Investigations on the Influence of Immunodepressive Means on the Chemical Carcinogenesis in Rats*

D. Schmähl
The Institute of Toxicology and Chemotherapy (Director: Prof. Dr. med. D. Schmähl),
German Cancer Research Center, Heidelberg

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Summary. The carcinogenicity of cyclophosphamide in rats could not be influenced by additional immunodepressive treatment with hydrocortisone. In the same way the carcinogenic effect of 3,4-benzopyrene could not be promoted by the immunodepressants cyclophosphamide and hydrocortisone.

Untersuchungen an Ratten zur Beeinflussung der chemischen Carcinogenese durch immunodepressive Maßnahmen

Zusammenfassung. Die carcinogene Wirkung von Cyclophosphamid bei Ratten konnte durch zusätzliche immunodepressiv wirksame Behandlungen mit Hydrocortison nicht verstärkt werden. Ebenso ließ sich die carcinogene Wirkung von 3,4-Benzpyren durch Immunodepression mittels Cyclophosphamid oder Hydrocortison nicht im fördernden Sinne beeinflussen.

The study of the carcinogenicity of cytostatic drugs in rats (Schmähl, 1967; Schmähl and Osswald, 1970) proved that particularly alkylating agents are able to produce malignant tumors, whereas no carcinogenic effects were found in antimetabolites (Schmähl and Osswald, 1970; Rustia and Shubik, 1973). Alkylating agents and antimetabolites both, however, have considerable immunodepressive activities. Scherf et al. (1970), therefore, examined whether the carcinogenicity of some cytostatic drugs must be led back to the immunodepressive activity of these compounds or has to be attributed to the chemical structure that is related to the alkylating activity. They failed to establish correlations between carcinogenesis and immunodepression of cytostatic compounds. These findings suggested that the carcinogenicity particularly of alkylating cytostatic substances is not connected with their immunodepressive activity, but must be expected on the basis of its chemical reactivity against essential cell constituents. On the other hand, clinical reports described an increased frequency of malignant tumors observed in organ transplant recipients and in children who had been born with immune insufficiencies (Penn, 1973).

It is, therefore, assumed that in man disorders of the surveillance functions of the immune system might be accompanied with malignant tumor growth, though other mechanisms have also been discussed (Gleichmann and Gleichmann, 1973).

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In the present study we examined whether the chemical carcinogenesis can be influenced when rats are treated with immunodepressants during carcinogenesis. Our models were the local carcinogenesis by 3,4-benzopyrene and the systemic carcinogenesis by cyclophosphamide.

**Materials and Methods**

We used 244 three months old male Sprague-Dawley-rats which were fed with Altromin®-cakes and water ad libitum. They were kept under observation until spontaneous death. Animals bearing tumors of considerable size were killed. All animals were dissected carefully and organs showing abnormalities examined histologically. Because of the immunodepressive treatment special care was necessary to prevent infective diseases.

In Experiment 1) we used the carcinogen cyclophosphamide that itself exerts also immunodepressive activity. As an additional immunodepressant we gave hydrocortisone to find out whether the carcinogenesis is hastened or fortified. Three groups of 32 rats each were formed:

- **Group 1)** Intravenous injection of cyclophosphamide only (single dose: 13 mg/kg body weight per week; total dose: 670 mg/kg).
- **Group 2)** Subcutaneous application of hydrocortisone only (single dose: 50 mg/kg/week; total dose: 2600 mg/kg).
- **Group 3)** Combination of cyclophosphamide and hydrocortisone. Dosage see Group 1 and 2.
- **Group 4)** Control without treatment (52 rats).

In this rat strain the applied dose of hydrocortisone leads to a depression of the humoral antibodies to ~ 25% of the initial level; the immunodepressive activity of cyclophosphamide in these rats has been described in detail by Scherf et al. (1970).

As a second model we investigated whether the local carcinogenic effect of 3,4-benzopyrene is influenced by additional immunodepressive treatment with hydrocortisone or cyclophosphamide. Again three groups of 32 rats each were formed:

- **Group 1)** Received one single subcutaneous injection of 3 mg/kg body weight (~ 0.6 mg/animal) 3,4-benzopyrene in oily solution. This relative small dosage was used to enable sufficiently long induction periods of the tumors.
- **Group 2)** Received 3,4-benzopyrene + hydrocortisone. Dosages see above.
- **Group 3)** Received 3,4-benzopyrene + cyclophosphamide. Dosages see above.

**Results**

The results of these studies are summarized in Table 1. In the cyclophosphamide series in 44% of the animals malignant tumors developed after a latency period of 510 ± 90 days. These observations are in accord with our previous findings (Schmähl, 1967). We noted: 3 rats with reticulo-sarcomas, 6 rats with hemangioendotheliomas in various organs, 1 neurogenic sarcoma of the mediastinum with metastases of the lung, 1 sarcoma of the heart, 1 leukemia; two animals showed two malignant tumors each, namely 1 osteosarcoma of the paranasal sinus combined with 1 pheochromocytoma and 1 angiosarcoma of the abdomen combined with 1 pheochromocytoma.

In the series given the combination of cyclophosphamide and hydrocortisone again 44% of the rats showed malignant tumors after 500 ± 140 days. Type and localization of these tumors corresponded with the cyclophosphamide series. We observed: 7 rats with hemangioendotheliomas, 3 rats with reticulo-sarcomas, 1 rat with pheochromocytoma, and 1 angiosarcoma of the abdomen combined with 1 pheochromocytoma.

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