Fibrinolysis in colonic disease

C. H. J. SWAN, J. ALEXANDER WILLIAMS, AND W. T. COOKE

From the Nutritional and Intestinal Unit, The General Hospital, Birmingham

SUMMARY   Fibrinolytic activity of colic venous and arterial blood has been studied at laparotomy in 18 patients with ulcerative colitis or Crohn's colitis and compared with that of 17 patients with colonic carcinoma or diverticulosis. Using the dilute blood clot lysis time technique, no difference was detected between the fibrinolytic activity in colic venous blood from the two groups. When the clinical complications of bleeding or thrombosis are compared with fibrinolytic activity the only important association is between a low peripheral venous fibrinolytic activity and the occurrence of postoperative thrombo-embolic complications.

Recurrent haemorrhage from the inflamed colonic mucosa is a common feature of both ulcerative colitis and granulomatous disease of the colon. Since haemorrhagic diatheses are rarely encountered in these diseases, a defect in local haemostasis may contribute to this phenomenon. Fleisher and Loeb (1915) suggested that tissue fibrinolysis was a feature of normal regenerative processes, and Demuth and von Reisen (1928) postulated that the tissues activated a proteolytic pro-enzyme in the plasma. This view was endorsed by Astrup and Permin (1947), while Astrup and Albrechtsen (1957) subsequently measured plasminogen activator in thiocyanate tissue extracts. The endothelial lining of veins and venules was identified as the site of release of plasminogen activator by a histochemical technique termed 'fibrinolysis autography' (Todd, 1958 and 1964). Marked activity of plasminogen activator has been observed in areas of acute inflammation, and Kwaan and his coworkers (Kwaan, Cocco, and Mendeloff, 1964; Kwaan, Cocco, Mendeloff, and Astrup, 1969) have demonstrated increased plasminogen activator at the bases of crypt abscesses and in the lamina propria of rectal biopsies from patients with acute ulcerative colitis.

After observing early postoperative haemorrhagic complications in two patients with inflammatory large bowel disease, we were led to

consider the colonic vascular bed as the source of plasminogen activator. We postulated that sufficient activaters might have been liberated in these patients in sufficient quantity to be significant in the systemic circulation. The present study was undertaken to compare the fibrinolytic activity of blood draining normal and inflamed colon.

Patients and Methods

CLINICAL MATERIAL

Thirty-five patients were studied before and during operations on the large bowel. For the purpose of analysis the patients were divided into those with inflammatory and those with non-inflammatory disease of the bowel as shown in Table I. The patients with non-inflammatory

	Male	Female	Total	Age Range
Inflammatory disease				
Ulcerative colitis	7	5	12	26-60
Crohn's colitis	3	3	6	24-45
Non-inflammatory disease				
Carcinoma	5	6	11	55-78
Diverticulosis	2	4	6	56-67

Table I   *Distribution of clinical material*

Patient	Dilute Blood Clot Lysis Time (mean of two readings in minutes)				Bleeding		Postoperative Thrombosis
	Peripheral Venous Blood		Colic Arterial Blood	Colic Venous Blood	Before Operation	After Operation	
	Before Operation	At Operation					
With inflammatory conditions							
1	—	60	60	17	—	—	Deep venous
2	—	110	75	44	—	—	thrombosis
3	555	155	160	35	—	—	Deep venous
4	—	160	104	108	—	—	thrombosis
5	—	210	132	45	—	—	Pulmonary
8	—	35	35	21	—	—	embolism
11	—	88	75	30	—	—	—
13	—	100	150	56	—	—	—
14	—	157·5	180	142·5	+	—	—
15	215	40	60	30	+	—	—
18	120	140	195	117·5	—	—	—
19	285	90	90	90	—	—	—
20	3,120	215	185	55	+	—	Deep venous
22	140	40	25	25	—	—	thrombosis
25	675	120	135	60	—	—	—
31	530	112·5	140	85	—	—	—
32	—	100	95	40	—	—	—
33	1,440	70	65	40	—	—	Deep venous thrombosis
With non-inflammatory conditions							
6	—	158	130	140	—	—	—
7	—	30	30	25	—	—	—
9	—	45	Not obtained	26	—	—	—
10	—	120	120	40	—	—	—
12	—	48	50	37	—	—	—
16	187·5	82·5	95	95	—	—	—
17	105	100	100	67·5	—	—	—
21	—	60	65	30	—	—	—
23	1,452·5	120	105	75	—	—	—
24	—	420	190	90	+	—	—
26	225	45	57·5	42·5	—	—	—
27	150	110	Not obtained	65	—	—	—
28	165	45	60	55	—	—	—
29	175	60	70	30	—	—	—
30	402·5	75	80	50	—	—	—
34	—	105	120	60	—	—	—
35	270	60	75	40	—	—	—

Table II   *Results of investigations in 35 patients with inflammatory and non-inflammatory conditions*

diseases were undergoing colonic resections for carcinoma or diverticulosis coli without inflammatory complications.

TECHNIQUE

Fibrinolytic activity
Specimens from the colic arteries and veins were obtained during laparotomy. In the group with non-inflammatory bowel disease, these specimens were taken at sites as far removed as possible from any colonic lesion, whilst those from patients with inflammatory conditions were taken from the sites involved in the disease process. Eighteen patients also had preoperative peripheral venous specimens taken.

The fibrinolytic activity during operation was assessed simultaneously in peripheral venous, colic venous, and colic arterial blood by the dilute blood clot lysis time technique of Fearnley, Balmforth, and Fearnley (1957). All specimens, after withdrawing, were immediately placed in tubes surrounded by ice. The blood was then diluted 1:10 in cooled phosphate buffer, to which thrombin had previously been added. Clot formed within five minutes and after refrigeration at 4°C for 30 minutes, the tubes were transferred to a water bath at 37°C. Dissolution of the clot was regarded as the end point and was determined visually. (Dilute blood clot lysis time varies inversely with fibrinolytic activity, which means that the longer the dilute blood clot takes to lyse, the lower the fibrinolytic activity.)

Other laboratory studies
All patients had a preoperative assessment of haemoglobin, prothrombin activity, platelet count, and bleeding and clotting times. In five patients with inflammatory conditions levels of plasma fibrinogen and platelet counts were estimated in both colic artery and colic vein.

Hypoprothrombinaemia in three patients with ulcerative colitis was corrected before operation by parenteral vitamin K_1.

Clinical evidence of complications
Preoperative bleeding was taken as having occurred when, during the year before presenting, the history mentioned overt rectal bleeding and

the haemoglobin count fell below 10·0 g %.

Thrombotic complications after operation were recorded whenever there was clinical evidence of thrombosis or emboli sufficient to justify anti-coagulant therapy.

Results

The results are shown in Table II.

COMPARISON OF THE TWO GROUPS

There appears to be no difference in the fibrino-lytic activity in the colic venous blood between patients with inflammatory and non-inflammatory conditions (Fig.). This impression is confirmed by the statistical analysis of the results. Similarly there was no difference in the colic arterial fibrinolytic activity between the two groups (Fig.).

ARTERIOVENOUS DIFFERENCE

In 31 of the 35 patients studied, fibrinolytic activity was greater in the colic venous blood than in the colic arterial blood. This increase in activity as the blood passed through the capillary bed showed no significant difference as between the inflammatory and non-inflammatory groups (Fig.). Furthermore, in the five patients studied no difference in fibrinogen levels or platelet counts could be detected across the capillary bed.
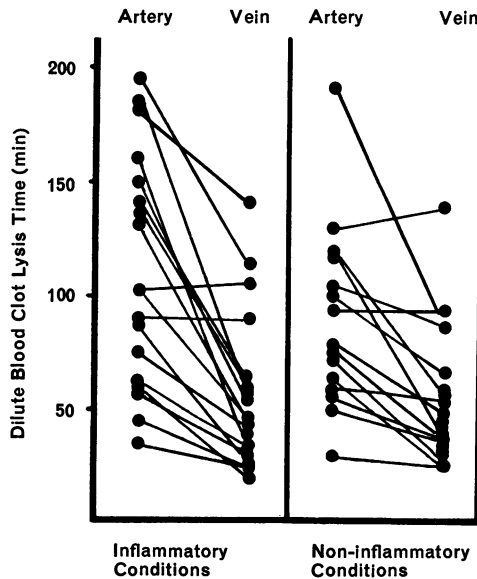

Fig. *The arteriovenous difference in fibrinolytic activity across the colonic capillary bed in patients with inflammatory and non-inflammatory conditions and the individual values for colic artery and vein.*

CLINICAL COMPLICATIONS

There was no correlation between the presence of preoperative bleeding and the lytic activity in the peripheral veins before operation or in any of the measurements during operation.

During the period of this study there were no postoperative haematomata or excessive operative bleeding. Four patients suffered post-operative peripheral deep venous thrombosis and one had recurrent pulmonary microemboli. In two of these five patients the dilute blood clot lysis time before operation was longer than the accepted range of normality which is from three to 11 hours (180 to 660 min) and a third patient had low but normal fibrinolytic activity before operation (Table I).

Discussion

There has been some published evidence to suggest that fibrinolytic substances might be liberated by inflammatory lesions of the alimentary tract and that these may play a part in producing alimentary bleeding. The earliest evidence came from the demonstration of plasminogen activator in extracts from cadaveric organs (Astrup, 1956; Albrechtsen, 1957 and 1958). Subsequently higher fibrinolytic activity was demonstrated in the venous blood, as compared with arterial blood, in limbs (Fearnley and Ferguson, 1957), in the thyroid (Bennet, Ogston, and McAndrew, 1967), in the uterus (Mackay, Das, Myerscough, and Cash, 1967), in the kidney (Holemans, Mann, and Cope, 1967), and in the stomach (Cox, Poller, and Thompson, 1967). Free plasmin was found in gastric venous blood and plasminogen activator in gastric mucosa by Cox *et al* (1967) who suggested that these factors may be important in patients with gastric bleeding. They concluded that the therapeutic application of an antifibrinolytic agent such as epsilon-aminocaproic acid might be useful.

Similar conclusions have been drawn from the results of investigating tissue fibrinolytic activity in ulcerative colitis. Histochemical assay of plasminogen activator in rectal biopsies during the acute phase of active ulcerative colitis has revealed greatly increased activity when compared with biopsies taken from patients with quiescent disease. It was therefore suggested that the release of excessive amounts of plasminogen activator from the bases of crypt abscesses might play a part in the mucosal bleeding of active ulcerative colitis. Furthermore, it has been suggested that antifibrinolytic agents might have a therapeutic role in ulcerative colitis (Sherry, 1966). Our study was originally undertaken to assess whether such increased local fibrinolytic activity was of a magnitude sufficient to play a part in postoperative haemorrhage in patients having proctocolectomy for colitis. The tech-

niques used in this study have revealed no differences between the fibrinolytic activity in the venous blood draining from an inflamed bowel and from a non-inflamed bowel. The fact that since this study began we have not experienced pelvic haematomata after more than 30 procto-colectomies suggests that this complication may be attributable to surgical technique rather than to disturbance of the blood-clotting mechanism. It is well recognized that proctectomy for colitis may be technically difficult when there is pararectal inflammatory infiltration and fibrosis.

Although the work of Kwaan *et al* (1964 and 1969) suggests that local antifibrinolytic therapy may be valuable in mucosal haemorrhage, our results reveal no indication for systemic antifibrinolytic therapy. In this regard, the incidence of thromboembolic complications in patients with low peripheral venous dilute blood clot lysis times before operation described in this series may be of particular importance. Graef, Baggenstoss, Sauer, and Spittell (1966) showed an increased tendency to thrombosis in patients with ulcerative colitis, which increased with age and debility. This association was not true of the patients investigated here, since both young and well patients experienced this complication. Nevertheless, since thrombotic complications have been described during epsilon-aminocaproic acid therapy (McNicol and Douglas, 1964), its indiscriminate systemic use in ulcerative colitis is considered inadvisable. Although the evidence is inconclusive at this stage, the dilute blood clot lysis time might prove useful as a preoperative screening test to select those patients who are at risk for postoperative thrombo-embolism, since in this series three patients who suffered deep venous thrombosis or pulmonary embolism were shown to have low peripheral venous fibrinolytic activity before operation.

References

Albrechtsen, O. K. (1957). The fibrinolytic activity of human tissues. *Brit. J. Haemat.*, 3, 284-291.

Albrechtsen, O. K. (1958). The fibrinolytic agents in saline extracts of human tissues. *Scand. J. clin. Lab. Invest.*, 10, 91-96.

Astrup, T. (1956). The biological significance of fibrinolysis. *Lancet*, 2, 565-568.

Astrup, T., and Albrechtsen, O. K. (1957). Estimation of the plasminogen activator and the trypsin inhibitor in animal and human tissues. *Scand. J. clin. Lab. Invest.*, 9, 233-243.

Astrup, T., and Permin, P. M. (1947). Fibrinolysis in the animal organism. *Nature (Lond.)*, 159, 681-682.

Bennett, N. B., Ogston, C. M., and McAndrew, G. M. (1967). The thyroid and fibrinolysis. *Brit. med. J.*, 4, 147-148.

Cox, H. T., Poller, L., and Thompson, J. M. (1967). Gastric fibrinolysis. A possible aetiological link with peptic ulcer. *Lancet*, 1, 1300-1302.

Demuth, F., and Riesen, I. von. (1928). Eiweissstoffwechsel normaler und bosartiger Gewebe in vitro. *Biochem. Z.*, 203, 22-49.

Fearnley, G. R., Balmforth, G., and Fearnley, E. (1957). Evidence of a diurnal fibrinolytic rhythm: with a simple method of measuring natural fibrinolysis. *Clin. Sci.*, 16, 645-650.

Fearnley, G. R., and Ferguson, J. (1957). Arterio-venous difference in natural fibrinolysis. *Lancet*, 2, 1040-1041.

Fleisher, M. D., and Loeb, L. (1915). On tissue fibrinolysins. *J. biol. Chem.*, 21, 477-501.

Graef, V., Baggenstoss, A. H., Sauer, W. G., and Spittell, J. A. (1966). Venous thrombosis occurring in non-specific ulcerative colitis. *Arch. intern. Med.*, 117, 377-382.

Holemans, R., Mann, L. S., and Cope, C. (1967). Fibrinolytic activity of renal venous and arterial blood. *Amer. J. med. Sci.*, 254, 330-333.

Kwaan, H. C., Cocco, A., and Mendeloff, A. I. (1964). Histologic demonstration of plasminogen activation in rectal biopsies from patients with active ulcerative colitis. *J. Lab. clin. Med.*, 64, 877.

Kwaan, H. C., Cocco, A., Mendeloff, A. I., and Astrup, T. (1969). Fibrinolytic activity in the normal and inflamed rectal mucosa. *Scand. J. Gastroent.*, 4, 441-445.

Mackay, A. V. P., Das, P. C., Myerscough, P. R., and Cash, J. D. (1967). Fibrinolytic components of human uterine arterial and venous blood. *J. clin. Path.*, 20, 227-230.

McNicol, G. P., and Douglas, A. S. (1964). ε-Amino-caproic acid and other inhibitors of fibrinolysis. *Brit. med. Bull.*, 20, 233-239.

Sherry, S. (1966). Fibrinolytic mechanisms in tissue injury. *Gastroenterology*, 51, 901-912.

Todd, A. S. (1958). Fibrinolysis autographs. *Nature (Lond.)*, 181, 495-496.

Todd, A. S. (1964). Localisation of fibrinolytic activity in tissues. *Brit. med. Bull.*, 20, 210-212.