Induction of Pituitary Tumors by Means of Ionizing Irradiation.*† (20608)

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The occurrence of pituitary tumors among mice exposed to X rays has been mentioned before(1,2), but no evidence has been presented thus far to indicate that these tumors were actually induced by ionizing irradiation. In all probability earlier workers did not examine the cranial cavity systematically, or the experimental animals were not observed long enough after irradiation.

Methods. Large numbers of mice of the LAF_1 strain were exposed to atomic detonation. Some were not shielded and received predominantly gamma rays of high energy; some were lead-shielded to eliminate most of the gamma rays. The latter group will be spoken of as neutron-exposed animals. A fuller account of the exposure conditions and energy calculations will be given later. Approximately 30 days following exposure the surviving mice were transported to Oak Ridge where they remained individually caged until natural death or were killed in extremis. All animals have been autopsied and are preserved. The tumor diagnosis, as tabulated, is based on gross examination confirmed by microscopic examinations. At autopsy most tumors replaced the anterior hypophysis completely and compressed the overlying brain. In animals bearing large tumors the posterior part of the skull was bulging. Numerous animals in which the clinical diagnosis was made on this basis, were sacrificed and the bulk of the tumors was used in transplantation studies(3). On microscopic examination the tumors appeared chromophobe usually with many cavernous vascular spaces. Invasion of the sella and its marrow cavity was frequent even though the cells appeared uniform, lacked hyperchromatophilia and nuclear abnormalities indicative of malignancy. A detailed description of the gross and microscopic features of these tumors will follow. Minute tumor nodules discovered on microscopic examination have not been included in the tabulation. Hemorrhage in the tumor or compression of the brain appeared to be the cause of death in most instances.

Results. Table I indicates that 4 to 12% of the females exposed to 192-733 r developed pituitary tumors as compared to 0.3% of the controls. No pituitary tumor occurred among the control males during this period of observation while 2 to 5% of the males exposed to 491-785 r developed such tumors. The dose acutely fatal to 50% of the animals was about 750 r. Most mice exposed to larger doses died within 10-14 months, and this probably accounts for the absence of pituitary tumors in mice exposed to higher doses, since, as Table II indicates, the period of latency of these tumors is very long.

Table II shows that pituitary tumors began to appear in larger numbers 16 months postirradiation, and they occurred with greatest frequency in the 23-25 months postirradiation groups. It is well known that chromophobe adenomas of the pituitary gland are common among old rats, but very little is known about pituitary tumors in mice.

That pituitary tumor-induction dose is low is indicated in Table III which lists the findings on neutron-exposed mice. It seems that a dose as low as 40 to 70 rem may induce pituitary tumors. Further work is required to establish the relatively greater efficiency of neutron as compared with gamma irradiation in the induction of these neoplasms, suggested by Table III.

These findings, representing only a part of a very large scale experiment, are released here in a preliminary form because:

(a) They indicate that ionizing irradiation can produce pituitary tumors in at least one strain of mice, and this knowledge might induce other investigators to a closer study of this organ in mice of other strains and of animals of different species exposed to ioniz-

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TABLE I. Longevity and Incidence of Pituitary Tumors in Mice Exposed to Atomic Detonation.

Dose (r)*	No. exposed,† ♂ and ♀	Female mice surviving‡ 30 days No.	%	1 yr No.	%	25 mo No.	%	Pituitary tumor No.	%	Male mice surviving* 30 days No.	%	1 yr No.	%	25 mo No.	%	Pituitary tumor No.	%
812-932	880	25	6	15	3	0	0	0	0	39	9	25	6	0	0	0	0
759-785	440	87	40	57	26	0	0	0	0	85	39	58	26	4	2	3	5
711-733	440	157	71	118	53	0	0	14	12	153	70	130	59	13	6	2	2
631-687	440	195	89	146	66	9	4	17	12	204	93	176	80	37	17	8	4
491-556	440	215	98	179	81	43	19	22	12	208	95	185	84	75	34	4	2
367-424	440	78§	—	66	—	23	—	7	11	108§	—	102	—	43	—	0	0
287-318	440	213	97	195	89	58	26	10	5	213	97	202	92	112	51	2	1
192	220	107	97	102	93	45	41	4	4	107	97	101	92	62	56	0	0
0	620	301	97	300	97	189	61	1	0.3	310	100	294	95	198	64	0	0

* Predominantly (over 90%) gamma radiation; the ratio of gamma rays to neutrons being somewhat greater in the lower dose range.
† Half males, half females.
‡ Post-irradiation. The mice were irradiated at 6-12 wk of age. This tabulation was prepared approximately 26 months post-irradiation.
§ These figures are incomplete due to loss of animals during transportation from field laboratories.

TABLE II. Incidence of Pituitary Tumors in Mice Exposed to Atomic Detonation.

Mo post-irradiation	Female No. dying	Female Pituitary tumor No.	%	Male No. dying	Male Pituitary tumor No.	%
1-10	139	0	0	115	0	0
11-13	83	3	4	56	0	0
14-16	148	3	2	81	0	0
17-19	244	22	9	178	6	3
20-22	231	21	9	241	7	3
23-25	215	26	12	226	4	2

TABLE III. Incidence of Pituitary Tumors in Female Mice Exposed to Neutron Radiation from Atomic Detonation.

Dose* (rem)	No. exposed	Mice surviving 30 days No.	%	1 yr No.	25 mo No.	Pituitary tumor No.	%
450	30	27	90	20	4	2	10
180	30	28	93	22	3	3	14
140	20	20	100	18	2	3	17
70	30	30	100	29	14	2	7
40	30	27	90	24	13	1	4
0	310	301	97	300	189	1	0.3

* The rem values were calculated on the basis of thymic wt loss following 230 kvp X radiation by Dr. R. E. Carter and associates.

ing irradiation.

(b) They indicate the long period of latency required for the development of these tumors, and this knowledge might induce others not to destroy irradiated animals prematurely.

(c) These data present the background to the transplantation studies of pituitary tumors described currently(3), indicating that the first 2 of these tumors successfully grafted on normal mice of this strain secrete ACTH.

(d) It is possible that these tumors are induced not by a direct action of ionizing irradiation on the pituitary but by some indirect mechanism, the elucidation of which calls for a renewed study of the effects of irradiation on endocrine and other organs under pituitary control.

It is generally believed that female mice live longer than males. The present data show the reverse, and this may be due to several factors, such as, strain differences, individual caging of the animals which prevented fighting among the males, or greater incidence of neoplasms and other diseases among females, at an earlier age.

Summary and conclusions. Pituitary tu-

mors were induced in mice by a single exposure to ionizing irradiation. The greatest incidence occurred among mice exposed to doses of gamma radiation somewhat below the LD_{50}. These tumors were about four times more frequent among females than among males. Neutrons appear more efficient in inducing these neoplasms than gamma rays, and the data suggest that doses as low as 40-70 rem may induce such tumors. The period of latency of these neoplasms is very long, the maximum incidence being at 17-25 months postirradiation.

1. Furth, J., and Butterworth, J. S., *Am. J. Cancer,* 1936, v28, 66.

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3. Furth, J., Gadsden, E. L., and Upton, A. C., PROC. SOC. EXP. BIOL. AND MED., 1953, v84, 253.

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