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