Time 16.00 cont.

0844 FIBRIN AND CANCER CELL GROWTH: PROBLEMS IN THE EVALUATION OF EXPERIMENTAL MODELS.

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Studies on the role of fibrin in experimental cancer growth should take into account the following problems: 1) during growth and dissemination of experimental tumours, haemostatic changes may occur which vary depending on the route of inoculation of cancer cells and on the tissue where the tumour grows. Thrombocytopenia, haemolytic microangiopathic anaemia and decreased survival of fibrinogen were observed during spontaneous dissemination to the lung of i.m. implanted Lewis Lung Carcinoma cells, not when metastatic growth occurred after surgical removal of the primary tumour or lung nodules developed following i.v. injection of the same cells. 2) Treatment of experimental tumours with drugs active on the haemostatic system may have different effects depending on the stage of growth of the tumour. This observation (which we have made with both warfarin and a defibrinating enzyme in murine metastasizing tumours) could suggest that fibrin may play different roles at different phases of cancer cell growth. 3) The supposed antitumoral activity of drugs active on the haemostatic system may be also influenced by other factors, such as a direct activity on cancer cells or on the host's immune system or on blood supply to the tumour. As an example, non steroidal antiinflammatory drugs may act not only as antiplatelet agent, but also as inhibitors of prostaglandin synthesis by cancer cells and some snake venoms may influence cancer cell growth not only through defibrination, but also with their immunodepressant properties. (Supported by Italian CNR and NIH.NCI, USA).

0845 COUMARIN ANTICOAGULATION AND EXPERIMENTAL METASTASES

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Under experimental conditions oral anticoagulants of the coumarin type retard primary tumour growth and drastically reduce the incidence of distant metastases from rodent tumours. Employing different dose schedules it was found that satisfactory therapeutic anticoagulation and long-term treatment are pre-requisites for the anti-tumour activity. The equivocal effects of other anticoagulants, such as snake venoms, heparin and "antiplatelet" drugs on tumour growth and dissemination suggest a unique mechanism of coumarin derivatives. There is experimental evidence that the anti-tumour action is not a direct drug effect on malignant cells but specifically mediated by the vitamin K antagonism of the coumarins. Altered blood coagulability appears not to be the sole mechanism by which oral anticoagulants exert their anti-metastatic effect.

There is a theoretical role for vitamin K dependent γ-carboxyglutamic acid containing proteins in interactions between tumour and host. Vitamin K deficiency increases the phagocytic activity of peritoneal macrophages after nonspecific immunostimulation; this might be an important factor in controlling tumour growth. The synthesis of serine proteases with clot promoting activity by tumour cells is partly vitamin K dependent; these proteases could also have considerable implications for the metastatic potential of blood borne cancer cells.

0846 A CLINICAL TRIAL OF WARFARIN IN CANCER (Ca)

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A 5-year study of the effect of warfarin on the natural history of human ca is in progress. The basis for this study is: the occurrence of clots at ca sites, uptake of tagged fibrinogen or anti-fibrinogen antibody into ca, occurrence of localized and disseminated intravascular coagulation with ca, evidence from experimental ca systems of involvement of the clotting mechanism in the growth and spread of ca, and preliminary evidence of such involvement in man. Patients with either limited or extensive ca of the lung or large bowel, advanced prostatic ca or recurrent head and neck ca are randomized by hospital and performance status within 1 of 9 different strata to receive standard therapy with or without warfarin. Study design includes: 1)definition of exclusion criteria, 2)comparison of included vs. excluded patients, 3)classification and recording of bleeding complications, 4)serial tests for intravascular coagulation, 5)blinded reading of x-rays and scans used to follow tumor responses and, 6)use of physician extenders for patient screening and data collection. Patients are evaluable only if on-study at least 2 weeks. Response criteria include survival, tumor response, changes in laboratory tests, causes of death and autopsy findings. Supported by the VA Cooperative Studies Program (CSP#75) of the VA Medical Research Service.