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Letter to the Editor

Effect of Progesterone Administration on Rat Endometrial Disease after Exposure to *N*-Nitrosomethylurea*

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WE RECENTLY reported the occurrence of estrous cycle abnormalities, polycystic disease of the ovaries, gross thickening of the uterine horns with accompanying hydrometria and endometrial hyperplasia in rats exposed to the mammary carcinogen *N*-nitrosomethylurea [1]. Eventually a proportion of these animals develop infiltrative adenomatous hyperplasia, squamous metaplasia and carcinomas of the endometrium (unpublished findings). Thus the uterine changes which occur over time after treatment with *N*-nitrosomethylurea (NMU) appear to provide a useful model for human endometrial cancer. We have now demonstrated low serum progesterone levels in rats exposed to NMU and found that the uterine abnormalities can be prevented by chronic administration of progesterone. Our model, therefore, also reproduces clinical situations in which uterine tissue is exposed to estrogen stimulation unopposed by progesterone.

Figure 1 illustrates the low serum progesterone levels and loss of the estrous cycle peak in NMU-treated rats. The carcinogen had been administered by i.v. injection on 3 occasions, the first when the rats were 50 days old, as previously described [2], except that the dose was 4 mg/100 g body weight. Serum samples were obtained from 6 NMU-treated rats 4.5 months after the first injection for 5 days between 7:00 and 7:30 p.m., and also from 10 controls. Progesterone was extracted from serum with petroleum ether [3] and measured by radioimmunoassay [4].

To demonstrate an inhibitory effect of progesterone administration on the development of uterine disease, 50-day-old female Sprague–Dawley rats were given 4 mg/100 g body weight of NMU by i.v. injection and a second dose 1 month later. One group of 20 animals received no further treatment, while another 21 were given progesterone (Sigma Chemical Co., St. Louis, MO), 2.5 mg dissolved in peanut oil twice daily by s.c. injection, commencing 7 days before initial exposure to NMU and continuing throughout the study. The rats were sacrificed and autopsied when they had developed a mammary carcinoma with a maximum diameter of 2 cm or, if this had not occurred, at 20 weeks from the first NMU injection. The average time intervals between NMU injection and sacrifice for the control and progesterone-treated groups were virtually identical, 124 ± 19 and 125 ± 20 days respectively,

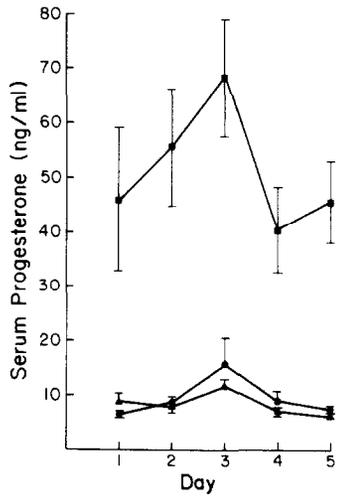

Fig. 1. Serum progesterone levels taken over a 5-day period at 7:00 to 7:30 p.m. from untreated controls (■), and rats 4.5 months after initial exposure to NMU with normal appearing uteri (●) or hydrometria (▲).

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although hormone administration did reduce the mammary tumor incidence (80 vs 62%).

Chronic treatment with progesterone had a pronounced inhibitory effect on the development of endometrial disease in rats exposed to NMU (Table 1). No abnormalities were detected on gross examination in this group, whereas 75% of the NMU-exposed controls had thickened uteri which were often distended with fluid. Similarly, while only 2 of the 21 progesterone-treated animals showed endometrial glandular hyperplasia, this was present in all but 1 of the controls. No endometrial carcinomas were seen, but our experience is that these occur only when survival is extended to 28 weeks after NMU administration by surgical excision of the mammary carcinomas. However, uteri from 9 of the NMU-exposed controls (45%) did contain benign neoplasms, whereas none were found in the progesterone-treated group. Progesterone administration did not influence the development of ovarian polycystic disease after exposure to NMU.

These results provide further evidence supporting the validity of our model for the preneoplastic endometrial disease. While the pathological mechanism by which NMU induces changes culminating in endometrial hyperplasia and neoplasia remains to be established, a distinctive feature of our model is the presence of polycystic disease of the ovaries. Women with the Stein–Leventhal syndrome are known to be at increased risk of endometrial cancer [5], and here anovulation and a deficiency of progesterone may be involved, as well as increased production of androstenedione and thence of estrone. So, it seems at least plausible that NMU may act by interference with the hypothalamo-pituitary-ovarian axis. This leaves open the question of whether the compound also performs as a chemical initiator of endometrial carcinogenesis.

Table 1. *Effect of progesterone administration on endometrial and ovarian disease in rats exposed to NMU*

Group	No.	Gross uterine abnormalities	Endometrial histopathology		
			Glandular hyperplasia	Adenomas	Polycystic ovaries
NMU-exposed controls	20	15/20 (75%)	19/20 (95%)	9/20 (45%)	20/20 (100%)
NMU, progesterone treated	21	0/21 (0%)	2/21 (9%)	0/21 (0/%)	21/21 (100%)

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