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Coagulation factors in chronic liver disease

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SYNOPSIS Coagulation studies were carried out on 30 patients with chronic liver disease. The clotting defect was complex and involved factors V, VII, IX (Christmas factor), and prothrombin. Some patients showed a significant depression of factor IX in the presence of a normal one-stage prothrombin time. Thrombotest was found to be a good indicator of factor IX deficiency in this group of patients and may be of use as an additional liver function test. The screening of patients with liver disease for surgery or liver biopsy should assess the coagulation factors involved in both intrinsic and extrinsic thromboplastin generation.

In 1935, Quick demonstrated a coagulation defect in liver disease when he introduced the one-stage prothrombin test (Quick, Stanley-Brown, and Bancroft, 1935). The defect has since been studied by several workers (Cowling, 1956; Rapaport, Ames, Mikkelsen, and Goodman, 1960; Hedenberg and Korsan-Bengsten, 1962; Kupfer, Gee, Ewald, and Turner, 1963) and is now known to be very complex. The finding of a marked depression of factor IX and a normal one-stage prothrombin time in one patient with cirrhosis of the liver stimulated the present detailed investigation of coagulation factors in other patients with chronic liver disease.

MATERIALS AND METHODS

Thirty patients were investigated. In most cases the diagnosis of hepatic cirrhosis was confirmed by needle biopsy of liver using the Vim-Silverman or Menghini needle or by operative liver biopsy. The main clinical details, results of routine liver function tests, and biopsy findings are given in Table I. The few patients who had received parenteral synthetic vitamin K (Synkavit) previously are indicated. Peripheral blood examination was carried out using standard haematological techniques (Dacie and Lewis, 1963).

The following tests of bleeding and clotting function were undertaken: Bleeding time (Ivy, Nelson, and Bucher, 1941); clotting time in glass and siliconized tubes (Lee and White, 1913); one-stage prothrombin time using an acetone extract of human brain (Quick, 1942), the results expressed as the ratio of patient time to control time; prothrombin consumption index (as described by Dacie and Lewis, 1963); factor V activity (Quick and Stefanini, 1948); factor VII level by comparing the patient's plasma with that of a patient with congenital factor VII deficiency (Biggs and Macfarlane, 1962); two-stage prothrombin time (Biggs and Macfarlane, 1962); Thrombotest activity (Owren, 1959); thromboplastin generation test (Biggs and Douglas, 1953); factor IX level by a modification of the thromboplastin generation test (Biggs and Macfarlane, 1962); fibrinogen as a concentration (Biggs and Macfarlane, 1962) and as a titre using Fibrindex[1] (Sharp, Howie, Biggs, and Methuen, 1958); and the euglobulin lysis time as an index of fibrinolytic activity (Biggs and Macfarlane, 1962).

RESULTS

The results of the peripheral blood counts and the various tests of bleeding and coagulation are given in Table II. Eleven patients had thrombocytopenia with platelet counts of less than 150,000/c mm; in each case this was in keeping with their degree of splenic enlargement from portal hypertension. A few subjects showed a slight prolongation of clotting time but in no case was this marked. Only two patients (nos. 16 and 17) showed a reduction in factor V activity, but the level of factor VII was found to be deficient in 10 patients. The one-stage prothrombin time was prolonged by more than three seconds in 12 patients. An abnormal prothrombin consumption index was obtained in only one patient (no. 10) who had low levels of factors VII and IX. The two-stage prothrombin time was slightly reduced in four patients (nos. 17, 18, 19, and 26).

The Thrombotest activity was considerably reduced in seven patients and was impaired in many patients. There was a serum abnormality in the thromboplastin generation test in 10 of these

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[1]Ortho Pharmaceuticals Ltd.

TABLE I

CLINICAL DETAILS AND RESULTS OF LIVER FUNCTION TESTS

Case No.	*Age*	*Sex*	*Clinical Diagnosis*	*Biopsy Confirmation*	*Given Vitamin K*	*Presenting Feature*	*Haematemesis (H) or Melaena (M)*	*History of Encephalopathy*
1	60	F	Portal cirrhosis	Yes	Yes	Haematemesis	Repeated H and M	Yes
2	47	M	Alcoholic cirrhosis	Yes	No	Anaemia	H and M	No
3	32	F	Portal cirrhosis	Yes	No	Haematemesis	Repeated H and M	No
4	49	M	Alcoholic cirrhosis	Yes	No	Anorexia	M × 1	No
5	55	F	Portal cirrhosis	Yes	No	Haematemesis	Repeated H and M	Yes
6	27	F	Portal cirrhosis	Yes	No	Splenomegaly	—	No
7	64	F	Portal cirrhosis	Yes	No	Anaemia	Repeated M	No
8	55	F	Portal cirrhosis	Yes	No	Haematemesis	H and M	No
9	30	F	Portal cirrhosis	Yes	Yes	Ascites	Repeated H	No
10	41	F	Alcoholic cirrhosis	Yes	No	Haematemesis	H × 2	Yes
11	19	F	Portal cirrhosis	Yes	No	Anaemia	Occult blood in stool	No
12	45	M	Wilson's disease	Fatty degeneration	No	Tremor	—	No
13	51	M	Alcoholic cirrhosis	Yes	Yes	Jaundice	Occult blood in stool	No
14	52	M	Secondary carcinoma	Yes	Yes	Ascites	—	No
15	51	M	Biliary cirrhosis	Yes	Yes	Pruritus	—	No
16	71	F	Portal cirrhosis	Yes	No	Splenomegaly	—	Yes
17	42	M	Portal cirrhosis	Yes	No	Melaena	Repeated H and M	Yes
18	46	M	Portal cirrhosis	Yes	No	Haematemesis	Repeated H and M	No
19	22	F	Portal cirrhosis	Yes	No	Malaise	H and M	No
20	60	M	Portal cirrhosis	Yes	No	Jaundice	—	No
21	67	M	Alcoholic cirrhosis	Yes	No	Jaundice	—	Yes
22	37	M	Portal cirrhosis	Yes	No	Jaundice	—	No
23	37	F	Alcoholic cirrhosis	Yes	No	Malaise	—	No
24	54	M	Alcoholic cirrhosis	No	Yes	Jaundice	—	No
25	63	F	Alcoholic cirrhosis	No	No	Haematemesis	Repeated M	No
26	66	F	Portal cirrhosis	Yes	No	Jaundice	M × 1	Yes
27	61	M	Portal cirrhosis	Yes	No	Oedema	M × 2	Yes
28	62	F	Portal cirrhosis	No	No	Subarachnoid haemorrhage	—	No
29	70	M	Portal cirrhosis	Yes	No	Angina	—	No
30	51	F	Portal cirrhosis	Yes	No	Haematemesis	Repeated H and M	Yes
			Normal range					

TABLE I—*continued*

CLINICAL DETAILS AND RESULTS OF LIVER FUNCTION TESTS

Splenomegaly[1]	*Serum Bilirubin (mg %)*	*Serum Alkaline Phosphatase (King-Armstrong units)*	*Serum Thymol Turbidity*	*Serum Transaminase SGPT*	*Total Serum Proteins (g%)*	*Albumin (% of total)*	*Globulin (% of total)*			
							α_1	α_2	β	γ
2 f.b.	3·6	36	7	<20	6·5	3·0 45	0·3 5	0·7 11	0·5 8	2·0 30
1 f.b.	1·6	12	5	<20	6·5	2·7 42	0·1 2	0·6 9	1·1 17	2·0 30
Splenectomy	1·7	18	6	<20	8·1	3·3 41	0·2 2	0·6 8	1·2 15	2·8 34
Tip	0·6	21	1	43	7·6	4·0 52	0·3 4	0·8 11	0·8 11	1·7 22
Splenectomy	0·8	7	1	<20	6·8	3·3 48	0·3 4	0·8 12	0·8 12	1·6 24
5 f.b.	0·9	6	1	<20	6·1	4·1 67	0·1 2	0·5 9	0·7 11	0·7 11
—	1·7	30	7	27	5·7	2·5 44	0·3 6	0·6 10	0·7 12	1·6 28
2 f.b.	0·6	19	6	<20	6·3	2·2 35	0·3 5	0·9 14	1·3 21	1·6 25
3 f.b.	2·2	45	3	30	6·9	3·8 56	0·3 4	0·8 11	0·8 11	1·2 18
Tip	0·5	40	8	20	7·1	3·1 43	0·3 4	0·5 7	0·6 8	2·7 38
—	0·3	6	1	<20	7·7	3·8 49	0·5 6	0·9 12	1·0 13	1·5 20
—	0·7	8	3	<20	7·6	3·8 50	0·3 4	1·1 14	0·8 11	1·6 21
—	14·6	11	3	62	6·8	2·7 40	0·7 10	1·2 17	1·0 14	1·3 19
3 f.b.	2·4	20	1	15	5·4	2·8 51	0·4 8	0·9 17	0·6 11	0·7 13
—	17·5	95	3	68	6·5	2·7 41	0·5 7	1·9 30	1·1 17	0·3 5
2 f.b.	1·2	20	3	25	6·2	3·6 58	0·6 10	0·8 13	0·4 6	0·8 13
—	4·0	9	>10	43	6·8	2·7 40	0·1 2	0·6 9	1·2 17	2·2 32
Splenectomy	0·4	16	2	<20	7·0	3·9 55	0·1 2	0·8 12	0·9 13	1·3 18
—	1·7	3	1	<20	6·9	4·2 61	0·3 4	0·8 12	0·9 13	0·7 10
—	0·6	30		75	6·2	2·9 46	0·3 4	0·7 11	0·9 14	1·6 25
—	0·6	12	2	<20	6·5	3·6 56	0·3 4	0·7 11	0·7 10	1·2 19
—	2·5	27	6	25	5·2	2·1 41	0·4 8	0·6 12	0·5 10	1·5 29
—	0·2	9	2	<20	6·1	3·8 63	0·1 2	0·5 9	0·7 11	0·9 15
—	1·2	9	5	25	6·8	2·5 37	0·5 7	0·8 12	0·8 11	2·2 33
3 f.b.	0·5	5	1	<20	7·1	4·5 64	0·2 3	0·9 13	0·8 11	0·6 9
—	0·8	7	4	<20	6·4	3·1 48	0·1 2	0·4 6	0·8 13	2·0 31
—	5·8	40	8	40	6·0	2·9 48	0·2 3	0·9 15	0·7 12	1·3 22
2 f.b.	1·1	14	6	<20	6·8	2·7 40	0·2 3	0·8 11	1·2 18	1·9 28
—	0·4	31	3	29	8·1	3·1 39	0·2 2	1·3 16	1·4 17	2·1 26
4 f.b.	1·3	50		52	7·2	2·5 34	0·2 3	0·7 10	1·0 14	2·8 39
	0·1–1·0	<13	1–4	<40						

[1]Fingerbreadths (f.b.) below costal margin.

TABLE II

PERIPHERAL BLOOD FINDINGS AND RESULTS OF TESTS OF BLEEDING AND CLOTTING FUNCTIONS

Case No.	Hb (g/100 ml) (100% value = 14·6 g/100 ml)	WBC per c mm	Platelets per c mm	Hess Test	Bleeding Time (Ivy)	Clotting Time		Prothrombin Ratio to Normal	Prothrombin Consumption Index
						Glass	Silicone		
1	10·5	3,300	60,000	–	3′ 2″	10′ 12″	27′ 34″	1·75	31
2	12·7	3,300	75,000	–	5′ 6″	10′ 11″	23′ 23″	1·25	40
3	13·6	5,100	150,000	–	6′ 0″	10′ 10″	28′ 34″	1·00	31
4	9·5	11,500	200,000	–	4′ 23″	10′ 10″	27′ 27″	1·00	30
5	11·0	5,700	185,000	–	6′ 30″	11′ 11″	26′ 28″	1·00	16
6	11·7	10,400	360,000	–	5′ 45″	15′ 15″	18′ 23″	1·08	25
7	6·0	3,500	85,000	–	2′ 30″	9′ 9″	21′ 32″	1·25	28
8	11·1	4,200	100,000	–	2′ 50″	11′ 11″	30′ 30″	1·00	33
9	14·2	9,700	180,000	–	4′ 25″	8′ 9″	31′ 32″	1·64	21
10	14·6	5,000	76,000	+	2′ 55″	11′ 13″	22′ 22″	1·36	63
11	8·3	8,400	550,000	–	3′ 20″	11′ 11″	24′ 24″	1·09	17
12	17·1	6,900	250,000	–	2′ 30″	5′ 30″	20′ 32″	1·1	27
13	12·0	7,800	365,000	–	3′ 25″	13′ 25″	26′ 30″	1·25	23
14	12·6	9,700	225,000	–	3′ 29″	10′ 30″	27′ 29″	1·25	30
15	12·0	13,200	325,000	–	4′ 8″	16′ 16″	34′ 34″	1·00	41
16	12·3	3,000	75,000	–	3′ 25″	10′ 10″	28′ 42″	1·25	27
17	13·3	5,600	100,000	–	2′ 28″	15′ 15″	30′	1·50	19
18	12·8	5,900	300,000	–	2′ 30″	9′ 11″	26′ 27″	1·08	40
19	11·7	4,900	125,000	–	3′	13′ 13″	20′ 30″	1·00	28
20	16·5	5,200	100,000	–	2′ 30″	8′ 30″	24′ 30″	1·00	21
21	14·9	4,900	150,000	–	1′ 45″	15′ 15″	31′ 40″	1·00	30
22	12·3	5,500	185,000	–	2′ 45″	10′ 10″	17′ 30″	1·00	21
23	14·6	9,500	177,500	–	3′ 18″	12′ 12″	25′	1·00	24
24	12·6	5,800	110,000	–	4′ 20″	6′ 6″	30′ 30″	1·36	33
25	10·2	3,300	150,000	–	2′ 30″	9′ 30″	25′	1·08	16
26	12·6	4,900	150,000	–	2′	8′ 30″	40′	1·23	27·5
27	14·3	5,500	50,000	–	2′	6′ 30″	24′	1·08	28
28	11·7	4,100	130,000	–	2′ 30″	9′ 9″	20′ 24″	1·00	34·5
29	16·1	6,000	95,000	–	1′ 45″	9′ 9″	29′	1·25	30
30	7·3	3,900	220,000	–	2′ 25″	7′ 7″	28′ 28″	1·18	17
Normal	Male 13·5–18·0 Female 11·5–16·4	4,000–10,000	150,000–400,000	—	2′ –8′	5′–10′	18′–25′	0·9–1·2	0–20 (normal) 20–40 (equivocal)

patients; this was corrected by normal serum but not by serum from a patient with Christmas disease. Factor IX was low in all of these 10 patients with abnormal thromboplastin generation and was also moderately reduced in two others.

In all patients the fibrinogen titre and concentration were normal. Patient no. 3 showed a euglobulin lysis time less than normal but as judged by this method no patient had evidence of gross fibrinolysis.

There was significant correlation between the assay of factor VII and the one-stage prothrombin time ($r = 0{\cdot}76$; $P < 0{\cdot}001$; $n = 30$). There was no significant correlation between the results of factor IX assay and the one-stage prothrombin time ($r = 0{\cdot}39$; $0{\cdot}05 > P > 0{\cdot}01$; $n = 30$). Good correlation existed between the results of the Thrombotest and the assay of factor IX ($r = 0{\cdot}78$; $P < 0{\cdot}001$; $n = 30$) (Fig. 1), and fair correlation between Thrombotest activity and factor VII level ($r = 0{\cdot}55$; $0{\cdot}01 > P > 0{\cdot}001$; $n = 30$).

DISCUSSION

The defect in coagulation in patients with chronic hepatocellular disease is rarely due to a single abnormality. Like others (Kupfer *et al*, 1963) we have found the clotting and bleeding times to be of little value. We have confirmed that reduction of factors V, VII, IX, and prothrombin may exist.

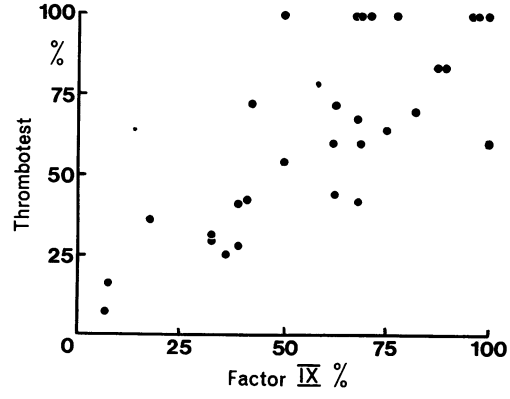

FIG. 1. *Correlation between results of the Thrombotest and the assay of factor IX.*

TABLE II—*continued*

PERIPHERAL BLOOD FINDINGS AND RESULTS OF TESTS OF BLEEDING AND CLOTTING FUNCTIONS

Factor V (%)	*Factor VII* (%)	*Two-stage Prothrombin* (%)	*Thrombotest* (%)		*Thromboplastin Generation Test*	*Factor IX* (%)	*Fibrinogen*			*Euglobulin Lysis Time* (*min*)
			Control	*Patient*			*Concentration* (*g*%)	*Thrombin Titre*		
								Control	*Patient*	
75	50	96	100	72	A[1]	42	0·3	1/64	1/16	140
90	65	107	100	60	N[2]	62	0·3	1/64	1/32	>330
100	100	112	100	100	N	77·4	0·2	1/64	1/64	85
100	95	95	84	60	N	100	0·45	1/64	1/32	325
100	86	91	100	70	N	82·2	0·5	1/64	1/64	320
96	74	98	100	100	N	97·0	0·2	1/64	1/32	100
96	64	102	84	64	N	75·0	0·2	1/64	1/32	180
96	87	100	80	36	A	17·5	0·3	1/64	1/16	320
90	56	87	80	44	N	62·5	0·3	1/64	1/16	310
99	52	86	100	7	A	6·8	0·15	1/64	1/32	130
82	93	106	100	72	N	62·5	0·2	1/64	1/64	140
72	80	116	100	100	N	100	0·3	1/64	1/64	140
80	36	97	100	30	A	32·5	0·7	1/64	1/32	330
90	36	82	100	31	A	32·5	0·35	1/64	1/64	230
90	100	110	100	100	N	70·8	0·5	1/64	1/16	225
46	42	96	100	100	N	68·7	0·25	1/64	1/16	205
46	25	62	100	25	A	36	0·25	1/64	1/16	180
95	86	56	70	16	A	7·5	0·4	1/64	1/16	140
87	92	65	90	100	N	50	0·35	1/64	1/64	125
70	100	87	100	60	N	68·7	0·40	1/64	1/64	>330
102	78	96	100	54	N	50	0·5	1/64	1/32	>330
116	100	79	100	90	N	87·5	0·4	1/64	1/32	210
136	89	83	100	100	N	96	0·2	1/64	1/32	160
97	53	102	84	28	A	39	0·3	1/64	1/32	150
97	86	102	100	90	N	89·5	0·5	1/64	1/64	155
67	42	59	100	41	A	39	0·2	1/64	1/32	225
66	87	92	80	68	N	68	0·2	1/64	1/64	300
76	80	96	100	100	N	68	0·2	1/64	1/64	300
86	42	86	100	42	A	41	0·2	1/32	1/16	120
90	62	97	42	42	N	68	0·2	1/128	1/64	>330
60–200	60–160	60–160	70–130		N	60–200	0·15–0·3	1/32–1/128		>120

[1]A = abnormal.
[2]N = normal

Cowling (1956) stated that a prolonged one-stage prothrombin time is caused mainly by combined deficiencies of factors V and VII. In his patients and in those of Finkbiner, McGovern, Goldstein, and Bunker (1959) lack of factor IX was found only in patients with prolonged prothrombin times. Our results indicate that prolongation of the one-stage prothrombin time correlates well with lack of factor VII but that factor IX deficiency, which was present in many patients, is not always accompanied by a prolonged one-stage prothrombin time. On the other hand we have found Thrombotest to be a good indicator of deficiency of factor IX (Fig. 1) in this group of patients, although Thrombotest has been reported as relatively insensitive in detecting deficiency of factor IX in the plasma of patients with Christmas disease or in patients who are receiving therapy with phenindione (Denson, 1961). We do not have an explanation for this (unexpected) finding, although we note that the occasional patient with congenital factor IX deficiency may have a prolonged Thrombotest (Kidd, Denson, and Biggs, 1963). Some of our patients showed depression of factor IX despite normal routine liver function tests and normal serum albumin levels. The one-stage prothrombin time is said to be a useful liver function test (Williams, 1965), but Thrombotest might be preferable as it may detect abnormalities of intrinsic as well as of extrinsic thromboplastin generation, both of which are affected by liver disease. Disorders of haemostatic function are extremely common in patients with liver disease (Hedenberg and Korsan-Bengsten, 1962) and Thrombotest may be of diagnostic use in the assessment of such patients as suggested originally by Owren (1959).

Haemorrhage in patients with liver disease may occur in the presence of apparently normal coagulation. Most authors consider that a clotting defect contributes to the severity of the bleeding although it may not precipitate it (Cowling, 1956; Finkbiner *et al*, 1959; Kupfer *et al*, 1963). It was not possible from a study of our patients to assess the relative importance of the coagulation defect in the causation of bleeding. In none of the patients studied was there abnormal bleeding after needle biopsy of the liver. Further, although some of our patients showed marked abnormalities of coagulation, there was no evidence in this group that such abnormalities

affected the prognosis. It is difficult to evaluate the significance of a single clotting defect, and even more difficult to assess minor deficiencies in several coagulation factors. Moreover the relative importance of defective coagulation, abnormal fibrinolysis, thrombocytopenia, portal hypertension, and the presence of oesophageal varices in precipitating or prolonging haemorrhage has still to be established.

It is commonly recommended (Sherlock, 1963) that the one-stage prothrombin time be estimated as a screening precaution before needle biopsy of the liver is undertaken. However, since lack of factor IX is not shown by this test, we suggest that in the meantime patients with liver disease in whom bleeding and clotting functions need to be assessed, *eg*, for liver biopsy, should be investigaged with a test to measure intrinsic thromboplastin generation, as well as with the more customary one-stage prothrombin time, which depends on extrinsic thromboplastin generation and the prothrombin content of the blood. We regard such a screen as a minimum and, in practice, we perform the following investigations for such patients: peripheral blood counts including platelet count; bleeding time; whole blood clotting time; one-stage prothrombin time; Thrombotest or partial thromboplastin time (Matchett and Ingram, 1965); prothrombin consumption index; and euglobulin lysis time.

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