Eur J Cancer Clin Onol, Vol. 17, No. 12, pp. 1357–1358, 1981.
Printed in Great Britain.

0277-5379/81/121357-02$02.00/0

Letter to the Editor

Hormone Dependence of Rat Mammary Tumors Induced by *N*-Nitrosomethylurea*

DAVID P. ROSE and JOHN J. NOONAN

Division of Clinical Oncology, Wisconsin Clinical Cancer Center, University of Wisconsin, Madison, WI 53792, *U.S.A.*

RAT MAMMARY carcinomas induced by *N*-nitrosomethylurea (NMU) frequently undergo regression after bilateral ovariectomy [1–3]. In contrast to dimethylbenz(a)anthracene (DMBA)-induced mammary tumors [4], these regressions continue during perphenazine treatment, suggesting that the carcinomas are principally estrogen, rather than prolactin, dependent [5]. We now report that the regression of NMU-induced mammary carcinomas after hypophysectomy is prevented by replacement doses of estradiol and also by prolactin administration.

Mammary tumors were induced in female Sprague–Dawley rats by 2 intravenous doses of NMU, 5 mg/100 g body weight given 7 days apart, the first being administered when the animals were 50 days old. When the surface area of 1 tumor had reached approximately 2 sq cm [1], the rats were randomized to 3 groups, treated as follows: Group I, untreated controls; Group II hypophysectomy by the parapharyngeal route; Group III hypophysectomy plus estradiol benzoate, 5 μg in 0.2 ml corn oil given daily by subcutaneous injection. The completeness of hypophysectomy was confirmed by arrest of body weight gain and uterine, ovarian and adrenal atrophy. The surface area of the designated tumor was determined twice a week for 2 weeks, at which time estrogen administration was discontinued and the tumors in Group III measured for a further 14 days.

Four other NMU tumor-bearing rats were hypophysectomized and the carcinomas observed for 7 days, when they had all regressed by approximately 50% of their preoperative size. Ovine prolactin (supplied by the Pituitary Agency, National Institutes of Health) was then given in a dose of 1 mg twice daily by subcutaneous injection for 7 days. Tumor measurements were then continued for a further 14 days.

Table 1 shows that, in contrast to the controls, the tumors of hypophysectomized rats regressed rapidly after surgery; 9 of 12 were no longer palpable by 14 days and the other 3 were 10–14% of their original size. Treatment with estradiol benzoate slowed or prevented hypophysectomy-mediated regression; only 1 was reduced in size by more than 50%, 2 were static and 2 of the 11 had grown by at least 25% after 14 days. Fourteen days after cessation of estrogen replacement, all tumors had undergone significant regression (Student's paired t test: $P < 0.001$).

Figure 1 shows the effect of prolactin on the 4 other tumors that had undergone partial regression after hypophysectomy. The growth of 3 was clearly stimulated by the hormone, while the fourth remained static. All 4 underwent second regressions when prolactin replacement was withdrawn.

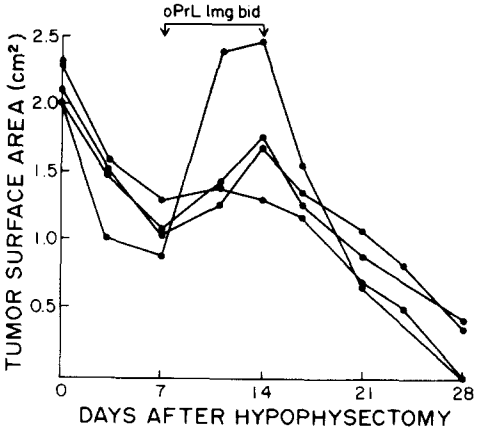

Fig. 1. The effect of prolactin administration on the hypophysectomy-mediated regressions of 4 tumors, each borne by an individual rat.

*Supported by USPHS Grant CA 14520 and CA 17579.

Table 1. The effect of hypophysectomy and estrogen replacement after hypophysectomy on the growth of NMU-induced rat mammary carcinomas

Group treatment	Tumor surface area (cm^2) Pretreatment	After 14 days
I Controls (12)	2.08 ± 0.30	3.83 ± 1.57*
II Hypophysectomy (12)	2.35 ± 0.33	0.09 ± 0.18*
III Hypophysectomy plus estrogen† (11)	2.53 ± 0.54	2.42 ± 1.53
Group III off estrogen (11) for 14 days	—	0.67 ± 0.84*

The number of rats and tumors in each group is given in parentheses.
*Significantly different from corresponding initial surface area by Student's paired t test, $P < 0.001$.
†Estradiol benzoate 5 μg/day.

These results indicate that both estrogens and prolactin influence the growth of NMU-induced rat mammary carcinomas. The observed effect of estrogen is of particular interest because the same dose of estradiol benzoate has no effect on the regression of DMBA-induced mammary tumors after hypophysectomy [6]. To this extent mammary carcinomas induced by NMU appear to provide the better model for human breast cancer. The failure of 1 tumor to re-grow during prolactin administration may reflect the additional requirement for estrogen, or indicate a need for a second pituitary factor, such as growth hormone.

REFERENCES

1. Rose DP, Pruitt B, Stauber P, Ertürk E, Bryan GT. Influence of dosage schedule on the biological characteristics of *N*-nitrosomethylurea-induced rat mammary tumors. *Cancer Res* 1980; **40**: 235–239.
2. Arafah BM, Gullino PM, Manni A, Pearson PH. Effect of ovariectomy on hormone receptors and growth of *N*-nitrosomethylurea-induced mammary tumors in the rat. *Cancer Res* 1980; **40**: 4628–4630.
3. Williams JC, Gusterson B, Humphreys J, Monaghan P, Coombes RC, Rudland P, Neville AM. *N*-Methyl-*N*-nitrosourea-induced rat mammary tumors. Hormone responsiveness but lack of spontaneous metastasis. *J Natl Cancer Inst* 1981; **66**: 147–151.
4. Manni A, Trujillo JE, Pearson OH. Predominant role of prolactin in stimulating the growth of 7,12-dimethylbenz(a)anthracene-induced rat mammary tumor. *Cancer Res* 1977; **37**: 1216–1219.
5. Pruitt B, Rose DP, Bryan GT. Hormone dependence of *N*-nitrosomethylurea (NMU)-induced rat mammary tumors: response to two modes of anti-estrogen therapy. *Proc Am Cancer Res* 1979; **20**: 87.
6. Sterental A, Dominguez JM, Weissman C, Pearson OH. Pituitary role in the estrogen dependency of experimental mammary cancer. *Cancer Res* 1963; **23**: 481–484.