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HISTOLOGIC AND PHYSIOLOGIC CHARACTERISTICS OF HORMONE-SECRETING TRANSPLANTABLE ADRENAL TUMORS IN MICE AND RATS*

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Adrenocortical tumors which occur spontaneously are infrequent in mice and rats.[1-7] They have been induced in several strains of mice by castration shortly after birth[8-11] and in the rat by implantation of estrone pellets[12] or by inclusion of the carcinogenic agent "butter yellow" in the diet.[13] Histologic studies of tissues of hosts bearing tumor transplants indicated the production of estrogenic or androgenic hormones, or both, by some experimental tumors. To our knowledge, adrenocortical tumors which secrete corticoids have not been observed in mice or rats. However, transplants of an adrenocortical carcinoma in the Osborne-Mendel strain of rats induced atrophy of the adrenal glands of the hosts, indicating inhibition of ACTH by adrenocorticoid secretions.[13]

The present investigation concerns two adrenocortical tumors, one occurring in the LAF_1 strain of mice and the other in the WR strain of rats. Neither of these tumors gives evidence of secretion of gonadal hormone of either type, feminizing or masculinizing, and both are characterized by the presence of excessive adrenocorticoid secretion.

MATERIALS AND METHODS

Origin of the Adrenal Tumor of Mouse. During April, 1951, a group of LAF_1 mice was exposed to the irradiation of a test atomic bomb explosion (Operation Greenhouse). Adrenal tumors were observed in less than 1 per cent, and it is questionable whether these were induced by the irradiation or arose spontaneously. One male mouse that re-

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ceived 318 rep and was sacrificed in October, 1953, had a tumor in the right adrenal cortex measuring 12 by 20 mm.; the left adrenal gland was atrophic. The tumor was excised and finely minced in a small amount of isotonic saline solution and implanted intramuscularly in the thigh of male and female LAF_1 mice.

Origin of the Adrenal Tumor of Rat. A group of young WR male rats was radiothyroidectomized with I^{131} (400 μc. injected subcutaneously) for the purpose of inducing pituitary tumors. Two of the animals were sacrificed 1½ years later, when a tumor measuring 8 by 10 mm. was found in the right adrenal cortex of one rat, and in the other a tumor with an average diameter of 6 mm. was found in the left adrenal cortex. It is uncertain whether radiothyroidectomy caused these tumors. The two tumors were combined, finely minced with a small amount of isotonic saline solution, and implanted in the thigh muscles of WR rats.

Animals. The WR rats were bred in our laboratory; the LAF_1 mice were obtained from the Jackson Memorial Laboratory, Bar Harbor, Maine. The animals were fed a standard diet of Purina Chow pellets. Rats that were to be radiothyroidectomized were given a low iodine diet* and distilled drinking water for several weeks before administration of the I^{131} (120 μc. subcutaneously). Following adrenalectomy, the mice were given a single intramuscular injection of 1 mg. of desoxycorticosterone trimethylacetate.†

All animals into which the tumors were implanted were subsequently necropsied. Tissues were fixed in Zenker's solution and stained with hematoxylin and eosin.

Electrolyte Studies. Blood was obtained by cardiac puncture of etherized animals. Twenty-four hour samples of urine were collected from animals placed in metabolism cages. The electrolyte analyses were made with a flame photometer.

Eosinophil Counts. The technique of Speirs[14] was followed.

Results

Adrenal Tumor of Mouse, Strain 2

Original Tumor. At necropsy, the mouse bearing the original tumor displayed the following changes: emaciation with no edema, atrophy of lymph nodes and thymus, atrophy of testes and seminal vesicles, and slight enlargement of the thyroid gland. The tumor cells were fairly uniform in size and shape; the cytoplasm was scanty and ill-defined. There were few mitotic figures. Metastases in the lungs were numerous.

* Obtained from Nutritional Biochemicals Corp., Cleveland, Ohio.

† Percorten, Ciba, generously supplied by Dr. Robert Gaunt.

Transplantations. The tumor transplants took well in mice of the host strain in all passages: in males nearly 100 per cent and in females, 92 per cent (Table I). The average latent periods of the original passage in males and females were 106 and 133 days, respectively. After several passages, the average latencies decreased to 23 days in females in the seventh passage and to 16 days in males in the ninth passage.

TABLE I

Growth of Transplants of an Adrenal Tumor of a Mouse, Strain 2, in Isologous Strain

Treatment of hosts	Recipients	
	Male	Female
None	201/202*	77/84*
Adrenalectomy	13/14	4/4
Gonadectomy	11/11	8/9
Hypophysectomy		4/4

* Number of takes over number grafted.

The tumor took in eight of nine female gonadectomized recipients, but in these the average latency was about 35 per cent longer than in untreated controls. No change in the latency was observed in gonadectomized males. Adrenalectomy did not affect the latency in males but increased it slightly in females. Hypophysectomy, performed only in females, doubled the latent period.

Necropsy Findings. At necropsy, the transplanted tumors weighed 5 to 10 gm. each, were brown, soft, well vascularized, and sometimes spotted with opaque areas of necrosis. Microscopic examination of the tumor showed solid sheaths of polygonal epithelial cells of uniform size with scanty cytoplasm, spherical nuclei, and a few mitotic figures (Fig. 1). Most tumor cells resembled those of the adrenal cortex; rarely, they were elongated or sarcoma-like. Connective tissue septa separated groups of cells into nodules. The absence of distinct anaplasia was significant in the almost invariable presence of pulmonary metastases. Some tumor cells possessed a certain degree of polarity, being lined up on a basement membrane with nuclei located close to the membrane. Calcification and ossification were noted in a few tumors. The tumor cells contained little fat and the impression was gained that it was more abundant in the degenerating parts of the tumor.

Minute metastatic tumor nodules were disseminated throughout all lobes of the lungs (Fig. 2). In several cases these were not seen on gross examination, but were present in all sections taken. Most metastases were intravascular "tumor emboli." Where tumor cells had gained entry into alveoli and bronchi, they appeared to have grown there uninhibited. Edema and cavernous dilatation of pulmonary capillaries frequently accompanied the pulmonary metastases.

The most characteristic change associated with this transplanted tumor was a very marked atrophy of all three layers of the adrenal

cortex (Fig. 3). The adrenal medulla appeared unchanged in all tumor-bearing hosts. Some adrenal glands were enlarged, but this was due to congestion of adrenal sinusoids and not to hyperplasia of the cortex (Fig. 4). Similar cavernous dilatation of vessels was noted in the liver, ovaries, lungs, and in a few other organs, suggesting that the tumor growth was sometimes associated with a marked hypervolemia.[15]

A marked thymic atrophy was evident in all tumor-bearing animals. It was present even in animals bearing only small tumors and was interpreted as due to secretion of corticoids by the tumor. Animals bearing tumors other than those secreting ACTH or steroid hormones did not cause thymic atrophy until the tumors were large, while involution of the thymus occurred soon in all mice bearing this adrenal tumor.

TABLE II

Polyuria and Polydipsia in Mice Bearing Transplants of an Adrenal Tumor, Strain 2

Mouse	Days of observation	Water consumed, mean (range)	Urine excreted, mean (range)
		ml./mouse/day	*ml./mouse/day*
Control*	38	6.5 (5.8–7.0)	1.2 (1.0–2.2)
Tumor-bearing	10	37 (29–43)	23 (18–27)
Tumor-bearing	10	23 (17–26)	13 (10–18)
Tumor-bearing	10	57 (53–67)	36 (30–44)
Tumor-bearing	10	61 (53–69)	34 (27–41)
Tumor-bearing	10	29 (27–34)	18 (15–22)
Tumor-bearing	5	31 (28–33)	16 (12–20)
Tumor-bearing†	5	50 (47–55)	28 (20–38)
Tumor-bearing‡	8	33 (29–35)	13 (9–19)
Tumor-bearing‡	6	24 (20–34)	16 (10–23)

* Five animals were used to secure the control values. Other values are for individual mice.

† Gonadectomized mouse.

‡ Adrenalectomized and gonadectomized mouse.

Thymic involution is, in our experience, the most sensitive indicator of hyperstimulation by adrenocorticoids.

The testes and ovaries appeared normal or atrophic. Leydig cells were fewer than normal. The latter observation suggested some secretion of androgenic steroids by the tumor, but this supposition was not supported by the finding that in castrated tumor-bearing animals the seminal vesicles remained atrophic.

In the ovaries, lutein bodies were conspicuously absent and luteinization of the stroma was deficient. The uterine horns were slightly elongated and dilated or thickened. The mammary glands were usually normal except for marked ductal hyperplasia in a few animals, a change

not uncommon in old female mice. In ovariectomized hosts, the uterine horns were sometimes dilated and elongated, and sometimes thin and atrophic. These changes suggested the possibility of some secretion of estrogens. The ovaries of female adrenalectomized hosts were atrophic; their uteri were slightly dilated and elongated.

The pituitary and thyroid glands of tumor-bearing mice appeared normal. The liver showed no conspicuous change other than that of an occasional slight congestion of the hypervolemic type and/or a leukemoid reaction. Hemopoiesis was evident in the spleen, but such changes are common in animals bearing diverse tumors of large size. The kidneys showed no noteworthy change. There was no indication of a masculinizing effect in female mice.

Water Balance and Electrolytes. When the adrenal tumor in the mouse grew to 2 or 3 cm. in diameter, a profound polyuria and polydipsia, with no edema, were observed in the hosts (Table II). The

TABLE III

Serum Electrolyte Values of Mice Bearing an Adrenal Tumor, Strain 2

Serum electrolyte	Control mice*	Tumor-bearing mice*
Na, meq./l.	166.7 ± 12.7†	189.1 ± 7.9†
K, meq./l.	5.6 ± 0.7	4.9 ± 0.5
Cl, meq./l.	115.2 ± 10.1	121.7 ± 10.6
Na/K ratio	30.3 ± 5.4	38.8 ± 4.4

* Five mice in each group.

† Standard deviation of the mean.

presence of these changes in adrenalectomized and gonadectomized mice indicated that they were caused by secretions of the tumor.

A study of the serum electrolyte changes was made in mice with grafted adrenal tumors of later passages when hormonal secretions appeared to have diminished (Table III). The serum sodium levels were elevated and the potassium levels were slightly depressed. Polyuria and polydipsia were not so prominent in these mice as noted earlier. Increased sodium retention and polyuria pointed to an increased secretion of aldosterone or of another mineralocorticoid by the tumor. It is noteworthy that adrenalectomized mice bearing the tumor could be maintained on tap water.

Eosinophils. The eosinophil counts of the blood in adrenal tumor-bearing mice (strain 2) dropped to very low levels soon after the grafted tumor became palpable (Table IV). This occurred also in adrenalectomized, adreno-gonadectomized, and hypophysectomized tumor-bearing hosts (Table IV).

The change in levels of eosinophilic leukocytes was followed in 12 mice. A representative example is shown in Table V. The tumor was not yet palpable at 26 days, when the level of eosinophils was 378 per cmm. and the leukocyte count was 25,800. As the tumor grew, both eosinophil and total leukocyte counts dropped progressively to 19 per cmm. and 9,800, respectively. Bilateral adrenalectomy was performed 57 days after the graft. In normal animals, adrenalectomy is followed promptly by regeneration of the thymus and recovery from eosinopenia. In these animals, the eosinopenia persisted, the progressive drop in the levels of leukocytes and eosinophils was not arrested (terminal counts 1,600 and 3 per cmm., respectively), while the animals gained weight and the tumors continued to grow (Table V). Additional gonadectomy had no effect on the levels of eosinophils.

Eosinopenia was consistent in all adrenal tumor-bearing mice, but leukopenia was variable and usually slight. There was, however, a marked lymphopenia which occurred late in the presence of large tumors. In tumor-bearing mice, adrenalectomy was not followed by regeneration of the thymus. These data indicate that adrenal tumors of strain 2 secrete glucocorticoids.

TABLE IV

Eosinophil Levels of the Blood in Mice Bearing Adrenal Tumors, Strain 2*

Tumor size†	Normal			Adrenalectomized			Adreno-gonadectomized			Hypophysectomized		
	No. of counts	Mean	(Range)	No. of counts	Mean	(Range)	No. of counts	Mean	(Range)	No. of counts	Mean	(Range)
+	14	33	(0–150)	1	9					1	16	
+ to ++	8	6	(0–19)	5	9	(3–25)	2	25	(12–37)	2	6	(3–9)
++ to +++	3	6	(3–12)	5	7	(3–12)	1	12				
+++ to ++++	3	22	(9–48)	3	8	(3–12)						
Controls	55	409	(75–1373)	37	178	(22–318)	5	259	(97–612)	8	573	(250–967)

* Eosinophil counts per cmm. Blood obtained from tails at 8:00 a.m.
† Each plus sign indicates an approximate average diameter of 1 cm.

Adrenal Tumor of Mouse, Strain 3

Another adrenal tumor occurring also in an irradiated mouse was studied earlier in four passages. This tumor grew very rapidly, causing death with large tumors in about 1 month. It caused only slight involution of the thymus; the gonads and adrenal glands of the hosts appeared normal or were only slightly altered. Transplantation of this malignant non-secreting or low-secreting adrenocortical tumor was discontinued.

TABLE V

Sequence of Changes in a Mouse Bearing an Adrenal Tumor, Strain 2

Days after graft	Body weight	Tumor size*	Eosinophils	White blood cells	Lymphocytes	
					%	Total
	gm.		c.mm.	c.mm.		c.mm.
26	26.3	o	378	25,800	91	23,478
33	27.2	?	150	26,750	82	21,935
41	28.6	±	41	20,100	87	17,487
47	28.0	± to +	12	8,600	83	7,138
54	30.2	+ to + ±	19	9,800	70	6,860
57†						
63	33.0	++	25	12,500	48	6,000
70	34.9	++±	12	8,300	37	3,071
77	36.0	++±	3	1,600		

* Each + indicates an average of 1 cm.
† Bilateral adrenalectomy.

Adrenal Tumor of Rat, Strain 1

Original Tumor. The two rats bearing the original adrenal tumors were emaciated and anemic. Malnutrition could be attributed to overgrown incisor teeth. There was advanced atrophy of the thymus and lymph nodes. The testes were small, with degenerative changes in spermatogenic tubules and reduction in number of Leydig cells. Small remnants of the thyroid gland were present; other changes at thyroid sites were those of "radiothyroidectomy." There were distinct "thyroidectomy cells" in the pituitary body[16] with decrease in the number of acidophils. The adrenal tumors appeared to be typical cortical adenomas with no evidence of malignancy. The adrenal glands of the opposite side also contained minute tumor nodules and the cortical layers were thin. No metastases were observed.

Transplantation. The original passage was made by grafting the pooled tumors on radiothyroidectomized and gonadectomized rats of the strain of origin. In untreated rats there were no tumor takes even

after 615 days. The thyroidectomized animals, on the other hand, developed tumors with an average latency of 221 days; and gonadectomized rats, of 485 days.

Table VI summarizes the results of transplantations in animals variously treated. The tumors grew best in hosts made deficient of thyroid hormone either by radiothyroidectomy or low iodine diet. They took well in gonadectomized males and females, but in the latter after a much longer latent period. These periods were longer in gonadectomized than in radiothyroidectomized animals, and longer in the females than in males. The tumors grew well in animals that were both adrenalectomized and gonadectomized, but the average latent period was still about twice that of the radiothyroidectomized rats.

TABLE VI

Transplantation of Adrenal Tumor of Rat, Strain 1

Treatment of hosts	Recipients	
	Males	Females
None	6/28*	0/8*
Gonadectomy	11/13	4/4
Adrenalectomy and gonadectomy	4/4	
Radiothyroidectomy	10/10	9/9
Low iodine diet	5/5	

* Number of takes over number of grafts.

In the course of successive transfers, there was a decrease in the latent periods, but the relative differences in latency in animals which were variously treated persisted. These data indicate that growth of this adrenal tumor is greatly influenced by some hormonal imbalance in the hosts. Growth promotion by adrenalectomy can be adequately explained by increase of ACTH, but that by thyroidectomy is puzzling.

Necropsy Findings. At death, the grafted tumors were approximately 4 cm. in average diameter and weighed 10 to 15 gm. They had a characteristic, yellow-brown hue and were spotted with hemorrhagic and necrotic areas. Rarely, disseminated areas of calcification, and sometimes of ossification, were noted. The adrenal tumor cells of the rat (Fig. 6) were similar to those of the mouse: polygonal, closely packed, often forming palisades. Mitotic figures were numerous, but anaplasia was scant. Pulmonary metastases were noted in a few animals (Fig. 7).

There was atrophy of all layers of the adrenal cortex of tumor-bearing hosts; the medulla appeared unchanged (Fig. 8). The thymus was atrophic. These observations indicate that the tumor secreted corticoids. The thyroid gland appeared normal in the gonadectomized and untreated hosts. There was marked atrophy of the testes and seminal vesicles (Fig. 10) of the non-operated animals. Leydig cells were few or absent and spermatogenesis was depressed. In the gonad-

ectomized males, there was advanced atrophy of the seminal vesicles. The testes and seminal vesicles of radiothyroidectomized hosts were atrophic. These findings indicate lack of secretion of androgens. The ovaries and uteri of female radiothyroidectomized hosts were of normal size or atrophic; in no case was there evidence of gonadal stimulation.

The pituitary bodies of the gonadectomized and thyroidectomized animals possessed large numbers of hypertrophied cells with hyalinization and vacuolization of the cytoplasm.[16] These changes were similar to Crooke's hyalinization of pituitary basophils, which is considered to be pathognomonic of Cushing's disease. They were absent in untreated rats bearing the adrenal tumor.

Obesity, a characteristic change in mice bearing grafted adrenotropic tumors,[23] was present in most rats, but absent in most mice with grafted adrenal tumors.

Preliminary studies have shown the tumor-bearing rats to be slightly polyuric, with about two or three times the daily urine output of controls. The serum sodium and potassium values appeared unchanged in the few tumor-bearing rats examined. However, adrenalectomized hosts survived well on tap water once the tumor started to grow.

Discussion

The physiologic effects of functional adrenocortical tumors in man and animals vary with the type of hormones secreted. In general, four types of hormonal effects have been noted: those influencing carbohydrate or electrolyte metabolism and male or female sexuality. The clinical picture most frequently observed suggests the simultaneous overproduction of a mixture of several hormones in various proportions, sometimes of only two types and rarely of only one type.[17] Table VII surveys functional adrenal tumors in several animal species. In earlier reports of others, only gonadal effects (masculinizing, feminizing, or both) were recorded, while our adrenal tumor strains in both mice and rats exhibited glucocorticoid and mineralocorticoid but no gonadal activities. Studies are now being made on the rates and types of corticoids secreted by the tumor slices *in vitro*[21] and on urinary steroidal products of the hosts.[22] The results of the former[21] indicate secretion of corticoids and responsiveness of the tumor cells to ACTH. The results of the latter[22] indicate a large increase in urinary 17-ketosteroids, particularly the 11-oxygenated 17-ketosteroids.

It is noteworthy that all three layers of the adrenal cortex of tumor-bearing hosts were inhibited. Atrophy of the zona glomerulosa and polyuria indicate secretion of mineralocorticoids. Confirmatory evi-

TABLE VII

Physiologic Effects of Functional Adrenocortical Tumors and Transplants in Several Animal Species

Host	Strain and sex	Induction procedure	Presumed secretion			
			Andro-genic	Estro-genic	Gluco-corticoid	Mineralo-corticoid
Mouse	NH ♂ and ♀,[8,11] DBA ♀ [18]	Castration	−	+	−	−
Mouse	A ♀ [11]	Castration	+	−	−	−
Mouse	CE ♂ and ♀,[9,10] C_3H ♀, CBA ♀, Bagg albino ♂ and ♀ [11]	Castration	+	+	−	−
Mouse	LAF_1 ♂ (Cohen *et al.*, 1957)	Irradiation(?)	−	−	+	+
Mouse	NH x A ♂ [3]	Irradiation(?)	−	?	−	−
Mouse	Old NH ♀ [3]	Spontaneous	−	+	−	−
Mouse	C ♀ [3]	Spontaneous	−	−	−	−
Rat	WR ♂ (Cohen *et al.*, 1957)	Radiothyroidectomy(?)	−	−	+	+
Rat	Osborne-Mendel ♀ [13]	Carcinogenic diet	−	−	?	−
Guinea pig	♂ [19]	Castration	+	−	−	−
Rabbit	♂ [20]	Spontaneous	−	−	−	−

dence for this is the hypernatremia co-existing with polyuria. The hypoplasia of the zona glomerulosa is probably caused by a process analogous to its inhibition by administration of salt. The early severe depression of eosinophil counts is indicative of excessive secretion of glucocorticoids and, correspondingly, the marked atrophy of the zona fasciculata and zona reticularis indicates inhibition of ACTH discharge.

In parallel studies the levels of eosinophils of mice bearing transplanted tumors of diverse types have been investigated. A marked and early drop in levels of eosinophils occurred in mice with grafted adrenal or adrenotropic pituitary tumors. Following this drop, adrenalectomy caused a rise in levels of eosinophils in mice bearing adrenotropic pituitary tumors, while in animals with adrenal tumors the drop continued until almost all eosinophils disappeared from the circulation.

It is most desirable to identify the corticoids secreted by such tumors. While it is possible that they merely represent a spectrum of the usual adrenocorticoids, it is also conceivable that some of them have little or no hormonal activity, yet exert a specific pituitary inhibition. Such compounds may characterize the neoplastic cell and be of therapeutic value in inhibiting secretion by adrenotropes.

Routine morphologic examinations disclosed no significant change in the mouse or rat pituitary bodies of the tumor-bearing hosts. Theoretically, one would expect atrophy or hypoplasia of the adrenotropic cells. The morphologic characteristics of adrenotropic cells are unknown. They are believed to be variants of basophils, but none of our three transplantable adrenotropic tumors is composed of distinctly basophilic cells.[23] All are chromophobic or amphophilic even though they are highly secretory. The absence of Crooke's change in the pituitary bodies of untreated mice and rats bearing adrenal tumor grafts is noteworthy. Crooke's change has been reproduced in man by administration of cortisone or hydrocortisone.[24] The literature on Crooke's change in rodents given ACTH or cortisone is contradictory. Our findings with adrenotropic pituitary tumors[23] and with adrenal tumors here described agree with those of Halmi and Barker,[25] who failed to find any changes in the pituitary bodies of rats and mice given corticoids or ACTH; we fail to explain the contradictory findings of Golden and Bondy.[26] A sharp differentiation of the changes in the pituitary gland caused by gonadectomy, thyroidectomy, and lack or excess of corticoids remains to be worked out.

Prolonged cortisone treatment in mice usually causes a fatal infection with a diphtheroid organism (*Corynebacterium pseudotuberculosis murium kutscheri*), with pleurisy and pericarditis and tumor-like

granulomas in the lung, kidneys, and liver.[27] Mice bearing transplantable ACTH-secreting tumors almost invariably die of a fatal infection by this microorganism[23] when the tumor measures barely more than a few millimeters. Absence of such changes in mice bearing the transplantable adrenal tumors can be taken as biologic evidence indicating that these tumors do not secrete cortisone, hydrocortisone, or a related steroid which depresses body resistance. Clarification of these problems awaits identification of the steroids secreted by these tumors and determination of the range of changes caused in the animal body by each of these.

Summary

Adrenocortical tumors originating in mice and rats were transplanted in series in the strain of origin.

In mice, the transplanted tumor of strain 2 grew in normal, gonadectomized, adrenalectomized, and hypophysectomized hosts. It caused marked atrophy of all layers of the adrenal cortex (but not the medulla), hypernatremia with profound polyuria, thymic involution, and marked depression of the levels of eosinophils. Grafted adrenotropic pituitary tumors also caused a marked and early drop in levels of eosinophils and involution of the thymus; however, while with adrenotropic tumors adrenalectomy is followed by regeneration of the thymus and a rise in levels of eosinophils, in adrenal tumor-bearing animals the eosinopenia and thymic involution persisted. These effects indicate that this adrenal tumor secretes glucocorticoids and mineralocorticoids. In preliminary experiments, the tumor responded to ACTH *in vitro*.

In spite of retention of secretory abilities and lack of anaplasia, this tumor is highly malignant, as indicated by extensive pulmonary metastases, a behavior rarely exhibited by common tumors of mice.

The transplants of the adrenal tumors in the rat grew best in adrenalectomized and in radiothyroidectomized, less well on gonadectomized, and least in untreated hosts. Males were much more susceptible than females.

Secondary changes produced by the adrenal tumors in the rat were similar to those of the tumors in the mouse and indicated secretion of glucocorticoids. Polyuria, however, was less extensive in the rat, and levels of serum electrolytes were normal. Obesity was common in the rat, but not in the mouse.

Evidence for secretion of feminizing or masculinizing gonadal hormones by adrenal tumors of either the mouse or rat was lacking.

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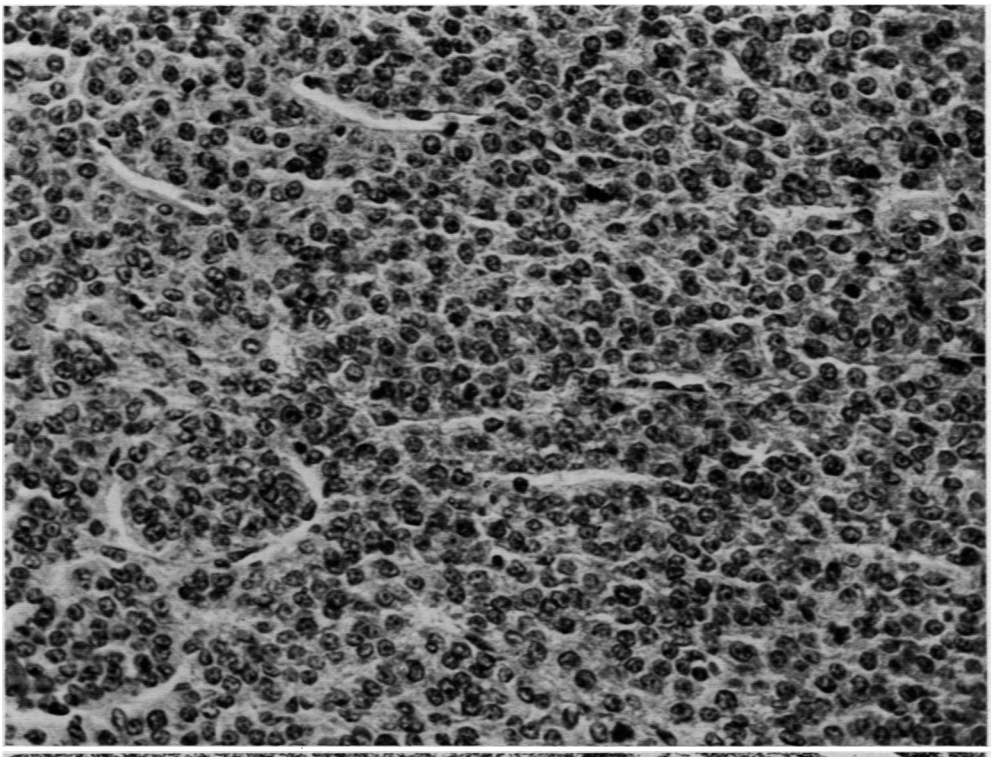
LEGENDS FOR FIGURES

FIG. 1. Grafted adrenal tumor of a mouse, strain 2. × 400.

FIG. 2. Extensive pulmonary metastases of grafted adrenal tumor of a mouse, strain 2. × 150.



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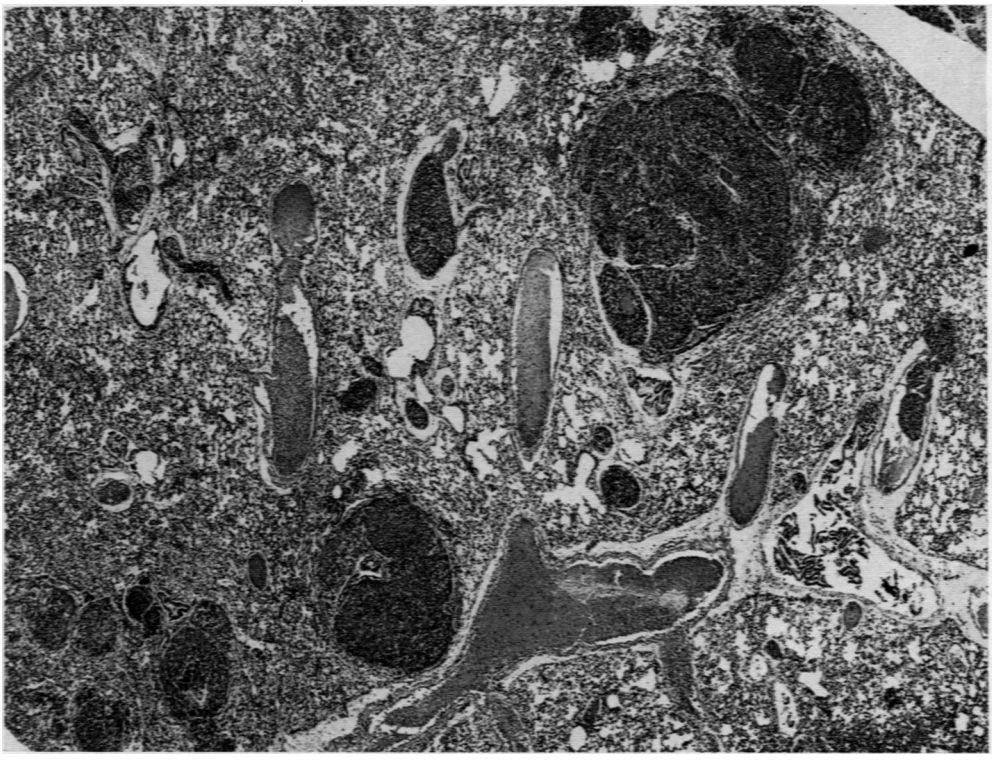

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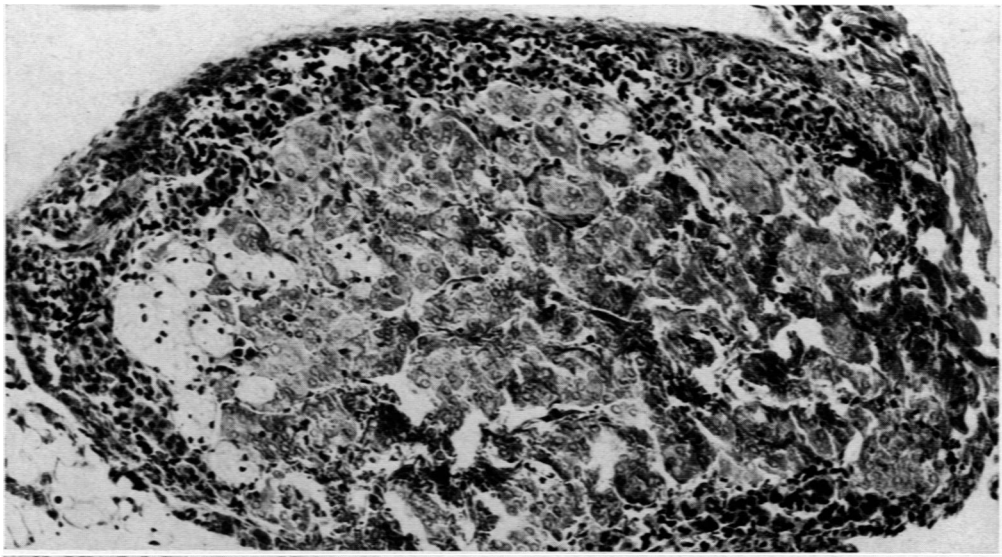
FIG. 3. Advanced atrophy of the adrenal cortex of a male mouse bearing transplanted adrenal tumor, strain 2. × 200.

FIG. 4. Advanced atrophy of the adrenal cortex with moderate congestion in a male mouse bearing a grafted adrenal tumor, strain 2. × 200.

FIG. 5. Adrenal cortex of a normal adult male mouse. × 200.



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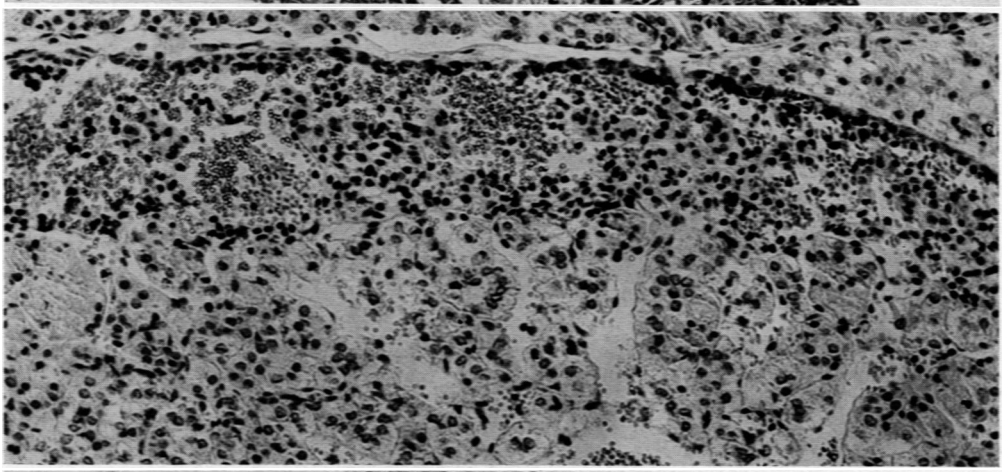

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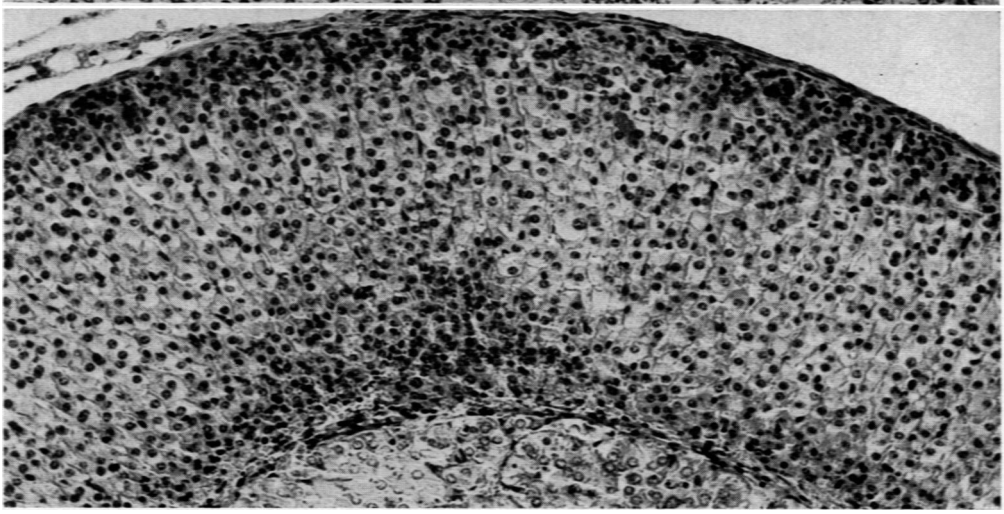

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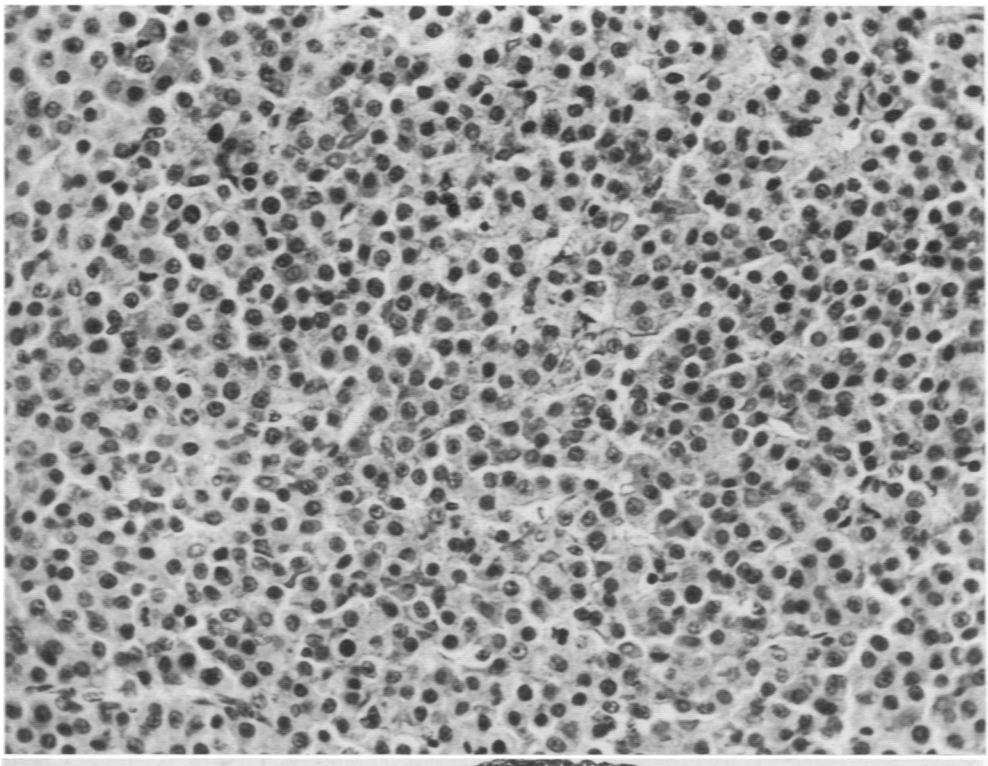
FIG. 6. Grafted adrenal tumor of rat, strain 1. × 400.

FIG. 7. Pulmonary metastases from grafts of adrenal tumor of rat, strain 1. × 100.



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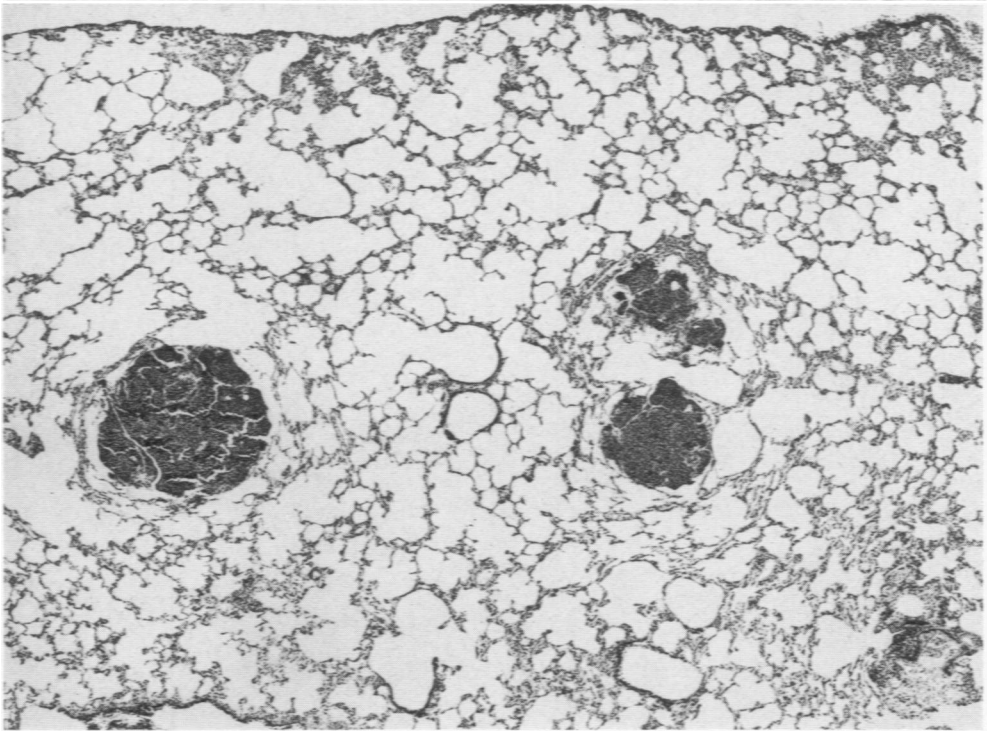

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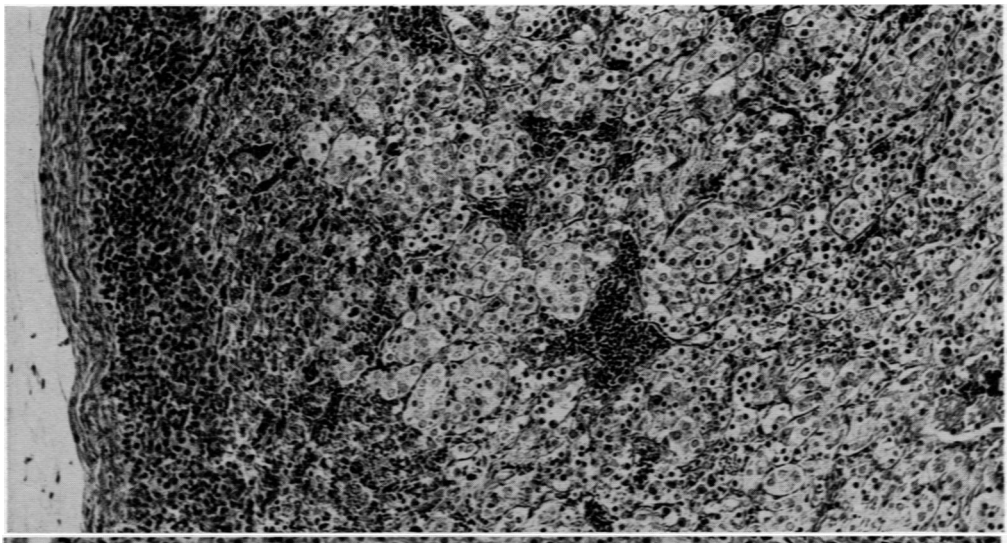
FIG. 8. Advanced atrophy of the adrenal cortex of a male rat bearing a grafted adrenal tumor, strain 1. × 150.

FIG. 9. Adrenal cortex of a normal male rat. × 150.

FIG. 10. Advanced atrophy of spermatogenic tubules with an area of calcification in a rat bearing a grafted adrenal tumor, strain 1. × 100.



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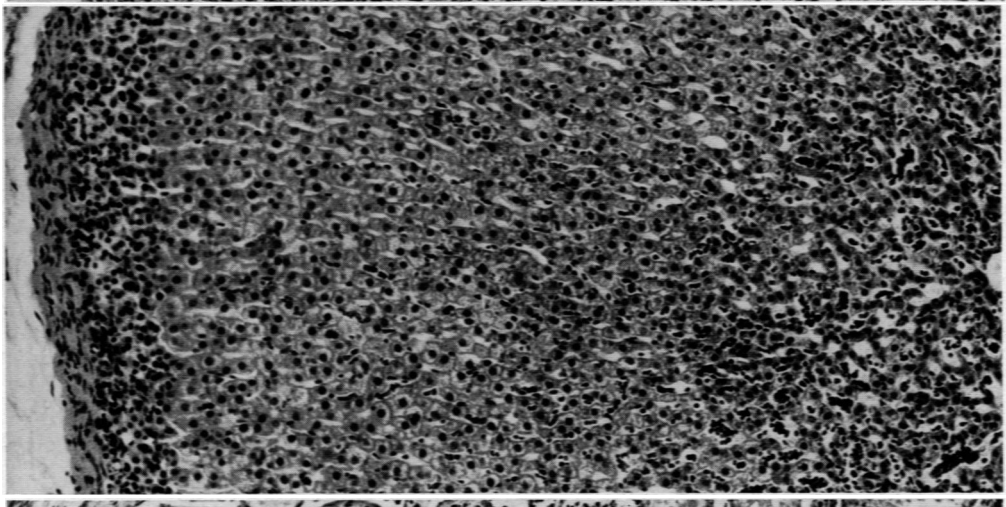

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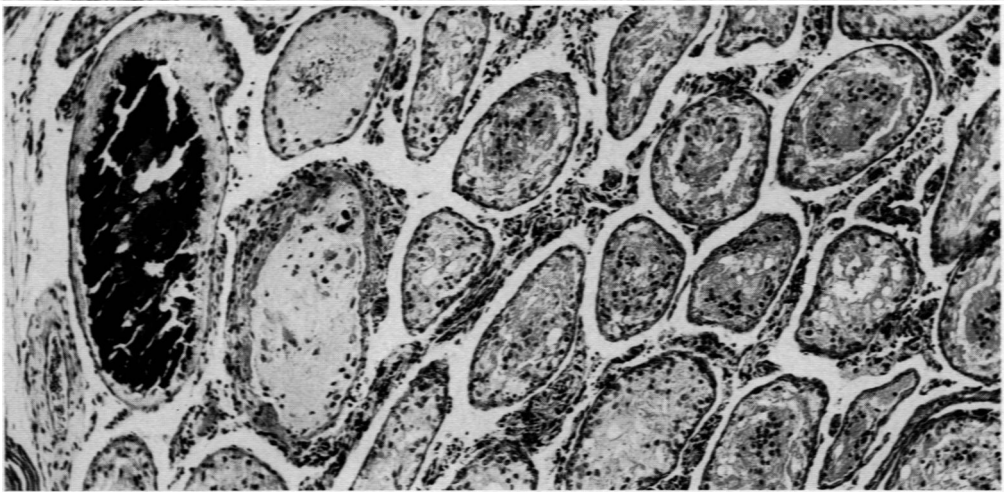

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