MORPHOLOGIC CHANGES ASSOCIATED WITH THYROTROPHIN-SECRETING PITUITARY TUMORS *

JACOB FURTH, M.D.†

(From the Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.)

Pituitary tumors can be induced readily in mice by radiothyroidectomy.[1] Transplantation of these growths is highly successful in mice in which thyroid function is depressed, but not in normal mice.[2] In the course of successful transplantation many of these conditioned pituitary growths acquire autonomy, can be grafted in normal mice, and after a few passages in normal hosts they grow even better in normal than in radiothyroidectomized animals.[3] Administration of thyroid hormone to radiothyroidectomized mice prevents the induction of such tumors[4] and retards or prevents the growth of grafted dependent tumors.[5] Morphologic evidence will be presented here to indicate that these tumors secrete large quantities of thyrotrophin. Changes in tumor-bearing hosts indicate secretion of gonadotrophin in some hosts. Acquisition of autonomy is associated with characteristic morphologic changes in tumor cells and in stromal reaction to them. The main purpose of this study is to describe and illustrate the remarkable morphologic changes observed in the tumors and tumor-bearing hosts; their pathogenesis remains to be studied.

MATERIAL AND METHODS

The induction and transplantation of these pituitary tumors have been described.[2,3,6] Seven tumors induced in C57 black mice have been carried in serial passages. Three of these have given rise to autonomous growths in the course of subpassages.

Normal mice, 6 to 10 weeks of age, were injected subcutaneously with 100 to 400 μc. of carrier-free I^{131} in 2 cc. of physiologic saline solution. These doses destroy the thyroid glands of mice kept on a standard diet consisting of Purina chow *ad libitum* supplemented once weekly with carrots or lettuce. Mice 2 weeks old were radiothyroidectomized with 50 μc. of I^{131}. The tumor grafts were made 2 to 5 weeks

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† Now at Children's Cancer Foundation, 35 Binney St., Boston, Mass.

following administration of I^{131}. The tumors were transplanted by injecting tumor fragments in physiologic saline solution into the thigh muscles of normal and radiothyroidectomized mice. All animals were necropsied. Microscopic examinations were made whenever gross inspection was inadequate to evaluate the changes, and for special studies. In addition to the common histologic staining techniques, Gude's[7] combination of Martins and Mallory's trichrome stain, the periodic acid-Schiff method, and the aldehyde fuchsin technique of Gomori were used.[cf. 8] Since the total number of mice examined was in the hundreds and the changes observed were fairly similar, it was considered proper to describe them without giving the numbers of specimens studied except when the number was small. Large numbers of mice have been preserved *in toto* and are available to those interested.

Nomenclature. As *dependent* or conditioned tumors will be designated those requiring for their growth destruction of the host's thyroid gland (absence of thyroid hormone); as *autonomous* tumors, those which grow in normal hosts. Dependency or autonomy are relative and quantitative terms.[6] By *late autonomy* is meant the development of small tumors in normal mice injected with dependent strains of tumors, after a very long (over 8 months) latency period; when transplanted, these tumors grew readily in normal hosts. Destruction of the thyroid by I^{131} is termed *radiothyroidectomy*. The term "gonad-stimulating hormone" will be used because a separation into follicle stimulating and luteinizing hormonal activities was not carried out. The histologic changes indicate that stimulation by these two hormones occurred concurrently, with the activity of one or the other in excess.

Pituitary Tumors

Halmi[8] traced the histogenesis of the pituitary tumors to beta cells even though they are chromophobic and give neither the periodic acid-Schiff reaction for 1, 2 glycols nor the aldehyde-fuchsin reaction of Gomori. Sudden loss of weight, slight bulging of the cranium over the occipital region, listlessness, ruffled fur (Fig. 1), and uncoordinated motions marked the terminal stage, when the animals either died suddenly or were sacrificed. At death the primary tumors (Fig. 2) measured 6 to 12 mm. across. The microscopic appearance of primary tumors is described and illustrated by Halmi.[8] Although some of the primary tumors exhibited a fair degree of anaplasia and many were locally invasive, none of 11 successfully grafted on thyroidectomized mice grew in normal animals.

The first generation grafted tumors (Figs. 3 to 7) had many features in common with the primary growth. The predominant cells were chromophobe and free of granules. The amount of cytoplasm was usually moderate. The clusters of very large cells of thyroidectomy type, often present in the first grafts (Fig. 3), soon vanished in the course of subpassages, the cytoplasm of well established tumors being scant or moderate in amount. Features of anaplasia were absent. The tumor cells usually formed solid masses with no definite pattern (Fig. 7). Rarely tubular formations (Fig. 5) were noted, with empty or sometimes blood-filled lumina lined more frequently by tumor cells than by endothelial cells. The large periodic acid-Schiff-positive intranuclear inclusions characteristic of primary tumors[8] were also frequently noted in grafted dependent tumors (Fig. 4). The stroma of the dependent tumors was invariably scant and correspondingly the tumors were soft, almost pulpy. Retrogressive changes occurred, as with other grafted tumors, when the tumors were large. Terminally, the bulk of the tumor often underwent necrosis. The grafted tumors weighed 4 to 8 gm. at death.

Retrogressive changes with fibrosis were much more marked with *autonomous* tumors which could usually be identified on gross inspection by their firmness and variegated appearance. The latter is due to scattered areas of necrosis, congestion, hemosiderosis, and fibrosis (Figs. 16 to 19). The greatest degree of retrogressive change occurred in late autonomous tumors which grew very slowly over long periods. While the dependent tumors were composed of masses lacking histologic criteria of malignancy, marked anaplasia developed in the course of transplantation as the tumors gained autonomy. A cytologic correlation of dependency and autonomy is yet to be made. Cells of autonomous tumors varied greatly in size and shape; cells with micro-nuclei and macro-nuclei and giant cells were common (Figs. 17 to 19). Nuclear chromatophilia increased and nuclear-cytoplasmic ratio decreased. These features of malignancy were acquired gradually. It has not been possible to state on the basis of microscopic appearances whether or not a tumor has already acquired autonomy. After several subpassages, however, the microscopic appearance of the autonomous tumors invariably indicated a high degree of malignancy. A study of frequency and character of mitotic figures in relation to tumor type remains to be made.

Metastases in the regional lymph nodes were common with both dependent (Fig. 8) and autonomous growths (Figs. 13 to 15), but they were larger with the latter and more widespread, extending

throughout the para-aortic abdominal chain of lymph nodes as far as the diaphragm (Fig. 14). The microscopic appearance of the metastases resembled that of the primary growth. In several mice there were extensive bilateral metastases in the ovaries (Fig. 15) and, in a few there were metastases also in the liver. A yellow-brown pigment present in large mononuclear cells of the tumor and in draining lymph nodes gave an iron reaction.

In one experiment transplantations were made with an iliac lymph node replaced by metastasis from a dependent tumor. The grafts took in radiothyroidectomized hosts but not in normal hosts, indicating that these metastatic tumors remained dependent.

In one experiment that will not be detailed, intrasplenic grafts were made in order to find out if the liver metabolizes the pituitary hormones of these grafts as it does those of gonadal grafts. In 2 of 4 mice grafted in the spleen there were extensive metastases in the liver (Figs. 9 and 11) and both animals developed a malignant lymphoma (Figs. 9, 10, and 12). The latter disease is very rare in this strain. The induction of lymphoma by growth hormone has been reported by Moon *et al.*[9] and following pituitary grafts by Silberberg and Silberberg[10] who attributed the leukemogenic effect to ACTH. The relation of anterior pituitary activity to tumor induction has been reviewed by Lipschutz.[11]

Thyroid Gland

The changes in the thyroid gland caused by radiothyroidectomy have been amply described by Gorbman,[12] Goldberg *et al.*,[4,13,14] Rugh,[15,16] and Maloof *et al.*[17] The following are observations on mice bearing grafted pituitary tumors with some supplementary findings on the effects of radiothyroidectomy.

Normal Hosts. Thyroid stimulation was apparent in all normal mice bearing autonomous tumors, the degree of enlargement and of adenoma formation being in direct relation with the length of the tumor-bearing period. In normal mice in which the tumors gained autonomy many months after the graft was made (late autonomy), the thyroid glands were tremendously enlarged (Figs. 34 and 35), the weight of this organ increasing from approximately 0.8 mg. to over 6 mg. even when the grafted tumors measured but a few millimeters across. In numerous mice the grafts were not identified but were suspected because of the greatly enlarged thyroid glands, and subsequently minute growths were located after some gross or microscopic search. The tumor nodules so identified measured but 1 to 2 mm. in diameter in many mice in which thyroid enlargement gave evidence of excessive

secretion of thyrotrophin by grafted pituitary tumors (Figs. 24 and 25). Whether these delayed minute growths represent the acquisition of late autonomy or failure of a normal host to restore its homeostatic balance in the presence of grafted, dependent pituitary tumors remains to be studied. If the cells were autonomous, explanation is needed why they remained localized at the site of injection; and if not normal, homeostasis would call for their depression.

Soon after establishment of autonomy the tumors gained in proliferative vigor and killed the mice a few months after grafting, when the tumors weighed 2 to 4 gm. The thyroid glands of these mice were several times the normal size but were not as large as those with late autonomous tumors; in sections they invariably gave evidence of marked thyrotrophic stimulation (Figs. 24 and 25). In the course of successive passages the thyroid stimulation was less pronounced. This is due in part to a decrease in the tumor-bearing period and in part to a diminution of thyrotrophin secretion by the tumors, as indicated by bioassays of tumors and of blood of tumor-bearing animals.

Microscopic examinations (Figs. 24, 25, and 36) have shown the well known evidences of stimulation by thyrotrophin, namely, resorption of colloid, enlargement of the epithelial cells, cytoplasmic colloid masses, vacuolization of the cells, and, after sustained stimulation, formation of increasing numbers of adenomas, some of which were papillary (Figs. 36 to 38, *cf.* normals: Figs. 20 and 21); colloid formation became diminished. Radioautographs have indicated a fairly uniform uptake in different follicles of the normal gland, a great variability in stimulated follicles, and almost complete lack of uptake in the adenomas.[6]

In mice with greatly enlarged thyroid glands the neck was markedly swollen over the gland, and frequently there was a brownish discoloration of hair (normally brown-black) in this region.

Radiothyroidectomized Hosts. In almost all mice receiving approximately 300 μc. of I^{131} the thyroid glands were absent and the characteristic chronic radiation damage, such as stenosing arteritis, hemosiderosis, and fibrosis, marked the site of the gland (Figs. 28, 32, and 33). Stenosing tracheitis, also noted by Silberberg *et al.*,[18] was occasionally encountered (Fig. 29). In animals receiving smaller doses (75 to 200 μc.) and in some receiving as much as 300 μc. some thyroid tissue was present (Figs. 22 and 23), but this was evidently incapable of being stimulated by thyrotrophin or undergoing compensatory hyperplasia, even though the blood of these animals contained large amounts of thyrotrophin.[19] Many of these thyroid cells often

failed to form acini and in those which did the lumina were devoid of, or poor in, colloid. The thyroid cells varied greatly in size and shape; the nuclei of many were hyperchromatic; the cytoplasmic-nuclear ratio was reduced and occasional cells had the morphologic features of carcinoma cells (Figs. 22 and 23). The presence of such cells in heavily irradiated fields is well known (*cf.* Maloof *et al.*[17]); their biologic potentialities have, however, not been analyzed, so far as I know. They appear soon after irradiation, remain *in situ,* and are not known to proliferate as cancers. Failure to respond fully to thyrotrophin may explain why thyroid glands partially destroyed by I^{131} do not inhibit the growth of dependent tumors.[6] The thyroid glands of mice receiving partially destructive doses of I^{131} exhibited cytologic evidence of stimulation, but proliferation to the extent of restoration to normal was absent. Rarely pituitary tumors coexisted with thyroid adenomas exhibiting morphologic evidence of stimulation by thyrotrophin (Fig. 26).

Metastases. Invasion of blood vessel by thyroid tissue (Fig. 39) and metastasis of thyroid "adenomas" in regional lymph nodes were rare findings, but no special search was made to detect the spread of thyroid adenomas. Pulmonary metastases of the thyroid adenomas (as occurring in thiouracil-treated animals) were not observed. The possibility of neoplastic transformation was tested by grafting these adenomas in muscle of mice bearing autonomous pituitary tumors or by injecting minute thyroid particles intravenously. Thus disseminated "tumor" nodules were produced in the lungs and these exhibited the same degree of stimulation as the animal's own thyroid gland (Figs. 40 and 41) but did not undergo malignant transformation. In control normal mice bearing grafted thyroid fragments, the latter could not be identified at necropsy. Four normal mice that had been given intravenous injections of thyroid cells and intramuscular grafts of autonomous tumors died suddenly when the grafted pituitary tumors measured but 1 to 2 cm. across. All had minute disseminated nodules of thyroid tissue in the lungs (Figs. 42 to 45), extensive central necrosis of the liver (Fig. 46), and thrombosis of the cardiac auricles. That these animals died of thyrotoxicosis was suggested by the sudden occurrence of death with heart failure and hepatic necrosis, with no anatomical change indicative of another mode of death. Further work is required to find out whether thyrotoxicosis was caused by the rapid discharge of thyroid hormone or by its heightened production from these pulmonary thyroid nodules and to establish if the lung might serve as an inactivator of excessive quantities of thyroid hormone.

Changes in the Thyroid Region by I^{131} Treatment. Hyperplasia in the tracheal epithelium, notably in juxtaposition to the irradiated thyroid gland, was seen only in the presence of inflammation, and it never proceeded to tumor development. On the contrary, the mucosa, submucosa, and cartilage of the larynx, notably the parts in juxtaposition to the thyroid gland, often appeared injured (*cf.* Figs. 27 to 29). There was atrophy of epithelium, replacement of ciliary epithelium by squamous cells, atrophy of mucous glands of the submucosa, chronic inflammation, degenerative changes in the cartilage with calcification (Fig. 28), but never changes known to be precancerous or cancer in any of these structures.

The only neoplasm observed about the thyroid gland occurred in an overlying submaxillary gland. The tumor measured 15 by 15 by 12 mm. across, involved symmetrically both lobes of the submaxillary gland, and did not invade the thyroid gland or skin. The microscopic appearance indicated an anaplastic growth, probably a carcinoma, with osteogenesis in the stroma (Figs. 68 and 69), or an extraosseous osteogenic sarcoma. Osteogenesis is a well known feature of salivary tumors. In view of this finding the morphologic changes in the submaxillary gland of radiothyroidectomized mice deserve special study. This organ, overlying the thyroid gland, must receive large quantities of gamma irradiation in the course of radiothyroidectomy.

A systematic study of the *parathyroid gland* was not made. In general, this organ, when identified in radiothyroidectomized mice, was smaller than normal and contained an excessive amount of connective tissue, notably in parts nearest to the thyroid gland (Figs. 30 and 31). The parathyroid damage was attributed by Rugh[15,16] to a diminished blood supply. In addition, local beta irradiation damage is indicated by the characteristic appearance of the lesion, that is, localization of fibrosis to parts in juxtaposition to the thyroid gland. Lack of morphologic evidence of compensatory hyperplasia is noteworthy.

Gonads and Accessory Sex Organs

Ovary. In radiothyroidectomized animals with *primary pituitary tumors* the ovaries were invariably small and yellow, due to overgrowth of luteinized cells, and ova were absent (Fig. 52). Occasional nodular areas of lutein cells (Fig. 53) suggested the beginning of a luteoma. Atrophy of the female gonads in mice with primary pituitary tumors, as noted by Gorbman,[12] is the rule but with small tumors and "pretumors" some ovarian stimulation was evident. In contrast to the ovaries of x-rayed mice, to which this picture bears close resemblance,

tubular down-growth of the germinal epithelium and formation of expanding nodules of granulosa cells were invariably absent. It is possible that the ovaries of these 13 to 16 months' old animals were non-responsive to gonadotrophins or, more likely, that the primary thyrotrophin-secreting pituitary tumors depressed or destroyed the gonadotrophin-secreting cells. Assessment of gonadotrophins of these pituitary tumors and of the blood of such tumor-bearing mice, and the study of the morphology and responsiveness of ovaries in the course of pituitary tumorigenesis by I^{131} may clarify this problem. The studies and assays of Anderson and Bates[20] suggest the presence of minute amounts of gonadotrophins in dependent tumors.

A remarkable difference was noted between radiothyroidectomized and normal mice bearing grafted pituitary tumors. The ovaries of *radiothyroidectomized* mice bearing large grafted tumors were greatly enlarged, measuring as much as 5 to 6 mm. across, and were studded with hemorrhagic and cystic follicles similar to those given by gonadotrophins, which characterize the pregnancy reaction of Aschheim-Zondek (Figs. 54 to 57). In several mice spontaneous rupture of a hemorrhagic follicle caused exsanguination into the peritoneal cavity. The sequence of changes appears to be as follows: hastened maturation of follicles, accumulation of liquor, hemorrhage in follicles, and luteinization of stromal cells. The relative degree of stimulation by follicle-stimulating hormone and luteinizing hormone, respectively, varied with different animals. Correlation of morphologic appearances with bioassays will be required to explain this variability. Luteinization of the stromal cells was predominant when the follicles were few or altogether absent ("burned out"). In some mice with slowly growing tumors the ovaries were yellow and of approximately normal size or even smaller than normal.

With *autonomous tumors* in normal hosts the gonads and accessory sex organs were either normal or, less often, smaller than normal, but never distinctly stimulated. Autonomous tumors carried in radiothyroidectomized mice did cause gonadal stimulation but this was slight and infrequent. To investigate this problem further, 8 animals bearing large grafted tumors were killed, all having received grafts of the same autonomous tumor on the same day, 4 recipients being radiothyroidectomized and 4 normal. All radiothyroidectomized mice exhibited a marked ovarian and uterine stimulation while in normal mice these organs were atrophic. This finding has since been amply confirmed in the course of routine necropsies of large numbers of mice, supporting the assumption that lack of thyroid hormone enhances sensitivity to

gonadotrophins. It is known (Bischoff *et al.*[21]) that thyroidectomy will increase the ovarian response to injections of hypophyseal gonadotrophins. Thyroxin is able to counteract the influence of thyroidectomy. Bischoff *et al.* have explained this by a decrease in the rate of exchange of the body fluids brought about by thyroidectomy, but reduced metabolism rate goes with conservation of gonadotrophin. Thyroidectomy alone (without grafted tumors) did not cause ovarian enlargement.

The *uteri* of mice bearing pituitary tumors in radiothyroidectomized hosts present one or a combination of the following changes: thickening of the uterine wall without dilatation and elongation (Fig. 54) due to predominantly stromal and muscular hyperplasia, or a marked elongation and dilatation. The former change was noted with transplantable granulosa cell tumors and was attributed to secretion of granulosa cells (estrogens); the latter was noted with luteomas and was attributed to secretion of lutein cells (progestins). The usual change with dependent tumors is that of hyperplasia with dilatation and elongation of the uterine horns indicative of a mixed type of stimulation. Less frequently the uterine horns exhibit a tremendous cystic dilatation as shown in Figure 55. This puzzling alteration has not been noted in hosts carrying granulosa tumors, luteomas, or Leydig cell tumors. The uterine changes, obviously secondary to ovarian stimulation and accordingly more marked with dependent than with autonomous tumors, are absent in normal hosts. Incidentally, this suggests the use of radiothyroidectomized animals in assays for gonadotrophins, including those of pregnancy.

Testes and Accessory Male Organs. In radiothyroidectomized mice bearing dependent tumors there is a marked hyperplasia and hypertrophy of the Leydig cells (Fig. 64). This change is analogous to the ovarian stimulation which has been discussed, and is not found in normal mice bearing autonomous tumors. In mice bearing dependent tumors (and having stimulated Leydig cells) the seminal vesicles are greatly enlarged and filled with secretions. In normal mice with autonomous tumors the seminal vesicles are smaller than normal. In mice with dependent tumors the sex features of the submaxillary glands are exaggerated in both sexes. The prostates of the males are likewise large. These organs have not been adequately studied.

Mammary Gland. In female mice bearing primary pituitary tumors and having atrophic luteinized ovaries the mammary ducts are greatly hypertrophied and hyperplastic (Figs. 65 to 67). Rarely the ducts are distended with some milky fluid. This change is noted also in females bearing slowly growing, grafted, dependent pituitary tumors and hav-

ing small lutein cell-laden ovaries, but not in males. Bates[20] failed to find lactogenic hormone in dependent pituitary tumors, and the normal cells of pituitary bodies in which this alteration is usually encountered are likely to be replaced by tumor cells. I am at a loss to explain the pathogenesis of this change. The mammary glands in the mice with greatly stimulated ovaries are not enlarged.

Hyperplasia and Ectasia of the Extrahepatic Biliary Ducts

A common finding in mice bearing large dependent tumors[22] is hyperplasia of the epithelium of the extrahepatic ducts, most marked at the ampulla of Vater, with hyperplasia of the submucosa and cystic dilatation of the anatomically patent ducts (Fig. 48).

The following confirmatory and supplementary information is based on newer observations. Rupture of the cyst, with large amounts of viscous, slightly bile-stained fluid in the peritoneal cavity, was a common terminal event; yet evidence of biliary tract obstruction was absent when tested post mortem by injection of fluid into the cysts. Figure 51 is a cross section at the ampulla of Vater; the arrow points to the orifice of the duct. Often fibrous adhesions were formed between the large cyst, the anterior abdominal wall, and loops of intestine adjacent to the cyst. The cystic duct was often thickened, the hepatic duct occasionally, but the gallbladder usually appeared normal; rarely it was somewhat dilated. Hyperplasia of the intrahepatic duct, if present at all, was localized to the region in immediate continuity with the extrahepatic duct (Figs. 49 and 50). Hyperplasia appears to precede dilatation. The changes were most marked in the region adjacent to the junction of hepatic, cystic, and common ducts or at the ampulla, with or without a macroscopic change at other sites. Obstructive jaundice was absent in spite of the tremendous dilatation of the extrahepatic biliary tract and, while acute inflammation of the head of the pancreas in the region of the ampulla was common, intrahepatic cholangitis was but rarely noted.

Cystic dilatation of the extrahepatic biliary tract occurred in most radiothyroidectomized mice bearing large, dependent, pituitary tumors. It was usually associated with evidence of gonadal stimulation and was seen but once without it, while gonadal stimulation without changes in extrahepatic biliary tract was frequent (Table I). Thus the two alterations appear to be caused by different and probably hormonal mechanisms. Dilatation of the extrahepatic biliary tract was not seen in mice bearing grafted hormone-secreting granulosa cell tumors, luteomas, or Leydig cell tumors. Thus the hosts exhibiting this change

are characterized by a lack of thyroid hormone, by hypersecretion of thyrotrophin, and usually by excessive stimulation by gonadotrophins; but how these factors act to bring about the biliary duct ectasia and whether other factors are involved are unknown. The report of Gardner *et al.*,[23] who noted a similar change in mice receiving estrogens

TABLE I

Relation of Tumor Size to Gonadal Stimulation and Cystic Dilatation of the Extrahepatic Biliary Tracts

No. of strain	Tumor dependent (D) or autonomous(A)	Host	Tumor size	Number of mice			
				Gonad+* Duct+	Gonad+ Duct−	Gonad− Duct+	Gonad− Duct−
77	D	Athyroid	++				9
			+++	7			
6	D	Athyroid	++				4
			+++				13
101	D	Athyroid	++		8		2
			+++	2	25		5
124	D	Athyroid	++	5			
			+++	13			
3	D	Athyroid	++	18	2		
			+++	7			
19	D	Athyroid	++	20	1		1
			+++	20	1		
163	D	Athyroid	++	25	1	1	4
Total	D	Athyroid	++	68	12	1	20
			+++	49	26		18
			++ and +++	117	38	1	38
19	Late A	Normal	+				13
163	Late A	Normal	++		5		
3	Late A	Normal	++				4
3	Late A	Normal	+++				5
Total	Late A	Normal	+ to +++		5		22
3	A	Athyroid	++		8		7
			+++		42		25
3	A	Normal	++		3		12
			+++				74

* Evidences of gonadal stimulation present (+) or absent (—).
Hyperplasia and dilatation of the extrahepatic biliary ducts present (+) or absent (—).

over long periods of time, is no less puzzling. In my experiments biliary duct ectasia occurs in mice of both sexes and may be present in mice with grafted tumors subjected to gonadectomy a few weeks or months before death.[22]

Adrenal Gland

Changes indicative of overproduction of ACTH have been consistently absent in mice bearing either dependent or autonomous tumors or in those used for bioassays of tumor extracts. Adrenal

glands of radiothyroidectomized mice with dependent tumors were normal or smaller than normal. A characteristic change noted consistently in the reticular zone was replacement by large cells with pyknotic nuclei and bulky "foamy" sudanophilic cytoplasm (Figs. 60 and 61). These degenerative changes in the reticular zone are similar to the "brown" degeneration seen by Cramer and Horning[24] in animals after prolonged administration of estrogens. Some of the yellow material in the "foam" cells was also acid-fast. Studies with transplantable luteomas suggest that the yellow material in degenerating lutein cells is probably derived from a steroid hormone of these cells. "Healthy" secreting lutein cells are not acid-fast and are weakly, if at all, sudanophilic, and acid-fast granules appear in the lutein cells in areas of degeneration.

In normal mice with autonomous tumors the adrenal glands were enlarged by excessive fatty deposit in cells of the reticular zone (Figs. 62 and 63) and not by hyperplasia. The beginning of this change is shown in Figure 63. Large fat globules accumulate in the cytoplasm of the cells and push the nucleus to the periphery, thus creating a "signet ring" cell. Such changes were consistently absent in normal control mice and in those bearing either feminizing granulosa cell tumors or masculinizing luteomas or Leydig cell tumors. The fascicular and glomerular zones showed no conspicuous changes. A special histochemical study of the adrenal glands remains to be undertaken.

Thymus

The thymus was characteristically atrophic in radiothyroidectomized mice or in those bearing grafted dependent tumors or large primary tumors, but in normal mice bearing autonomous tumors and in those with small primary tumors it was frequently normal. If the latter is taken as supporting evidence for the assumption that the autonomous tumors do not secrete ACTH, an explanation is needed for the characteristic atrophy of the thymus in radiothyroidectomized mice bearing dependent tumors. Atrophy (accidental involution) of the thymus is a usual event in mice bearing large transplanted tumors, and a "chronic stress" with non-specific hypersecretion of the adrenal cortex is the usual explanation. Radiothyroidectomized mice lose much weight, while normal tumor-bearing mice are well nourished. Radiothyroidectomized mice are hypothyroid, normal tumor-bearing mice are hyperthyroid, and the latter state is known to be associated with lymphoid hyperplasia. Persistence of the thymus with autonomous

tumors is therefore the more meaningful finding indicating lack of hypersecretion of the adrenal gland.

Pancreas

In normal mice bearing autonomous tumors the pancreas was gray-pink and conspicuously enlarged. Microscopic examinations disclosed, in addition to hyperplasia, the fusiform cleft-like spaces in exocrine cells illustrated in Figure 47. The character of this change, its frequency and meaning, require special studies.

Increase in Blood Volume in Normal Mice Bearing Autonomous Tumors

The increase in blood volume in normal mice bearing autonomous tumors was indicated by the unusually large amount of blood (1.5 to 2 ml.) obtained for assays by cardiac puncture. Blood volume determinations were not made, but the amount obtained from normal hosts in the same transplantation series was almost double that from radiothyroidectomized hosts. Absence of the characteristic morphologic features of hypervolemia[25] indicates that the blood volume increase was only moderate as compared to that in mice with granulosa tumors.

Survey of Frequency and Constancy of Secondary Changes

Table II surveys the salient secondary changes observed in different hosts. The presence or absence of gonadal stimulation and formation of cystic dilatation of the extrahepatic biliary tracts is tabulated in Table I on the basis of a random sampling of 392 mice.

Dilatation of biliary ducts occurred only in radiothyroidectomized hosts and was always accompanied by gonadal stimulation with a single exception. This mouse, preserved *in toto,* was carefully re-examined. It was found to have atrophic gonads and uterus and an enormously distended common duct. The reverse, gonadal stimulation in the absence of biliary duct ectasia, was encountered frequently.

The following strain differences are suggested by Table I: Tendency to give rise to autonomous cells (strains 19, 163, and 3) or the lack thereof (strains 77, 6, 101, and 124); marked gonadal stimulation with very large tumors, in absence of biliary tract ectasia (strain 101); almost invariable presence of both ductal ectasia and gonadal stimulation with large tumors (several strains), or the lack of both (strain 6); consistently slow growth rate during a period of 2½ years (strains 6 and 77) or steadily gaining proliferative vigor (strain 3). Whether

these differences, noted at the conclusion of these studies, are significant and can be correlated with morphologic and cytologic features of the pituitary tumors and of the pituitary bodies of their hosts remains to be studied.

Thyroid stimulation was apparent in all normal mice bearing tumors, without distinct changes in the gonads and extrahepatic biliary tract. Several normal mice grafted with autonomous pituitary tumors, in which the tumor-take was not identified on gross examination, exhibited evidence of thyroid stimulation. Gonadal changes were conspicu-

TABLE II

Changes Secondary to I^{131} Induced Pituitary Tumors in Different Hosts

	Thyroid gland	Ovaries, uteri	Biliary tract ectasia	Adrenal glands	Thymus
Primary tumor	Absent	o	o	o	Normal or atrophic
Dependent tumor Host I^{131} treated	Absent	o to +++	o to +++	Degenerative changes in reticularis	Atrophic
Autonomous tumor					
Host normal	+ to +++* enlargement	o	o (to +)	Degenerative changes	Normal or atrophic
Host I^{131} treated	Absent	o to ++	o to ++	Degenerative changes	Atrophic

* Plus signs indicate degree of specific hormonal stimulation.

ous at necropsy in most radiothyroidectomized mice bearing dependent tumors of medium or large size. They were less often present and were much less marked in mice with autonomous tumors in radiothyroidectomized hosts, and lack of gonadal stimulation or gonadal atrophy were the usual findings with autonomous tumors in normal hosts.

Changes in the extrahepatic biliary tract occurred only in mice bearing large tumors and were often absent in mice with tumors of medium size and exhibiting gonadal changes (Tables I and II).

Quantitative Assays for Thyrotrophin in Different Types of Tumors

The quantity of thyroid-stimulating hormone in tumors and in the blood of tumor-bearing hosts, assayed in numerous experiments in chicks and mice, will be fully reported later.[19] In each experiment three parameters were recorded: morphologic stimulation of the thyroid glands examined as unknowns, thyroidal retention of a tracer dose of I^{131}, and total body retention of I^{131}. The results indicate that dependent tumors contain about as much thyrotrophin as primary

tumors and the latter several times as much as the normal pituitary body calculated on the basis of unit weight. Because of the uncertainty of identifying thyrotrophin-secreting cells in the normal pituitary body, no calculation can be made on the basis of the number of such cells. Autonomous tumors contain much less hormone than dependent tumors. Similarly the blood of mice with dependent tumors contains large quantities of thyrotrophin and that of mice with autonomous tumors contains much less.

Discussion

Dependency and Autonomy. Dependent tumors are those in which apparently normal cells proliferate in an altered host; autonomous tumors are those in which permanently altered cells proliferate in normal hosts.[26] All of 11 primary tumors bioassayed proved dependent, even though they regularly metastasized to regional lymph nodes in athyroid hosts. Such lymph node metastases assayed were found to be as dependent as the primary tumors. The thyroid adenomas occurring in normal hosts bearing thyrotrophin-secreting autonomous pituitary grafts and in hosts treated with thiouracil are likewise dependent tumors even though they can metastasize to regional lymph nodes or lungs. Thyroid tumors induced by thiouracil have the ability to metastasize to the lungs and yet are dependent on interference with thyroid hormonal synthesis.[cf. 26] Their driving force is thyrotrophin excess. Successive transplantation of conditioned thyroid tumors by Morris *et al.*[27] led to autonomous thyroid tumors, as successive transplantation of our dependent pituitary tumors led to the development of autonomous pituitary growths. It is being debated whether dependent pituitary or thyroid growths should be called true neoplasms. A discussion of the terminology of "neoplasia" and "cancer" is, at present, fruitless; what is wanted is better knowledge of the alterations in the hosts and in the cells, which accompany formation of dependent and autonomous growths.[cf. 26]

Identity of the Thyrotrophin-Secreting Cells. The essential identity of all seven pituitary tumors induced by radiothyroidectomy and transplanted in series deserves special emphasis. All are chromophobic and possess similar cytologic features, behave similarly in the course of serial transplantations, and cause the same secondary changes. All produce thyrotrophin in large quantities in radiothyroidectomized hosts. Subtle differences among the various strains may exist, but the essential identity of the seven strains studied deserves emphasis.

According to current concepts, reviewed by Halmi,[8] the thyrotropes are beta cells characterized by giving a positive periodic acid-Schiff's

and aldehyde-fuchsin reaction. The tumor cells here described are doubtless thyrotropes and, although they are probably derived from beta cells,[8] they give neither of the above reactions. The explanation that in radiothyroidectomized hosts the tumor cells discharge thyrotrophin almost as fast as they produce it, carries with it some uncertainty. With autonomous tumors secreting thyrotrophin and growing in normal hosts, the thyroid hormone produced should retard release of thyrotrophin and therefore give the periodic acid-Schiff reaction. The present studies indicate that current criteria are inadequate to identify a thyrotrophin-secreting cell.

Experimental Pituitary Tumors of Different Types. Adenomas of the pituitary body have been described in gonadectomized mice.[28] Control data are wanting on the spontaneous incidence of these tumors and on the types of hormones, if any, they secrete. Compensation by cells of the adrenal cortex might prevent complete absence of estrogens and progestins, but complete absence of gonadal hormones could be achieved by combined removal of gonads and adrenal glands and maintaining life with cortisone. Dunning *et al.*,[29] confirming others, induced pituitary tumors by sustained treatment of rats with stilbestrol, and have shown by transplantation tests that these tumors are conditioned neoplasms, but they did not study their secretions. Monomorphous transplantable ACTH-secreting pituitary tumors have been isolated recently.[30] Thus, if the estrogen-induced tumors secrete gonadotrophin, at least three types of pituitary tumors can be made available for controlled investigations for further research on cell type and function. The question is whether the conditioned tumors are composed of essentially normal cells and whether the chromophobes are reserve cells; if so, it may be possible to bring about a change in the tumor cell types in hypophysectomized mice by creating a need for one hormone while substituting for all others.

Retrogressive Changes in Autonomous Tumors.[cf. 26] The pathogenesis of retrogressive changes is complex, and its better understanding calls for special studies. The rôle of deficient vascular supply in causing retrogressive changes is well documented. Greene[31] has shown that such changes may be due to immunity reactions and it is conceivable that, as the tumor becomes autonomous, an antigenic change accompanies a genic change. Furthermore, the remote possibility that thyroid hormone or related substance may exert some effect on thyrotrophin-secreting cells has to be considered. If the latter factor is operative, the same tumor strain is expected to behave differently in normal and radiothyroidectomized hosts. The maximum degree of

retrogressive changes with fibrosis was noted with highly secreting, slowly growing, late autonomous tumors. In rapidly growing autonomous tumors retrogressive changes, notably fibrosis, were less marked.

Further Unsolved Problems. Formation of adenomas in the thyroid glands of mice with autonomous tumors and their spread to regional lymph nodes deserve emphasis. Malignant transformation of thyroid adenomas could probably be achieved by successive grafts of thyroid adenomas in mice bearing autonomous thyrotrophin-secreting tumors. Since such a transformation of thiouracil-induced adenomas to carcinomas has already been demonstrated by Morris *et al.*,[27] this problem was not pursued further.

Secretion of some gonadotrophins by the tumor cells in radiothyroidectomized hosts probably occurs.[20] The observations made indicate that several factors might determine the presence or absence of gonadal stimulation in mice with pituitary tumors: (a) gonadotrophin secretion by the tumor cells, (b) enhancement of sensitivity of the gonads to gonadotrophins in the absence of thyroid hormone, (c) influence on gonadotrophin secretion by the normal pituitary cells, (d) altered responsiveness of gonads (*e.g.*, I^{131} injured or aged) to gonadotrophins.

The hyperplasia of the pancreas and the formation of cleft-like spaces in acinar cells in normal hosts bearing autonomous tumors remain to be elucidated. Laqueur[32] is of the opinion that this is related to functional activity of the cells and may represent negative images of unstained mitochondria. He noted that the clefts were more prominent when the zymogen granules were less densely packed or even absent and when the basophilic substance was prominent.

One lesson learned from the study of transplanted hormone-secreting tumors is that changes in the host in which the tumor originates seldom disclose the hormone-secreting potentialities of the tumor cells. This is true for estrogen, thyrotrophin, and ACTH-secreting tumors studied by me, injury to the target organ being the main inciting factor of these tumors. When the primary pituitary tumors are large, compression atrophy of normal elements causes a secondary atrophy of all organs stimulated by the pituitary body. The hormonal potencies of "spontaneous" or primary pituitary tumors are better analyzed in hosts bearing small tumors which have not destroyed this organ completely.

Summary and Conclusions

Morphologic characteristics of dependent and autonomous transplanted pituitary tumors, originally induced by radiothyroidectomy, and the secondary changes caused by these tumors are described. De-

pendent tumors are composed of chromophobe cells fairly uniform in size and shape; they lack the features of cancer cells. Autonomous tumors exhibit features of anaplasia characteristic of a malignant neoplasm. Retrogressive changes (necrosis, fibrosis, hemorrhage, and hemosiderosis) are more often encountered and are more marked in autonomous growths. Factors to explain the latter are discussed.

Chromophobe cells are capable of secreting large quantities of thyrotrophin as indicated by assays of the tumors and of blood of tumor-bearing animals.

Secretion of thyrotrophin by these tumors occurs invariably, more by dependent than by autonomous growths. In autonomous tumor-bearing normal hosts secretion of thyrotrophin causes extensive stimulation of the thyroid gland of the host with formation of adenomata which may invade the blood vessels and spread to regional lymph nodes.

Gonadal stimulation is common in radiothyroidectomized hosts bearing large tumors but is absent in normal hosts bearing autonomous tumors. This may be due to secretion of minute quantities of gonadotrophin by some of the tumor strains studied and to some other factors which are discussed.

The morphologic changes in hosts bearing these tumors suggest lack of secretion of pituitary hormones other than thyrotrophin, with the possible occasional exception of traces of gonadotrophin.

Cystic dilatation of the biliary tract was common in radiothyroidectomized mice, notably in the presence of gonadal stimulation.

The following alterations seen in mice bearing pituitary tumors remain to be explained: retrogressive changes in the reticular zone of the adrenal gland; hyperplasia with cystic dilatation of the extrahepatic biliary tracts; extensive ductal hyperplasia of the mammary gland of female radiothyroidectomized mice; cleft-like spaces in pancreatic cells; pathogenesis of sudden death with signs suggestive of thyrotoxicosis in mice bearing intrapulmonary thyroid grafts.

I gratefully acknowledge the skillful assistance and devotion to this work of William D. Gude in preparing the sections, Evelyn L. Gadsden in the animal experimentation, and Bonnie Anderson in the radioisotope assays.

REFERENCES

1. Gorbman, A. Tumorous growths in the pituitary and trachea following radiotoxic dosages of I^{131}. *Proc. Soc. Exper. Biol. & Med.*, 1949, **71**, 237–240.
2. Furth, J., and Burnett, W. T., Jr. Hormone-secreting transplantable neoplasms of the pituitary induced by I^{131}. *Proc. Soc. Exper. Biol. & Med.*, 1951, **78**, 222–224.

3. Furth, J., Gadsden, E. L., and Burnett, W. T., Jr. Autonomous transplantable pituitary tumors arising in growths dependent on absence of the thyroid gland. *Proc. Soc. Exper. Biol. & Med.*, 1952, **80**, 4–7.

4. Goldberg, R. C., and Chaikoff, I. L. On the nature of the hypertrophied pituitary gland induced in the mouse by I^{131} injections, and the mechanism of its development. *Endocrinology*, 1951, **48**, 1–5.

5. Gadsden, E. L., and Furth, J. Effect of thyroid hormone on growth of thyrotrophin-secreting pituitary tumors. *Proc. Soc. Exper. Biol. & Med.*, 1953, **83**, 511–514.

6. Furth, J., Burnett, W. T., Jr., and Gadsden, E. L. Quantitative relationship between thyroid function and growth of pituitary tumors secreting TSH. *Cancer Research*, 1953, **13**, 298–307, and unpublished data.

7. Gude, W. D. Modified Martins-Mallory stain for mouse pituitary gland. *Stain Technol.*, 1953, **28**, 161–162.

8. Halmi, N. S., and Gude, W. D. The morphogenesis of pituitary tumors induced by radiothyroidectomy in the mouse and the effects of their transplantation on the pituitary body of the host. *Am. J. Path.*, 1954, **30**, 403–419.

9. Moon, H. D., Simpson, M. E., Li, C. H., and Evans, H. M. Neoplasms in rats treated with pituitary growth hormone. I. Pulmonary and lymphatic tissues. *Cancer Research*, 1950, **10**, 297–308.

10. Silberberg, M., and Silberberg, R. Malignant lymphoid tumors in orchidectomized mice receiving hypophyseal and ovarian grafts at various ages. *Proc. Soc. Exper. Biol. & Med.*, 1949, **72**, 547–550.

11. Lipschutz, A. Les hormones préhypophysaires dans la tumorigénèse expérimentale. *Ann. d'endocrinol.*, 1952, **13**, 9–23.

12. Gorbman, A. Functional and structural changes consequent to high dosages of radioactive iodine. *J. Clin. Endocrinol.*, 1950, **10**, 1177–1191.

13. Goldberg, R. C., and Chaikoff, I. L. The cytologic changes that occur in the anterior pituitary glands of rats injected with various doses of I^{131} and their significance in the estimation of thyroid function. *Endocrinology*, 1950, **46**, 91–104.

14. Goldberg, R. C., Chaikoff, I. L., Lindsay, S., and Feller, D. D. Histopathological changes induced in the normal thyroid and other tissues of the rat by internal radiation with various doses of radioactive iodine. *Endocrinology*, 1950, **46**, 72–90.

15. Rugh, R. Radioiodine and histopathological effects. *J. Morphol.*, 1951, **89**, 457–499.

16. Rugh, R. The mouse thyroid and radioactive iodine (I^{131}). *J. Morphol.*, 1951, **89**, 323–365.

17. Maloof, F., Dobyns, B. M., and Vickery, A. L. The effects of various doses of radioactive iodine on the function and structure of the thyroid of the rat. *Endocrinology*, 1952, **50**, 612–638.

18. Silberberg, R., Silberberg, M., and Dixon, F. J. Obliterating tracheitis, a complication following administration of radioactive iodine. *J. Lab. & Clin. Med.*, 1952, **39**, 256–259.

19. Furth, J., Burnett, W. T., Jr., Gadsden, E. L., and Anderson, B. Quantitative assays for TSH in relation to thyrotrophin-secreting pituitary tumors. To be published.

20. Anderson, E., and Bates, R. W. Unpublished data.

21. Bischoff, F., Clarke, G. J., and Epps, C. H. Influence of the thyroid on the resorption of gonadotropic hormones. *Endocrinology,* 1941, **28,** 48–52.

22. Furth, J., Gadsden, E. L., and Upton, A. C. Hyperplasia and cystic dilatation of extrahepatic biliary tracts in mice bearing grafted pituitary growths. *Cancer Research,* 1952, **12,** 739–743.

23. Gardner, W. U., Allen, E., and Smith, G. M. Hyperplasia and hypertrophy of the mucosa of larger biliary ducts in mice receiving estrogens. *Proc. Soc. Exper. Biol. & Med.,* 1941, **46,** 511–513.

24. Cramer, W., and Horning, E. S. Adrenal changes associated with oestrin administration and mammary cancer. *J. Path. & Bact.,* 1937, **44,** 633–642.

25. Sobel, H., and Furth, J. Hypervolemia in mice bearing granulosa cell growths; time of onset and some associated physiological and chemical changes. *Endocrinology,* 1948, **42,** 436–447.

26. Furth, J. Conditioned and autonomous neoplasms: A review. *Cancer Research,* 1953, **13,** 477–492.

27. Morris, H. P., Dalton, A. J., and Green, C. D. Malignant thyroid tumors occurring in the mouse after prolonged hormonal imbalance during the ingestion of thiouracil. *J. Clin. Endocrinol.,* 1951, **11,** 1281–1295.

28. Dickie, M. M., and Woolley, G. W. Spontaneous basophilic tumors of the pituitary glands in gonadectomized mice. *Cancer Research,* 1949, **9,** 372–384.

29. Dunning, W. F., Curtis, M. R., and Segaloff, A. Strain differences in response to diethylstilbestrol and the induction of mammary gland and bladder cancer in the rat. *Cancer Research,* 1947, **7,** 511–521.

30. Furth, J., Gadsden, E. L., and Upton, A. C. ACTH secreting transplantable pituitary tumors. *Proc. Soc. Exper. Biol. & Med.,* 1953, **84,** 253–254.

31. Greene, H. S. N. A conception of tumor autonomy based on transplantation studies: a review. *Cancer Research,* 1951, **11,** 899–903.

32. Laqueur, G. L. Personal communication.

LEGENDS FOR FIGURES

FIG. 1. Characteristic appearance of a mouse with a pituitary tumor induced by I^{131}.

FIG. 2. Two primary pituitary tumors (4077 and 5001) induced by I^{131} with a normal pituitary body in the center. Mouse 4077 died 12½ months after subcutaneous injection of 50 μc. of I^{131}.

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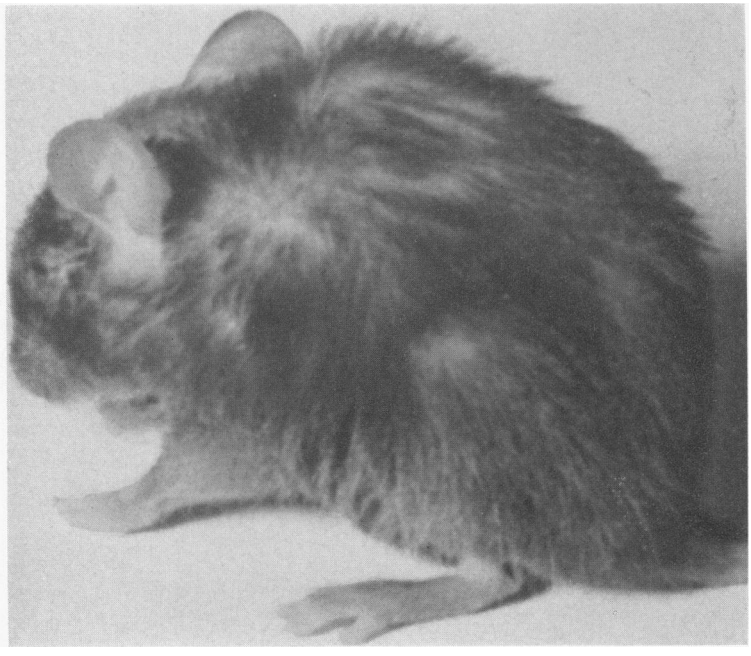

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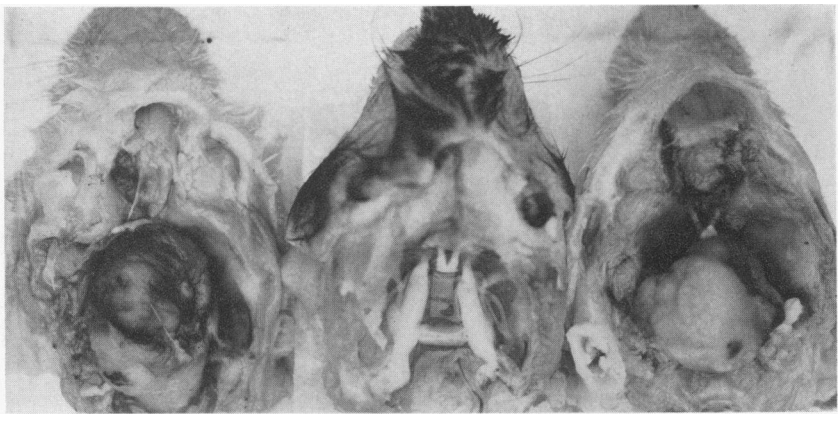

Figures 3 to 8 illustrate dependent tumor strain 3.

FIG. 3. The large cells shown were rarely present in first generation grafts. They vanished on subsequent passages and their character is not known. × 450.

FIG. 4. Same tumor as in Figure 3, showing the numerous intranuclear inclusions frequently present in thyrotrophin-secreting dependent tumors. × 470.

FIG. 5. Gland-like structures occasionally seen in primary tumors and first generation grafts. × 470.

FIG. 6. Characteristic appearance of dependent tumor cells. There is uniformity in shape and size of cells and the cytologic features of cancer cells are lacking. Martins and Mallory's trichrome stain. × 450.

FIG. 7. Early growth of a dependent tumor with lack of degenerative changes. Cavernous sinusoids, as in this field, were numerous. × 120.

FIG. 8. Metastasis to regional lymph node. × 470.

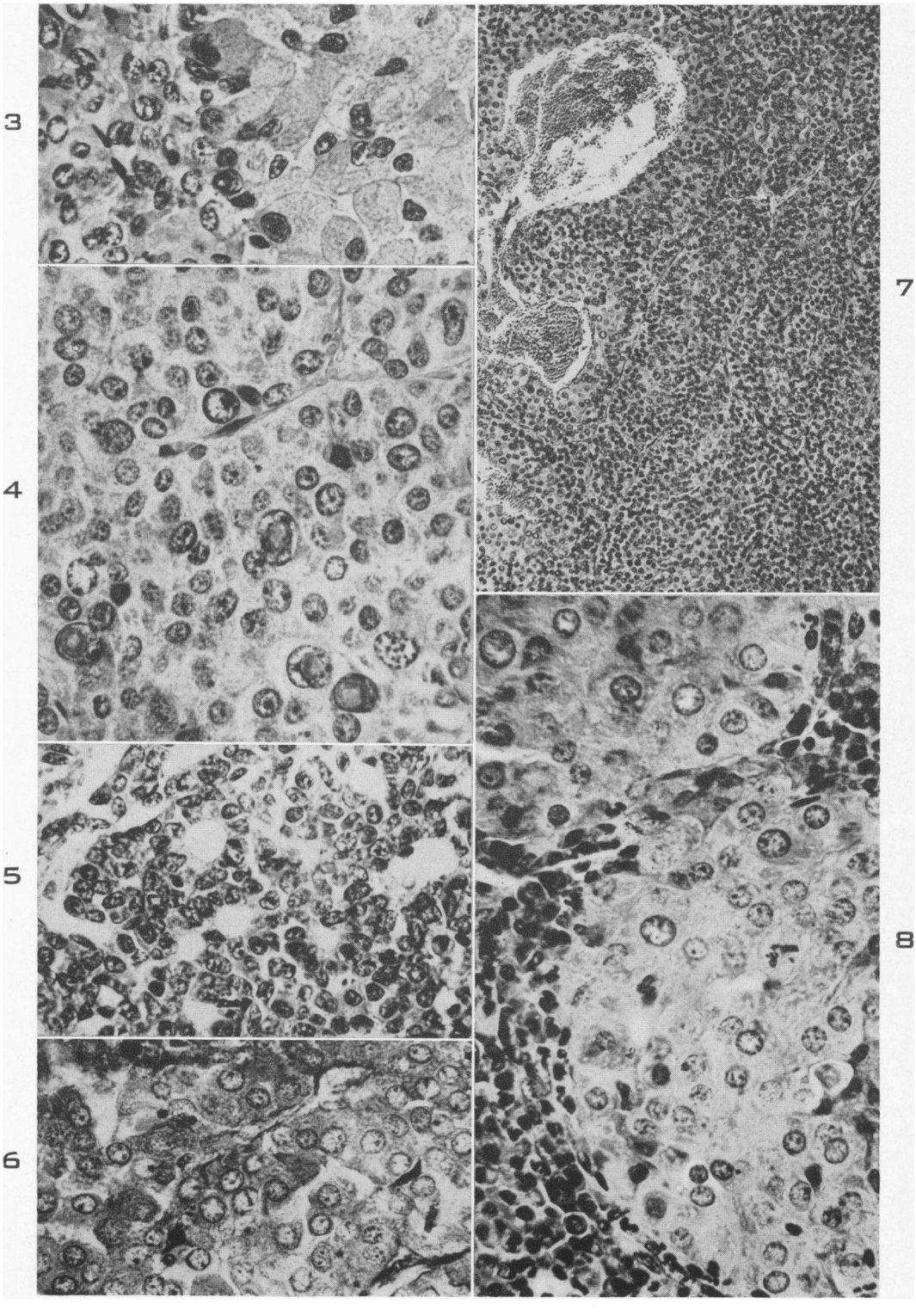
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FIG. 9. Metastasis to liver following intrasplenic graft (strain 3D), with malignant lymphoma. × 120.

FIG. 10. Same as Figure 9 showing, at magnification × 470, lymphomatous infiltration about a bile duct.

FIG. 11. Same as Figure 9 showing, at magnification × 470, liver cells and tumor cells.

FIG. 12. Malignant lymphoma and dependent pituitary tumor cells following subcutaneous graft (strain 124D). × 120.

FIG. 13. Autonomous pituitary tumor graft (strain 3A) in the right thigh. Extensive metastases to lymph nodes. Atrophy of uterine horn.

FIG. 14. Tumor 3A graft. Extensive metastases to retroperitoneal lymph nodes. Atrophy of seminal vesicles.

FIG. 15. Tumor 3A graft. Extensive metastases in retroperitoneal lymph nodes and ovaries.

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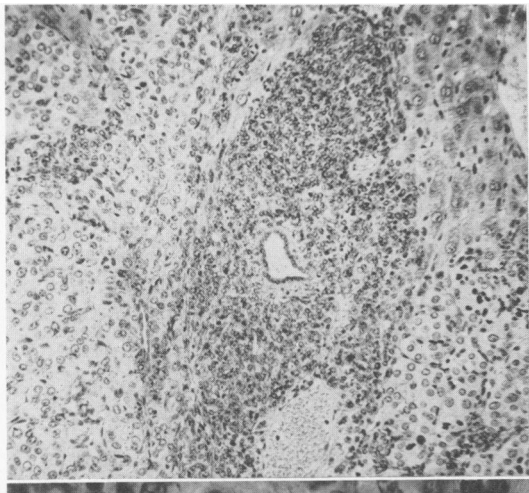

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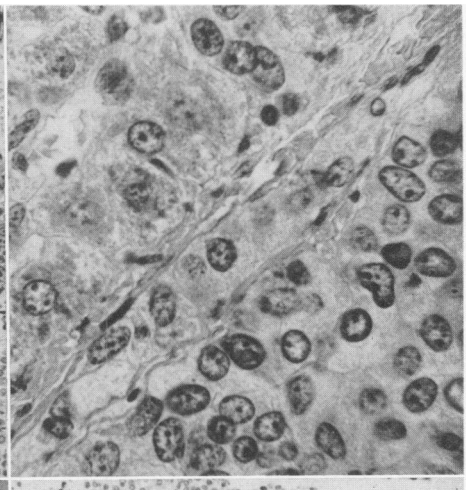

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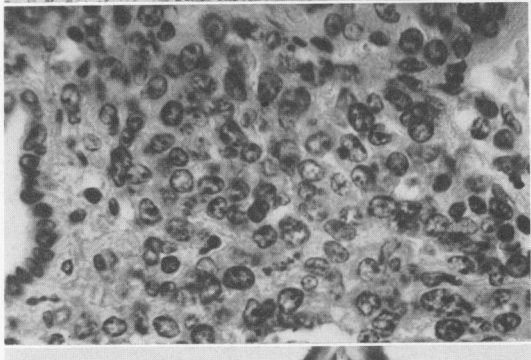

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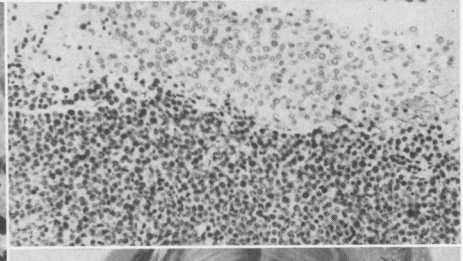

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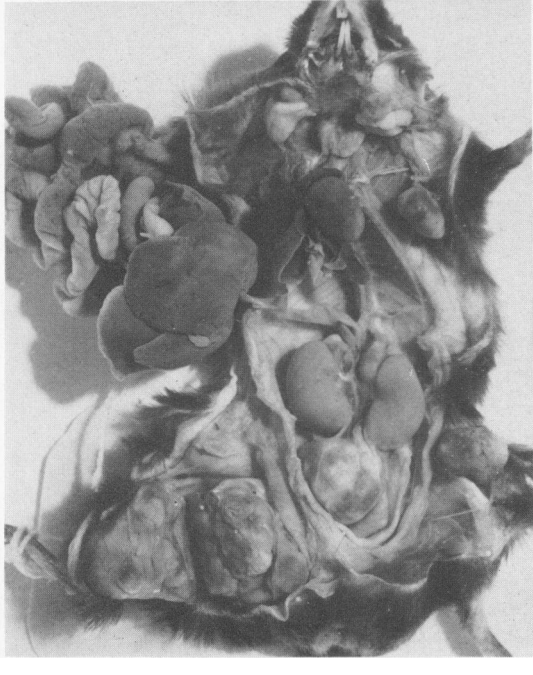

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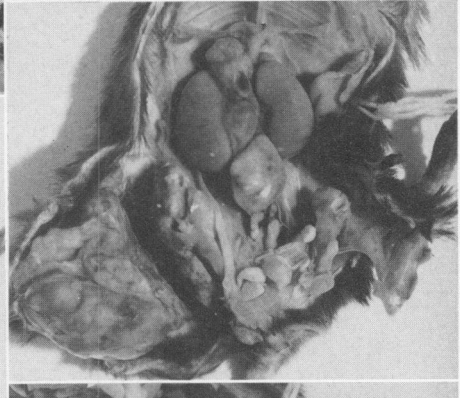

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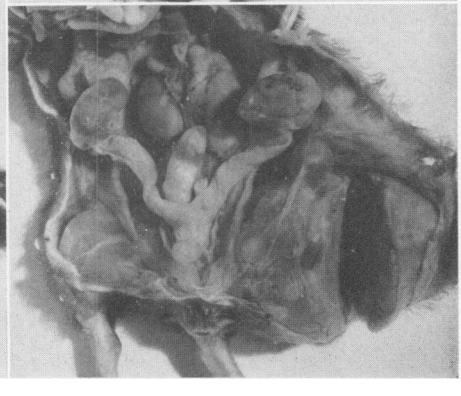

Figures 16 to 19 illustrate the autonomous tumor strain 3A.

FIG. 16. Extensive hemorrhage, moderate fibrosis, and necrosis. × 120.

FIGS. 17 to 19. Several fields of the autonomous tumor shown in Figure 16, at magnification × 470, exhibiting features of a malignant growth.

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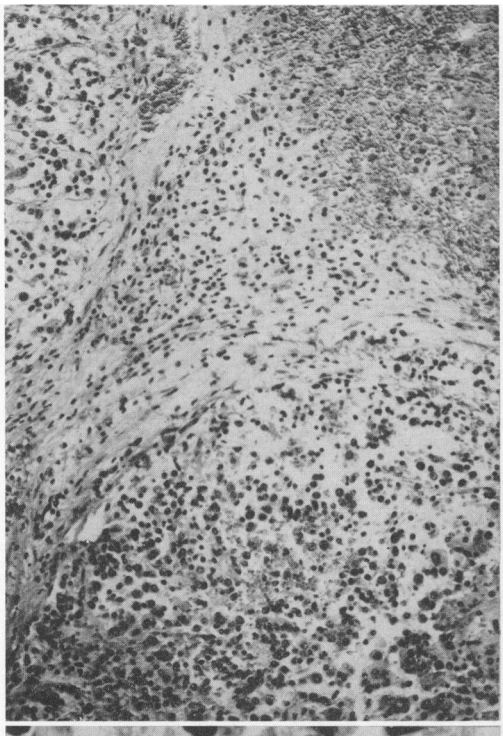

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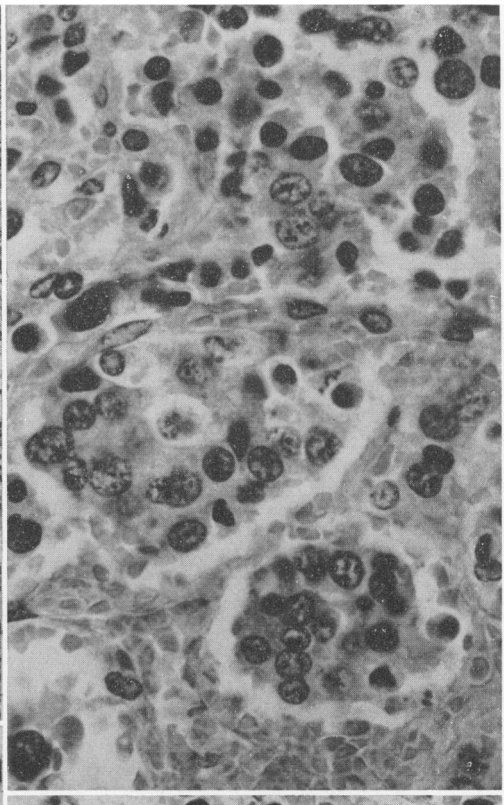

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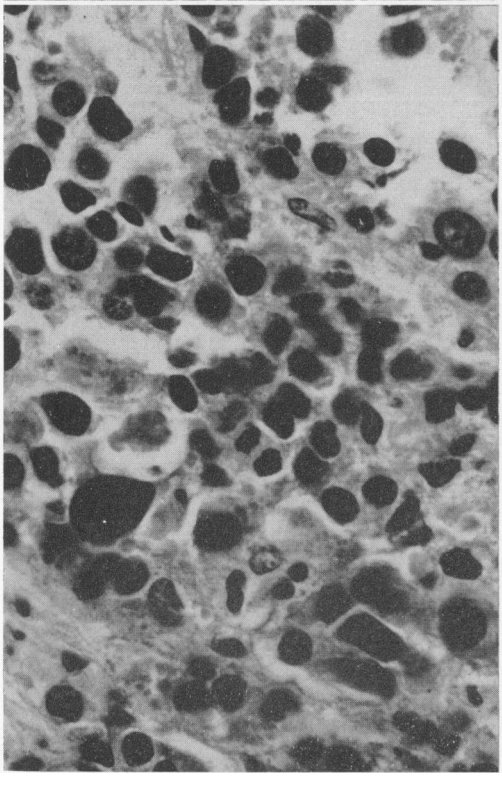

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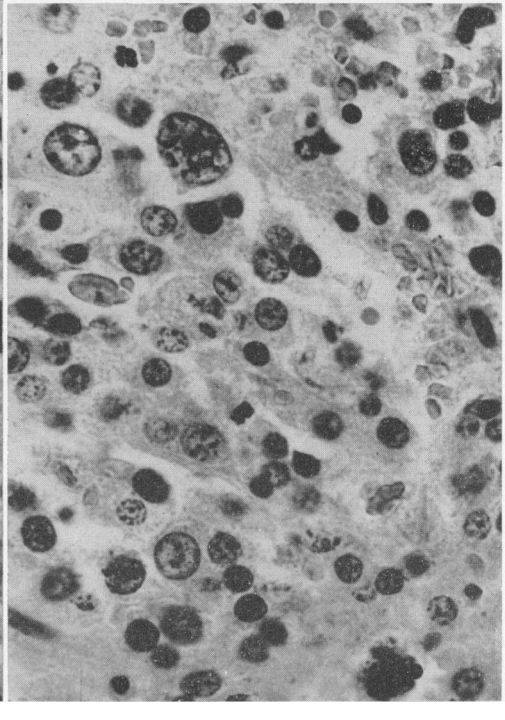

FIGS. 20 and 21. Normal thyroid gland. × 33 and 250.

FIGS. 22 and 23. Near-complete radiothyroidectomy. These atypical thyroid cells are apparently incapable of regeneration. This mouse died 223 days after administration of I^{131}. × 33 and 470.

FIGS. 24 and 25. Diffuse stimulation of the thyroid gland by late autonomous pituitary tumor. The animal died 7 months following graft of a tumor 3D. × 33 and 470.

FIG. 26. A thyroid adenoma following near-complete destruction of this organ with 100 μc. of I^{131}; this animal had a pituitary tumor of about 4 by 6 mm., 14 months following administration of I^{131}. × 120.

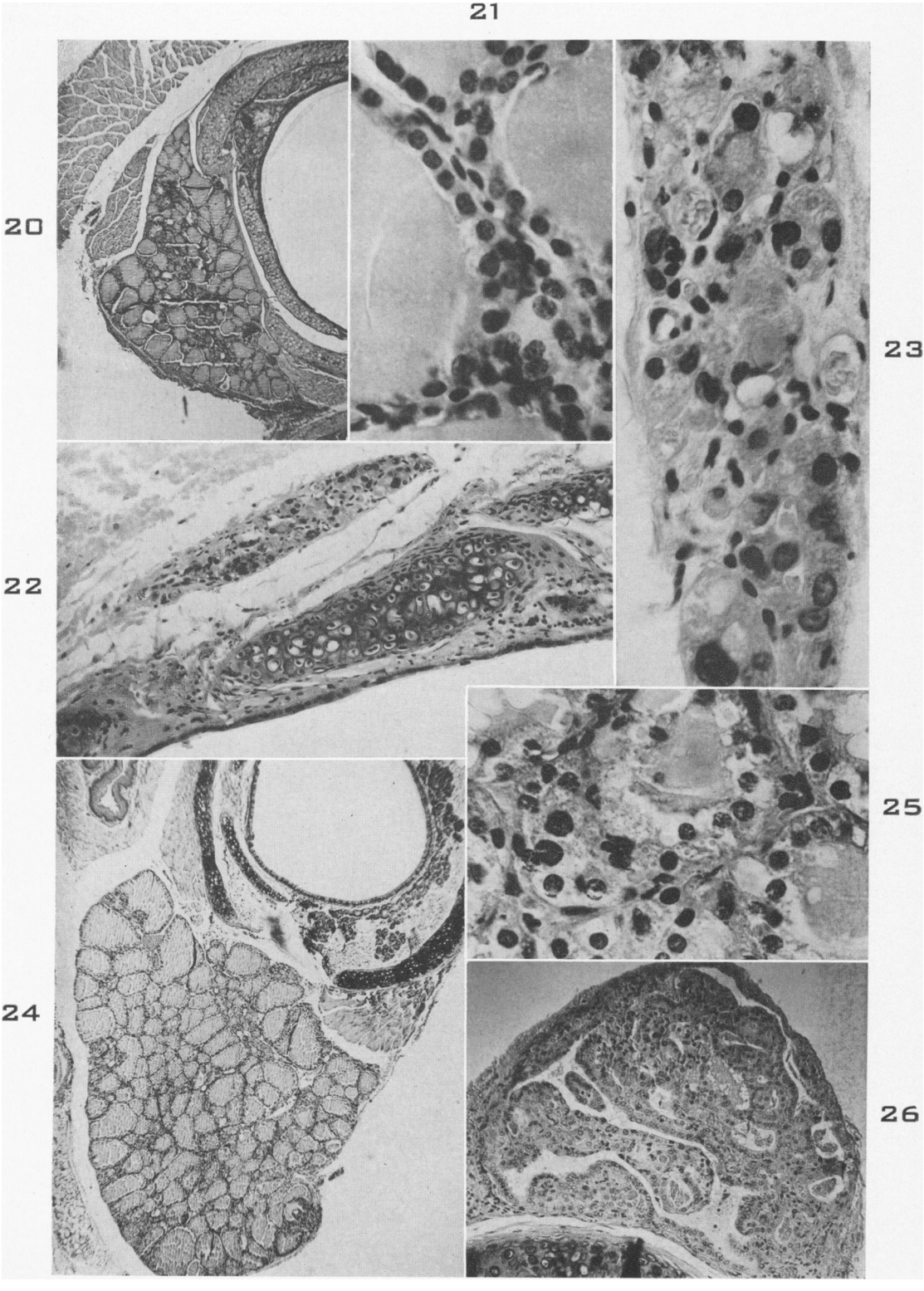
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FIG. 27. Cross section of normal trachea. × 120.

FIG. 28. Incidental changes 367 days after radiothyroidectomy. Arterial stenosis; fibrosis at site of the thyroid gland. Calcification of cartilage. Fibrosis of submucosa with absence of mucous glands. × 120.

FIG. 29. Stenosing tracheitis 300 days after radiothyroidectomy. × 33.

FIGS. 30 and 31. Partial destruction of the parathyroid gland following radiothyroidectomy. Stenosing arteritis; adjacent area of fibrosis marks the site of the thyroid gland. × 120.

FIGS. 32 and 33. Arterial changes 8 days following administration of 270 μc. of I^{131}. × 120.

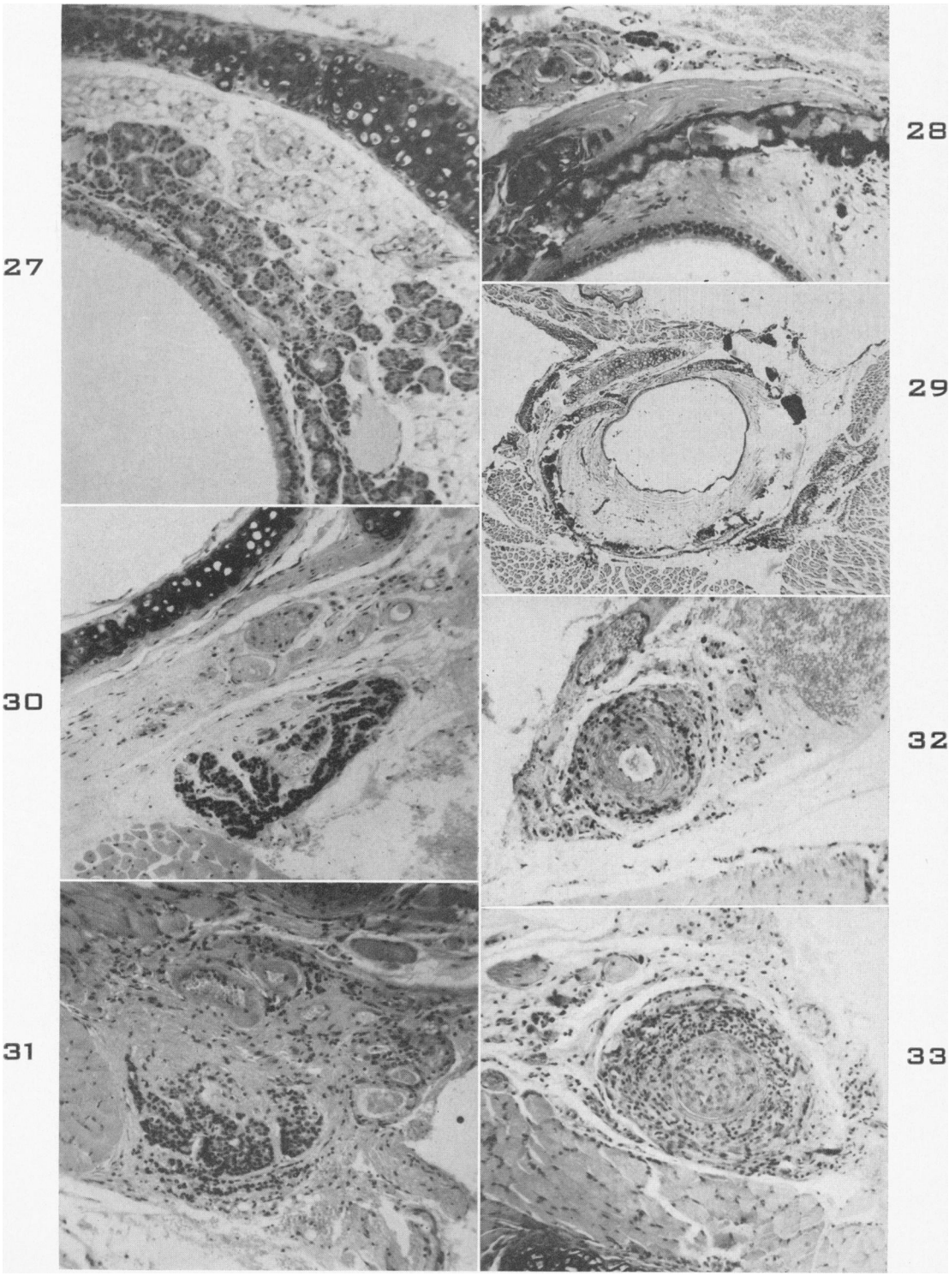
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FIG. 34. Enormous enlargement of the thyroid gland with adenomas caused by grafted late autonomous pituitary tumor (strain 3).

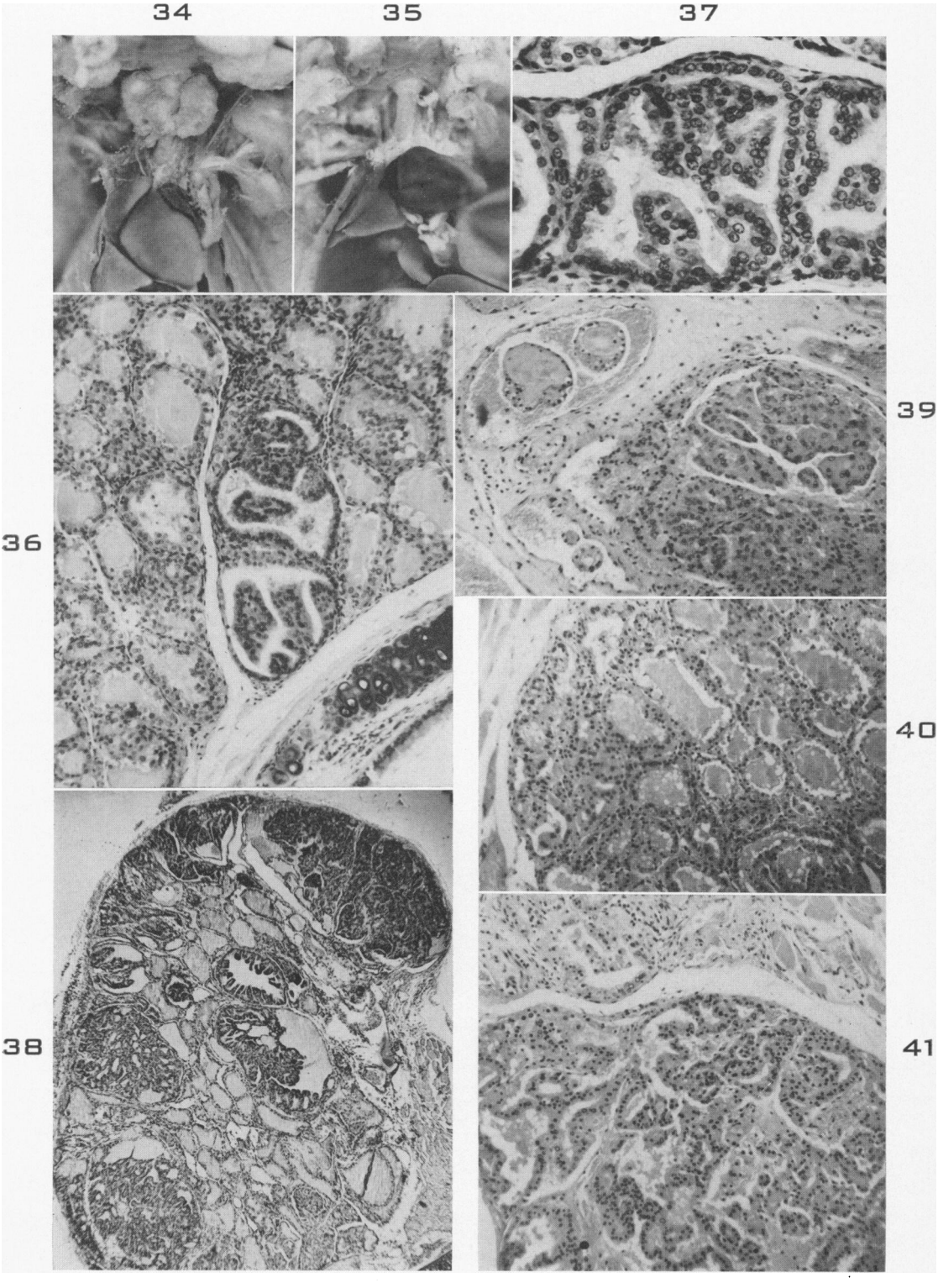
FIG. 35. Normal thyroid gland shown for comparison with Figure 34.

FIGS. 36 and 37. Hyperplasia of the thyroid gland with adenomas, in a mouse bearing a late autonomous tumor (strain 3). × 120 and 240.

FIG. 38. Enormous enlargement of the thyroid gland with numerous adenomas, in a mouse bearing a late autonomous pituitary tumor (strain 3). This animal died 7 months after the graft. × 33.

FIG. 39. Invasion of a blood vessel by thyroid tissue in a mouse with greatly enlarged adenomatous thyroid gland caused by a late autonomous pituitary graft (strain 3). Necropsy 15 months after the tumor graft. × 120.

FIGS. 40 and 41. Intramuscular thyroid grafts showing evidence of stimulation, in mice bearing grafted autonomous pituitary tumors (3A). × 120.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FIGS. 42 and 43. Intrapulmonary thyroid tissue following intravenous injection of thyroid cells in a mouse bearing an autonomous pituitary tumor (strain 3A). × 120 and 450.

FIGS. 44 and 45. Intrapulmonary thyroid tissue following intravenous injection of thyroid cells in a mouse bearing an autonomous pituitary tumor (strain 19A). × 450.

FIG. 46. Massive hepatic necrosis in a mouse having thyroid tissue grafted in the lung and an autonomous pituitary tumor in the thigh. (Most mice of this group died suddenly, probably of thyrotoxicosis). × 120.

FIG. 47. Cleft-like spaces in the acinar cells of the pancreas of a mouse bearing an autonomous pituitary tumor (3A). × 450.

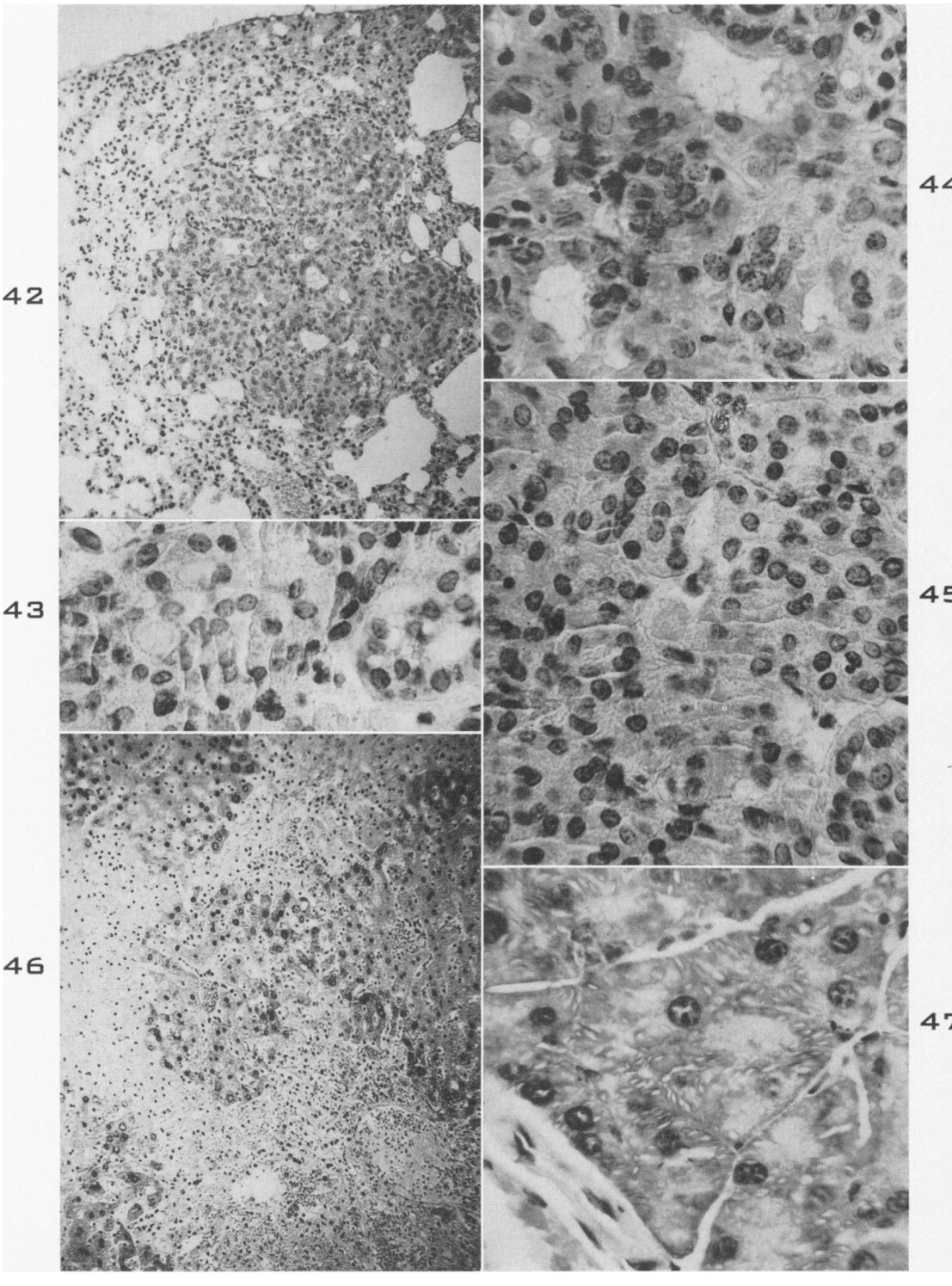
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FIG. 48. Two mice bearing grafted dependent tumors (not seen in the picture) with cystic dilatation of the extrahepatic biliary tracts.

FIGS. 49 and 50. Hyperplasia and dilatation of the hepatic duct in a mouse bearing a grafted dependent tumor. × 33.

FIG. 51. Hyperplasia and dilatation at ampulla of Vater. Arrow points to the patent lumen near the orifice. × 33.

FIG. 52. Atrophic ovary with lutein cells in a mouse with a primary pituitary tumor induced by radiothyroidectomy. × 120.

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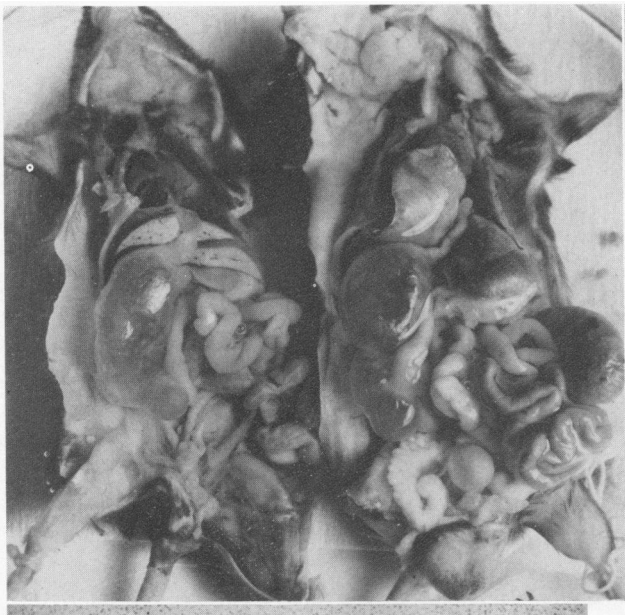

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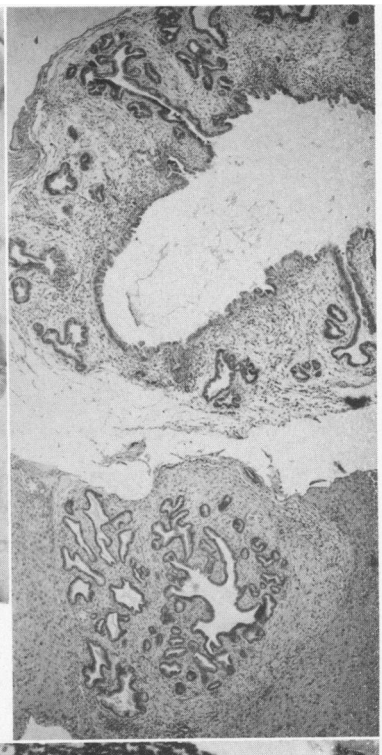

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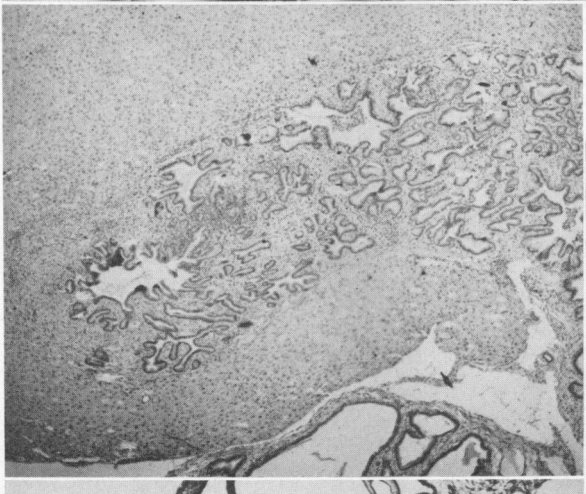

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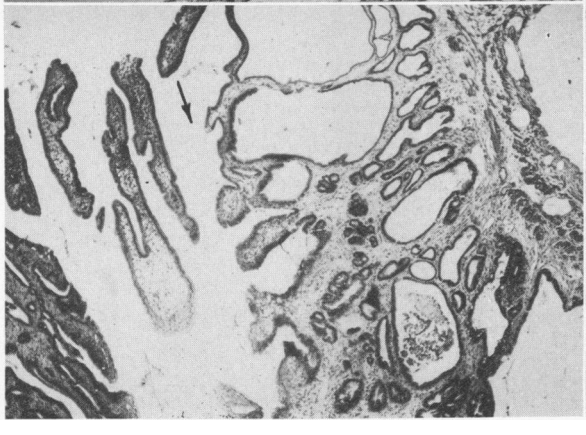

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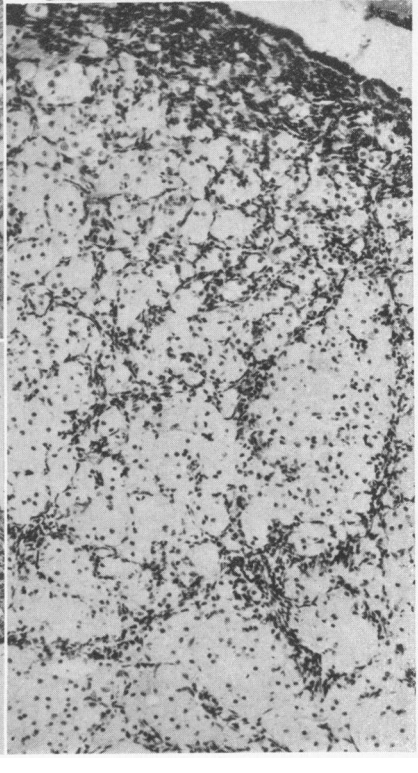

FIG. 53. Atrophic ovary with a lutein body (microluteoma?) in a mouse with pituitary tumor induced by radiothyroidectomy. × 120.

FIG. 54. Extensive gonadal stimulation ("A-Z reaction") in a radiothyroidectomized mouse bearing a grafted dependent tumor. Estrogenic type of uterine stimulation (strain 3D).

FIG. 55. Gonadal stimulation ("A-Z reaction") in a radiothyroidectomized mouse bearing a grafted dependent tumor. Cystic dilatation of the uterine horn (strain 3D).

FIGS. 56 and 57. Greatly stimulated ovaries ("A-Z reaction") in mice bearing grafted dependent tumors; phase of follicular ripening with hemorrhage and luteinization of stroma cells. × 33 and 120.

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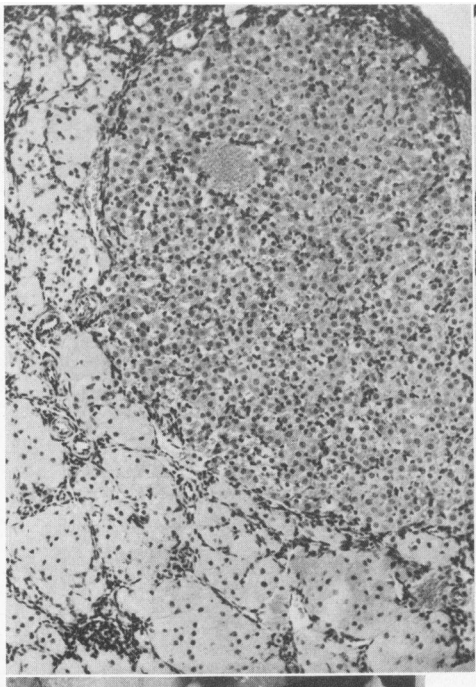

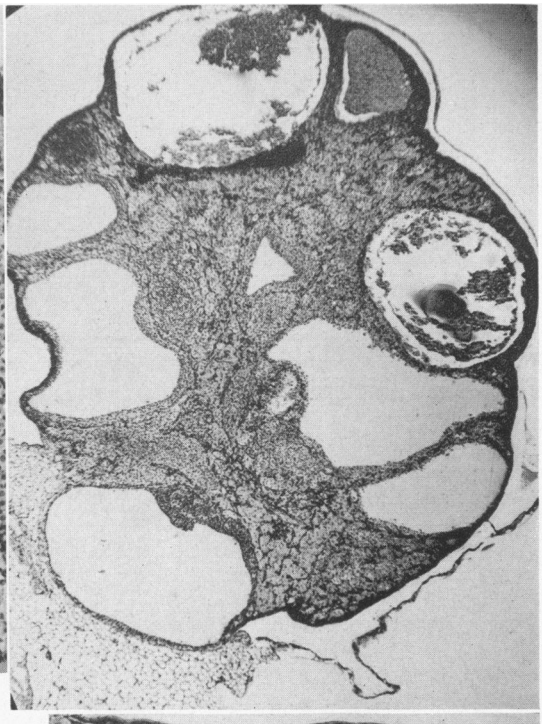

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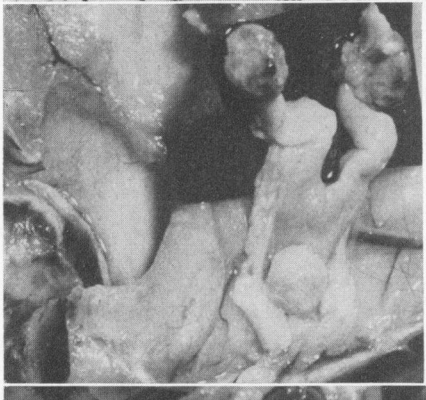

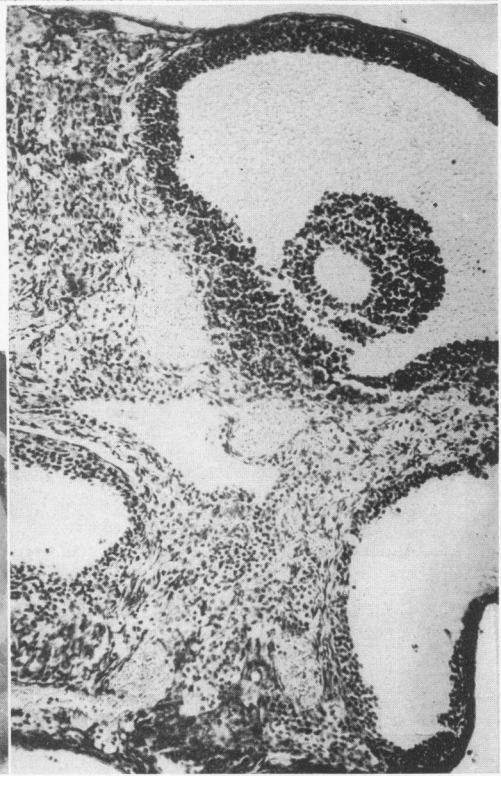

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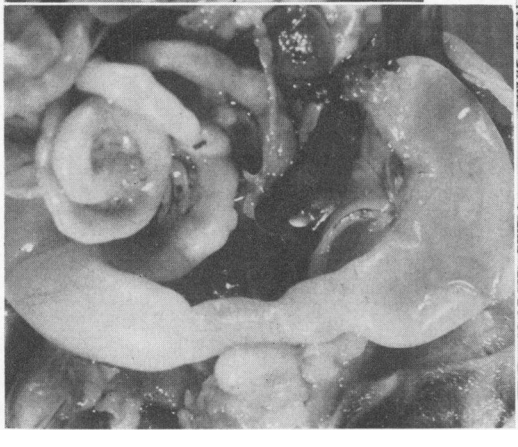

FIG. 58. Normal adrenal gland of an adult mouse. × 120.

FIG. 59. Atrophic adrenal cortex of a mouse with primary pituitary tumor induced by radiothyroidectomy. × 120.

FIGS. 60 and 61. Replacement of the reticular zone of the adrenal cortex with "foam" cells; a characteristic change secondary to dependent tumors. × 120 and 470.

FIGS. 62 and 63. Characteristic lipid degeneration in the region of the reticular zone of the adrenal gland in a normal mouse bearing a late autonomous tumor. × 120 and 470.

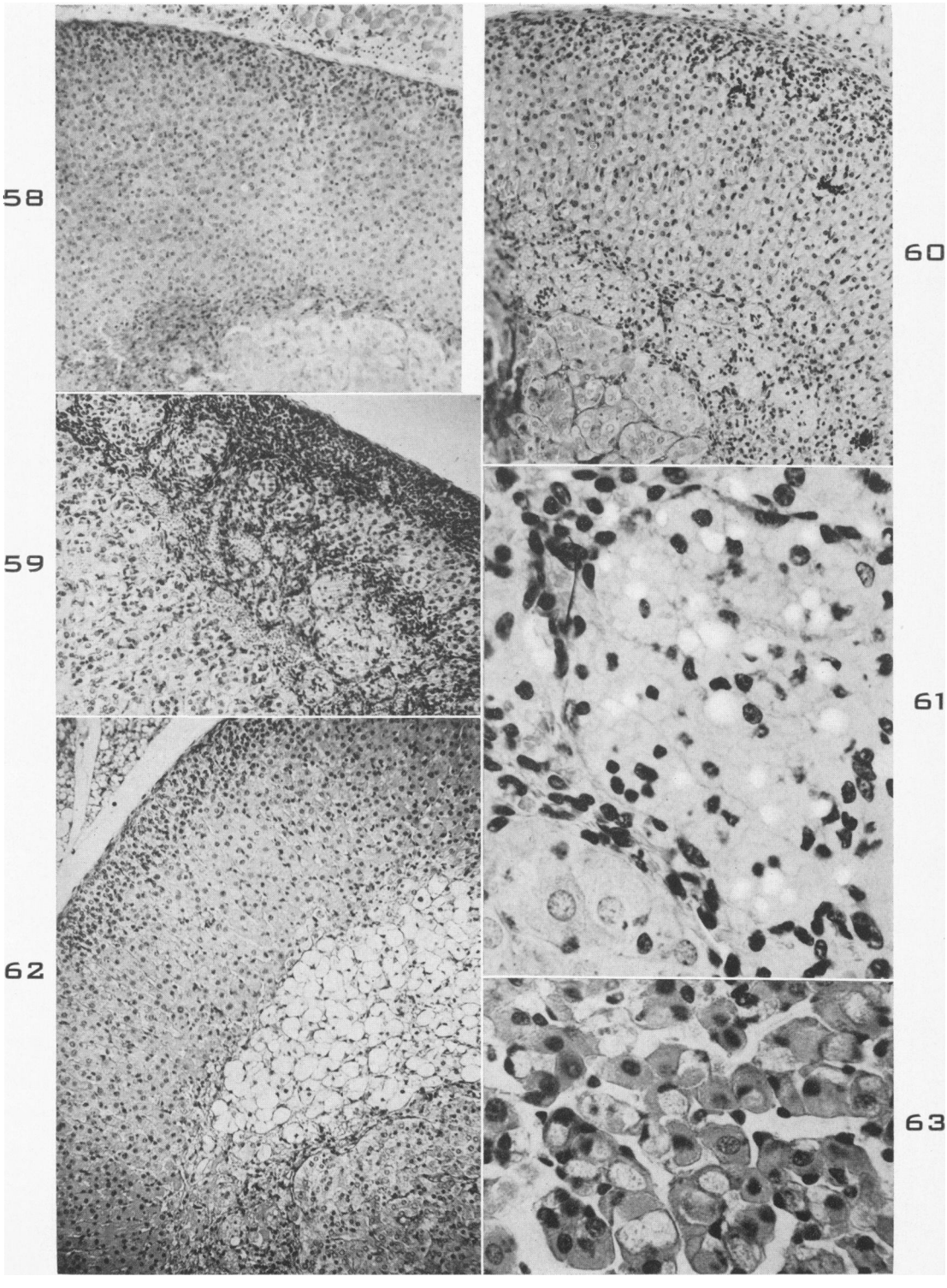
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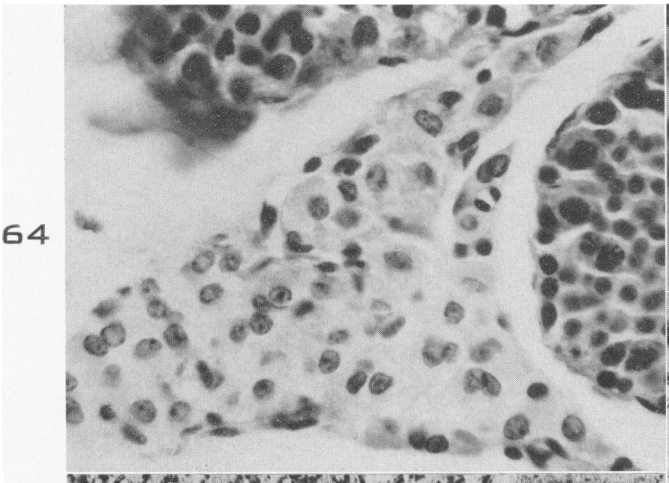
FIG. 64. Hyperplasia of Leydig cells in a radiothyroidectomized mouse bearing a dependent tumor. × 470.

FIG. 65. Hyperplasia of the mammary gland of a radiothyroidectomized mouse bearing a grafted dependent tumor (strain 19D).

FIG. 66. Hyperplasia of the mammary gland of a radiothyroidectomized mouse bearing a primary pituitary tumor. × 120.

FIG. 67. Grafted dependent pituitary tumor with hyperplasia of the adjacent mammary gland. × 120.

FIGS. 68 and 69. Tumor of the submaxillary gland with osteogenesis in a mouse 345 days following radiothyroidectomy. × 120 and 470.



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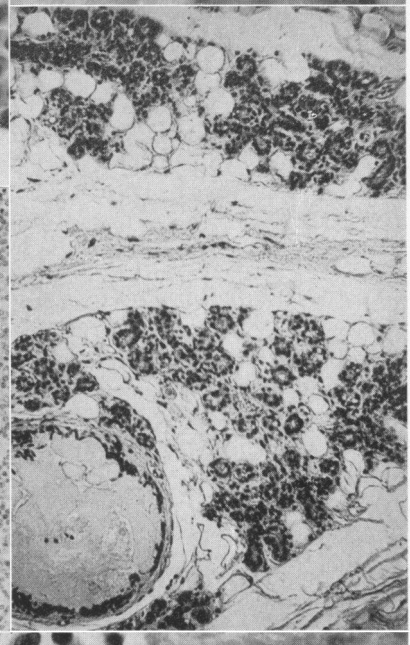

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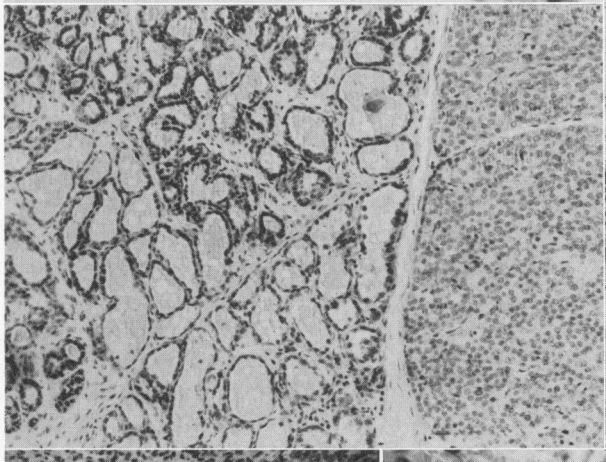

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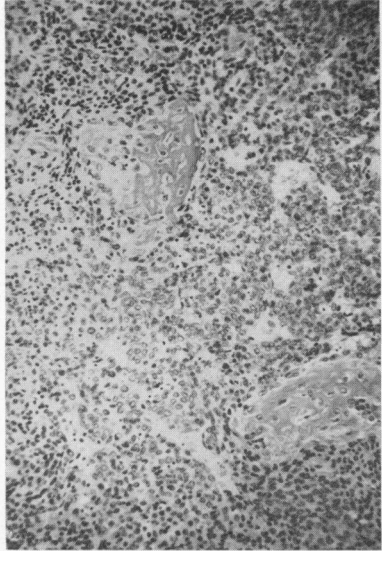

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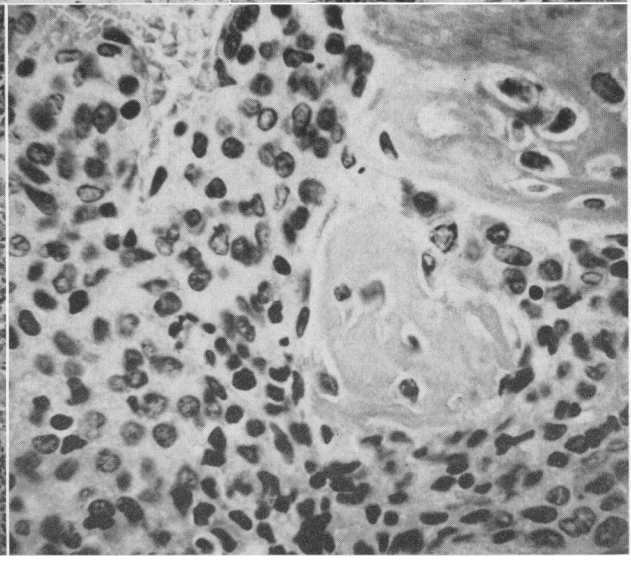

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