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

EIGHT DIFFERENT HUMAN BREAST CANCER CELL LINES

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Cytochromes P-450 are a family of haemoproteins involved in the metabolism of both endogenous and exogenous compounds, i.e. carcinogens. P-450c is inducible by TCDD. Induction of this gene measured by slot blot analysis of cellular RNA, and its effect on the metabolism of BP7,8-diol was studied in eight human breast cancer cell lines. The cells were grown under well defined conditions and treated with different concentrations of TCDD for 24 hr prior to addition of tritium labelled BP7,8-diol (675 nM). The basal level of P-450c mRNA was the same in all cell lines. The TCDD induced levels of P-450c mRNA followed the order: MCF-7>T47-D>ZR-75-1>3909>3522 in a dose-dependent manner. Three lines, AL-1, BT-20 and CAMA-1 did not respond at all to TCDD. Pretreatment of the cells with TCDD changed the BP7,8-diol metabolite profile. An unidentified compound with the retention between that of 9,10- and 7,8-diol was the major metabolite in TCDD treated cells. These results demonstrate that human breast cancer cell lines differ greatly from each other with respect to inducibility of P-450c by TCDD and that the induction influence the BP7,8-diol metabolite profile.

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DORMANCY AND PROGRESSION OF B LEUKAEMIC CELLS IN AKR MICE

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The high incidence of spontaneous T-cell lymphoma in AKR mice (arising predominantly in the thymus) can be abolished almost completely by thymus removal at the age of 1 to 3 months. Only 10 to 15% extrathymic lymphoid tumours occur late in life following thymectomy, nevertheless each of the thymectomized AKR mice is a carrier of dormant potential lymphoma cells (PLC). Transplantation of lymphoid cells from 8 to 14 months old AKR mice (thymectomized at the age of 40 to 60 days) into the appropriate intact or thymectomized recipients caused B cell leukaemia development of AKR origin in 100% of the recipients. Immunosuppressive treatment involving preferentially T-cell function like ATS, corticoids, X-rays and retroviruses isolated from AKR (DTV) were found to stimulate the progression of dormant PLC present in thymectomized AKR mice towards B-cell lymphoma development. Splenectomy of 8 to 12 months old thymecytomized mice and intravenous reinjection of their own splenocytes back resulted in breakdown of dormancy in 50 to 60% of the mice, suggesting the possible restrictive spleen microenvironment role on PLC dormancy.

A SHORT SYNTHETIC PEPTIDE FRAGMENT OF HUMAN INTERLEUKIN 1 β (hIL-1β) INCREASES HUMAN NATURAL KILLER (NK) ACTIVITY

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We previously characterized a synthetic peptide of IL-1β (fragment 163-171), which has immunostimulatory but not inflammatory activity. In this study we examined the effects of this peptide on natural cytotoxicity of human cells. Peripheral blood mononuclear cells (PBMC), preincubated in medium containing interleukin 2 (IL-2), exhibited a dose-dependent augmentation of NK activity against K562 leukaemia cells. In contrast, both IL-1β and the synthetic peptide were unable to stimulate the cytotoxicity of these cells. However, when PBMC were further depleted of monocytes by adherence to plastic, a marked increase of NK activity occurred in the presence of the peptide, but not in the presence of hIL-1α or β . Significant augmentation in cytotoxicity was obtained by preincubating lymphocytes for 18 hr with 10 to 100 µg per ml of the peptide. This effect is likely to be the result of the induction of IL-2 by the peptide, which, in contrast to the entire IL-1 molecule, does not stimulate the synthesis of prostaglandin E2, a potent inhibitor of NK activity.

GROWING CELL CULTURES EXERT DISTINCTIVE COLONY MORPHOGENESIS

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Morphogenesis of colonies of transformed or malignant cells <u>in vitro</u> requires feeder cells or enriched medium and