

ACTH Secreting Transplantable Pituitary Tumors.*† (20607)

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Pituitary tumors can be induced by ionizing irradiation(1). In order to find out whether these tumors are hormone-secreting and if so, to ascertain the type of hormones they secrete, attempts were made to transplant them in mice of the strain in which the tumor originated (LAF₁). Furthermore, it was thought possible that these tumors, like those induced by I¹³¹, are conditioned neoplasms(2), and that the necessary conditioning procedures(3) might yield information as to the pathogenesis of pituitary tumors induced by ionizing irradiation. Accordingly, recipients were subjected to gonadectomy or radiothyroidectomy or X irradiation before grafting on them the tumors induced by ionizing irradiation.

The first attempt to graft a pituitary tumor occurring among mice exposed to ionizing irradiation yielded a transplantable growth which, contrary to expectations, proved autonomous, that is, transplantable to normal mice as well as to those variously pretreated (conditioned). The salient changes produced in the recipients were: obesity, with atrophy of the thymus and spleen, polyuria sometimes with glycosuria, hyperglycemia, and leukopenia, notably lymphocytopenia. These findings constitute sufficient presumptive evidence that the tumors secrete ACTH. Correspondingly, the adrenal glands of mice bearing these grafted tumors were hyperplastic while the gonads, thyroid, and other organs examined gave no indication of stimulation by other types of pituitary hormones. The following is supporting evidence:

Transplantation data. The original tumor (O.G. 1) was grafted in the thigh muscle of 23 mice of the strain of origin, of which all but 2 exhibited most, or all, of the changes stated above. Four males of this group were castrated 5 days after the tumor graft; 4

sibling males were non-castrated. Three females received 250 μ c of I¹³¹ 3 days after the tumor graft; 3 female siblings remained untreated. Nine females received 200 r of 250 kvp X rays approximately 1 year before the tumor graft. The period of latency of tumor development as ascertained by palpation varied from 110 to 207 days. Following identification of the tumor, the hosts lived for periods of several weeks; most of them were sacrificed. At death the tumor measured a few mm to 10 mm across. Two subpassages were made with success as indicated by leukopenia or polyuria, after a somewhat shortened period of latency in all 16 mice that were grafted with tumor fragments.

Polyuria and glycosuria. The urinary volume of normal mice placed in a metabolism cage averages about 1-2 cc per day. The urinary volumes of mice bearing grafted tumors observed in the metabolism cage for at least 1 week varied between approximately 20 to 30 cc/day. The water intake was correspondingly increased. Of 15 mice with polyuria 2 had severe glycosuria. None of the numerous uninjected controls studied gave significant quantities of sugar in the urine.

Hyperglycemia. Blood sugar determinations were made on 8 tumor-bearing mice with leukopenia or polyuria. The animals were fasted for 16 hours. Samples of 0.05 ml of blood were obtained from the tail vein of heparinized mice and analyzed by the Folin-Wu method, slightly modified. Heparin had no effect on blood sugar levels. An approximately double number of normal mice were tested simultaneously with tumor-bearing mice in each experiment. The values for reducing sugars in mg per 100 ml blood were as follows:

Blood sugar, mg %	
Normal mice†	Mice with tumor grafts*
88	104
115, 120	160, 200, 230
150, 160	170, 208, 210, 830

* Individual values on animals with polyuria and leukopenia.

† Mean values of 2-3 mice.

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The high normal values may be due to inadequate fasting of mice in the respective experiments.

White cell counts. The white cell count of 9 tumor-bearing mice ranged from 300 to 3,150, averaging 1,150. The % of lymphocytes ranged from 4 to 44, averaging 15. The control white cell counts made simultaneously on 3 normal animals varied from 9,650 to 12,050 with an average of 11,233. The lymphocytes averaged 84.7%.

Obesity. Every tumor-bearing animal was either moderately or highly obese.

Microscopic observations. The adrenals of all tumor-bearing mice were slightly to greatly enlarged. The cells of all 3 layers of the cortex were swollen. The tumor cells were fairly uniform in size and shape. The nucleus was nearly normal in size and appearance; the cytoplasm was abundant and all cells contained in their cytoplasm numerous minute granules which were distinctly stained with hematoxylin. None of the other endocrines exhibited noteworthy changes. Detailed description and illustration of the tumors, adrenals, and other organs will follow.

Surgical removal of the adrenal was successful in one tumor-bearing mouse in which the 24-hour urinary volume, 20 cc before operation, dropped to 2 cc after the operation and remained within the normal range until death, 24 days after operation.

Comments. Thirteen pituitary tumors induced by radiothyroidectomy in 3 strains of mice were transplanted in series to a total of well over 1000 mice. Transplantation of these tumors succeeded at first only in radiothyroidectomized and not in normal mice. All secreted thyrotrophin and none ACTH. In contrast, the tumors which originated in a mouse exposed to ionizing irradiation and analyzed in this study produce secondary changes indicative of ACTH secretion. A second tumor of similar provenance currently analyzed is

identical in every respect with that here described. The evidence presented elsewhere(1) strongly suggests that the tumors occurring among mice exposed to ionizing irradiation are actually induced by the latter either by a direct or indirect action, their incidence among controls 25 months after exposure being 0.15% as compared to 4 to 12% in groups receiving about 200-700 r. The present study indicates that these tumors might be related to the original insult of the adrenal-pituitary mechanism caused by a single exposure of gamma rays or neutrons.

Excessive doses of cortisone produce in mice lymphopenia, loss of body weight, atrophy of thymus and spleen(4). The animals in our experiment did not lose and usually gained weight. This suggests that obesity and gain in weight are due to hormones other than cortisone produced in excess (directly or indirectly) by the grafted pituitary tumors.

Summary and conclusions. Two pituitary tumors occurring in mice exposed to ionizing irradiation proved readily transplantable causing in the recipients obesity with thymic atrophy, hyperglycemia, polyuria, sometimes with glycosuria, severe lymphocytopenia, and hypertrophy of the adrenal cortex. On the basis of these findings it is concluded that this tumor secretes ACTH. There is lack of evidence of stimulation of any endocrine organ other than the adrenal.

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