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The role of natural killer (NK) cells in retrovirus induced leukaemogenesis was studied. Neonate BALB/c mice infected the Moloney murine leukaemia virus (MoLV) develop leukaemia. The MoLV infected mice showed a progressive loss of endogenous or augmented NK activity, correlated with the development of the leukaemic state. Mixing of spleen cells from tumour bearing mice with NK augmented splenocytes, resulted in suppression of NK activity. In addition, mixing of T cell lines isolated from MoLV induced tumours with augmented splenocytes also resulted in the down regulation of NK cell activity. It is postulated that after MoLV infection, the progression of virus transformed T cells to a fully developed tumour depends on the ability of these cells to down regulate NK cell activity and thus evade immune surveillance.

REGULATION OF MAMMALIAN DNA REPAIR ENZYMES DURING THE CELL CYCLE

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We have studied the regulation of mammalian DNA repair enzymes as a function of the cell cycle. Synchronous populations of L-929 cells in early G1 were obtained using centrifugal elutriation. Synchronous populations of early G1 cells were reestablished in culture and harvested at different intervals during the cell cycle. Enzyme extracts were prepared by a high salt wash of purified nuclei. The results indicate that DNA repair enzymes redoxy-endonuclease, ^{3}Me-adenine-DNA-glycosylase, uracil-DNA-glycosylase and Ap-endonuclease all have an increased activity in late G1 prior to the onset of DNA synthesis. The O^{6}-Me-guanine transferase activity, however, was present at the same level in all stages of the cell cycle studied. We conclude from these experiments that the majority of mammalian DNA repair enzymes are cell cycle dependently expressed.

BIOLOGICAL AND MOLECULAR PROPERTIES OF p53

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p53 is a cellular protein found in elevated levels in a variety of tumour-derived and *in vitro* transformed cells. To investigate the possible role of p53 in transformation, we cloned p53-specific DNA and used it to construct p53 expression plasmids. The introduction of such plasmids into non-transformed cells, either alone or together with Ha-*ras*, led to neoplastic conversion, thus implicating p53 as an oncogenic protein possessing *myc*-like activities. This notion was also confirmed by experiments indicating that p53 can serve as a competence factor in the control of normal cellular proliferation. Finally, p53 was shown to form a tight complex with a major heat-shock protein, raising the possibility that stress proteins may also play a role in proliferation-related processes.

CORRELATION BETWEEN HLA-A,B,C EXPRESSION ON HUMAN UROTHELIAL CELL LINES AND TRANSFORMATION GRADE *IN VITRO*

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Various characteristics of human urothelial cell lines permit a classification of these cell lines according to grade of transformation (TGr) *in vitro*. Of special interest here is that the slightly transformed (TGrI) and pre-tumourigenic (TGrII) cell lines all express the appropriate HLA-A,B epitopes in contrast to the tumourigenic (TGrIII) cell lines. Using the immunofluorescence test and a complement dependent cytotoxicity test we have investigated 3 TGrII and 7 TGrIII cell lines for their expression of the monomorphic part of HLA-A,B,C antigens. We provide evidence that the apparent loss of HLA-A,B epitopes observed in TGrIII cells is due to a significantly (4 to 6 fold) lower concentration of HLA-A,B,C antigens on TGrIII cells as compared to that on TGrII cells. Furthermore, treatment of TGrIII cells with neuraminidase partly restored the expression of HLA-A,B,C antigens.

THE EFFECT OF CELLADAM ON EHRLICH AND S180 TUMOURS

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A new anticancer and immunostimulant

drug Celladam (DCM) and a simple cancer diagnostic method (MTA) have been developed by Kovacs and his group. In animal experiments, including various immune diagnostic methods, therapeutic effect of CDM was as follows: 0.025 mg/kg CDM pretreatments administered 5 and 1 days before the tansplantation of Ehrlich tumours had increased the survival time of mice by 70%. CDM treatment in doses of 0.025 to 0.1 mg/kg twice a week inhibited the growth of subcutaneously transplanted Ehrlich and S180 tumours, increased survival time and stimulated PHA-induced blastogenesis. In the Ehrlich tumour bearing animals we found elevated transferrin, -glycoprotein and -lipoprotein levels in serum and ascitic fluid. On CDM treatment, the level of these plasma proteins, as well as the results of MTA diagnoses had approached the control levels: these results may be attributed to the mechanism of action of CDM.

CLONAL SENSITIVITY TO DIFFERENTIATION INDUCERS AND TO CYTOSTATIC DRUGS OF HETEROGENEOUS TUMOUR CELL POPULATIONS

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Heterogeneous responses of individual cells of tumour cell populations to inducers of differentiation, e.g. phorbol myristate acetate (TPA), were observed using various human tumour cell lines including HL-60 promyelocytic, K562 erythrocytic leukaemia, and A 2058 and BHM-97 melanomas of human origin. Clonal lines were isolated from the A 2058 melanoma line, which showed different cell morphology, kinetic parameters and different sensitivity against inducers of differentiation. The sensitivity to various cytostatic drugs of these clones was studied and compared with their sensitivity to the inducers. Evaluation of the effects was made with clonogenic assay, morphological alterations such as dendrite formation, cytotoxic effects, change in melanin production. The importance in the therapy of tumours of the correlation existing between the sensitivity to inducers of differentiation and to cytostatic drugs of cell clones has been evaluated.

UTILIZATION OF THE QUANTITATIVE COMPONENT OF THE INFORMATION OBTAINED FROM SHORT TERM TESTS: INTEGRATED USE OF POSITIVE AND NEGATIVE RESULTS

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Carcinogenicity in small rodents and short term test results are to some extent correlated phenomena, but at the same time profoundly different in their biological significance. For this reason usually only qualitative correlations between the two phenomena are investigated. In the perspective of risk assessment studies, we have attempted to establish a logical and mathematical bridge between the two formalisms of studying qualitative or quantitative correlations. We have shown that, as expected, the two formalisms are completely compatible and interchangeable. However, we have found that a not completely negligible amount of information is discarded using only the qualitative component of the information. Under certain reasonable hypotheses it is possible to transform coherently in a quantitative value of very low potency even negative results. This allows for a homogeneous treatment of the globality of the data. Using the quantitative component of the information a multiple correlation approach can be applied to batteries of tests, obtaining a more straightforward gain in predictivity than using the qualitative approach.

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BEN, AGE AND SCE

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Balkan endemic nephropathy (BEN) is a chronic renal disease often combined with uroepithelial tumours. It occurs in some regions of Bulgaria, Yugoslavia and Romania. The cause of the disease is unknown. One of the most likely explanations is the presence of genetic predisposition combined with some environmental agent.

Here are reported data from a study on the level of sister chromatid exchanges (SCE) in patients with BEN, matched controls with other kidney diseases living in non-endemic regions, children from endemic families and matched controls. It was found that the level of spontaneous SCE in peripheral lymphocytes was not higher in the patients with BEN and children from BEN families. However, it nearly doubled the control frequency following <u>in vitro</u> treatment with mitomycin C.

INDUCTION OF THE CYTOCHROME P-450c GENE AND THE METABOLISM OF BENZO(a)PYRENE-7,8-DIOL (BP7,8-DIOL) IN