

## THE METABOLIC ACTIVATION OF CHRYSENE

R.M. Hodgson, P.L. Grover and P. Sims

Chester Beatty Laboratories, Institute of Cancer Research, London SW3 6JB, U.K.

The polycyclic hydrocarbon chrysene is a weak carcinogen on mouse skin, but the dihydrodiol precursor of its 'bay-region' diol-epoxide is more carcinogenic than the parent compound. The chrysene-nucleoside adducts formed in cultured hamster embryo cells, a rat-liver microsomal metabolising system containing DNA and mouse skin *in vivo* treated with  $^3\text{H}$ -chrysene were examined. In hamster embryo cells, the major DNA-adducts had chromatographic properties identical to those of adducts formed when the *anti* isomer of the 'bay-region' diol-epoxide of chrysene reacts with DNA. Both guanosine- and adenosine-hydrocarbon adducts were detected. NMR studies on the guanosine adducts showed that the hydrocarbon is attached at the exocyclic amino group of guanine. In the rat-liver microsomal preparations and in mouse skin treated with  $^3\text{H}$ -chrysene, adducts having chromatographic properties identical to those formed when *anti*-chrysene 1,2-diol 3,4-oxide reacts with DNA were also detected. Additional adducts were detected in these systems which differed in their chromatographic mobilities from synthetic DNA-chrysene adducts formed from *anti*-chrysene 1,2-diol 3,4-oxide. The results show that metabolic activation of chrysene occurs via this 'bay-region' diol-epoxide but suggest that, in some biological systems, this may not be the sole route for the metabolic activation of chrysene.

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MONOCLONAL ANTIBODIES IN HEPATOCARCINOGENESIS. C.H. Holmes, E.B. Austin, B. Gunn, M.J. Embleton and R.W. Baldwin. Cancer Research Campaign Laboratories, University of Nottingham, Nottingham NG7 2RD, U.K.

In order to examine the cellular events associated with the progression to malignancy in experimental hepatocarcinogenesis we have produced a panel of 3 monoclonal antibodies which are directed against normal adult rat hepatocytes. We have used an immunohistochemical technique to examine the reactivity of these antibodies with normal adult liver, with foetal and neonatal liver, and with azo dye induced premalignant and malignant liver lesions including a range of 32 primary liver carcinomas. Three antibody-defined phenotypes were sequentially expressed during normal hepatocyte differentiation and these same 3 phenotypes were also expressed by the 32 liver carcinomas. The phenotype expressed by any particular tumour depended largely on its histological type. Premalignant liver lesions such as enzyme-altered foci and neoplastic nodules expressed only one or two of these phenotypes respectively. This approach may provide a means to examine the relationship between differentiation and malignancy in the liver and might also allow for the isolation of premalignant cell populations important for hepatocarcinogenesis.

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THE MODE OF UPTAKE OF 5-FLUOROURACIL (5-FU) BY DIMETHYL-HYDRAZINE (DMH) INDUCED RAT COLO-RECTAL TUMOUR TISSUES. L.S.F. Hsu and D. Burston. Department of Experimental Pathology, Westminster Medical School, London SW1, U.K.

The transport of 5-FU by colonic tumour tissue has been studied in order to find an improved method of administration of this drug in colo-rectal cancer. Colo-rectal cancer was induced in rats by weekly subcutaneous injection of DMH (20 mg/Kg) for 20 weeks. Colon from DMH treated rats was classified as "normal", "transitional" and "tumour" tissue. 2 min uptake of 5-FU by everted rings, or pieces of these and control tissues was measured *in vitro* over a range of substrate concentrations from 0.5 - 40 mmol/l 25 weeks after the start of induction. Tissue extracts were analysed by high-pressure liquid chromatography and uptakes were expressed in  $\mu\text{mol/g/min}$  after correction for 5-FU in the inulin space. Uptake was found to be linear over the concentration range studied suggesting a non-mediated process. The  $K_d$  values for the process were 0.058, 0.048, 0.086, and 0.078  $\mu\text{mol/g/min/mmol}$  in control, "normal", "transitional", and "tumour" tissues respectively. The linear mode of transport and greater uptake by the "transitional" and "tumour" tissues suggests that anal administration of 5-FU at high concentration may have a greater killing effect on malignant cells and may also avoid the systemic toxic effects arising from intravenous administration of the drug.