

Short Communication

PLASMA CONCENTRATIONS OF THE PLATELET-SPECIFIC
 β -THROMBOGLOBULIN IN MALIGNANT DISEASE

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MALIGNANCY is commonly associated with disorders of haemostasis. Patients with malignant disease show evidence of hyper- and hypocoagulable states (Miller *et al.*, 1967). The latter state may arise from the former as clotting factors are consumed, for example by fibrin deposition around the tumour. O'Meara (1958) proposed that deposition around tumour cells is caused by procoagulant activity of the tumour itself and provides a matrix on which the tumour can grow. In addition to coagulant and fibrinolytic activity, many human tumour-cell lines promote platelet aggregation *in vitro* (Gasic *et al.*, 1976).

Platelet aggregation is associated with the release of a number of proteins, including a platelet-specific β -globulin, β -thromboglobulin (Moore *et al.*, 1975). Plasma levels of β -thromboglobulin should therefore reflect platelet aggregation *in vivo*. We report here our findings on β -thromboglobulin in patients with malignant disease.

β -Thromboglobulin was measured in platelet-poor plasma by radioimmunoassay, using a commercial kit (Radiochemical Centre, Amersham). Blood samples were handled and plasma separated and stored as recommended by the manufacturers. Control samples were taken from hospital staff and patients without evidence of thromboembolic or malignant disease.

Three patients were originally referred to the Department of Nuclear Medicine with pulmonary embolism (confirmed by ventilation-perfusion lung scan). Blood was taken at the time of scanning for plasma β -thromboglobulin determination. On further investigation these 3 patients were found to have carcinoma (pancreas, lung and kidney).

The remaining patients did not suffer thromboembolic episodes and had been referred to the Department of Nuclear Medicine for bone scanning or to St Luke's Hospital for radiotherapy and/or chemotherapy. Patients were investigated by conventional clinical, radiological and radioisotope methods, and were staged according to the TNM system (IUCC, 1968). Patients with a staging of T₄, N₃ or M₁ were classed as having advanced malignancy. In addition to plasma β -thromboglobulin, the platelet count, prothrombin time and serum fibrinogen/fibrin degradation products (FDP) were measured. Of the 23 patients assessed in this manner, 17 had advanced malignancy and the remainder had early tumours.

Plasma β -thromboglobulin levels in controls and patients with early tumours, advanced malignancy and malignancy complicated by pulmonary embolism, are shown in the Figure. Mean values were, respectively, 25.8 ng/ml, 26.0 ng/ml, 48.2 ng/ml and 100.6 ng/ml. Plasma β -thromboglobulin levels were significantly raised in

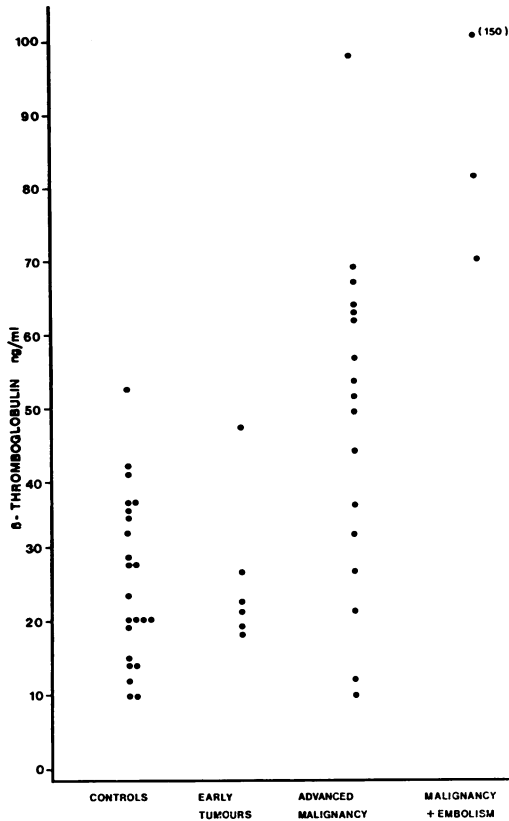


FIG.— β -Thromboglobulin in controls and patients with malignancy.

Table.—Plasma β -thromboglobulin in patients with various malignancies

Diagnosis	β -Thromboglobulin (ng/ml)
Early tumours	
Breast	23
Prostate	27
Larynx	21
Brain (astrocytoma)	48
Myeloma	18
Lymphoma (non-Hodgkin's)	19
Advanced malignancy	
Lung (squamous)	52
Lung (squamous)	10
Lung (undifferentiated large-cell)	54
Lung (oat cell)	69
Lung (oat cell)	57
Breast	63
Breast	12
Breast	45
Breast	98
Kidney (hypernephroma)	27
Bladder	64
Ovary	62
Larynx	67
Testis (teratoma)	21
Nasopharynx	32
Antrum	36
Malignancy with pulmonary embolism	
Pancreas	150
Lung	82
Kidney (hypernephroma)	70

patients with advanced malignancy when compared with controls ($P < 0.001$; Mann-Whitney U test) and with those with early tumours ($P < 0.025$). When malignancy was complicated by pulmonary embolism, higher levels of plasma β -thromboglobulin were found ($P < 0.01$).

Among the patients with advanced disease without thromboembolism, 1 had a low platelet count and 4 had raised serum FDP levels. None of these findings was statistically significant (χ^2 test). No correlation was found between plasma β -thromboglobulin and platelet count, prothrombin time or serum FDP levels.

β -Thromboglobulin has been suggested as a screening test for deep-vein thrombosis (Ludlam *et al.*, 1975). However, it appears from our findings that patients with malignant disease would produce a

significant number of false-positive results. Nevertheless the results in our 3 patients with malignancy and pulmonary embolism suggest that the effects of malignancy and venous thromboembolism on plasma β -thromboglobulin levels may be additive, though further studies are needed to confirm this. It may be that, following the determination of "baseline" values for an individual patient, serial determinations of β -thromboglobulin could be used to detect thrombotic complications in cancer patients. The effects of surgery, radiotherapy and chemotherapy must first, however, be investigated.

Plasma β -thromboglobulin concentrations appear to correlate inversely with platelet survival (Doyle *et al.*, 1979). Patients with advanced malignancy have shortened platelet survival (Harker & Slichter, 1972). Our results are not, therefore, unexpected. Experimental studies have shown that platelet aggregation may occur at several stages of blood-borne

metastasis (Warren, 1976). Elevated plasma β -thromboglobulin suggests that such processes also occur in patients with malignant disease. Metastasis formation in animals can be inhibited by induction of thrombocytopenia or by inhibition of platelets by aspirin (Gasic *et al.*, 1973). Should such therapeutic measures be applied to human cancer, β -thromboglobulin could be used as a marker for monitoring treatment.

It is not yet certain whether the high plasma β -thromboglobulin levels in advanced malignancy reflect the greater tumour load or the aggressive nature of the tumours. Whilst murine tumours with platelet-aggregating activity have greater metastatic potential (Gasic *et al.*, 1973), this has yet to be established for human tumours. Furthermore a small, localized tumour may not cause sufficient aggregation to increase peripheral plasma β -thromboglobulin levels. Nevertheless the *in vitro* studies of Gasic *et al.* (1976) are encouraging, and we suggest that platelet behaviour deserves further investigation in patients with cancer.

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