Pituitary Cytology of Rats with Leydig-Cell Tumors Induced by Low-Level Testicular Irradiation[1] (34827)

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Benign interstitial-cell (Leydig) testicular tumors have been induced in Long–Evans rats by local X-irradiation of the testes. A pituitary feedback mechanism of gonadotropic stimulation, secondary to testicular radiation injury, was suggested as a possible promoting factor in the development of interstitial-cell hyperplasia and neoplasia in these rats (1).

The present study involved the cytologic examination of pituitary glands from 181 rats including 45 control animals and 136 still surviving 2 years after local testicular irradiation with either 150 or 500 R X-rays (1). The relationships between gonadotropic basophilic hyperplasia and adenomas in these pituitary glands and the testicular lesions, degenerative and neoplastic, resulting from irradiation were investigated.

Materials and Methods. The techniques of the testicular irradiation employed have been described elsewhere (1). The rats were killed with ether and the pituitary glands were fixed *in situ* in 10% neutral formalin, embedded in paraffin, and sectioned. Multiple sections from each gland were stained by the orange G/periodic acid–Schiff (PAS) (2) and by the aldehyde–fuchsin (AF) (3) methods, the latter without prior oxidation by permanganate. Adenomas in the pituitary pars anterior were classified according to their staining characteristics as designated by Griesbach (4).

Results. Types of pituitary adenomas. Three types of adenoma were found in the pituitary pars anterior of control and irradiated rats. The structure and characteristic locations of these tumors in the pars anterior have been described in detail by Griesbach (4).

Diffuse gonadotropic hyperplasia without nodule formation was evident in many rats (control, 13%; 150-R-irradiated, 21%; and 500-R-irradiated, 13%), although differential counts of pars anterior cells were not performed.

Gonadotropic adenomas. These adenomas were composed of cells containing PAS-positive, AF-negative cytoplasmic granules (Figs. 1 and 2), either coarse and flocculent (Type I, FSH cells) or fine and uniformly dispersed (Type II, LH cells). Approximately equal numbers of gonadotropic adenomas of both types were found in the three groups of rats. Type III adenomas were not identified in this study. Most of these adenomas were small; only one occupied a lateral lobe. While the majority were single, two or more were found in some glands. Types I and II adenomas frequently occurred together.

Thyrotropic adenomas. Cells containing PAS-positive, AF-positive cytoplasmic granules compised this type of adenoma. Characteristically, these cells were irregular in shape, with angular outlines. No multiple thyrotropic adenomas were found.

Chromophobe adenomas. The cells of these adenomas were devoid of granules that stained with either orange G–PAS or AF. All of the grossly enlarged pituitary glands of 10 rats receiving testicular irradiation in this study (1) were found to contain chromophobe adenomas, which were invariably larger than the other tumor types.

Incidence of pituitary adenomas. The numbers of control and irradiated rats in

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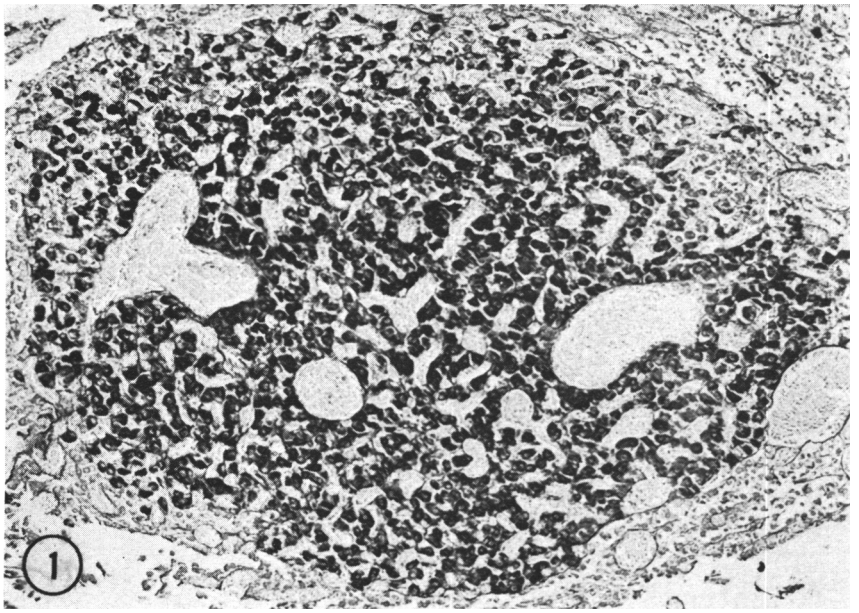

FIG. 1. Gonadotropic adenoma (Type I) in rat anterior pituitary. The nodule is circumscribed but unencapsulated. The granules are coarsely flocculent and PAS-positive (FSH cells). Control rat, age 2 years; orange G–PAS stain (×125).

which three types of pituitary adenomas developed are listed in Table I. The frequency of gonadotropic adenomas in irradiated animals was slightly lower than in control rats, whereas the frequency of thyrotropic adenomas was decidedly lower and that of chromo-

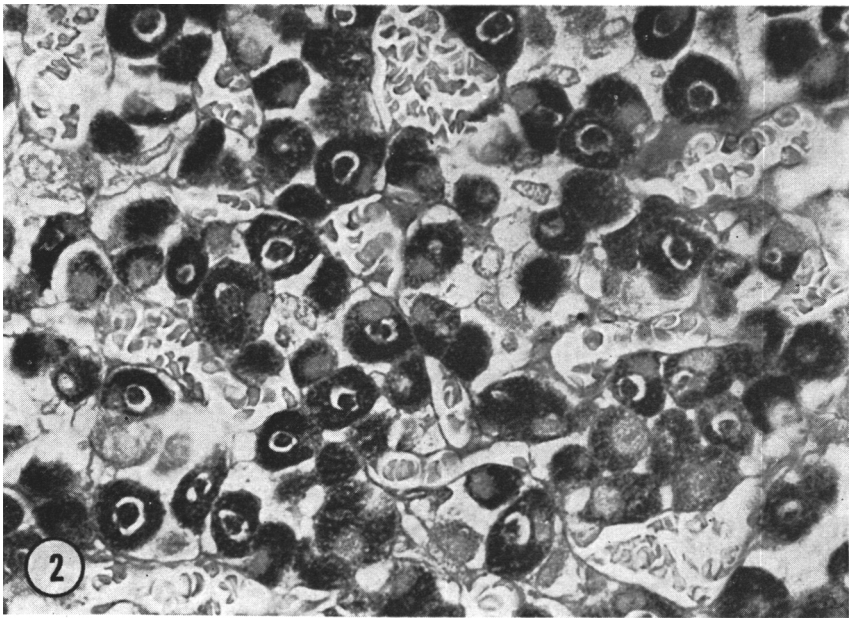

FIG. 2. Gonadotropic rat adenoma (Type I). The cells are coarsely granulated and PAS-positive. Note negative Golgi images. Rat treated with 500 R X-rays, age 2 years; orange G–PAS stain (×630).

TABLE I. Pituitary Adenomas in Control and Irradiated Rats.

Treatment	Type					
	Gonadotropic		Thyrotropic		Chromophobe	
	No.	%	No.	%	No.	%
None	18	40	5	11	3	6
150 R	14	22	1	1	10	16
500 R	23	31	0	0	14	18

phobe adenomas was higher in irradiated animals compared to controls. In the present study, the incidence of gonadotropic adenomas was significantly lower than that reported by Griesbach in either controls or thyroid-irradiated, male Long–Evans rats (4).

Correlation of pituitary and testicular lesions. The incidence of gonadotropic adenomas and hyperplasia together with the incidence of testicular Leydig-cell tumors, interstitial-cell hyperplasia, and testicular tubular atrophy is recorded in Tables II and III. Expected and observed incidences of each pituitary lesion (adenoma and hyperplasia) occurring with each testicular lesion (Leydig-cell neoplasm, hyperplasia, and tubular atrophy) in the same rat were almost identical, indicating the absence of a statistical relationship between pituitary and testicular pathologic lesions.

Comment. Previous reports have demonstrated that thyroxine deficiency in the rat, induced by subtotal thyroidectomy or radiation with either X-rays or various doses of ^{131}I, increased the incidence of thyrotropic adenomas in the pituitary (4–8). Supplementing the diets of similarly treated rats with desiccated thyroid powder caused a significant decrease in the incidence of these thyrotropic adenomas (7, 8) as well as a decrease in the incidence of thyroid adenomas induced by subtotal thyroidectomy or irradiation (5, 6).

In the present experiment, tubular atrophy, interstitial-cell hyperplasia, and Leydig-cell tumors resulted from localized testicular irradiation. The incidence in rats irradiated with 500 R was higher than in those treated with 150 R. Since these radiation-induced, degenerative, hyperplastic, and neoplastic lesions were considered comparable to those found in the thyroid gland after irradiation, the pituitary glands were studied for evidence of increased gonadotropic activity, *i.e.*, gonadotropic hyperplasia and/or adenoma, which might be expected to result from gonadal

TABLE II. Correlation of Gonadotropic and Testicular Lesions.

Treatment	No. of rats	Gonadotropic adenoma		Gonadotropic hyperplasia		Leydig-cell tumor	
		No.	%	No.	%	No.	%
None	45	18	40	6	13	1	2
150 R	62	14	22	13	21	6	9
500 R	74	23	31	10	13	40	54

		Gonadotropic adenoma and Leydig-cell tumor together			Gonadotropic hyperplasia and Leydig-cell tumor together		
		Expected	Observed		Expected	Observed	
		%	No.	%	%	No.	%
None	45	0.8	0	0	0.2	0	0
150 R	62	2	1	1.5	1.9	2	3
500 R	74	16	14	19	7	6	8

TABLE III. Further Correlation of Gonadotropic and Testicular Lesions.

Treatment	No. of rats	Interstitial-cell hyperplasia		Gonadotropic adenoma and interstitial-cell hyperplasia together			Gonadotropic hyperplasia and interstitial-cell hyperplasia together		
				Expected	Observed		Expected	Observed	
		No.	%	%	No.	%	%	No.	%
None	45	0	0	0	0	0	0	0	0
150 R	62	0	0	0	0	0	0	0	0
500 R	74	28	37	11	9	12	5	6	8
		Testicular tubular atrophy		Gonadotropic adenoma and testicular atrophy together			Gonadotropic hyperplasia and testicular atrophy together		
				Expected	Observed		Expected	Observed	
		No.	%	%	No.	%	%	No.	%
None	45	8	17	7	2	4	2	0	0
150 R	62	6	9	2	0	0	2	0	0
500 R	74	45	60	18	16	21	8	9	12

deficiency and which might in turn be related to or promote testicular interstitial-cell hyperplasia and neoplasia.

Although gonadotropic hyperplasia and adenomas were found in the irradiated rats, the incidences were the same or actually lower than in non-irradiated control rats. Analysis of the frequencies of pituitary and testicular lesions revealed no significant relationship between the two (Tables II and III). The finding of an extremely high incidence of gonadotropic adenomas in rats which had undergone gonadectomy (9) as contrasted with a relatively low incidence after radiation injury suggests that the doses employed (150 and 500 R) were insufficient to cause gonadal hormone deficiency and evidence of secondary gonadotropic hyperactivity. Since Leydig-cell tumors appear to develop from stimulated hyperplastic interstitial cells (1), it is likely that these cells had indeed been subjected to gonadotropic stimulation, although cytologic evidence of increased gonadotropic activity was not apparent.

Summary. The pituitary gland cytology of rats subjected to local testicular irradiation was studied. Although rats treated with 500 R X-rays had a high incidence of testicular atrophy, interstitial-cell hyperplasia, and Leydig-cell tumors, increased incidences of gonadotropic hyperplasia and adenomas were not found. We could find no statistical relationship between degenerative, hyperplastic, and neoplastic lesions of the testes and pituitary gonadotropic hyperplasia and adenomas.

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