Generally, there was a significant and reproducible increase in survival time of deuterated, tumor-bearing mice treated with MTX. Further, it appeared that deuteration at an effective antineoplastic level does not markedly affect proliferation of normal cell renewal systems, as examined by the incorporation of tritiated thymidine into the DNA of bone marrow and small intestine following prolonged exposure of normal mice to moderately deuterated drinking water.
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HYDANTOIN INDUCED LYMPHOMAS : BENIGN OR MALIGNANT ?

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Hydantoin derivatives are the most commonly used antiepileptic drugs with well-known, mostly harmless side-effects. One of the most controversial complications of long-term hydantoin therapy is the appearance of lymphomas. They are mostly multiple, self-limiting with signs of an allergic reaction and complete remission after withdrawal of the drug. However there is an increasing number of observations of clear-cut malignant lymphomas after long-term hydantoin therapy, progressing after discontinuation of the drug. We have seen 8 cases of malignant lymphomas after antiepileptic treatment with predominantly hydantoin derivatives of 7-23 years duration. 2 are Hodgkin's, 6 Non-Hodgkin's lymphomas of various histological types. We have added 4 new cases to those already presented (Schweiz. med. Wschr. 105, 1735, 1975). The only common characteristic of these 8 cases - as in most others reported - is the unalterable fatal outcome of the disease despite all therapeutic measures. There is no conformity in type or course of the epilepsy nor in the clinical or histological presentation of the ensuing lymphomas. Hydantoin derivatives have a well documented carcinogenicity. Long-term hydantoin treatment may occasionally lead to the development of malignant lymphomas, which is only seldom preceded by a typical hydantoin lymphadenopathy (documented in one of our cases). There is no way to identify potential candidates for this detrimental, irreversible complication of an otherwise well tolerated routine drug therapy. Close observation of hydantoin-treated epileptics and central registration of all cases of hydantoin-induced lymphomas are warranted.

TUMOR PROMOTION AND CELL CULTURE STUDIES

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The carcinogenic process is multifactorial in its causation and multistage in its development. The two-stage model of chemical skin carcinogenesis is one of the best known experimental systems to study the mechanisms underlying the different steps in the cocarcinogenesis processes. Operationally two clearly separate events and mediated by different agents have been defined, namely tumor initiation and promotion. Tumor promoters are compounds which lack significant carcinogenic activity when tested alone, but markedly enhance the yield of tumors when applied after a low dose of an initiating carcinogen. The best known promoters are the phorbol-type diterpene esters and their promoting activity has also been shown in other organs than skin. Cell culture studies provided important clues to the unterstanding of tumor promotion and have revealed interesting biologic effects of the phorbol esters. These effects can be devided in four categories :

1) Mimicry of transformation in normal cells and enhancement of transformation by chemical carcinogens, viruses and X- or UV-rays,
2) Modulation (inhibition or enhancement) of differentiation and maturation,
3) Alteration of membranes resulting in changed receptor functions and intercellular communication,
4) gene modifications by chromatid and chromosomal changes.

Recent evidence suggests that phorbol esters bind to specific membrane receptors, lead to rapid alteration of membrane phospholipids and produce signals or mediators which lead to the subsequent cytoplasmic and nuclear effects. Although promoter effects can be observed with a variety of cell types, there is no unique alteration which is specific for phorbol-ester tumor promoters. The expression of the pleiotropic effects vary with tissue origin and functional state of cells and they were predominantly studied in mesenchyme-type cells. Although promotion related effects have been observed as well in epithelial cell cultures, they may vary qualitatively and quantitatively from those observed in fibroblast cultures. Stimulation of cell proliferation, inhibition of differentiation, enhancement of transformed phenotype and chromosomal modifications have been documented in epithelial cultures. Although promotion in vivo has so far nearly exclusively been demonstrated in epithelial tissues, two-stage transformation in vitro has only been demonstrated with mesenchymal cells. However, this has been predominantly realized with cells from permanent

lines, i.e. cells with an already altered phenotype. Whether these cells may be termed initiated and are thus the appropriate targets for promotion is not clear. Following recent observations phorbol esters interfere with intercellular communication processes and thus may well act not only on initiated cells but also on their normal surrounding cells, thus rendering the tissue permissive for the expression of the transformed phenotype and for the development of the initiated cells to visible tumors.

BLOOM'S SYNDROME : A DEFICIENCY IN THE DETOXIFICATION OF ACTIVE OXYGEN SPECIES ?

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Bloom's Syndrome (BS) is an autosomal recessive disease which is characterized clinically by growth retardation, skin sensitivity to sunlight, immunodeficiency and increased susceptibility for development of cancer. Increased frequencies of spontanenous chromosomal aberrations and sister chromatid exchanges have been observed on the cellular level. In studies of the near-ultraviolet photobiology of skin fibroblasts of BS patients we have investigated the survival of the colony forming ability and the formation of DNA single strand breaks following exposure to monochromatic light at 313 nm. Near-ultraviolet represents a major portion of the solar radiation which reaches the surface of the earth. Abnormal survival curves were observed in 6 of 7 BS strains, 4 strains being hypersensitive to the lethal action of 313 nm light. In 6 of 8 strains 313 nm light induced excessive DNA fragmentation. These abnormalities in the response of cultured BS fibroblasts to near-ultraviolet light may be reflection in vitro of the skin sensitivity of BS patients to sunlight.
Further insight into the pathology of BS was obtained in cytogenetic studies. A low molecular weight component was identified in concentrated media from 6 BS fibroblast strains which induces chromosomal aberrations in phytohemagglutinin stimulated lymphocytes from normal donors. The activity of this clastogenic factor could be decreased substantially by the addition of bovine CU-Zn superoxide dismutase. The clastogenic factor also induced sister chromatid exchanges in normal lymphocytes, albeit with low efficiency. In analogy to collagen diseases such as systemic lupus erythmatosus, Crohn's disease and periarteritis nodosa it is speculated that BS fibroblasts are deficient in the detoxification of active oxygen species ($O_2^{\cdot}$, $OH^{\cdot}$). On the basis of our photobiological and cytogenetic results a new hypothesis for the pathology of BS will be discussed.
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PROGNOSTIC FACTORS IN THE TREATMENT OF METASTATIC GERM CELL CANCER

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91 patients with metastatic germ cell cancer were classified as having either advanced disease (AD) or minimal disease (MD). Criteria for staging are given. All patients were treated similarly according to protocol 01/76 of the Swiss Group for Clinical Cancer Research (SAKK). Complete remission (CR) rates (95 % vs 35 %) and survival (84 % vs 33 %) were significantly better ($p < 0.001$) for the MD group than for the AD group. Disease sites did not influence the therapy results. Patients with MD had higher CR rates ($p = 0.003$ to 0.009) than AD patients at all sites (lung, abdomen or combined sites). The incidence of MD was higher in patients with embryonal cell carcinoma than in all other histology groups (54 % vs 31 %, $p = 0.026$). This was reflected in a higher CR rate (77 %) for the embryonal cell carcinoma patients than in the other histological groups (46 %, $p = 0.003$). The CR rate for patients with MD was the same in all histology groups (89 % to 100 %). In AD the 50 % CR rate for embryonal cell carcinoma patients versus the 28 % rate for other patients showed a definite trend but did not reach statistical significance. The dosages of chemotherapy given had no apparent effect upon CR rates. Relaps rates were significantly affected by dosage reduction, and in AD patients, by the number of chemotherapy cycles given.

LONG TERM SURVIVORS WITH SMALL CELL CARCINOMA OF THE LUNG

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Several authors have recently reported long term, disease-free survival in patients with small cell carcinoma of the lung (SCCL) after aggressive initial treatment. In an attempt to identify long term, potentially cured survivors with SCCL in Switzerland a questicnnaire was sent to all medical oncology centers throughout the country. 14 patients with SCCL were reported achieving disease-free survival for over 24 months after initial therapy. Median age was 61 (39 - 80), median performance status 0 (0 - 2), 2 were females and 12 were males. 13 patients were classified as limited