ADAPTIVE REACTIONS TO PHENOBARBITAL IN PUTATIVE PRENEOPLASTIC LIVER FOCI. R.Schulte-Hermann, J.Schuppler[1] and I.Timmermann-Trosiener. Institute of Toxicology and Pharmacology, University of Marburg. [1]Department of Experimental Toxicology, Schering AG., Berlin 65, F.R.G.

Phenobarbital (PB) appears to promote tumour development in rat liver and accelerates the growth of putative preneoplastic (ppn) foci which appear after treatment with initiating carcinogens. The mechanism of promotion is not known. In normal liver PB induces adaptive responses such as an increase in cytochrome P_{450} and other drug-metabolizing enzymes associated with hepatocyte proliferation. By means of immunocytochemistry with antibodies against cytochrome P_{450}-PB and GSH transferase B and by autoradiography following infusion of ^{3}H-thymidine for 2 weeks we have now found that ppn foci still express the adaptive responses. However, there are certain regulatory defects resulting in atopic, autonomous and excessive expression of some of these responses that lead to preferential proliferation of focal cells during PB promotion. We currently view foci as being "over-specialized" for adaptation to lipophilic compounds. Known changes in carbohydrate metabolism within foci seem to fit into this concept.

REDUCED AUTOPHAGY MAY GIVE PRENEOPLASTIC HEPATOCYTES A SELECTIVE SURVIVAL ADVANTAGE Per E.Schwarze and Per O.Seglen. Department of Tissue Culture, Norsk Hydro's Institute for Cancer Research, The Norwegian Radium Hospital, Montebello, Oslo, Norway.

The purpose of this study was to compare aspects of protein metabolism in normal and preneoplastic hepatocytes. Preneoplastic hepatocytes - comprising approximately 35% γ-GT-positive cells - were induced by sequential carcinogen-treatment with diethylnitrosamine and 2-acetylaminofluorene. Hepatocytes were isolated by the collagenase perfusion technique. Protein synthesis was measured as the incorporation of [^{14}C]valine, protein degradation as the release of isotope from pre-labelled protein. Autophagy was measured as the intracellular uptake of sucrose into autophagic vesicles. The Trypan Blue exclusion method was used to determine the number of surviving cells in culture. Preneoplastic and normal hepatocytes showed similar rates of protein synthesis and no significant differences in the degradation of predominantly short-lived protein. Predominantly long-lived protein was degraded at a 35% slower rate in preneoplastic hepatocytes, reflecting a lower rate of autophagy. In the absence of amino acids preneoplastic hepatocytes survive much better than normal hepatocytes. In the presence of amino acids or the specific inhibitor of autophagy, 3-methyladenine, normal and preneoplastic hepatocytes survive equally well. The reduced autophagic activity may give preneoplastic hepatocytes a selective advantage to survive and grow.

ALTERATIONS OF ANGIOTENSIN-I-CONVERTING ENZYME IN LUNG CANCER.
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Serum angiotensin-I-converting enzyme (SACE), E.C.3.4.15.1, in 60 patients with histologically confirmed untreated (n = 34) and treated (n = 26) lung cancer was determined spectrophotometrically using the synthetic substrate hippuryl-L-histidyl-L-leucine. 64 healthy subjects served as controls. SACE was significantly ($p<0.001$) reduced in patients with lung cancer (7.4 ± 4.5 (± SD) U/ml) compared to healthy controls (10.8 ± 4.4 U/ml). According to the histological types of cancer we found: squamous cell (untreated): 8.1± 6.0 (n = 10), treated by radiotherapy 6.0 ± 5.4 (n = 10); oat cell (untreated) 6.8 ± 3.3 (n = 11), treated by chemotherapy (cisplatin, adriamycin, VP-16, vindesine) 5.9 ± 4.3 (n = 16); bronchioalveolars: 6.1 ± 3.6 (n = 4); adeno: 9.2 ± 4.7 (n = 4); non classified carcinomas: 8.7 ± 2.9 (n = 5). The differences between the subgroups were not significant. These results indicate a reduction of SACE in all types of lung cancer, probably caused by spread of cancer into the pulmonary vasculature. A decrease of SACE is observed after radio- or chemotherapy. In individual cases, very low SACE suggests a poor prognosis.

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