On the Relation between Thyroid Depression and Pituitary Tumor Induction in Mice*

JAMES NORMAN DENT, EVELYN L. GADSDEN, AND JACOB FURTH

(Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn.; Children's Cancer Research Foundation, Boston, Mass.; and the Department of Biology, University of Virginia, Charlottesville, Va.)

The development of tumorous growths in the pituitary glands of mice following the injection of radioiodine and subsequent radiothyroidectomy was first reported by Gorbman (8), who reasoned that thyroid destruction was not the principal factor in the production of these growths, since pituitary tumors had not been induced when the thyroid gland was chronically depressed by goitrogens. Later, Gorbman (10) and Gorbman and Edelmann (11) obtained findings on which they based the conclusion that the radioiodine must act in a dual rule—indirectly by damaging the thyroid gland, and directly through some unexplained effects of its radiation on the treated mice. Moore, Brackney, and Bock (15) attempted to test this hypothesis by prolonged treatment with propyl thiouracil and by surgical removal of the thyroid gland. By the first procedure they produced evidence that tumors can be induced in the unirradiated pituitary gland. Tumors were not produced by surgical thyroidectomy; however, considerable residual, functioning thyroid gland tissue was found at necropsy. In the present paper, findings are presented indicating that near-complete surgical thyroidectomy will induce pituitary tumors in mice. In addition, observations made on the histological nature of thyroid damage at various levels of radioiodine treatment are described, and the following questions are considered: (a) What is the minimal dose of radioiodine necessary to induce pituitary tumors? (b) Are the changes seen in radiation-damaged thyroid glands identical with the senile changes described by Andrew and Andrew (1)? (c) What is the regenerative capacity of the thyroid gland after radiation damage or subtotal thyroidectomy? and (d) Will dependent pituitary tumors (3, 5) persist and grow in surgically thyroidectomized mice? Also, data suggesting a sex variation in susceptibility to pituitary tumor induction are presented. Some of these findings are documentations or amplifications of material presented in a paper read before the American Goiter Association (4).

MATERIALS AND METHODS

The animals used in this investigation fall into four principal groups: (a) 25 surgically thyroidectomized C57BL mice; (b) approximately 800 C57BL mice injected with 5, 50, 100, or 500 µc. of 131; (c) six each surgically thyroidectomized, radiothyroidectomized, and normal C57BL mice implanted in the thigh with pieces of pituitary tumor (dependent strain 101-D); and 81 senile or near senile mice. Of these 81 old mice, 40 (twenty each males and females) were of the LAF1 strain and were 25-30 months old at death; seventeen were 21-month-old female RF mice; and 44 (5 males and 19 females) were C57BL mice, 14-26 months old. All animals were maintained at a controlled temperature of approximately 27° C. They were given water and Purina Chow ad libitum with occasional supplementation of carrots, lettuce, and hemp seed.

Necropsy was performed on each animal when it died or was killed, and thyroid and pituitary glands were sectioned and stained routinely with hematoxylin and eosin. Martins-Mallory trichrome stain (12) and periodic acid-Schiff's reagent were often used as supplemental stains. Other organs were studied microscopically when gross diagnosis appeared to be inadequate.

The procedure used in surgical removal of the thyroid gland was as follows: The mouse was anesthetized with sodium nembutal and affixed ventral side up to a small paraffin-filled dissecting pan under a binocular dissecting microscope. After shaving away the hair from the throat region, a midventral incision was made through the skin, exposing the submaxillary gland. With fine but blunt forceps, the submaxillary gland was divided into two parts along the median sagittal plane, and the two halves of the sternohyoid muscle were separated. Next, these structures together with the sternothyroid muscles were reflected laterally by means of retractors devised from pieces of paper clips and attached to the dissecting pan by means of rubber bands. Thus, the thyroid gland was exposed. It was then dissected free (avoiding damage to the recurrent laryngeal nerve) with fine watchmaker's forceps and a microscalpel ground on the tip of a dissecting needle. During the process of retracting the adjacent muscles, the right parathyroid gland ordinarily became separated from the thyroid and was handily left in place. The left parathyroid was usually partially imbedded in the left lobe of the thyroid. In this study it was dissected from the thyroid and left behind when the thyroid was removed. However, it is so difficult to completely separate the left parathyroid from the thyroid that it is probably better to ablate both. The mouse will survive with one parathyroid,
Fig. 2.—Electron micrograph of a section of Novikoff tumor, ×30,000. At the upper right and lower right, portions of nuclei appear, and the double nature of their membranes is apparent. The membranes of the two cells that come into contact may be seen passing from the lower left corner to the right middle part of the illustration, and the irregular nature of the cell membranes is apparent. Rows of ergastoplasmic vesicles are present just below the cell membrane (middle right).
Fig. 3.—Electron micrograph of a section of a 20-day rat embryo liver, ×80,000. A mitochondrion may be seen at the upper left. Through the remainder of the figure, vesicles of the ergastoplasm, flattened to different extents, are abundant. Associated with these, and scattered among them, are small dark granules of the ergastoplasm.

Fig. 4.—Electron micrograph of a section of Novikoff tumor, ×17,000. The cytoplasm of the cell at the left illustrates the considerable variation in diameter exhibited by the mitochondria of these tumor cells. Some Golgi material may be seen in the lower right part of the illustration.
and chances of performing complete thyroidectomy are increased if the left parathyroid is removed along with the thyroid tissue.

When the thyroid vessels were necessarily cut, bleeding was usually so profuse as to obstruct the view of the gland but was controlled by the use of small pledgets of Gelfoam.1 Occasional use of a microcautery was also helpful. At the completion of the operation, the wound was closed by application of a single metal wound clip to the skin. No special attempt was made to maintain sterile conditions.

During the course of brief iodine-uptake studies (not to be discussed in this paper), each of these mice received one, and in some instances two, injections of 5–9 µc. of I131.

The radioiodine used in these uptake studies and in radiothyroidectomy was obtained from the Isotopes Sales Department of the Oak Ridge National Laboratory in the form of NaI. After its radioactivity had been measured in a 100 per cent geometry gamma ionization chamber, it was diluted to the desired strength for injection with 0.9 per cent sterile saline solution and injected subcutaneously in the thigh region.

**OBSERVATIONS AND RESULTS**

**HISTOLOGY OF THE THYROID REGION**

*In surgically thyroidectomized mice.*—Examination of serial sections disclosed thyroid remnants in 25 of the 31 mice operated upon, including the six animals which received tumor implants. Most of these remnants were composed of a few typically formed follicles with greatly thickened epithelium containing considerable intracellular colloid (Figs. 1 and 3). The other remnants were evident as sharply circumscribed nodular structures containing irregularly shaped follicles and also considerable numbers of interstitial cells. These structures closely resemble the thyroid adenomas described in the mouse (16) and the rat (14) and are designated as thyroid adenomas (Fig. 2). The difference between nodular hyperplasia and adenoma is admitted arbitrarily.

*In mice given 25–200 µc. of I131.*—In the thyroid site of those mice which had received 100 and 200 µc. of I131 were found regions of fibrosis containing sometimes (more frequently in the 100- than in the 200-µc. group) a few abnormal and atretic follicles accompanied by scarring of adjacent tissues. This is the typical response to thyroid-destructive doses of I131 in the mouse as described by several investigators (see, e.g., 9, 17).

The thyroids from the animals injected with 25 µc. of I131 were characterized, in general, by the presence of interfollicular hyaline connective tissue. This condition varied from one extreme in which the fibrous accumulation was light and was largely confined to the central region of the gland (Fig. 4) to another in which the greater part of the thyroid was composed of hyaline material (Fig. 5). The follicles of these glands were usually intact and usually had swollen epithelia made up of cells

1 The Upjohn Company, Kalamazoo, Mich.
TUMOROUS CONDITIONS IN PITUITARY GLANDS

The pituitary glands from the various mice of this investigation were classified after histological examination as being normal, as exhibiting thyroidectomy changes, as having a microtumor (or microtumors), or as having a gross tumor. We have used the term "thyroidectomy change" as described by Halmi and Gude (13) to stipulate the presence of large, pale cells ("thyroidectomy cells") among the closely associated acidophils which make up the greater part of the normal gland (Fig. 13). These large cells have nuclei 2-4 times as large as those of the acidophils and, in animals showing the thyroidectomy change, are usually distributed fairly uniformly throughout the adenohypophysis. A discrete nodular collection of these cells is referred to as a microtumor or a microadenoma (Fig. 14). Gross tumors are those which cause marked enlargement (2 or more times normal size) of a part of or the whole anterior pituitary gland with distortion of its shape (Fig. 15). The cytological characteristics of these tumors and changes associated with their development have been described most recently by Halmi and Gude (15).

RELATION OF CERTAIN VARIABLE FACTORS TO THE DEVELOPMENT OF PITUITARY TUMORS

The experiments under discussion were not designed for proper comparison of tumorous conditions at various times subsequent to thyroid injury. Such a comparison would have been possible had subgroups of animals been killed after equivalent intervals of time following surgical or radiological damage to the thyroid gland. Yet, perusal of the data in Table 1 produces some indication

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Fig. 5.—Electron micrograph of a section of Novikoff tumor, ×30,000. This illustrates a small area of cytoplasm, and it shows the prominent cristae of the mitochondria and the irregular cell membrane characteristic of these liver tumor cells in areas where they are separated from one another. The insert represents a magnification of 86,000 and shows clearly the double nature of the transverse membranes (cristae) of the mitochondria, and also that they represent folds of the inner layer of the double limiting membrane which surrounds each mitochondrion. Vesicles and granules of the ergastoplasm are also demonstrated to advantage.
FIG. 6.—Electron micrograph of a section of Novikoff tumor, ×30,000. A little of the nucleus of a cell shows above; the remainder of the field is cytoplasm. This figure illustrates the prominent and branching cristae of the mitochondria to advantage. It also illustrates degenerating mitochondria. A large one is to be seen at the right, middle. The insert represents a magnification of 51,000 and shows the granular material present in a degenerating mitochondrion, the double limiting membrane of which can still be seen.
Figs. 7 and 8.—Electron micrographs of sections of liver tumor 124, X14,000. These figures illustrate the high nuclear-cytoplasmic ratio of the cells, their scanty mitochondrial contents, and the few organized ergastoplasmic structures in their cytoplasm. At the upper right corner of Figure 8, a portion of a cell with abundant organized ergastoplasmic structures can be seen; this may not be part of a tumor cell, for this was a very unusual appearance in this material.
that, following thyroid depression, there tends to be an increase in the incidence of tumors with increase in time.

Although some of the female mice receiving 25 μc. of I^{131} developed tumors within about 13 months after injection, the male mice of that group had developed none after 19 months. Likewise, at the 50-μc. level, female mice were consistently found to harbor gross tumors, although the incidence of tumors was only about 50 per cent among the males.

In general, an increase in the amount of radioactive iodine injected is accompanied by an increase in tumor incidence and also, within limits, by a decrease in the period of time required for tumor development. Although the time factor is again largely obscured by the design of the experiments, the damage done to the thyroid by surgery appears to have been about as effective in tumor induction as the injection of 50 μc. of I^{131} (Table 1).

In an attempt to correlate the degree of damage done to the thyroid with the response in the hypophysis, a survey was made of the sectioned thyroid and pituitary glands from nineteen male mice which had been injected with 50 μc. of I^{131} and maintained for 377 days before they were killed. All animals were killed on the same day. The results of this survey, recorded in Table 2, indicate that there is a direct relation between thyroid damage and the extent of tumorigenesis in the pituitary.

### Conditioning of Hosts for Growth of Dependent Tumors by Surgical Removal of the Major Portion of the Thyroid

Six each of surgically thyroidectomized, radiothyroidectomized, and control mice were given implants of small pieces of a tumor which had previously been found to grow only in radiothyroidectomized hosts (5). These animals were killed approximately 4 months following tumor implantation, except for four which died of pneumonia a few days earlier. The grafts grew in all experiments.

<table>
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<tr>
<th>Damage to Thyroid Gland</th>
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<th>Thyroditectomy Cells</th>
<th>Microtumor</th>
<th>Gross Tumor</th>
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<td>2</td>
<td>1</td>
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<tr>
<td>Fibrosis general; follicles undamaged</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>6</td>
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<tr>
<td>Fibrosis general; central follicles atretic</td>
<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Fibrosis extensive; most follicles atretic</td>
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DISCUSSION

The production of pituitary tumors after surgical thyroidectomy in this investigation and after prolonged treatment with propyl thiouracil in the investigation of Moore, Brackney, and Bock (15) appears to establish the thesis that radiation is not an essential factor in pituitary tumor induction. While it is true that most of our surgically thyroidectomized animals received very small amounts (5-9 μc.) of I^{131}, these doses are far below the 25-μc. level which is apparently minimal for tumor induction in normal mice. Also, pretumorous changes and one microtumor were found in surgically thyroidectomized mice which received no I^{131} but were implanted with pieces of dependent tumor. Further, two microtumors were found in surgically thyroidectomized mice (from another investigation) which had received neither I^{131} nor tumor implants. It is puzzling that pituitary tumors were not found among the mice treated by Gorbman (8) with 0.1 per cent thiouracil for 400 days or those treated by Dalton, Morris, and Dubnik (2) with 0.375-0.5 per cent thiouracil for 404-540 days. Probably, Moore, Brackney, and Bock (15) obtained tumors because they used the more potent propyl thiouracil in greater concentration (0.8 per cent).

Surgical depression of the thyroid has also been shown here to be as effective as radiological depression in the conditioning of hosts for bearing grafts of a dependent pituitary tumor. The implanted tumor, which produces TSH, did not protect the pituitary gland of the surgically thyroidectomized host against tumorous changes. In fact,
some indication that the appearance of these changes in the host's pituitary is hastened by the implantation of pieces of tumor was seen. This obtains also for radiothyroidectomized hosts (4).

Several factors appear to be involved in the mechanism of pituitary tumor induction, a primary factor being, obviously, the depression of the thyroid gland. Development of tumors in surgically treated mice retaining thyroid remnants and in mice receiving low (25- and 50-μc.) doses of I131 makes it clear that complete destruction of the thyroid is not necessary. The precise level of thyroid function required to prevent tumor formation remains to be ascertained, although Goldberg and Chaikoff (6) have demonstrated that feeding of desiccated thyroid to radiothyroidectomized mice protects them against pituitary tumor formation, and Gorbman (10) achieved the same end by implantation of thyroid glands and by injection of thyroxin.

A long latent period follows the depression of thyroid activity and precedes tumor formation. Some indication that the length of this latent period varies inversely with the extent of thyroid depression was seen, but the information necessary to express this relation in quantitative terms was not obtained.

The data shown in Table 1 indicate either that the pituitary glands of male mice are less susceptible to tumor induction than those of female mice or that thyroid damage is greater in the female for a given dose of I131. Some reported findings appear to disclose a relation between the pituitary tumors under discussion and the gonads or gonadal secretion. Gorbman (7) observed vaginal cornification, enlargement of mammary glands and uteri, and loosening of the pubic symphysis in female mice bearing tumors. Furth, Gadsden, and Burnett (5) found morphological evidence of gonadal stimulation in both sexes, notably in females bearing large grafted pituitary tumors, and Dr. Evelyn Anderson and associates (personal communication) have concluded that, since hypophysectomy of the host did not abolish this effect, these tumors secrete, in addition to large quantities of thyrotrophic hormone, very small quantities of gonadotrophic. However, attempts to demonstrate gonad-stimulating hormones in these tumors have met with failure, and Gorbman (7, 10) has found that neither gonadectomy nor ovarian implantation affects tumor induction. Thus, there is little sound knowledge upon which to base speculations regarding sex variation in susceptibility to pituitary tumor induction, and such speculation has not been attempted.

Although radiation is not essential to the development of tumors in the adenohypophysis, it is conceivable that, when that gland is irradiated, its cells become more competent for tumor induction. This view is supported in general by a large body of literature on the carcinogenic effects of radiation.

It is well known that the thyroid-destructive dose for mice is approximately 200 μc. of I131 following maintenance on a usual laboratory diet containing moderate amounts of iodine (9, 3), but the damage done to the thyroid by lower doses of radioiodine has received relatively little attention. Gorbman (8) states that doses of 10 and 50 μc. of I131 produced no changes in the pituitaries of his mice, but he did not describe the histology of their thyroids. It is of considerable interest that thyroids of mice receiving 25 μc. of I131 in the present study not only showed marked histological changes but also physiological changes great enough to induce tumors in female mice. Perhaps most of the mice of Gorbman's series were males or were not maintained long enough for tumor induction.

At the thyroid-destructive dosage of I131, Gorbman (9) found surviving bits of thyroid which functioned subnormally but which did not show growth or change in form. Partial survival of the thyroid was observed at each of the dose levels of

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Fig. 1.—Thyroid remnant in a surgically treated male mouse which received no I131 and which was implanted with a particle of a dependent tumor. Killed 157 days after subtotal thyroidectomy. The host pituitary showed thyroidectomy cells but no tumor. Note that the follicles appear to be somewhat stimulated and that the surrounding tissues are compressed, indicating that the remnant increased in size after the operation. X125.

Fig. 2.—Two residual pieces of thyroid gland left after surgical removal of most of the gland from a female mouse which received 5.8 μc. of I131 15 days after surgery. Died 409 days after surgery. Microtumors were found in its pituitary gland. The remnant in the lower part of the photograph is near normal, whereas the one in the upper part is adenomatous. X125.

Fig. 3.—Residual portion of thyroid lying between two pieces of parathyroid tissue in a female mouse which received 7 μc. of I131 30 days after surgery. Died 437 days after surgery. X55.

Fig. 4.—Thyroid region of a male mouse which received 25 μc. of I131. Killed 577 days after injection of I131. The pituitary was near normal. The follicles are fairly normal, but some fibrosis is seen particularly in the central regions of both lobes of the gland. X55.
FIG. 5.—Thyroid tissue from a female mouse injected with 25 μc. of I131 and killed 541 days postinjection. Microtumors were found in the pituitary. Extensive deposition of hyaline material is seen surrounding the irregularly shaped follicles with swollen epithelia. X200.

FIG. 6.—PAS-stained thyroid tissue of a female mouse injected with 25 μc. of I131 and killed 543 days postinjection. Pituitary near normal. This high-power photograph demonstrates the presence of intracellular droplets of colloid in the epithelial cells. X535.

FIG. 7.—Thyroid region of a female mouse injected with 25 μc. of I131 and killed 541 days later. Microtumors were present in the pituitary. Here is shown the maximal fibrosis and follicular breakdown found among mice injected with 25 μc. of I131. X75.

FIG. 8.—Adenomatous thyroid tissue from a male mouse injected with 50 μc. of I131 and killed 577 days thereafter. X75.

FIG. 9.—Opposing thyroid lobe of the animal shown in Figure 8. Note that, whereas about half of this lobe is markedly adenomatous, the remainder approaches a highly stimulated normal condition. X120.
Fig. 10.—Thyroid region of a 22-month-old normal female C57BL mouse showing marked senility changes. ×75.

Fig. 11.—High-power view of a part of the section shown in Figure 10. ×190.

Fig. 12.—Thyroid section from another 22-month-old normal C57BL female mouse. Here milder senility changes are demonstrated. ×75.
FIG. 13.—Anterior pituitary section from a male mouse implanted with a dependent pituitary tumor and killed 122 days after subtotal surgical thyroidectomy. Note the presence of multifocal microtumors in early stages of development. ×50.

FIG. 14.—Enlarged view of part of another section from the same gland showing large pretumorous cells in detail. ×300.

FIG. 15.—Pituitary tumor tissue from the mouse whose thyroid is shown in Figure 3. ×300.
this study; but at the 50-μc. level many, and at the 100-μc. level some, of these remnants (in male but not female mice) underwent distinct adenomatous hyperplasia. Thyroid remnants left after surgical treatment also were seen to have undergone hyperplastic change with some regulation in form and, possibly, some regeneration (Figs. 1 and 2).

Andrew and Andrew (1) described a type of involution of the thyroid gland which they attribute to senility. These authors examined three groups of mice which they classified as young (41–50 days old), middle-aged (362–381 days old), and senile (586–719 days old). The thyroids of the senile group contained distended and atrophic follicles and enormous amounts of interfollicular connective tissue. Our observations confirm those of Andrew and Andrew with regard to C57BL mice but indicate that the changes they describe are extremely rare in old animals of the LAFl and RF strains.

The deposition of interfollicular hyaline material seen in the thyroids of animals injected with 25 μc. of I131 was similar to that resulting from aging alone. However, the amount of fibrous substance was in general much greater in the radiiodine-treated animals than in control animals of equivalent age, and, whereas the follicular epithelium of the former were swollen, those of the latter were quite thin.

SUMMARY

1. Histological observations have been made on the pituitary glands and thyroid regions of C57BL mice at various periods of time following (a) near-complete thyroidectomy by surgical means, (b) near-complete surgical thyroidectomy and subsequent grafting of pieces of dependent thyrotrophin pituitary tumor, and (c) injection of I131 in doses of 25, 50, 100, and 200 μc. Thyroid glands from senile LAFl, RF, and C57BL mice have been examined.

2. Evidence has been presented in support of the view that radiation is not an essential factor in the development of pituitary tumors.

3. Near-complete surgical thyroidectomy has been shown to be as effective as radiiodine depression of the thyroid in conditioning hosts for bearing grafts of dependent pituitary tumors.

4. Pituitary tumors have been found to develop following doses of 50 μc. of I131 in male mice and 25 μc. of I131 in female mice, both maintained on normal laboratory diet.

5. Thyroid remnants in surgically thyroidectomized mice of both sexes and in male mice which had received 50 and 100 μc. of I131 were seen to have undergone adenomatoid hyperplasia.

6. Senility changes have been observed in the thyroids of 2-year-old C57BL mice but have been found to be extremely rare in 2- to 3-year-old mice of LAFl and RF strains.

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