and spleen cells, it is weak in bone marrow and the thymus, and virtually absent in peripheral lymph nodes.

## LITERATURE CITED


1. J. Djeu, H. Heinbaygh, H. Holden, et al., J. Immunol., 122, 175 (1979).
2. S. Helfand, J. Werkmester, and S. Roder, J. Exp. Med., 156, 492 (1982).
3. J. Flexman and R. Shellma, Immunology, 44, 311 (1981).
4. N. Minato, L. Reid, H. Cantor, et al., J. Exp. Med., 152, 124 (1980).
5. S. Targan and F. Dorey, J. Immunol., 124, 2157 (1980).
6. G. Trinchiery and D. Santoni, J. Exp. Med., 143, 1314 (1978)
7. A. Silva, B. Bonavida, and S. Targan, J. Immunol., 125, 479 (1980).
8. R. Welsh, K. Karre, M. Hansson, et al., J. Immunol., 126, 219 (1981).


# TUMORS INDUCED BY 1,2-DIMETHYLHYDRAZINE IN HYBRID MICE WITH PITUITARY GRAFTS IN THE KIDNEY


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Development of tumors of the large intestine and the anal region in mice, and also a high percentage of tumors of the uterus or ovaries in some strains of mice can be induced by 1,2-dimethylhydrazine (DMH) [3, 4, 8, 11]. Hormonal factors play an important role in the development of DMH-induced sarcomas of the uterus and vascular tumors of the ovaries in CBA mice [2, 3, 5].

The object of this investigation was to study the effect of prolactin, secreted by a pituitary graft beneath the capsule of the kidney, on carcinogenesis in hybrid mice treated with DMH.

## EXPERIMENTAL METHOD

Experiments were carried out on 112 female (CBA × C57BL/6)$F_1$ mice aged 3 months (Table 1). The pituitary gland from 2-month-old female CBA mice was grafted into mice of groups 1 and 3 beneath the capsule of the left kidney, and a mock operation on the kidney was performed on the mice of group 2. DMH in aqueous solution was injected subcutaneously in a dose of 8 mg/kg once a week into mice of groups 2 and 3 for 30 weeks, starting with the 8th week after the operation on the kidney. The animals were kept under observation until their natural death, but some mice with large tumors were killed in an agonal state; these last mice were killed 60 weeks after the beginning of DMH administration. The material was subjected to a histological analysis and sections were stained with hematoxylin and eosin. The frequency of tumors was determined relative to the number of mice surviving up to 20 weeks — the time of discovery of the first tumor. Differences in frequency were assessed by the $\chi^2$ method.

## EXPERIMENTAL RESULTS

The frequency of the most commonly encountered tumors in the different groups of mice is shown in Table 1. DMH induced the development of polyps and adenocarcinomas of the large intestine as well as ademomas and carcinomas of the sebaceous glands of the anal region, in agreement with data in the literature. An increase in the frequency of vascular tumors of the liver was observed in the groups of mice receiving DMH, compared with group 1 ($P < 0.001$). In group 1, for instance, one angioma of the liver and three hepatomas were found, in group 2 there were eight angiomas, three hepatomas, one hepatocellular carcinoma, and one cholangi-


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TABLE 1. Frequency of Tumors in (CBA × C57BL/6)$F_1$ Mice after Treatment with DMH and Pituitary Grafting into the Kidney

| Group of mice | Treatment | Number of mice | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | in group | with tumor (with malignant tumor in parentheses) | | | | | | | | | | | | | |
| | | | of large intestine | | of anal region | | of liver | | of ovaries | | of uterus | | of mammary gland | | in pituitary graft | |
| | | | absolute | % | absolute | % | absolute | % | absolute | % | absolute | % | absolute | % | absolute | % |
| 1 | Pituitary grafting | 45 | 0 | 0 | 0 | 0 | 4 | 8,9±4,2 | 1 | 2,2±2,2 | 6 | 13,4±5,1 | 27 (27) | 60,0±7,3 | 32 | 71,2±6,8 |
| 2 | DMH | 32 | 14 (3) | 43,9±8,8 | 5 (4) | 15,6±6,4 | 13 (2) | 40,6±8,7 | 16 | 50,0±2,8 | 8 (8) | 25,0±7,6 | 0 | 0 | — | — |
| 3 | Pituitary grafting + DMH | 35 | 15 (5) | 43,0±8,4 | 7 (4) | 20,0±6,8 | 18 (4) | 51,5±8,4 | 3 | 8,6±4,7 | 5 (4) | 14,3±5,9 | 3 (2) | 8,6±4,7 | 1 | 2,9±2,8 |

ocarcinoma; in group 3 there were nine angiomas and two angiosarcomas of the liver, four hepatomas, and three hepatocellular carcinomas. Grafting the pituitary into the kidney inhibited the formation of DMH-induced angiomas of the ovaries ($P < 0.001$) but did not affect carcinogenesis in the intestine, liver, and uterus ($P > 0.1$, $P > 0.05$). Sarcomas of the endometrium were found in eight mice of group 2 and in four mice of group 3; in the remaining mice, glandular polyps of the uterine cornua were found. In most animals of group 1, 50 weeks after grafting of the pituitary into the kidney a tumor (chromophobe adenoma) was found in the pituitary graft, in agreement with data in the literature [7, 9]. It is interesting to note that treatment with DMH inhibited tumor formation sharply in the grafted pituitary ($P < 0.001$). Histological investigation showed that the grafted tissue preserved the structure of the normal anterior lobe of the pituitary for a long time.

Pituitary isografting stimulates the development of mammary gland carcinoma in rats and mice, and this effect is connected with prolactin hypersecretion by the grafted pituitary [7, 12, 13]. In the present experiment mammary gland carcinoma was observed (60%) in the mice of group 1, in which frequency conversion of the pituitary graft into a tumor was observed, but it was found only rarely (8.6%) in group 3 ($P < 0.001$), where DMH almost completely prevented conversion of the graft into a tumor. In one mouse of group 3 a fibroadenoma of the mammary gland was observed.

Tumors of other organs were found as follows: three adenomas of the lungs, two pituitary adenomas, and one case of leukemia in group 1, five cases of leukemia in group 2, and two cases of leukemia in group 3.

The reduction in the frequency of formation of DMH-induced vascular tumors of the ovaries in mice with a pituitary graft can evidently be explained by the higher level of prolactin, secreted by the graft. This is in agreement with data in the literature showing that exogenous estrogens, increasing prolactin production by the pituitary itself [10], reduced the frequency of development of angiomas of the ovaries in inbred mice [6]. On the other hand, the absence of tumors in the pituitary graft of mice receiving DMH cannot be explained by the effect of the carcinogen on the level of biogenic amines in the hypothalamus [1], since prolactin secretion and transformation of pituitary cells into tumor cells took place independently in this case, unconnected with the hypothalamus. It can be tentatively suggested that DMH has a direct inhibitory action on proliferation of prolactin-forming cells in the grafted pituitary, and in that way prevents the development of tumors in it.

Analysis of the results thus shows that prolactin inhibits the formation of vascular tumors of the ovaries induced by DMH in hybrid mice, but does not affect carcinogenesis in the intestine, uterus, and liver. DMH inhibits tumor formation in a pituitary graft in the kidney and thereby prevents the development of mammary gland carcinoma.

## LITERATURE CITED


1. V. N. Anisimov, V. K. Pozdeev, L. Yu. Dmitrievskaya, et al., Byull. Éksp. Biol. Med., No. 11, 1359 (1976).
2. E. A. Ird and I. O. Smirnova, Éksp. Onkol., No. 1, 68 (1979).
3. V. S. Turusov, L. S. Bazlova, and V. A. Krutovskikh, Byull. Éksp. Biol. Med., No. 5, 458 (1979).
4. V. S. Turusov, N. S. Lanko, and L. S. Bazlova, Vopr. Onkol., No. 7, 39 (1977).
5. V. S. Turusov, A. B. Linnik, and O. V. Morozova, Byull. Éksp. Biol. Med., No. 11, 599 (1980).
6. V. S. Turusov, A. N. Murovannyi, and O. V. Morozova, Éksp. Onkol., No. 2, 20 (1982).
7. L. Boot and G. Röpcke, Cancer Res., 26, 1492 (1966).
8. J. T. Evans, T. S. Hauschka, and A. Mittelman, J. Natl. Cancer Inst., 52, 999 (1974).
9. A. Liebelt and R. Liebelt, Cancer Res., 21, 86 (1961).
10. A. Ratner, P. K. Talwalker, and J. Meites, Proc. Soc. Exp. Biol. Med. (N.Y.), 112, 12 (1963).
11. V. S. Turusov, N. S. Lanko, V. A. Krutovskikh, et al., Carcinogenesis, 3, 603 (1982).
12. C. Welsch, T. Jenkins, and J. Meites, Cancer Res., 30, 1024 (1970).
13. R. Yanai and H. Nagasawa, J. Natl. Cancer Inst., 48, 715 (1972).