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Erythrocyte Stearic to Oleic Acid Ratio in Prostatic Carcinoma

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Summary—The red cell membrane stearic acid to oleic acid ratio was analysed in 34 men with histologically proven carcinoma of the prostate and distant metastases. This ratio was expressed as the saturation index (SI). A mean SI of 0.97 was found in control patients without evidence of any malignancy whereas all patients with advanced prostatic cancer showed a reduced stearic to oleic acid ratio (mean SI 0.466). Untreated patients had a significantly lower SI (mean 0.36) than those who had responded to hormonal therapy (mean 0.547; $P<0.0001$). A drop in SI correlated well with more advanced disease as judged by radiological findings and serum PSA.

It is suggested that red cell membrane SI correlates well with radiological and biochemical markers of advanced prostatic carcinoma and may be used as a marker to assess progress and response to treatment.

Carcinoma of the prostate is now the second commonest cause of death from cancer in men in the United Kingdom. A total of 7500 new cases are diagnosed annually and the incidence of the disease appears to be increasing. Since 60% of patients present with established metastases, the prognosis is poor. The most efficacious treatment is androgen withdrawal either by orchiectomy, oestrogens, LH–RH analogues or antiandrogens. Response rates of up to 80% can be expected after treatment and on average the response will last for 12 months before relapse occurs. It would be valuable to have an indicator of response and prognosis for patients with advanced prostatic cancer.

It is now well established that the properties of plasma membranes of transformed and malignant cells differ from those of normal cells (Wood *et al.*, 1985a; Habib *et al.*, 1987). A general and concurrent finding has been that in the malignant cell there is an increased membrane fluidity (as judged by fluorescent probe and magnetic resonance analysis). These changes have been found to occur not only in the cell membranes of the malignant tissue itself but also in the cell membranes of erythrocytes from patients with malignancy. The increased membrane fluidity is due to a higher content of unsaturated fatty acids than in normal cells. It has also been shown that the major change in the fatty acids is in the stearic and oleic acid fractions and that the ratio of these 2 fatty acids could be used as an index of fatty acid saturation in the cell membrane (referred to as the "saturation index" (SI)).

We present the results of a study of the cell membrane fluidity of red cells in patients with advanced prostatic cancer and the significance of the primary findings is discussed.

Patients and Methods

A total of 34 men with histologically proven carcinoma of the prostate were studied; 30 had metastases, 2 had liver metastases and 2 had locally advanced tumours with pelvic lymph node involvement. In 11 cases no treatment had been given. Seventeen patients were undergoing hormone treatment, 9 with the antiandrogen cyproterone acetate and 8 with a combination of cyproterone acetate and an LH-RH analogue. Six other patients had progressive disease following previous hormonal therapy. Five cases were studied sequentially before

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and after treatment. Twelve healthy male volunteers were taken as controls.

A 5 ml blood sample in EDTA was taken from all patients and centrifuged at 1000 rpm to precipitate red blood cells. All samples were stored at −20°C until processed. Total lipid extraction was carried out following the method used by Apostolov and Barker (1981) and Folch *et al.* (1957). The extracts were analysed by temperature programmed (160–260°C at 4/min) gas liquid chromatography of the fatty acid methyl-esters using a 2.1 × 2 mm 1D glass column packed with a 3% SP-2310/2% SP-2300 on 100/120 mesh chromosorb W (Supelco Inc). This allowed separation of C16, C18, C20 and C22 fatty acids. The stearic to oleic acid ratio was taken as the indication of membrane fluidity or saturation index.

Statistical analysis was performed using the Mann-Whitney U test.

Results

Normal male controls had a mean saturation index of 0.944 (range 0.86–1.057). In all 3 groups of patients, significantly lower ratios of stearic to oleic acid were found than in the control group ($P = <0.05$). The untreated group exhibited significantly lower saturation indices (mean 0.485, range 0.34–0.59) than the group undergoing hormone treatment (mean 0.64, range 0.41–0.69) ($P = <0.05$). There was no significant difference between the treated and the relapsed group (Fig. 1).

In all 5 patients in whom sequential pre- and post-treatment erythrocyte saturation indices were measured, a rise was seen after treatment commenced (Fig. 2). It was not possible with such small numbers to relate the saturation index to the grade or local stage of the tumour.

Further studies are required to look at the changes in prostatic tissue cell membrane fluidity in addition to red cell membrane fluidity.

Discussion

The cell membrane is an essential component of cellular homeostasis (Cooper, 1977), providing a fluid barrier to the passage of some components whilst facilitating transport of others. In general, higher membrane fluidity leads to increased cell metabolism and higher division rates (increased metabolism and capacity for division are the essential characteristics of malignant cells). The lipid bilayer determines the fluidity of the cell membranes. The degree of this fluidity is dependent

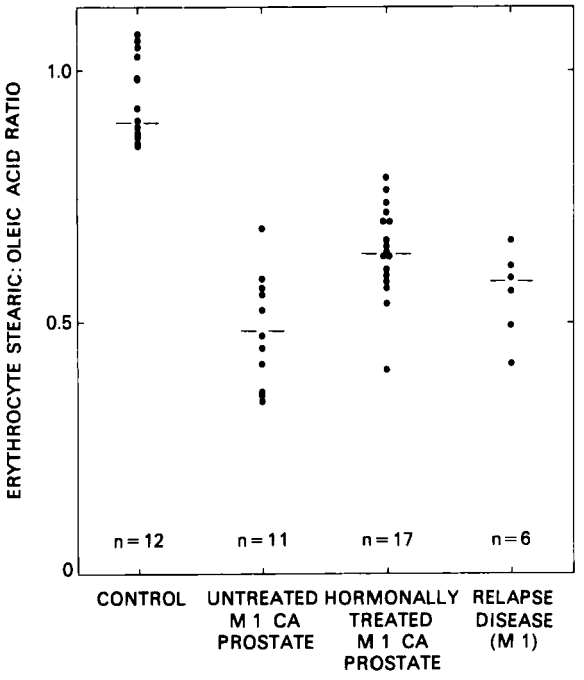

Fig. 1 Erythrocyte stearic:oleic acid ratio in controls and patients with advanced prostatic cancer.

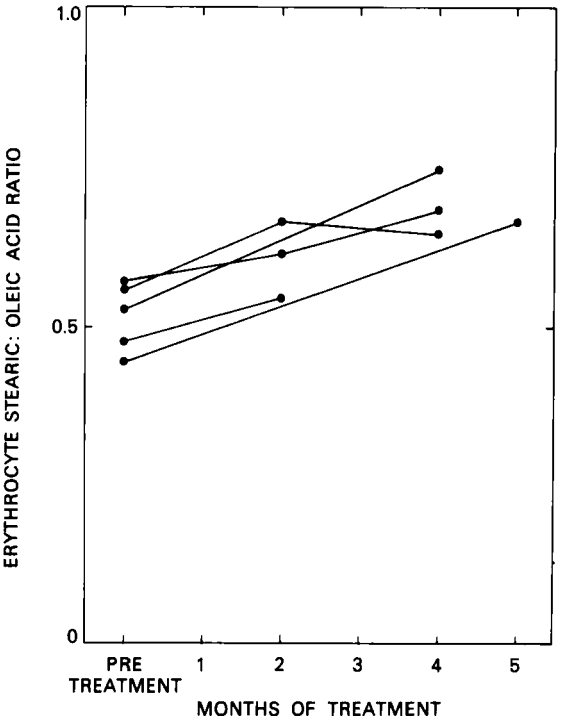

Fig. 2 Change in erythrocyte stearic:oleic acid ratio following hormonal therapy for advanced prostatic cancer.

on the ratio of saturated to unsaturated fatty acids: the greater the degree of unsaturation the more fluid the cell membrane. It has been shown that a significant decrease in cell membrane saturation occurs in liver tumour cells (Wood *et al.*, 1985a) and in leukaemic white blood cells (Apostolov *et al.*, 1985) as compared with normal cells. A similar change has been found in the circulating erythrocytes of patients with solid tumours (Wood *et al.*, 1985b), possibly due to an effect on the bone marrow produced by factors released by the tumour tissue. The available evidence suggests that a decrease in fatty acid saturation index is a feature of malignant transformation in human cells.

This study has confirmed that a decrease in fatty acid saturation is seen in patients with advanced prostatic carcinoma. Further study will be necessary to ascertain any relationship between tumour stage and grade and the level of desaturation. The study has also shown an increase in saturation index in patients after starting hormone treatment. This seems to imply a general beneficial effect of hormone treatment in patients with prostatic cancer. The reasons for these changes in erythrocyte fatty acid saturation have yet to be determined, but it seems to offer an opportunity for study of the mechanisms involved in prostatic carcinogenesis.

Membrane fluidity may play an important part in determining the spatial orientation of receptor molecules in the cell membrane. It would also be of interest to establish whether alterations in the fatty acid composition of the malignant cell membrane could alter receptor configuration and in so doing enhance or reduce the cell's affinity for hormonal interaction.

Further studies are being conducted in this field.

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