two groups.

In high-altitude controls the platelet count increased significantly on the first day and this increase persisted on the third, seventh and the fourteenth days. There was no significant change in platelet adhesiveness throughout. Platelet factor 3 showed an insignificant increase on the first and third days, significant increase on the seventh day which persisted on the fourteenth day. Clot retraction was significantly decreased on the first day, fluctuated with insignificant decrease on the third day, significant decrease on the seventh day and insignificant increase on day 14. The cause of decreased clot retraction during the first week is not obvious. During this period the haematrocit and plasma fibrinogen showed no significant changes. Therefore, there is a possibility that decrease in clot retraction may have been related to alterations in the platelet surface in spite of increase in their numbers. In patients, it has been found that decreased clot retraction is associated with decreased electrophoretic mobility of platelets; we have not done this study in controls.

In comparison with high-altitude controls, on the first day, the patients showed a numerical decrease in platelet count, a significant increase in platelet adhesiveness and platelet factor 3. It thus seems platelet aggregation is increased and intravascular clotting is favoured in patients at the onset of the disease. Decreased fibrinolytic activity would itself be associated with increased platelet adhesiveness (Poplawski, Skorulska and Niewiarowski, 1968; Prokopowicz et al., 1967). There was a significant decrease in clot retraction. As there was no significant difference in platelet numbers in high-altitude controls and patients, the significant decrease in clot retraction in patients may have been associated with higher plasma fibrinogen levels in them.

Several factors seem to be involved in the alteration of platelet adhesiveness, aggregation and mobility. Platelet adhesiveness may be based on rapid lipid mobilisation (Haslam, 1964; Hoak, Warner and Connor, 1967; Shore and Alpers, 1963; Whitten and Janoski, 1969) and increased sympathetic activity (Cunningham, Becker and Kreuzer, 1965; Mitchell and Sharp, 1964; O'Brien, 1963; Pace, Griswold and Grunbaum, 1964; Surks, Beckwitt and Chidsey, 1967) on arrival at high altitude. Possibly in some cases epinephrine is inactivated by hypoxia before its full action takes place or that hypoxic tissues are less sensitive to epinephrine (Surtshin, Rodbard and Katz, 1948; Van Loo, Surtshin and Katz, 1948). When such inactivation does not occur platelet cyclic 3'-5'-adenosine monophosphate may be diminished (Salzman and Levine, 1971; Sutherland, 1965) and platelet aggregation may be promoted. Local defibrination and platelet aggregation (Born,

1968; Salzman and Neri, 1969) may be associated with increased release of catecholamines and decreased inactivation of serotonin in the lungs.

The electrophoretic mobility of platelets in plasma and of washed platelets was decreased in patients as compared with sea level controls. The corresponding plasma fibrinogen levels were increased in patients as compared with sea level controls (Table 4).

TABLE 4. Electrophoretic mobility of platelets and plasma fibrinogen levels of patients in comparison with sea level controls

	Platelets in plasma	Washed platelets	Plasma fibrinogen
	μ/(sec. V. cm)		(mg/100 ml)
Sea level controls	0.882 ± 0.045	0.891 ± 0.045	325.2 ± 48.3
Patients	0.635 ± 0.044	0.779 ± 0.03	619.6 ± 55.3
Significance of difference	< 0.001	<0.01	< 0.001

With increasing concentrations of plasma fibrinogen the electrophoretic mobility decreased in both patients and controls. Reduction in the electrophoretic mobility of platelets in patients therefore seems to be related to increased plasma fibrinogen levels. However, in both patients and controls the electrophoretic mobility is perhaps optimal when the plasma fibrinogen level is 300 mg/100 ml. Whether there is any relationship of reduced electrophoretic mobility of platelets with increased plasma coagulation factors remains to be determined. Since factor XII is a sialo-glyco protein (Schoenmakers et al., 1965) and is easily adsorbed on the platelet surface (Iatridis and Ferguson, 1965) it can alter the charge on the platelet membrane. As factor XII is diminished in high-altitude pulmonary oedema (vide supra) diminished platelet mobility could be the result.

Immunoglobulin levels of IgG, IgA and IgM were raised in high-altitude controls as compared with sea level controls and in patients as compared with high-altitude controls (Table 5).

TABLE 5. Comparative immunoglobulin levels of high-altitude controls versus sea level controls and patients versus high-altitude controls

	IgG (mg/100 ml)	IgA (mg/100 ml)	IgM (mg/100 ml)
High-altitude controls	4285.0 ± 139.7	369.0 ± 74.4	207.0 ± 65.4
Sea level controls	1139.0 ± 253.9	204.8 ± 48.6	156.3 ± 50.4
Significance of difference	0.01	0.01	0.05
Patients	6975.0 ± 1014.0	754.0 ± 240.0	689.0 ± 247.0
High-altitude controls	4285.0 ± 139.7	369.0 ± 74.4	207.0 ± 65.4
Significance of difference	0.01	0.01	0.01

It is possible that on account of their increased levels, IgG and IgM get adsorbed on to the platelet surface, alter their mobility and increase aggregation (de Gaetano, Vermylen and Verstraete, 1970a). IgG is also known to promote release of ADP (de Gaetano, Vermylen and Verstraete, 1970b) which in turn can release platelet factor 3 (Hardisty, 1968; Horowitz and Papayoanou, 1968; Mustard and Packham, 1968).

In high-altitude controls the ADP levels were higher in arterial blood than in venous blood. In patients both arterial and venous blood ADP levels were decreased (Table 6).

TABLE 6. Showing the means, standard deviation of means, difference of means, and t values of ADP levels in arterial and venous blood in high-altitude controls and patients

	ADP levels mg/100 ml blood				Difference of means	t value(*
	High-altitude controls		Patients			
	Mean	SD	Mean	SD		
Arterial	4.6	1.3	2.5	0.3	- 2.1	3.62*
Venous	3.3	0.9	2.6	0.5	- 0.7	1.48

* $p < 0.01$ (* degree of freedom 15 t value at 1% level 2.95

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 blood from the right ventricle is deprived of ADP as well as replenished with it during its passage through the lungs.

ADP in varying concentrations had no significant effect on the mobility of platelets in sea level controls. On the other hand, the mobility of platelets in patients was significantly increased even at lower concentrations of ADP. The platelets of patients therefore seem to be more sensitive to lower concentrations of ADP.

In light microscropy of peripheral blood smears both large and small sized platelets were seen in high-altitude controls as well as patients. However, the larger ones were more numerous in patients. While the platelets remained distinct in high-altitude controls, they were found in aggregates in patients.

Electronmicroscopic studies of platelets in patients did not reveal any gross abnormality. The integrity of the plasma membrane, capacity for pseudopodia formation and ability of degranulation were intact. Platelet factor 3 and the substrate for thrombin generation and fibrin formation are therefore provided for abundantly. As 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 platelets, further release of factor 3 and more fibrin formation (Hardisty and Hutton, 1966). The coagulation process is cut short by the patient's recovery.

The possible inter-relationships between the various abnormalities in fibrinolytic activity, blood coagulation and platelet function described above and the pathogenesis of high-altitude pulmonary oedema are summarised in Fig. 1 and Fig. 2.

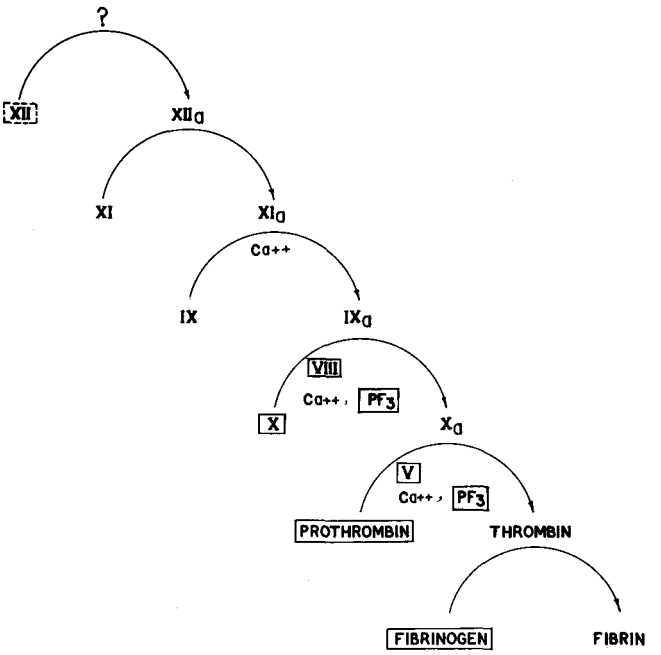

Fig. 1. Changes in the coagulation cascade in high-altitude pulmonary oedema. Unbroken enclosures signify an increase and broken enclosure indicates decrease.

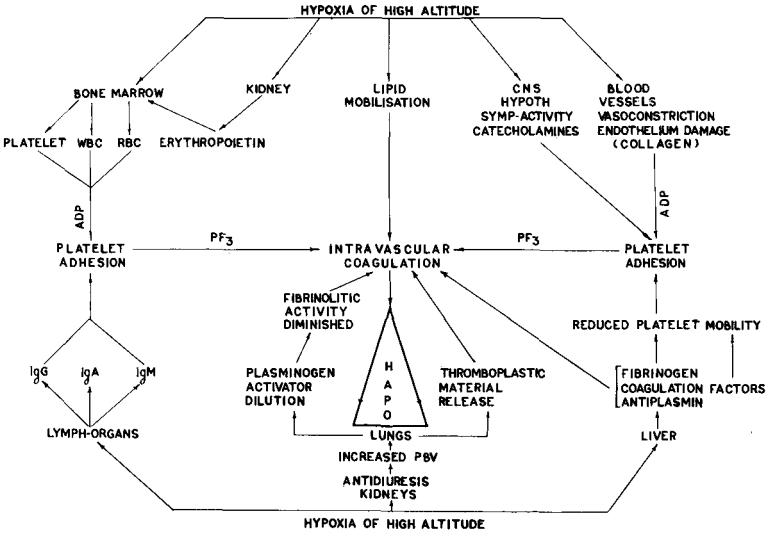

Fig. 2. Tentative origin of adverse changes in fibrinolytic activity, plasma fibrinogen, blood coagulation factors and platelet function predisposing to intravascular coagulation in high-altitude pulmonary oedema.

There is a time lag from 6 to 96 hours between arrival at high altitude and onset of pulmonary oedema. The majority of cases occur within the first 4 days and the chances of developing pulmonary oedema become remote after 7 to 14 days (Singh et al., 1965a). This incidence seems to run parallel with adverse changes in fibrinolytic activity, blood coagulation factors and platelet function as reported. While other factors may be involved in the pathogenesis of high-altitude pulmonary oedema, intravascular sludging of RBCs and thrombus formation at the pulmonary, capillary and venular level, with proximal congestion, seen in necropsy studies suggest that these changes impede the pulmonary blood flow and aggravate the disease.

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ABSTRACT.- Blood coagulation studies were undertaken in patients of high-altitude pulmonary oedema at 3,700 m, comparable controls, and sea level subjects to determine the possible causal connection between changes in fibrinolytic activity, blood coagulation factors, and formation of thrombi within the alveolar capillaries, venules and some branches of pulmonary arteries. The following changes have been observed: Fibrinolytic acitivty was reduced. Plasma fibrinogen and factor VIII were increased. Factor XII was decreased. Platelet adhesiveness and platelet factor 3 were increased and electrophoretic mobility of platelets reduced. The integrity of platelet plasma membrane and release reaction remained intact. Both arterial and venous ADP levels were low and there was evidence of excessive utilisation of ADP in the pulmonary bed. The findings suggest that sludging of RBCs and formation of thrombi possibly result from these changes, impede the pulmonary blood flow, and aggravate the disease.

ZUSAMMENFASSUNG.- An Patienten mit Lungenödem und vergleichbaren Kontrollen in 3700 m Höhe und Personen in Meereshöhe wurden Blutgerinnungsstudien vorgenommen, um die möglichen kausalen Beziehungen zu bestimmen zwischen den Veränderungen der fibrinolytischen Aktivität, den Gerinnungsfaktoren und der Bildung von Thromben im arteriellen und venösen Teil der Alveolarkapillaren und einiger Äste der Pulmonalarterien. Folgende Änderungen wurden gefunden: die fibrinolytische Aktivität war vermindert; Plasmafibrinogen und Faktor VIII waren erhöht; Faktor XII war vermindert; Plättchenklebrigkeit und Plättchenfaktor 3 waren erhöht und die elektrische Beweglichkeit der Plättchen herabgesetzt. Die Plasmamembran der Plättchen und die Release-Reaktion bleiben unbeschädigt. Der arterielle und venöse ATP-Spiegel waren niedrig und es zeigten sich Hinweise auf vermehrte ATP-Utilisation in den Pulmonargefässen. Die Ergebnisse deuten

darauf hin, dass als Folge der Veränderungen die Erythrozyten träge werden und sich Thromben bilden. Dies hemmt den pulmonalen Blutstrom und verstärkt die Krankheit.

RESUME.- On a mesuré les différentes propriétés de coagulation du sang de patients atteints d'oedème pulmonaire et de gens en santé (contrôle) et cela aussi bien à 3700 m d'altitude qu'au bord de la mer. Ces essais ont été effectués pour déterminer les relations de cause à effet possibles entre les changements de l'activité fibrinolytique et des facteurs de coagulation du sang d'une part, la formation de thromboses dans les capillaires alvéolaires, les veinules et diverses branches des artères pulmonaires d'autre part. On a alors pu observer les modifications suivantes chez les personnes du premier groupe (malades): l'activité fibrinolytique est réduite, la fibrinogène du plasma et le facteur VIII sont augmentés, le facteurs XII est diminué, l'adhésivité des plaquettes et le facteur 3 des plaquettes sont augmentés et la mobilité électrophorétique des plaquettes est réduite. L'intégrité des membranes plasmatiques des plaquettes et la réaction de décontraction sont restées inchangées. Le niveau de l'ADP aussi bien artériel que veineux a été très bas ce qui démontre une surconsommation au niveau des poumons. Les résultats obtenus laissent à penser que, par suite des modifications mentionnées, les érythrocytes perdent de leur vitalité et que des thromboses se forment. Ceci a pour conséquence de ralentir le flot sanguin pulmonaire et d'aggraver la maladie.