

# Studies on Spontaneous Fibrinolytic Activity In Patients with Cirrhosis of the Liver and Its Inhibition by Epsilon Amino Caproic Acid \*

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DEFECTS in the blood coagulation mechanism of cirrhotic patients have been reported in all stages of clot formation and dissolution.<sup>3,4,32</sup> In addition to abnormalities in thromboplastin generation,<sup>35</sup> and prothrombin formation,<sup>26</sup> spontaneous fibrinolytic activity has been observed in the plasma of many of these patients.<sup>11,12,27</sup>

Notwithstanding the fact that spontaneous fibrinolytic activity has been studied in a variety of disease processes,<sup>8, 28, 33</sup> and also during the course of certain extensive surgical procedures,<sup>6, 7, 23, 31, 35, 36</sup> its clinical and surgical significance in cirrhotic patients as well as the evaluation of any corrective measures seems to deserve more careful attention.

The investigation of the whole subject of spontaneous fibrinolysis has been recently stimulated by the demonstration of the effective *in vitro* inhibitory action of Epsilon amino caproic acid upon streptokinase activated plasminogen.<sup>1, 2, 10, 18</sup> Several experimental and clinical assays of its effects on streptokinase activated plasminogen and on spontaneous proteolytic activity have been recently reported.<sup>15-17, 20, 30</sup> However, with the exception of one patient included in a recent report,<sup>19</sup> no studies on

the effects of Epsilon amino caproic acid upon the spontaneous fibrinolytic activity associated with many cases of cirrhosis of the liver have been found in the literature. Although it would appear highly improbable that abnormal fibrinolytic activity could be a significant etiologic factor in the abrupt bleeding from esophagogastric varices associated with portal hypertension, it is conceivable that the hemorrhagic tendencies exhibited by many cirrhotic patients may be related to the presence of this abnormal proteolytic activity.

The present study was undertaken with the purpose of establishing the actual incidence of spontaneous fibrinolytic activity in a well documented series of cirrhotic patients and of correlating, at the same time, the presence of this abnormal activity with the bleeding tendencies observed in many of these patients. Additional aims included the evaluation of the inhibitory effect of Epsilon amino caproic acid on the spontaneous fibrinolytic activity of cirrhotic patients, and the effect of this inhibition on the control of clinical hemorrhage.

## Materials and Methods

Fifty-one patients with well-documented cirrhosis of the liver and a control group of 20 preoperative surgical patients with normal liver function constituted the clinical material for this study. All cirrhotic

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TABLE 1. *Fibrinolytic Activity in Cirrhotic Patients*

No.	Patient	Hospital No.	Euglobulin Fibrinolytic		Whole Clot Lysis	
			hrs.	min.	hrs.	min.
1	C. M.	105452	3	30	24	
2	W. E.	45807	2	40	24	
3	A. K.	107174	3	30	24	
4	L. C.	107823	1	20	3	
5	J. G.	108589	1	50	3	45
6	A. K.	017487	20		24	
7	M. P.	107483	16		48	
8	W. W.	VAH (1)	18		24	
9	J. R.	VAH (2)	20		48	
10	M. T.	105566	2	40	24	
11	J. W.	075916	2	30	16	
12	G. K.	110664	1	40	12	
13	B. V.	105647	1	30	6	
14	R. M.	107391	12		24	
15	J. F.	055984	4		24	
16	D. S.	110614	2	50	8	
17	P. B.	110683	3	45	24	
18	N. P.	000741	2	45	12	
19	A. F.	110535	2		10	
20	J. P.	112197	24		48	
21	A. R.	E58332	4	30	24	
22	L. A.	077111	8	30	48	
23	G. R.	E51766	2	55	25	
24	H. B.	112429	6	30	18	
25	J. R.	112623	5		24	
26	W. B.	112661	3	10	16	
27	W. K.	097518	4	10	27	
28	K. S.	112841	4	30	24	
29	J. M.	113055	5	15	28	
30	J. C.	113292	24		48	
31	J. M.	113458	12		48	
32	M. G.	113645	4	30	24	
33	V. T.	114584	6	30	18	
34	F. H.	114520	7	15	24	
35	B. S.	114707	8	30	48	
36	E. R.	114946	14	30	48	
37	M. M.	E12192	4	30	24	
38	B. C.	061044	5	45	5	30
39	H. M.	117607	3	30	26	
40	J. D.	90537	2	30	20	
41	E. T.	118041	3	30	16	
42	P. H.	119032	5	15	48	
43	A. M.	114311	1	15	2	30
44	J. S.	71783	3	18	3	45
45	J. J.	E68517	24		48	
46	D. V.	095520	24		48	
47	J. M.	118079	20		48	
48	G. L.	107736	24		48	
49	J. F.	110386	10		48	
50	M. T.	114584	18	30	18	
51	T. K.	117075	14		24	

patients had liver function and histological studies and a complete evaluation of their portal hemodynamics as determined by splenoportography and splenic and portal manometrics.<sup>21, 22, 29</sup> No patients with jaundice due to common duct obstruction were included in this series.

The inhibitory effects of Epsilon amino caproic acid were studied in the absence of hemorrhage, hypotension or blood transfusions. With the purpose of avoiding any complicating influence arising from hyperlipemia, a liquid diet from which fats were excluded was maintained at the time of the tests. In the unusual case of a patient with a high level of spontaneous fibrino-

lytic activity and a readily observable bleeding site, studies were repeated at the time of hemorrhage. Epsilon amino caproic acid\* was used. Two grams of this agent were diluted in 300 milliliters of 5 per cent dextrose in water and given intravenously over a period of two hours.

Proteolytic enzyme and coagulation studies included an evaluation of all the phases of the clotting mechanism. Samples of blood were drawn freely to prevent venostasis and its activating effect upon the plasminogen system.<sup>5</sup> Potassium citrate crystals were used in the samples for proteolytic enzyme studies and a one to nine proportion of 0.1 molar sodium oxalate was used for the determination of the blood coagulation factors. The following technics were used:

#### A. First phase of coagulation

1. Thromboplastin generation test. Zucker's<sup>34</sup> modification of Biggs and MacFarlane<sup>3</sup> method using barium sulfate absorbed plasma and inosithine.

2. Platelet count. Direct smear counting on capillary blood.

#### B. Second phase of coagulation

1. Prothrombin time. Quick's method.<sup>24</sup> Normal values were less than 14 seconds.

2. Factor V (accelerator globulin), Factor VII (proconvertin) by a modification of Owren's one-stage assay.<sup>14</sup> Normal values were above 70 per cent.

#### C. Third phase of coagulation

1. Plasma fibrinogen. Quick's modification of the method of Cullen and Van Slyke.<sup>24</sup>

2. Whole clot lysis. The time required for complete lysis of a whole blood clot was determined at 37° C. Normal range is 24 to 48 hours.

3. Fibrinolytic activity—euglobulin fraction. Method of Downie and Clifton,<sup>9</sup>

\* Caprocid® supplied by Merck, Sharp and Dohme, West Point, Pa.

TABLE 2. Associated Coagulation Defects in Cirrhotic Patients

No.	Patient	Hospital No.	Quick (sec.)	Factor V %	Factor VII %	Fibrinogen (mg.%)	Platelets (× 1000)
1	C. M.	105452	18	110	100	450	250
2	W. E.	45807	18.7	100	80	650	280
3	A. K.	107174	18	75	60	460	340
4	L. C.	107823	27	40	30	350	150
5	J. G.	108589	21	25	70	320	120
6	A. K.	017487	19.4	65	75	380	260
7	M. P.	107483	26	40	50	320	175
8	W. W.	VAH (1)	18	80	100	450	—
9	J. R.	VAH (2)	17.4	100	100	380	—
10	M. T.	105566	17.2	70	100	640	—
11	J. W.	075916	21.4	100	100	230	—
12	G. K.	110664	22	30	42	360	265
13	B. V.	105647	25.2	40	42	368	—
14	R. M.	107391	17.2	60	90	418	95.2
15	J. F.	055984	21	54	75	440	110
16	D. S.	110614	19	74	100	380	250
17	P. B.	110683	23	58	82	520	—
18	N. P.	000741	23.4	45	66	280	209
19	A. F.	110535	20.4	76	64	486	200
20	J. P.	112197	22	60	75	440	12
21	A. R.	E58332	18.6	55	77	466	190
22	L. A.	077111	15.2	100	100	418	—
23	G. R.	E51766	16	100	95	432	280
24	H. B.	112429	20	—	—	376	180
25	J. R.	112623	17	42	64	486	—
26	W. B.	112661	17.9	64	59	342	50
27	W. K.	097518	20	84	76	436	288
28	K. S.	112841	19.4	35	58	460	289
29	J. M.	113055	22.8	84	76	494	84
30	J. C.	113292	17.8	100	100	415	250
31	J. M.	113458	17.2	100	82	404	156
32	M. G.	113645	17.4	68	90	356	78
33	V. T.	114584	23.2	40	30	295	110
34	F. H.	114520	23.4	62	48	402	175
35	B. S.	114707	20	65	70	336	383
36	E. R.	114946	21	72	90	438	200
37	M. M.	E12192	24	30	45	288	137
38	B. C.	061044	25	19	24	170	142
39	H. M.	117607	28	66	35	465	42.9
40	J. D.	90537	21	35	40	334	200
41	E. T.	118041	24	35	40	—	169
42	P. H.	119032	27	—	—	—	150
43	A. M.	114311	21	—	—	235	204
44	J. S.	71783	35	—	—	180	339
45	J. J.	E68517	24.2	—	—	—	105
46	D. V.	095520	25	—	—	184	—
47	J. M.	118079	20	80	75	—	87
48	G. L.	107736	15	100	100	—	319
49	J. F.	110386	19	55	75	460	180
50	M. T.	114584	22	58	75	—	202
51	T. K.	117075	21	65	80	485	142

TABLE 3. *The Effect of Two Grams of Epsilon Amino Caproic Acid on Euglobulin Fibrinolytic Activity of Plasma*

Patient	Chart No.	Time After Infusion (Hours)				
		0	2	4	6	20
L. C.	107823	3 hr. 11'	20 hr.	1 hr. 30'	—	2 hr. 30'
J. G.	108584	2 hr. 10'	24 hr.	3 hr. 45'	—	6 hr.
A. F.	110535	3 hr. 45'	18 hr.	48 hr.	—	2 hr. 15'
J. F.	055984	2 hr. 5'	24 hr.	24 hr.	—	6 hr. 30'
L. A.	077111	8 hr. 30'	24 hr.	24 hr.	—	24 hr.
G. R.	E51766	2 hr. 55'	24 hr.	18 hr.	—	8 hr.
J. M.	113055	5 hr. 15'	7 hr. 30'	24 hr.	—	4 hr. 10'
W. K.	097578	4 hr. 10'	24 hr.	24 hr.	22 hr.	11 hr.
G. H.	114520	8 hr. 15'	24 hr.	24 hr.	12 hr. 30'	7 hr. 15'
V. T.	114584	8 hr. 30'	24 hr.	24 hr.	—	11 hr.
M. M.	E12192	5 hr. 30'	24 hr.	24 hr.	—	5 hr.
J. D.	90537	2 hr. 30'	24 hr.	24 hr.	16 hr.	3 hr. 15'
B. S.	114707	8 hr. 30'	24 hr.	24 hr.	15 hr.	10 hr. 30'
E. T.	118041	3 hr. 30'	24 hr.	24 hr.	18 hr.	6 hr.
B. C.	061044	5 hr. 45'	24 hr.	16 hr.	19 hr.	9 hr. 7'

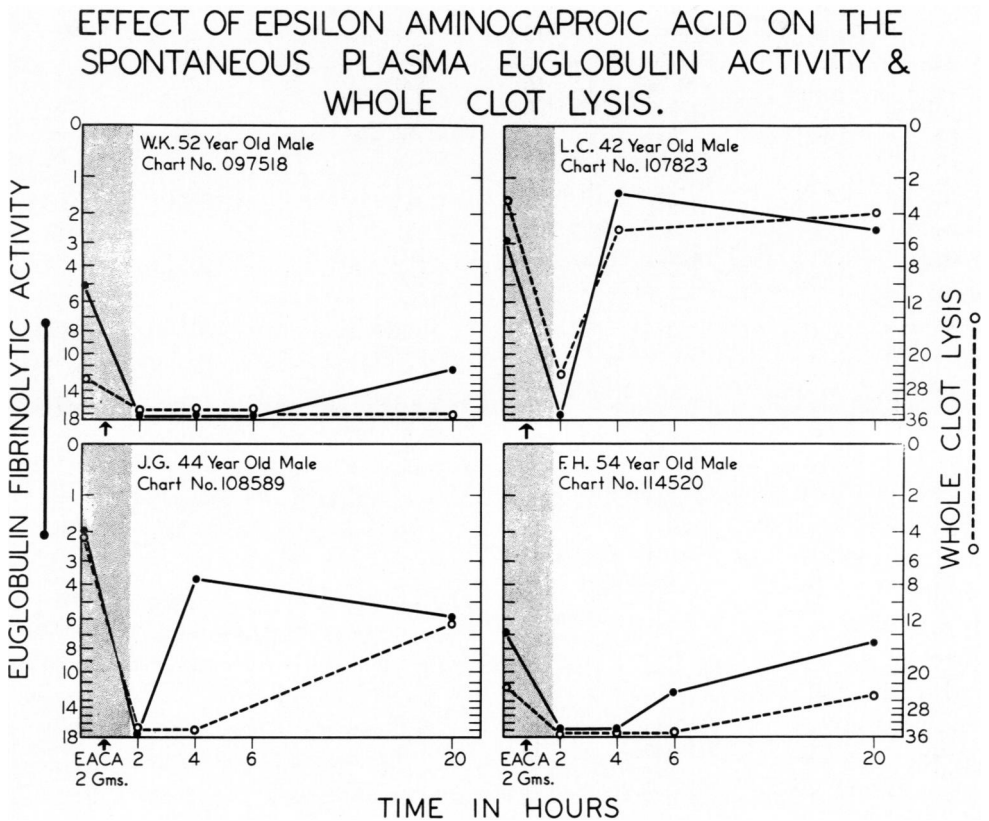


FIG. 1. Four patients are presented in this graph. The effect of a two gram infusion of Epsilon amino caproic acid given in two hours on the plasma euglobulin fibrinolytic activity and on the whole blood clot lysis activity is shown. Both activities are measured in hours. The effect of the drug over a period of 24 hours is presented. The four patients are: L. C. No. 107823, W. K. No. 097518, J. G. No. 108589, G. H. No. 114520.

employing 1 unit of Thrombin.\*\* Normal range is 16 to 24 hours. The greater the activity the shorter the time of lysis.

4. Clotting time. Lee-White.<sup>13</sup>

Results

In the series of 51 patients with cirrhosis of the liver studied in this investigation, 25 patients were found to have clear evidence of an increase in spontaneous plasma euglobulin fibrinolytic activity and 17, an abnormally increased spontaneous whole blood clot lysis (Table 1). The combined incidence of spontaneous proteolytic activity as shown by these two tests was 49 per cent. Use of less strict criteria (euglobulin activity beyond the five-hour mark and whole clot lysis beyond the ten-hour mark) could increase the incidence of spontaneous proteolytic activity to 78 per cent (Table 1). As a reflection of the severe liver damage present in this series of patients, associated defects in the blood clotting mechanism were frequently observed (Table 2).

These defects were mainly represented by a prolongation of the one-stage Quick prothrombin time observed in all the patients and by abnormal serum thromboplastin generation tests observed in the 10 patients in whom these tests were carried on. No improvement in the one-stage Quick prothrombin time was observed following large amounts of vitamin K.

The effect of the intravenous infusion of 2 Gm. of Epsilon amino caproic acid was assayed in 15 of the 25 patients showing an abnormal degree of spontaneous euglobulin fibrinolytic activity and the results are presented in Table 3. In general, the effect of this agent was noted toward the end of the infusion and was characterized by a rapid decrease to normal levels in spontaneous fibrinolytic activity (Fig. 1). This effect lasted between two and four hours after the end of the infusion and usually the values went back to pre-

TABLE 4. Effect of Two Grams of Epsilon Amino Caproic Acid on the Whole Blood Clot Lysis

Patient	Chart No.	Time After Infusion (Hours)				
		0	2	4	6	20
L. C.	107823	3½	24	5	—	3½
J. G.	108589	4½	48	48	—	12
A. F.	110535	22	48	48	—	48
J. F.	055984	8	48	48	—	24
L. A.	071111	48	48	48	—	48
G. R.	E51766	25	48	48	—	24
J. M.	113055	24	36	48	—	36
W. K.	097578	27	36	48	—	36
G. H.	114520	24	48	48	48	24
V. T.	114584	18	48	48	—	24
M. M.	E12192	26	48	48	—	24
J. D.	90537	20	48	48	48	18½
B. S.	114707	48	48	48	48	48
E. T.	118041	16	48	48	48	24
B. C.	061044	5½	48	48	48	5½

infusion levels after 20 hours. In a few patients with very high euglobulin fibrinolytic activity, the effect lasted only a short time beyond the end of the infusion.

The effect of Epsilon amino caproic acid upon the whole blood clot lysis of the same 15 patients is presented in Table 4. It is noted that two of these patients had no increase in whole blood clot lysis and that these two individuals did not have very high euglobulin fibrinolytic activity. The Epsilon amino caproic acid produced a definite and prolonged inhibition of the spontaneous whole blood clot lysis. This effect was present for four to six hours after the end of the infusion of the Epsilon amino caproic acid and in three patients the inhibitory effect was still present 22 hours later. In these three patients the whole blood clot lysis activity was back to pretreatment levels by 36 hours.

The changes in euglobulin fibrinolytic activity and whole blood clot lysis after the administration of Epsilon amino caproic acid were almost parallel, as indicated in four representative patients presented in Figure 1. Inhibitory effect was seen in both determinations of proteolytic activity at about the same time, but the effect on whole blood clot lysis seemed to last longer than on the euglobulin fibrinolytic activity. Abnormal proteolytic activity was lowered to normal levels for four to six hours.

Simultaneous serial determinations of

\*\* Bovine Thrombin, Parke Davis and Co., Detroit, Michigan.

TABLE 5. *Effect of Two Grams of Epsilon Amino Caproic Acid*

Patient	Chart No.	Test	Time After Infusion (Hours)				
			0	2	4	6	20
L. C.	107823	Quick (sec.)	30	30	28	—	26
		Factor V (%)	42	33	30	—	28
		Factor VII (%)	40	33	35	—	30
		Fibrinogen (mg.%)	470	456	480	—	420
J. G.	108589	Quick (sec.)	20.4	24.2	23	—	22
		Factor V (%)	80	74	55	—	—
		Factor VII (%)	33	52	64	—	—
		Fibrinogen (mg.%)	340	—	—	—	356
A. F.	110535	Quick (sec.)	20.4	21	20.8	—	17.1
		Factor V (%)	76	82	70	—	56
		Factor VII (%)	68	55	60	—	65
		Fibrinogen (mg.%)	486	—	—	—	422
J. F.	055984	Quick (sec.)	19.4	19.8	19.6	—	19.0
		Factor V (%)	75	80	72	—	100
		Factor VII (%)	64	66	68	—	69
		Fibrinogen (mg.%)	376	398	—	—	345
L. A.	077111	Quick (sec.)	15.2	15.6	14.8	—	15.2
		Factor V (%)	100	100	100	—	—
		Factor VII (%)	100	90	100	—	—
		Fibrinogen (mg.%)	410	—	—	—	402
G. R.	E51766	Quick (sec.)	16.0	15.8	16.6	—	16.2
		Factor V (%)	100	100	100	—	100
		Factor VII (%)	95	100	100	—	100
		Fibrinogen (mg.%)	432	—	—	—	—
J. M.	113055	Quick (sec.)	22.8	23	22	—	23
		Factor V (%)	84	90	80	—	75
		Factor VII (%)	76	70	75	—	65
		Fibrinogen (mg.%)	494	—	—	—	478
W. K.	097578	Quick (sec.)	20	21	22	23	22
		Factor V (%)	84	85	80	75	80
		Factor VII (%)	76	80	75	80	85
		Fibrinogen (mg.%)	436	—	—	420	455
G. H.	114520	Quick (sec.)	23.4	23	22.4	22	23.4
		Factor V (%)	70	65	55	50	62
		Factor VII (%)	45	46	50	45	48
		Fibrinogen (mg.%)	416	—	—	430	401
V. T.	114584	Quick (sec.)	23.2	24	23.8	—	24.5
		Factor V (%)	40	30	36	—	30
		Factor VII (%)	30	50	30	—	62
		Fibrinogen (mg.%)	295	—	—	—	324
M. M.	E12192	Quick (sec.)	24	26.2	25.4	—	23.4
		Factor V (%)	30	20	30	—	25
		Factor VII (%)	45	35	20	—	20
		Fibrinogen (mg.%)	288	281	—	—	306

TABLE 5. (Continued)

Patient	Chart No.	Test	Time After Infusion (Hours)				
			0	2	4	6	20
J. D.	90537	Quick (sec.)	21	21.4	22.8	23	22
		Factor V (%)	35	—	—	—	46
		Factor VII (%)	40	—	—	—	38
		Fibrinogen (mg.%)	334	—	—	341	352
B. S.	114707	Quick (sec.)	20	20.4	20.6	21	19.8
		Factor V (%)	65	40	—	—	—
		Factor VII (%)	70	66	—	—	—
		Fibrinogen (mg.%)	336	—	—	—	—
E. T.	118041	Quick (sec.)	24	23.6	24.2	23	23.8
		Factor V (%)	35	30	—	25	—
		Factor VII (%)	40	33	—	38	—
		Fibrinogen (mg.%)	—	—	—	—	—
B. C.	061044	Quick (sec.)	25	25	22	—	19
		Factor V (%)	—	—	—	—	—
		Factor VII (%)	—	—	—	—	—
		Fibrinogen (mg.%)	—	—	—	—	—

the Quick prothrombin time, Factor V, Factor VII, plasma fibrinogen, and Lee-White clotting time showed that, although the majority of values were at below normal levels, no significant change could be detected as a result of the Epsilon amino caproic acid infusion (Table 5). No deleterious effect on liver function was found and there were no allergic or toxic reactions to the medication. The Epsilon amino caproic acid solution was given to other patients in hypovolemic shock and during surgery without any ill effects. It was also given to a normal subject without affecting coagulation factors.

The unusual opportunity of studying one of these cirrhotic patients concurrently hemorrhaging profusely from a readily observable bleeding site, permitted the obtaining of simultaneous data on the effect of Epsilon amino caproic acid on the proteolytic activity of the plasma and the clinical course of hemorrhage.

### Case Report

L. C., Chart No. 166270, a 42-year-old man, was readmitted because of edema of the legs

and ascites three months after a portacaval shunt had been performed in this hospital for cirrhosis of the liver, portal hypertension and bleeding esophagogastric varices. Following portal decompression he had not had any more episodes of gastrointestinal hemorrhage. At this second admission, liver function tests showed a 4+ cephalin flocculation, Quick prothrombin time 25 seconds, Factor V 25%, Factor VII 30%, platelet count 93,000/mm.<sup>3</sup>, and an albumin-globulin ratio of 1. Euglobulin fibrinolytic time was 3 hours and 30 minutes, and whole blood clot lysis, 4 hours. On May 6, 1960, a right second lower molar tooth was extracted. Following the dental procedure, he bled profusely, requiring in addition to several repackings, vitamin K, seven units of blood, and two units of fresh frozen plasma over the next 72 hours in order to replace the blood loss. In spite of this, the oozing from the alveolar wound continued so that on the third post-extraction day (5/9/60), he was losing about 250 cc. of blood every four hours. Blood studies done at this point revealed the platelet count to be 150,000/mm.<sup>3</sup>, the Quick 26 seconds, Factor V 30%, Factor VII 25%, plasma fibrinogen 235 mg.%, the euglobulin fibrinolytic activity 30 minutes, and the whole clot lysis 4 hours and 30 minutes (Fig. 2). The clotting time was 6 minutes. The patient was given 2 Gm. of Epsilon amino caproic acid intravenously between 11 a.m. and 1 p.m. on 5/9/60, and then another 2 Gm. from 1 p.m. to 9 a.m. the following day. The plasma euglobulin activity at 1 p.m. was 1 hour

EFFECT OF EPSILON AMINOCAPROIC ACID  
ON SPONTANEOUS ENZYME ACTIVITY AND  
THE COURSE OF CLINICAL HEMORRHAGE

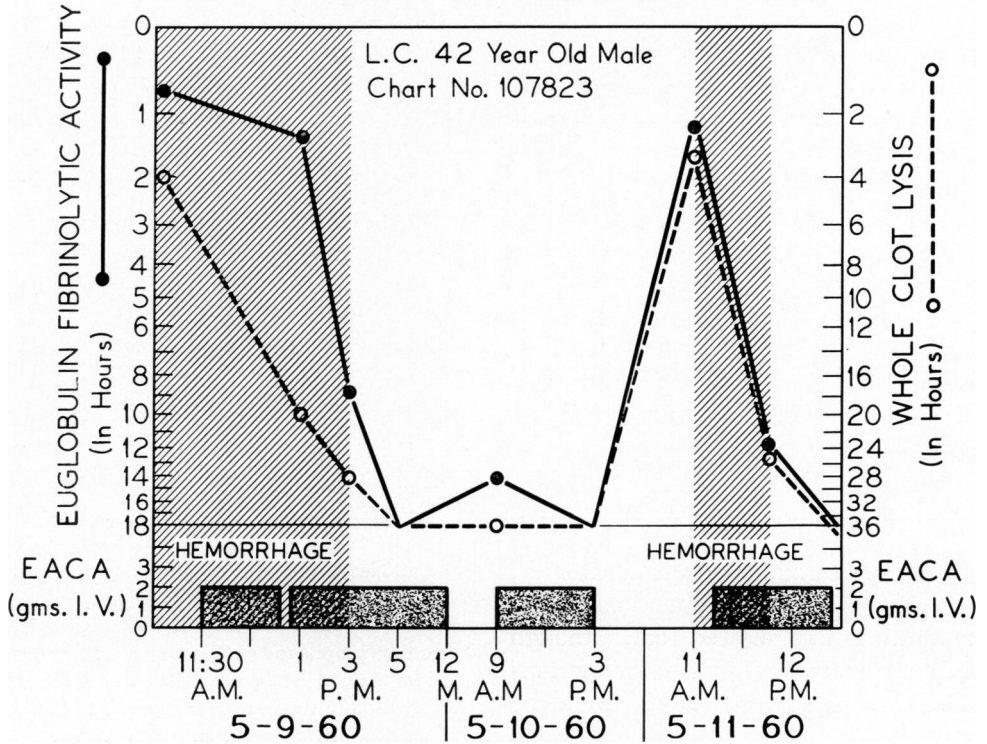


FIG. 2. The clinical course of patient L. C. No. 107823 is shown, demonstrating the relationship between the bleeding from the tooth socket and plasma proteolytic activity. Both plasma euglobulin fibrinolytic activity and whole blood clot lysis are shown as well as the time and amount given of Epsilon amino caproic acid. This patient had received Epsilon amino caproic acid on previous occasions as seen in Figure 1.

and 40 minutes, and the whole blood clot lysis was 20 hours and the Quick 25 seconds. The amount of blood oozing began to diminish rapidly after the first infusion in that he lost only 100 cc. in 4 hours, and by 3 p.m. on 5/9/60 the oozing had stopped completely. The dental packing was changed and there was no more oozing during the next day. By 5 p.m. of the first day the euglobulin fibrinolytic activity and the whole blood clot lysis were both down to normal levels. The infusion of Epsilon amino caproic acid was continued overnight. The next day another infusion of 2 grams was given over six hours and the fibrinolytic activity remained in the very low range. No more Epsilon amino caproic acid was given after 2 p.m. on 5/10/60. The dental packing was not changed. On 5/11/60 at 11 a.m., the patient was again complaining of oozing from the site of the dental extraction, losing about

200 cc. of blood in 2 hours. Coagulation studies revealed euglobulin fibrinolytic activity of 2 hours and 30 minutes and whole blood clot lysis of 3 hours and 45 minutes. He was again given 2 grams of Epsilon amino caproic acid over a period of 6 hours and bleeding stopped within an hour. The dental packing was removed the next day and hemorrhage did not recur.

### Discussion

The study of the derangement of the blood coagulation mechanism, blood clot dissolution, and of the abnormal bleeding tendencies associated with many cases of cirrhosis of the liver is a subject of a highly complex nature. Much further research will be necessary before a reasonable



understanding of the fundamental problems involved is reached and before an evaluation of the clinical significance of these problems is attained. In the meantime, from the results thus far obtained in this investigation it would appear that some partial tentative answers may be discussed more in expectation of attracting further thought than in trying to establish the value of their clinical implications.

In the first place, it became clear that in association with a variety of blood clotting defects, a varying degree of spontaneous proteolytic activity was present in the plasma of approximately one half of the cirrhotic patients studied in this investigation. Secondly, it was observed that this abnormal proteolytic activity could be effectively, although temporarily, inhibited by the intravenous infusion of Epsilon amino caproic acid. The data obtained indicate that following the administration of Epsilon amino caproic acid, definite inhibition to normal levels of spontaneous proteolytic activity was regularly obtained and that this inhibition lasted from two to four hours after the end of the administration of the drug. The inhibitory action was manifest in both the whole blood clot lysis and the euglobulin fibrinolytic activity and these changes paralleled each other. The effect on the whole blood clot lysis seemed, however, to be of longer duration. The inhibition of spontaneous proteolytic activity by an inhibitor of plasminogen activator may perhaps indicate that an activator rather than free plasmin was circulating in the blood of these cirrhotic patients. On the other hand, Epsilon amino caproic acid may be also an "in vivo" inhibitor of the enzyme plasmin itself. There did not seem to be any changes produced in Factor V, Factor VII, or fibrinogen in this short term experiment.

Due to the limitations inherent in clinical research, it has been difficult to separate the role of spontaneous proteolytic activity

from that of coagulation defects in the production of clinical hemorrhage, particularly in these patients with severely deteriorated liver function. However, the unusual opportunity of studying a cirrhotic patient with a marked degree of spontaneous proteolytic activity, severe defects in practically every stage of the blood clotting mechanism, and a readily observable bleeding site may contribute to effect such a separation. In this patient severe clinical bleeding following a minor surgical procedure, i.e., dental extraction, coincided with a high degree of plasma proteolytic activity and the hemorrhage failed to be stopped by orthodox therapeutic measures directed to compensate the deficiencies in the blood clotting process. On the other hand, when the inhibitory action of Epsilon amino caproic acid upon the spontaneous plasma proteolytic activity was at its peak, the hemorrhage ceased, only to reappear when this inhibitory action was exhausted and to stop again when the administration of Epsilon amino caproic acid was renewed. It would therefore appear that inhibition of the plasma proteolytic activity even in the presence of uncorrected blood coagulation defects was sufficient to modify the bleeding tendency of this patient. As a corollary, it could be assumed that, at least in this particular case, severe hemorrhage was specifically related to the presence of a high degree of spontaneous plasma proteolytic activity. Again, more research will be necessary before this assumption may be generalized. This will be particularly difficult in cases of gastro-intestinal bleeding in which the precise times of initiation and cessation of hemorrhage are not easily determined. However, since no toxic effects have followed the administration of Epsilon amino caproic acid its further evaluation may be justified.

It should also be kept in mind that spontaneous fibrinolytic activity, as was demonstrated by other patients in this

series, may not necessarily be associated with unusual bleeding following surgical trauma.

It seems improbable, finally, that spontaneous proteolytic activity may be significant in the production of the abrupt bleeding associated with portal hypertension and ruptured gastro-esophageal varices. In these situations powerful hemodynamic factors will be dominant. On the other hand, spontaneous proteolytic activity may be responsible for less severe episodes of gastro-intestinal hemorrhage sometimes observed in patients in whom gastro-esophageal varices have disappeared after adequate portal decompression.

### Summary and Conclusions

From the results obtained in this investigation the following conclusions may be permissible.

1. Definite abnormal spontaneous proteolytic activity was observed in the plasma of 49 per cent of the patients with cirrhosis of the liver in this series.
2. The intravenous infusion of Epsilon amino caproic acid resulted regularly in effective although temporary inhibition of spontaneous plasma proteolytic activity.
3. Epsilon amino caproic acid did not affect other clotting factors or fibrinogen levels.
4. The role of spontaneous proteolytic activity appeared to have been separated from that of the clotting mechanism defects in the production of severe bleeding tendency in the unusual case of one cirrhotic patient with a readily observable bleeding site.
5. Spontaneous fibrinolytic activity was not associated in other patients with unusual bleeding following surgical trauma.
6. It would appear improbable that spontaneous proteolytic activity could be significant in the abrupt hemorrhage associated with portal hypertension and ruptured gastroesophageal varices.
7. The use of plasmin inhibitors in cases

of cirrhotic patients with uncontrollable oozing seems to merit further study.

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