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# Fibrinolytic activity in malignant disease

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SYNOPSIS Resting fibrinolytic activity and fibrinolytic capacity were compared in 31 patients with malignant disease and in 24 control subjects without malignant disease.

Patients with malignant disease had a lower mean fibrinolytic activity: this was particularly marked in those with disseminated disease. In contrast, patients with malignant disease had a fibrinolytic capacity which did not differ from that of the control subjects.

The association of overt or latent malignancy with thrombosis has been recognized for over 100 years with the observations of Trousseau (1865) and Welch (1899). Both Trousseau and Welch pointed to a possible change in the composition of the blood to explain the association.

A number of studies have demonstrated abnormalities in the haemostatic mechanism in patients with malignant disease. A pathological increase in blood fibrinolytic activity was observed in some patients with carcinoma of the prostate with metastases (Tagnon *et al*, 1952, 1953), although Swan and Kerridge (1965) were unable to detect any increase in fibrinolytic activity in a series of 61 patients with carcinoma of the prostate. Soong and Miller (1970) observed increased fibrinolysis in nine of their 100 patients with disseminated malignancy.

In this study resting fibrinolytic activity and the fibrinolytic activity induced by venous occlusion (fibrinolytic capacity) have been measured in a series of patients with malignant disease.

## Methods

### FIBRINOLYTIC ACTIVITY AND FIBRINOLYTIC CAPACITY

A sphygmomanometer cuff (22 × 12 cm) was applied to the upper arm and inflated to midway between the systolic and diastolic arterial blood pressure for 10 minutes. Blood was then withdrawn from an antecubital vein of both the occluded and non-occluded arm, and plasminogen activator levels were measured in the plasma separated from each sample. The activator levels were assessed by performing euglobulin clot lysis times by the method of Nilsson and Olow (1962). The results are expressed by plotting the times logarithmically against units of fibrinolytic activity (Sherry *et al*, 1959), 10 units being arbitrarily equated with a lysis time of 50 minutes.

Plasminogen activator was also measured by applying 30 $\mu$l samples of resuspended euglobulin precipitate to fibrin plates prepared from 0·2% human fibrinogen (Grade L, A.B. Kabi, Stockholm). After incubation at 37°C for 24 hours the area of lysis was estimated for the product of two diameters at right angles to each other. Urokinase (Leo Pharmaceutical Products, Ballerup, Denmark) was used as a reference standard. The areas of lysis produced by the urokinase standard dilutions were plotted on a log-log scale, and the fibrinolytic activity of the euglobulin precipitate was obtained by interpolation and expressed as Ploug units of urokinase (Ploug and Kjeldgaard, 1957).

### Patients

Thirty-one patients with malignant disease were studied (15 men and 16 women) with an age range of 21 to 85 (mean 65) years. The group comprised patients with carcinoma of the colon or rectum (8), carcinoma of the breast (7), carcinoma of the prostate (4), carcinoma of the oesophagus (4), carcinoma of the bronchus (3), renal carcinoma (2), carcinoma of the ovary (1), teratoma of testis (1), and disseminated melanoma (1). Eighteen patients were judged to have localized disease and 13 had distant and widespread metastases.

Twenty-four volunteers (12 men and 12 women) aged 27 to 82 (mean 55) years acted as a control group. Most were hospital inpatients suffering from a

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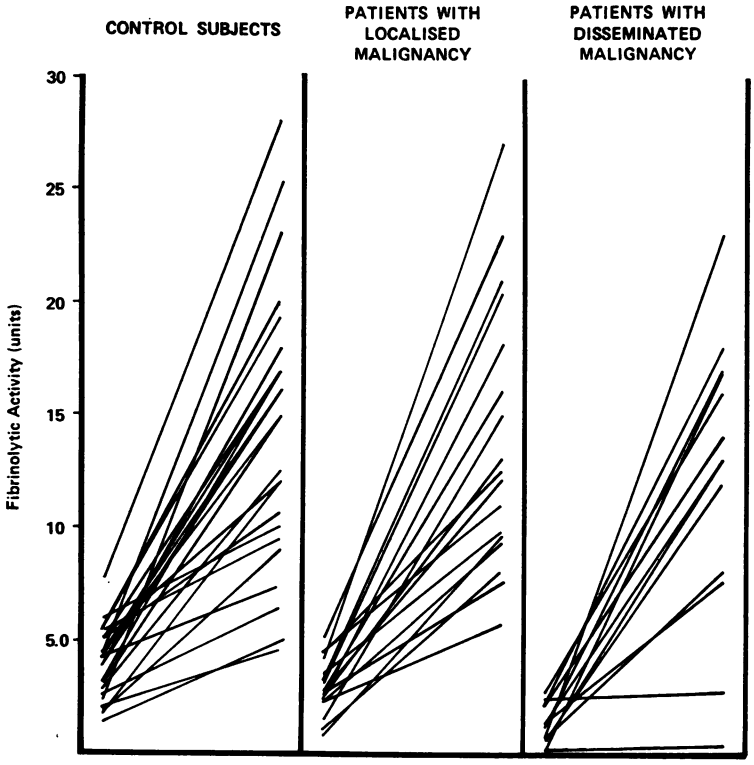


Figure *Individual fibrinolytic activities before and after venous occlusion ('fibrinolytic capacity') in control subjects and in patients with localized and disseminated malignant disease.*

variety of non-malignant diseases; the remainder were healthy members of the medical staff.

## Results

The individual values for the pre- and post-occlusion fibrinolytic activity, as assessed by the euglobulin clot lysis time, in the control subjects and the patients with malignant disease are illustrated (figure). The total group of 31 patients with malignant disease had a substantially lower mean fibrinolytic activity (2·2 ± 1·4 units) than the control subjects (4·0 ± 1·6 units): the difference was highly significant ( $P < 0.001$). The difference between the means for the patients with localized malignant disease and the control subjects (table) was also significant ($P < 0.05$) while the difference between the patients with disseminated malignant disease and those with localized malignant disease was highly significant ( $P < 0.001$).

The differences between the groups studied, as shown by the euglobulin clot lysis technique, were mirrored by those obtained using the activity of euglobulin precipitates on unheated fibrin plates to assess plasma fibrinolytic activity (table).

| | *Group* | | |
|---|---|---|---|
| | *Control Subjects (24)* | *Localized Malignant Disease (18)* | *Disseminated Malignant Disease (13)* |
| Fibrinolytic activity | | | |
| Lysis time (units) | 4·0 ± 1·6 | 3·0 ± 1·2 | 1·3 ± 0·9 |
| Fibrin plate (units) | 0·65 ± 0·32 | 0·44 ± 0·19 | 0·31 ± 0·12 |
| Fibrinolytic capacity | | | |
| Lysis time (units) | 14·3 ± 6·1 | 14·3 ± 5·8 | 12·4 ± 6·3 |

Table *Mean values (± 1 SD) for fibrinolytic activity and fibrinolytic capacity in the control subjects and in patients with localized malignant disease and disseminated malignant disease*

In contrast to the differences in the pre-occlusion fibrinolytic activity between the patients with malignant disease and the control subjects the mean values for the post-occlusion fibrinolytic activity (fibrinolytic capacity) did not differ significantly when patients with malignancy and control subjects were compared. Indeed, the mean rise in fibrinolytic

activity induced by venous occlusion was almost identical in the three groups studied.

## Discussion

This study has demonstrated that malignant disease is associated with a reduction in plasma fibrinolytic activity. This reduction was seen in both techniques used—the euglobulin clot lysis time and the activity of the euglobulin precipitate on plasminogen-rich fibrin plates. Since the latter technique is not influenced by the fibrinogen or plasminogen content of the patient's plasma it is likely that the low activity results from decreased activator levels rather than the effect of increased substrate in the assay procedure. It is notable that no patient with malignant disease studied had a level of fibrinolytic activity above the normal range. The explanation for the low levels of fibrinolytic activity in patients with malignant disease is uncertain. The major source of plasminogen activator in the circulation is probably the vascular endothelium (Todd, 1959), and the origin of the increase in circulating activator during venous stasis is considered to be the venous endothelium or the vasa vasorum (Pandolfi *et al*, 1967). In the present study the output of activator in response to venous occlusion or 'fibrinolytic capacity' (Robertson *et al*, 1972) was normal in the patients with malignant disease, indicating that the low circulating level is not due to decreased synthesis in the vessel wall or to some factor preventing its release. It is possible that it results from rapid neutralization by inhibitors in the plasma: indeed, high levels of fibrinolytic inhibitors have been described in patients with malignant disease (Soong and Miller, 1970).

Reduced fibrinolytic activity has been noted in patients with hepatic metastases (Ogston *et al*, 1971). The present study suggests that low levels of fibrinolytic activity in patients with malignant disease are not specifically secondary to the presence of hepatic metastases since a number with low activity had no clinical or laboratory evidence of such metastases.

Although the relationship of fibrinolytic activity to thrombosis is not established impaired activity would theoretically favour thrombus formation and persistence. The results of this study suggest that reduced fibrinolytic activity may be one explanation for the high incidence of thrombosis in malignant disease.

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