Experimental Investigations on the Influence upon the Chemical Carcinogenesis. 1st Communication: Studies with Ethylnitroso-urea

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Summary. Pregnant Sprague-Dawley-rats were given 30 mg/kg ethylnitroso-urea orally on day 19 of pregnancy. ~90% of 1068 offsprings developed 1847 neurogenic malignomas after a medium induction period of ~240 days which were predominantly situated in the cerebrum (gliomas), spinal cord (gliomas and malignant neurilemmomas) and n. trigemini (malignant neurilemmomas). 6 days after birth treatments were started to influence the carcinogenesis by immune depressive or immune stimulating measures, neurotropic poisons, enzyme-stimulating substances, sensorial stimulants or physical activity. The carcinogenesis could neither be promoted nor inhibited by these measures. In 3.5% of the males (19/538) extraneural tumors developed whereby Wilms’ tumors were most frequently seen. In 530 females 182 (34%) extraneural carcinomas occurred; 167 of these tumors were mammacarcinomas. The incidence of mammary cancer was significantly increased by postnatal applications of cyclophosphamide or Freund's adjuvant.

Experimentelle Untersuchungen zur Beeinflussung der chemischen Carcinogenese

1. Mitteilung: Versuche mit Äthylnitroso-harnstoff


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Introduction

The carcinogenesis by chemical agents in man and laboratory animals is characterized by at least five parameters that have to be taken into consideration when the promotion or inhibition of cancer is studied,

a) incidence of malignant tumors;
b) induction period;
c) dose of the carcinogen;
d) localization and biological reaction of tumors (i.e. formation of metastases);
e) histology of tumors.

We started an extensive study to investigate whether the once induced chemical carcinogenesis can be inhibited or promoted by more or less "specific" or also unspecific measures. Particularly cancer promotion seemed to be of interest since by an acceleration of cancer growth mechanisms could be detected that must be broken through to allow such an acceleration. These investigations might have practical significance for "high risk groups" (i.e. heavy smokers, certain occupational groups), because these populations could possibly be protected against cancer disease if — in the ideal case — it would succeed to prevent or at least slow down the process of cancer formation.

The efforts so far made i.e. to "stimulate the endogenous power of resistance" by a series of more or less scientifically grounded drugs revealed entirely disappointing results. We therefore attempted to examine by scientific methods whether at present it is at all possible to influence the chemically-induced carcinogenesis.

The present communication describes the first part of such investigations.

In this work rats were treated prenatally with a single dose of the carcinogen ethynitroso-urea (ENU). Particularly by the investigations of Ivankovic (reviews 1968, 1972) it is known that a single diaplacental application of this compound suffices to cause malignant tumors particularly of the nervous system in a high percentage of the offsprings after an induction period that can be determined exactly. This model appeared to be particularly suitable for this study because the animals get into touch with a chemical carcinogen only one time and for a very short period of their prenatal life and thereafter can be exposed to a series of measures in order to influence the prenatally originated process of cancerisation. For this purpose immunological means were applied as well as some neurogenic poisons, metabolic stimulants and sensorial stimuli since predominantly neurogenic tumors were expected. Furthermore some physical methods were used.

Methods

The investigations were carried out in almost 3000 Sprague-Dawley-rats of either sex. They were housed in macroclone cages in groups of 3—4 animals each and fed with Altromin®-pellets and water ad libitum. Usually they were kept under observation until spontaneous death. They were dissected carefully and organs showing abnormalities examined histologically. Previously toxicity tests of the applied substances had been performed in newborn rats of ~ 6 days of age weighing ~ 10 g. Thereby special care was necessary to prevent cannibalism after returning them to the mothers. In the present studies a weekly dosage of 5% of the LD₅₀ was applied since it had revealed that a higher dose (10% of the LD₅₀) i.e. of cyclophosphamide or Amethopterin was not tolerated. The applied dose was thus maximal for newborns and young animals.