PERSISTENCE OF CHROMOSOMAL DAMAGE INDUCED BY (M)ETHYLATING AGENTS IN RAT HEPATOCYTES IN RELATION TO ALKYLATION PATTERN OF LIVER DNA. Gerda J.Menkveld[1], Ad D.Tates[2] and Leo Den Engelse[1]. [1]The Netherlands Cancer Institute, Amsterdam; [2]Department of Radiation Genetics, University of Leiden, The Netherlands.

Micronucleus (MN) formation (indicative for chromosome breaks) was studied in rat hepatocytes. Partial hepatectomy (PH) was used to express preclastogenic damage. ENU, DEN and DMN resulted in an increased MN formation up to 56 days. Fractionated administration of DEN gives an accumulation of preclastogenic damage. MMS did not induce MN, except when administered at the peak of DNA synthesis after PH. Parallel data on the alkylation pattern of liver DNA was obtained. Results indicate that (1) DNA O-alkylation is much more efficient than N-alkylation in inducing MN in hepatocytes; (2) preclastogenic damage (at least after DEN) accumulates; (3) the stabilities of alkylphosphotriesters and possibly also some other O-alkyl product(s) (O^2-Cyt, O^2- and possibly O^4-Thy) parallel MN frequencies. Further DEN and ENU were compared for their potencies to enhance O^6-MeGua repair in rat liver. Both compounds induced an enhanced repair. These enhancing activities might reflect promoting activities since preliminary results indicate that feeding of the liver tumour promoter phenobarbital also resulted in an enhanced repair.

ROLE OF CELLULAR ONCOGENES IN VIRAL AND RADIATION INDUCED OSTEOSARCOMAGENESIS J.Merregaert, L.Michiels, M.Janowski, F.S.Pedersen[1] and J.R.Maisin
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Radiation induced osteosarcomagenesis might be the result of the activation of a "cellular oncogene", whose expression is switched on or amplified by an unknown mechanism. In order to develop specific probes to detect the expression of cellular oncogenes in a variety of osteosarcoma cell lines, we studied the structural organisation of an osteosarcoma inducing virus, Finkel-Biskis-Reilly murine sarcoma virus.

The FBR-Viral complex was isolated from an ^{90}Sr induced bone tumour of a X/Gf mouse and causes the rapid appearance of osteosarcomas in newborn mice and transforms fibroblasts *in vitro*. The two components of the FBR-viral complex have been isolated separately in tissue culture: FBR-MuLV by endpoint dilution and FBR-MuSV by the establishment of non-producer cell lines. A 5.2 kbp HindIII fragment containing FBR-MuSV provirus has been processed for molecular cloning in charon λ 21A. The transduced oncogene of FBR-MuSV is related to *v-fos* and different from *v-mos*, *v-abl* and *v-bas*. The host range properties and RNase T1 fingerprint analysis of FBR-MuLV genome demonstrated a pattern very closely related to, but distinguishable from the genome of AKR-MuLV.

The FBR-MuSV v-oncogene will be very useful to study its expression and its topography in osteosarcoma versus normal cells in order to understand its possible role in induced osteosarcomagenesis.

EFFECT OF 7,8-BENZOFLAVONE ON THE METABOLISM OF DIETHYLSTILBESTROL IN THE SYRIAN GOLDEN HAMSTER. M.Metzler. Institute of Pharmacology and Toxicology, University of Würzburg, Versbacher Strasse 9, D-8700 Würzberg, F.R.G.

The synthetic estrogen diethylstilbestrol (DES) induces renal tumours in male Syrian hamsters. In DES-treated animals fed a diet containing 7,8-benzoflavone (7,8-BF), no renal but hepatic tumours in high incidence were recently observed (Li and Li, J.Steroid Biochem. 15, 387, 1981). As 7,8-BF is a known inhibitor of drug metabolism, we have compared the pattern of oxidative DES metabolites in the urine of untreated and 7,8-BF-pretreated (4 days in the diet at 0.2%) hamsters. Untreated animals excreted mostly hydroxylated metabolites and little Z,Z-dienestrol (Z,Z-DIES), whereas pretreated hamsters produced significantly smaller amounts of hydroxylated compounds and an increased amount of Z,Z-DIES. As Z,Z-DIES is a product of peroxidative metabolism of DES (Metzler and McLachlan, Biochem. Biophys. Res. Comm. 85, 874, 1978), 7,8-BF appears to inhibit hydroxylation of DES but not its peroxidation. It is proposed that this shift in the metabolism of DES, which presumably takes place in the liver, is associated with the organ susceptibility, supporting the hypothesis that metabolic activation is a crucial step in the mechanism of DES carcinogenicity.