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A COMPARISON OF THE ABILITY OF HYDRALAZINE AND CADRALAZINE TO ENHANCE THE ANTI-TUMOUR ACTION OF HYPOXIC-CELL CYTOTOXIC AGENTS.

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The anti-hypertensive drug hydralazine (HDZ) can significantly decrease blood flow in certain tumours, leading to a concomitant increase in tumour hypoxia. Such an effect sensitizes solid tumours to various modalities including certain drugs and hyperthermia. Cadralazine (CDZ) is a new agent believed to be as effective as HDZ, yet far less toxic. The aim of our current study was to compare CDZ with HDZ in terms of its ability to modify tumour blood flow and to enhance the action of various hypoxic-cell cytotoxins. Using the techniques of Hoechst 33342 fluorescent labelling and 86-RbCl extraction we found that both HDZ and CDZ could reduce tumour blood flow to between 10-20% of control values within 1 hour following drug injection. But, whereas the HDZ-induced changes in blood flow had almost returned to normal by 12 hours, the tumour blood flow in CDZ treated mice was only 50% of that measured in controls. Additional data will be presented on the ability of these agents to enhance the damage produced by RSU-1069 and hyperthermia in tumours and normal tissues, and these results related to the blood flow changes.

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EFFECT OF CANCER CHEMOTHERAPY ON RADIATION RESISTANT HYPOXIC CELLS IN SOLID TUMOURS

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Radioresistant hypoxic cells may also be resistant to anti-cancer drugs due to their low rate of proliferation or because they are situated in poorly vascularized environments. We have investigated the effect of five major anti-cancer drugs on the hypoxic cells of a C3H mammary carcinoma by the clamped Local Tumour Control assay. The hypoxic fraction for untreated tumours was estimated to be 5.4%. Following Mitomycin C, Adriamycin or Cyclophosphamide treatment (administered 4 hours after irradiation) both the hypoxic fraction and the absolute number of hypoxic cells were significantly reduced. These three drugs have previously been shown to enhance the radiation response. On the other hand, Cisplatinum and Bleomycin did not significantly change the number of hypoxic cells or size of the hypoxic fraction from that measured in untreated tumours. This correlates with the lack of any effect on tumour control by these two agents. In a similar study, using the Tumour Regrowth Delay assay, no correlation between hypoxic cytotoxicity and the ability of drugs to cause regrowth delay could be demonstrated. We conclude that the ability of adjuvant drugs to enhance radiation damage and improve local tumour control is related to the specific hypoxic cell killing by these agents.

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INDUCTION OF CYTOCHROME P-450IA1 IN HUMAN BREAST CANCER CELL LINES.

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The objective of the study is to investigate the determinants of inter-individual variation in the induction of human cytochrome P-450IA1. High inducibility of enzyme activities associated with the gene product has previously been suggested to confer an increased risk of developing lung cancer.

The induction of IA1 was studied in human mammary cell lines. Confluente cultures were treated with TCDD, and the expression of IA1 was measured by slot blot analysis. The cell lines could be divided into high, medium and low/non-responders. To investigate if the lack of response is due to a defective or missing receptor for TCDD or altered regulatory sequences, the cells were transfected with a construct containing the complete regulatory sequence fused to chloroamphenicol acetyl-transferase gene, using a polybrene-DMSO protocol. The CAMA-1 cell line was non-responsive in both assays, suggesting that this cell line is missing or having an altered TCDD receptor. MCF-7 cells are responsive in both assays.

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OVEREXPRESSION OF C-MYC ONCOGENE IN V-RAF TRANSFORMED HUMAN BLADDER EPITHELIAL CELLS.

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The objective of this study has been to study the multistage process of human bladder carcinogenesis by introducing molecular cloned, activated oncogenes into cells. Non-malignant, human bladder epithelial cells (HCV 29) have been transformed by transfection with a plasmid carrying the v-raf oncogene. The tumorigenic transfectants were identified as human and of HCV 29 origin by HLA-typing and Southern blot analysis. As expected both the primary tumorigenic transfectants and cell lines obtained from the induced tumors expressed v-raf mRNA and v-raf protein. In addition we observed that c-myc was over-expressed in both primary transfectants and cell lines established from tumors. This experiment suggests that raf may enhance the expression of the c-myc oncogene and cooperate with c-myc in the transformation of human bladder cells in vitro.