

EFFECT OF PHENOLIC ANTIOXIDANTS AND METHYLCHOLANTHRENE ON BENZO(A)PYRENE METABOLISM, GENOTOXICITY IN SOS CHROMOTEST AND ITS METABOLITES BINDING TO BACTERIAL DNA

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The effect of butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and 3-methylcholanthrene (MC) on BP metabolism, genotoxicity and its metabolites binding to bacterial DNA was studied using, for activation BP, S9 fractions from the liver of mice fed diet containing BHA or BHT or mice injected i.p. with MC. BHA, BHT and MC-treatment elevated the total BP metabolism. Estimation of the distributions of organic and water soluble products indicated a marked increase of water soluble BP-metabolites formed in the presence of S9 fractions from antioxidant-fed mice. BP genotoxicity was checked in bacterial test SOS Chromotest. Findings from these experiments indicated strong inhibition of BP genotoxicity when the S9 fraction from BHT-fed mice was used for its activation. BHA had only a moderate, but not significant inhibitory effect on BP genotoxicity. The study has shown that these results were clearly correlated with the effect of antioxidants and MC on BP metabolite binding to bacterial DNA

EXPERIMENTAL LOCAL CHEMOTHERAPY IN BONE TUMOURS

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Cement is often used in the treatment of bone tumours. The effects of local chemotherapy produced by adding an antimitotic drug to the acrylic cement have been analysed in the present investigation. Diffusion of methotrexate (MTX) from cement loaded with MTX was studied *in vitro*; its liberation begins immediately and continues for as long as 3 months. 14 osteosarcomas of dogs were operated and bone loss created by the excision of the tumour was filled with cement containing MTX: this local administration produced a general chemotherapy during 3 to 5 days and seems to reduce local recurrence of the tumour. The effectiveness was tested on 107 rat experimental osteosarcomas (pellets were introduced in the tumour). By the tumour

growth and on histological examination, the effectiveness of such a method was confirmed. Pharmacological data, collected from patients who received cement with MTX during surgical treatment have identified the high concentration of MTX in the tumour drainage indicative of the general chemotherapeutic effect during the first days after treatment.

EXPRESSION OF THE N-myc PROTOONCOGENE IN HUMAN FOETAL BRAIN, RETINA AND KIDNEY

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The *myc* family of cellular proto-oncogenes consists of three known members, that are believed to regulate cell growth and differentiation. In embryonic and foetal tissues, distinct tissue and stage specific expression patterns of the *myc* family genes are observed. This suggests that the differential expression of the *myc* genes may have a key role in regulating multiple differentiation pathways.

The N-*myc* gene codes for a nuclear phosphoprotein of yet unknown function. It is expressed mainly in cells of neural origin, but during foetal development also in a variety of other tissues. High expression levels are found also in various tumours displaying neuroectodermal characteristics, such as neuroblastomas, retinoblastomas and in small cell lung carcinomas. Amplifications of the gene have also been found in these malignancies.

We analysed the expression of N-*myc* in human foetal brain, retina and kidney at 16 to 19 gestational weeks by Northern blotting and by *in situ* hybridization. By Northern blotting, we found expression of the N-*myc* gene to be 4 to 10 fold higher in the brain than in the kidney. The *in situ* hybridizations showed the expression to be rather generalized in the brain, though highest in the ependymal zone where the proliferation of the neuroepithelial cells takes place. The gene was also expressed in neuroblasts already located in the cortex, as well as in cells still migrating there. In the kidney, N-*myc* mRNA was localised in developing glomeruli and tubular walls. In the retina, N-*myc* was expressed at high levels in all the retinal cell layers. We conclude that expression of N-*myc* foetal tissues is

pronounced in cells of neural origin, but not strictly confined to any certain subset of cells. The foetal expression patterns may reflect the types of tumours preferably expressing the *N-myc* gene during post-natal life.

#### POTENTIAL MARKERS OF CELLULAR DIFFERENTIATION AND NEOPLASIA IN THE URINARY BLADDER

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Using the rat bladder-MNU carcinogenesis model, attempts are being made to establish a relationship between changes in selected properties of bladder urothelium and stroma and their biologic behaviour placing particular emphasis on changes during neoplastic transformation in luminal plasma membrane, intermediate filament (viz. cytokeratin), and extracellular matrix properties. Extra criteria for defining structure-function correlations in normal and abnormal differentiation involve: (a) histopathological and ultrastructural markers; and (b) probes targetting selected cell surface antigens and glycoconjugates, keratin proteins and extracellular matrix components.

The results, based on luminal surface and vertical tissue section analysis document a broad spectrum of changes in the course of differentiation, hyperplasia and neoplasia. Mapping studies of overt neoplastic change suggest associated 'field changes' of apparently uninvolved bladder mucosa. The data is interpreted within a conceptual model of stromal-epithelial regulatory/deregulatory processes in bladder.

#### KARYOTYPIC CHANGES IN HUMAN MALIGNANT MELANOMA

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Chromosome studies of the six melanoma patients were performed on direct preparations from primary and/or metastatic tumour explants. Abnormalities in ploidy demonstrated by the addition or loss of normal chromosomes and other structure rearrangements were noted in all cases. In one of the primary lesions 30% cells showed in direct karyotype analysis evidence of gene amplification in form of homogeneously

staining region (HSR) on chromosome 6 at band q16 as well as two other characteristic chromosomes (7p14+ and 14q32+) among numerous defined and undefined markers. No double-minute bodies (DMs) were observed in primary tumour specimens. Cells from primary cultures, cell lines and cell strains from both primary lesion and metastatic node shared the same alterations, suggesting their origin from a common precursor.

#### HETEROTRANSPLANTATION OF HUMAN ENDOMETRIAL TUMOURS TO NUDE MICE

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Established tumour lines of human endometrial tumours are few, because of low take rate and tumour heterogeneity. Thirteen specimens of human endometrial tumours were transplanted. Twelve were biopsy samples of varying histology obtained at curettage, one was a metastasis, obtained from paraaortic lymph nodes at laparotomy.

Serial transplantation was successful in five cases and two tumours grew 2 respectively for 1 passage.

Thymidine incorporation into DNA in the successfully transplanted tumours was increased during the first passages. The take rate was 100% in the fifth and subsequent passages. Twelve original tumours had detectable cytosol estrogen receptor and eight had detectable progesterone receptor content.

The success of heterotransplantation seems to be based initially upon the tumour subtype and progesterone receptor content.

#### AMPLIFICATION OF *myc*-FAMILY GENES IN SMALL CELL LUNG CANCER (SCLC) CELL LINES

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We studied 18 SCLC cell lines established in Groningen. *Myc*-family gene amplification was found in 11 cell lines: 7x *c-myc*, 2x *N-myc*, 2x *L-myc*. Out of 8 cell lines with a *myc* amplification, 7 appeared to contain numerous DMs. *In situ* hybridization was carried out to find the location of the amplification. In 3 cell lines we found amplified *c-myc* on DMs, in