Formation of Adenomata in Hypophyses of Rats Subjected to both Subtotal Thyroidectomy and Administration of $^{131}$I, and its Prevention by Feeding of Desiccated Thyroid

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SUMMARY

The tumorigenic effect of subtotal thyroidectomy on the pituitary was studied in 212 Long-Evans female rats. Of the 133 pituitaries that contained adenomata after 2 years, 76% were of the thyrotropic cell type. This finding confirms earlier work on the effect of long-term thyroxine deficiency.

The feeding of desiccated thyroid reduced the percentages of thyrotropic cell adenomata from a mean of 60 to a mean of 33. Thyroid feeding reduced the percentages of all adenomata from a mean of 72 to a mean of 53.

A single administration of 1 μc of $^{131}$I did not increase the number of, or tendency towards, anaplastic changes in pituitary adenomata of subtotaly thyroidectomized rats fed a stock diet. The same dose of $^{131}$I did not increase the incidence of pituitary adenomata in unoperated animals fed either the stock diet or the stock diet supplemented with desiccated thyroid. Two rats that developed malignant thyroid carcinomata after receiving 1 μc of $^{131}$I did not show cell changes or adenomata in the pituitary. The absence of cytologic signs of thyroxine deficiency in the pituitary cells of these rats supports the view that irradiation per se might well have been the cause of the neoplasms found in their thyroid glands.

The pituitary adenomata found in 124 unoperated rats, treated in the same way as the subtotaly thyroidectomized groups with respect to $^{131}$I dosage and thyroid feeding, closely resembled those found in the normal control group in number as well as in cell type.

It has been known for almost 2 decades that hyperplasia as well as benign and malignant neoplasms develop in thyroid glands of mice and rats in which, for prolonged periods, a state of thyroxine deficiency has been established by any one of the following means: the feeding of a low-iodine diet (1, 2); the administration of anti-thyroid substances (5, 15, 25); irradiation of the gland by $^{131}$I, astatine ($^{211}$At), or X-rays (7, 12, 14, 19); and subtotal thyroidectomy (6, 14). There is good evidence for the belief that the neoplastic changes should be attributed to the hyperplasia of thyrotropic hormone (TSH)–producing cells in the anterior pituitary glands of the animals suffering from long-term thyroxine deficiency. Assays of TSH contents of the hypophysis and blood, as well as cytologic study of the TSH-producing cells in the pituitary, lend support to this interpretation. The literature dealing with this subject has been reviewed by Bielschowsky (2) and Bielschowsky and Horning (3).

A matter of some interest as well as practical importance arose in the case of experiments in which irradiation was applied to the rodents' thyroid gland, either alone or in combination with chemical or surgical means, for inducing the thyroxine deficiency. In most cases, especially in the early work with large doses of $^{131}$I (up to 875 μc), the irradiation had been sufficiently strong to destroy much or all of the thyroid tissue (11, 12). In later experiments the $^{131}$I was given in a considerably reduced dose (25–40 μc). It was shown that hereby the number of experimentally induced malignant thyroid neoplasms was definitely higher (22). It could further be seen that hyperplasia of the thyroid epithelium surrounding the neoplasms was a constant feature of these glands. It was assumed that this was significant for the strong and permanent action of thyrotropic hormone. No signs of radiation damage were found. The question whether irradiation per se can induce thyroid tumors was discussed in another study in which either both lobes or a single lobe of the thyroid gland had...
TABLE 1
ADENOMATA IN PITUITARIES OF INTACT FEMALE RATS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
<th>NO. OF RATS EXAMINED</th>
<th>PITUITARIES WITH ADENOMATA</th>
<th>CYTOLOGIC CLASSIFICATION OF ADENOMATA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>%</td>
</tr>
<tr>
<td>I</td>
<td>None</td>
<td>47</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>VI</td>
<td>1 μc ¹³¹I injected</td>
<td>34</td>
<td>10</td>
<td>29</td>
</tr>
<tr>
<td>VII</td>
<td>Desiccated thyroid in diet</td>
<td>57</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>VIII</td>
<td>1 μc ¹³¹I plus desiccated thyroid in diet</td>
<td>33</td>
<td>17</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>171</td>
<td>71</td>
<td>42</td>
</tr>
</tbody>
</table>

TABLE 2
ADENOMATA IN PITUITARIES OF SUBTOTALLY THYROIDECTOMIZED FEMALE RATS

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
<th>NO. OF RATS EXAMINED</th>
<th>PITUITARIES WITH ADENOMATA</th>
<th>CYTOLOGIC CLASSIFICATION OF ADENOMATA</th>
<th>NO. OF ADENOMATA CLASSIFIED</th>
<th>ANAPLASTIC CHANGES IN:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>%</td>
<td>Thyrotrophs</td>
<td>Gonadotrophs</td>
</tr>
<tr>
<td>II</td>
<td>Subtotal thyroidectomy only</td>
<td>67</td>
<td>42</td>
<td>63</td>
<td>36 (86%)</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>Subtotal thyroidectomy plus 1 μc ¹³¹I injected</td>
<td>49</td>
<td>40</td>
<td>82</td>
<td>33 (83%)</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>Subtotal thyroidectomy, 1 μc ¹³¹I injected plus desiccated thyroid fed</td>
<td>60</td>
<td>32</td>
<td>53</td>
<td>22 (69%)</td>
<td>3</td>
</tr>
<tr>
<td>V</td>
<td>Subtotal thyroidectomy plus desiccated thyroid fed</td>
<td>36</td>
<td>19</td>
<td>53</td>
<td>10 (53%)</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>212</td>
<td>133</td>
<td>63</td>
<td>101 (76%)</td>
<td>12 (9%)</td>
</tr>
</tbody>
</table>

been irradiated (21). There, most of the carcinomata were found in rats in which both lobes had been irradiated, but 2 carcinomata also appeared in singly-irradiated lobes and 1 in an opposite, shielded lobe. Hence, it could not be decided whether thyroid carcinogenesis resulted from prolonged TSH stimulation or was a direct consequence of the irradiation. In a more recent paper, Goldberg et al. (14) reported finding a papillary and a follicular carcinoma in intact thyroid glands of rats that received but a single μc of ¹³¹I. The present report deals with the 383 pituitaries excised from the rats whose thyroids had been described in this latter study (14). In these pituitaries, many adenomata were found; they are described in detail, particularly with regard to the hormonal conditions that may have influenced their development.

MATERIALS AND METHODS

A total of 876 female, Long-Evans rats were randomly selected at 5-6 weeks of age, divided into 8 groups, and treated as shown in Tables 1 and 2. After weaning, all rats were maintained on a nutritionally adequate diet (Diablo Double-Check Labration) containing 3 μg of iodine/gm (20).

Subtotal thyroidectomy was performed under light ether anesthesia. Both lateral lobes of the thyroid were removed, leaving only the isthmus, which weighed about 0.1 mg. One week later, each rat of certain groups (Tables 1 and 2) received by i.p. injection 1 μc of carrier-free ¹³¹I in 0.1 ml of normal saline. Twenty-four hr later the isthmus contained about 2% of the radioactivity.

One week after either the subtotal thyroidectomy or ¹³¹I injection, feeding of the thyroid-supplemented diet was begun. The diet was prepared by adding desiccated thyroid powder (Lilly Thyroid, U.S.P., No. 58) to the stock diet to yield a concentration of 250 μg/kg. It was shown in a separate experiment that the uptake of ¹³¹I by the thyroid glands of the rats fed this diet was almost completely suppressed.

The rats were maintained for 2 years, and the survivors were killed with ether. Those that failed to survive for the 2 years usually died of chronic respiratory disease, and autopsies were not performed on all of these animals.

The thyroid glands of the rats of Groups I and VI-VIII were excised and weighed. In all other rats, the tracheas along with the paratracheal tissues were removed en bloc and fixed in 10% neutral formalin. The pituitary glands were removed and fixed in sublimate-formol (9:1, v/v). These glands were sectioned at 2.5 and 5 μm, and sections from each were mounted on 4 slides, with equal distribution onto each slide of the material cut at various depths of the block. They were treated as follows: Slides 1 and 2 with periodic acid-Schiff (PAS) stain and PAS stain in combination with Orange G-phosphotungstic acid (PTA), respectively; Slide 3 with aldehyde fuchsin (AF) usually followed by Orange G-PTA, without previous oxidation.

We are indebted to Dr. G. La Roche for this determination.

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with permanganate; and Slide 4 with the rapid Mallory stain of Churg and Prado (4). The last is well suited for counterstaining AF-stained tissues.

RESULTS

GENERAL REMARKS

Considerable numbers of adenomata were found in the anterior hypophyses of both unoperated (Table 1) and subtotally thyroidecomized (Table 2) rats. Such pituitary neoplasms were seen in 71, or 42%, of the unoperated animals and in 133, or 63%, of the operated ones. A cytologic examination revealed, however, that the adenomata were constituted of quite different cell types in these 2 major groups of rats. In the unoperated rats, the chro-

mophobe cell type of adenoma predominated; its incidence here was 29%, as compared with 12% in the operated rats. On the other hand, nearly half of the operated rats—101, or 48%—had adenomata composed principally of thyro-

trophs; the corresponding figure for the unoperated rat was 9, or 5%. Thus, subtotal thyroidectomy induced an almost 10-fold increase in thyrotrhoph adenomata and at the same time reduced the incidence of chromophobe adenomata 2.5-fold. There was no significant difference between the numbers of gonadotroph adenomata in un-

operated and operated groups (see "Histology").

EFFECT OF THYROID FEEDING ON INCIDENCE

OF ADENOMATA

No effect of thyroid feeding on the general pituitary cell picture of the unoperated rats was detected. The presence of a large number of acidophil cells was obvious and was to be expected in the anterior pituitary of normal rats fed the desiccated thyroid-containing diet continu-

ously.

The number of acidophil cells in the pituitary glands of the subtotally thyroidecomized rats fed the normal diet was quite low. The addition of desiccated thyroid to the diet of the rats changed the acidophil cell picture to normal.

The number of thyrotrhoph adenomata in Groups II and III (fed the stock diet) was 69, or 60%. Under the in-

fluence of thyroid feeding, the number of thyrotrhoph adenomata in Groups IV and V fell to 32, or 33%.

The number of gonadotroph adenomata was not changed by thyroid feeding, but that of chromophobe adenomata was increased—29%, as compared to 12% in rats fed the stock diet.

EFFECTS OF I31I ADMINISTRATION

In Groups VI and VIII (unoperated rats, Table 1), in which the majority of adenomata were of the chromophobe cell type, no significant effect of the I31I injection was de-

tected. Among the subtotally thyroidecomized rats, Groups III and IV, comprising 109 animals (Table 2), re-

ceived 131I, whereas Groups II and V (103 animals) received no 131I. Groups IV and V (96 rats) were fed the desiccated thyroid-containing diet. The incidence of thyrotrhoph cell adenomata was not significantly altered in Group III by the I31I administration as compared with Group II, which received no 131I. Of all adenomata found in Group III, 83% were thyrotrhoph cell adenomata. The corresponding figure for Group II was 86%. In the thyroid-fed rats, the higher percentage (69%) of all adenomata belonged to Group IV (I31I-injected). Group V (I31I not injected) contained the lower percentage of 53%. Anaplasia was found more frequently in the adenomata of the rats fed the stock diet than in those of rats fed the desiccated thyroid-containing diet—21% versus 13% (Table 2).

The 2 unoperated rats in which Goldberg et al. (14) found malignant thyroid neoplasms following the administration of 1 μc of I31I did not show pituitary adenomata or any deviation from the normal cell picture in their anterior pituitary glands (Table 3).

HISTOLOGY OF NEOPLASMS FOUND IN ANTERIOR PITUITARY GLANDS

Neoplasms were found in the pituitaries of all 8 groups of rats. These neoplasms contained primarily 1 type of cell, and each neoplasm was therefore classified according to its main cell type. Difficulties in classification arose in a few cases because of anaplastic areas in some of the neo-

plasms.

Chromophobe cell adenomata.—These were found in 30% of the anterior pituitaries of all unoperated rats and in 12%
of all thyroidectomized rats at the end of 2 years. They were composed of small cells that did not contain stainable granules. In many neoplasms of this type, the cells had a follicular arrangement. The follicles were filled with blood. Grossly visible hemorrhages were often found; these, in combination with rapid growth (mitoses), compressed the surrounding areas of otherwise intact pituitary tissue. Almost regularly, macrophages containing hemosiderin (clasmatoocytes) were seen in the chromophobe adenomata, and these macrophages were stained with PAS. So typical were the hemosiderin-containing cells that this type of adenoma was easily recognized in unstained sections by the presence of brown pigment (27).

Thyrotroph and thyroidectomy cell ("T"-granulated cell) adenomata.—Neoplasms composed of thyrotrophs were found in 9 pituitaries of the unoperated rats (5 %) and in 101 pituitaries of the thyroidectomized groups (48 %). In the former, the neoplasms were small and never anaplastic. The thyrotroph cells, which were multangular and irregular, sometimes bizarre, in shape, stained well with aldehyde fuchsins; the sections had not been previously oxidized by permanganate (Figs. 1–3, 11). The intensity of staining was not constant throughout the adenoma (Fig. 10), probably because the degree of granulation in the cells varied.

The pleomorphic cells of partially anaplastic neoplasms often contained aldehyde fuchsins-positive granules (Figs. 7, 8). Such neoplasms occasionally contained large hypertrophic cells with mitoses of unusual size (Fig. 17). The type of thyrotroph adenoma most frequently encountered, however, contained relatively uniform, tightly packed cells that stained intensely with aldehyde fuchsins and had vesicular, round or oval nuclei with 1 nucleolus (Figs. 4, 5, 14).

The adenomata varied greatly in size and shape. Usually they were multiple, and as many as 6 discrete foci have been noted in a single gland. Since these would not be expected to grow at the same rate or to possess identical degrees of neoplastic change, it is not surprising that quite different structures were seen in a single pituitary or even in a single adenoma (Figs. 5–8). The presence in such growths of aldehyde fuchsins stained cells having the angular shape characteristic of thyrotrhop simplified the differential diagnosis of such neoplastic alterations (Figs. 12, 15, 18). The area in the anterior lobe with the highest incidence of thyrotroph adenomata was the posterior edge near the pars intermedia.

The pituitaries of the subtotaly thyroidectomized rats contained a large number of hyalinized basophilic cells, the so-called thyroidectomcy cells, which are known to be thyrotrhophs that were transformed during the state of thyroxine deficiency. According to Purves and Griesbach (24), such cells, found in the pituitaries of rats in which thyroxine deficiency has been established for at least 2 weeks, contain coarse PAS-stainable granules ("T" granules) that differ from normal thyrotrhopic granules in being insoluble in water and not implicated apparently in thyrotrhopic hormone production. "T"-granules may also be stained by intense aldehyde fuchsin treatment (24), especially after preoxidation with permanganate. Recently, it has been shown by Doniach and Williams (6) that "T"-granulated cells can form adenomata. In the present study we found, in nearly 50 % of adenomata, "T"-granulated cell nodules adjacent to typical thyrotrhop adenomata in a single pituitary gland. The fact that the "T" granules seen here always stained with AF helped avoid confusion with the gonadotrophs (Fig. 13; see also Ref. 24).

Fully hyalinized cell areas were found in 14 % of the pituitaries with thyrotrhop adenomata. Such hyalinized cells resembled "thyrotrhopcy" cells and sometimes formed large parts of the neoplasms. Even mitoses were found among them (Fig. 9; see Ref. 18).

Gonadotroph adenomata.—The number of gonadotroph adenomata was small and was not affected by subtotal thyroidectomy. The cell type was the pale central variety (luteinizing hormone) described by Purves and Griesbach (17, 23). These cells are round or oval and have dark-red-stained Golgi areas near the nuclei, surrounded by pale cytoplasm (after PAS). Rapidly growing neoplasms of this type with many mitoses and compression of the neighboring area were noted (Fig. 16). In contrast to the thyrotrhop adenoma, the gonadotroph adenoma always preserved its acinar structure and manifested strongly PAS-positive vascular membranes. This helped to differentiate the 2 adenoma types, even at low magnification.

**DISCUSSION**

**GENERAL CONSIDERATIONS**

This paper deals with the cytology of the anterior hypophyses of the rats used in the experiments of Goldberg et al. (14). A large number of pituitary adenomata were found in these rats and were classified according to their morphologic appearance as thyrotrhop, gonadotrophic, or chromophobe. Their size was small, measuring 1–2 mm in diameter, and they could not be separated from the surrounding pituitary tissue even when their presence was known before autopsy. This fact prevented an assay of the neoplastic tissue for its hormone content by biologic means. The presence of thyrotrhopic cells in the adenomata therefore had to be based on their characteristic multangular form and their specific stainability with aldehyde fuchsins without previous oxidation of the section.

Goldberg et al. (14), 2 years after starting the experiments, found, in addition to many adenomata, 5 carcinomata in the thyroid glands of their rats. One papillary and 1 follicular carcinoma developed in the intact thyroids of rats that received only 1 μc of 131I, and it was believed possible that these neoplasms were induced solely by the radiation. A single papillary carcinoma developed in a rat that had been subjected to subtotal thyroidectomy, given an injection of 1 μc 131I, and fed the desiccated thyroid-containing diet. The question arose whether the tumor-producing mechanism could be deduced from a study of the pituitary glands (Table 3).

It is now widely acknowledged that enhanced and prolonged thyrotrhop secretion from the pituitary gland may provoke hyperplasia of thyroid cells, adenoma formation in the thyroid gland, and provided a state of thyroxine deficiency is established for a prolonged period, even carcinogenesis of the thyroid gland (1, 2, 6, 25).
creased thyrotropin secretion is manifested in the pituitary by greater numbers of thyrotropin-secreting cells (thyrotrrophs) and by the appearance of thyroidectomy cells. It would, therefore, have been of interest if this had happened in the pituitaries of the 2 rats bearing careinomata in their otherwise intact thyroid glands. This was not the case, however. The dose of $^{131}I$ administered was too small to have been destructive to the rats' thyroid glands, and this accounts for the absence of thyrotroph hyperplasia and adenoma formation in their hypophyses. We found no evidence that the injected $^{131}I$ increased the effect of subtotal thyroidectomy on the pituitaries (see Groups II and III). The numbers of pituitary adenomata in these groups of operated rats, regardless of whether the thyroid glands were irradiated, were not significantly different. We therefore have no reason to believe that the administered $^{131}I$ had induced neoplastic changes in the pituitary cells.

**CONCERNING THE MECHANISM OF PITUITARY TUMOR INDUCTION**

Old rats of either sex have been shown to contain a large number of spontaneous pituitary adenomata (27). These vary from microscopic to grossly visible tumors, and they probably arise because of hormonal changes due to aging. Chromophobe adenomata were found in 30% of the pituitaries of the unoperated rats in the present study. In another paper for which the same rat strain (Long-Evans) was used, Van Dyke et al. found a similar incidence (26). Wolfe et al. (27) reported an occurrence of 29% and 68% of pituitary tumors in Vanderbilt and Wistar rats, respectively, and Griesbach and Purves (17), using a Wistar strain, found that of a total of 31% adenomata, 23% were of the chromophobe type.

Cramer and Horning (cited in Ref. 3) were the first to produce neoplastic lesions in the rat pituitary experimentally by the administration of estrogen. These neoplasms consisted of chromophobe cells and manifested a strong tendency to hemorrhage; they thus resembled the many chromophobe tumors reported in the present study. Deficiency of sex hormones, induced by gonadectomy in mice and some strains of rats, may also cause the development of chromophobe cum acidophil and of gonadotroph cell adenoma. Griesbach and Purves (17) reported that rats with such neoplasms secrete milk and that this is observed occasionally even in males.

**FIG. 1.—**Medium-sized adenoma (0.9 x 0.8 mm) situated at caudal edge of anterior lobe. Individual cells show varied intensity of staining. Group II, AF. X 400.

**FIG. 2.—**Higher magnification of Fig. 1, showing irregular cell shape and variety of content of AF-stained granula. Group II, AF. X 900.

**FIG. 3.—**TSH cell adenoma covering nearly half of the anterior lobe and reaching far onto the rostral edge towards portal vessels. Group II, AF. X 900.

**FIG. 4.—**The adenoma seen is one of several in this pituitary, and its cells are similar to typical TSH cells. Group III, AF. X 400.

**FIG. 5.—**This and Figs. 6-8 show the variety of cells in a single adenoma. Here are typical TSH cells with strong AF staining. Group II, AF. X 400.

**FIG. 6.—**Area of "T"-granulated cells, some hyalinized. Group II, AF. X 900.
Fig. 7, 8.—The same tumor shows more atypical cells stained with AF. Group II, AF. × 400.

Fig. 9.—Adenoma with area of hyalinized thyroidectomy cells. Mitoses near center. Group III, PAS. × 400.

Fig. 10.—TSH cell adenoma. Generally small cells varying greatly in shape and uptake of AF. Group III, AF. × 400.

Fig. 11.—TSH cell adenoma showing the "stretched out" appearance not infrequently seen. Group III, AF. × 150.

Fig. 12.—This pituitary contains adenomata, some with "T" granules and others, like the one depicted, with a tendency towards anaplasia. Group III, AF. × 400.
FIG. 13.—Higher magnification of “T”-granulated cells giving a good picture of the coarse granules. Group III, PAS. × 900.

Fig. 14.—Very large adenoma with uniformly small cells. Group IV, AF. × 400.

Fig. 15.—Large adenoma showing unusual arrangement of the TSH cells. Group III, PAS. × 400.

Fig. 16.—PAS-positive, AF-negative adenoma of “pale cells” with intensely PAS-stained Golgi bodies, unoperated, ¹³¹I treated. Group VI, PAS. × 900.

Fig. 17.—Adenoma with very large AF-positive and PAS-positive anaplastic cells, one showing a large mitotic figure. Group IV, PAS. × 900.

Fig. 18.—Anaplastic part of otherwise typical AF-positive TSH cell adenoma. The cells seen are not densely granulated. Golgi rings visible. Group III, PAS. × 900.
the same time by Gorbman (15) and by Furth and Burnett (9). The pituitary tumors produced by these workers were of unusual size and could be transplanted. In the earlier experiments, the hormone content of such tumors was mainly thyrotropic, but in later experiments adrenotropic, mammotropin, somatotropin, and mixed tumors were also discovered (7–10). These were rich sources of hormones. In the blood serum of mice with large tumors, the concentration of thyrotropin was approximately 2000 times the normal level. A number of publications by Furth and his associates on this subject have appeared (7, 8). Halmi and Gude have given an excellent description of the cytology of tumors induced by radiothyroidectomy (18).

A recent paper (28) on the induction of pituitary tumors in rats with astatine (211At) is interesting in this context. Although, as Hamilton et al. showed earlier (19), 211At, 0.3 μc per gm of body weight, destroys the thyroid gland of the rat, no TSH-pituitary tumors were found in spite of ample signs of thyroxine deficiency (thyrotroph hyperplasia) in the pituitary. The authors state that "radiothyroidectomy (in contrast to mice) does not elicit thyrotropic pituitary tumors in rats."

The Present Experiment with 1 μc of 131I

The thyroid glands of the 3 groups of unoperated rats (VI–VIII) described by Goldberg et al. (14) showed a histologic pattern similar to that of their control group (I). The suppression of thyroid activity in Groups VII and VIII by feeding the thyroid-containing diet was to be expected. In all 4 groups, including the control Group I, a certain number of alveolar or lobular thyroid carcinomas were found (24–36%), as previously described in normal Long-Evans rats (14, 20, 21). However, 1 papillary and 1 follicular carcinoma developed in the otherwise intact thyroid glands of rats that received only 1 μc of 131I. These malignant neoplasms were possibly induced by the 131I irradiation. A single papillary carcinoma was found in a subtotally thyroidectomized rat (Group IV) that had been given 1 μc of 131I in addition to the thyroid-containing diet. This neoplasm could have been the result of either prolonged thyrotropic hormone stimulation or 131I irradiation (14).

In the present paper, possible cytologic changes in the pituitaries have been chosen as indicators of thyroxine deficiency caused by inadequacy of thyroid function. Subtotal thyroidectomy in all instances provoked the appearance of such cytologic changes, but it was impossible to decide whether the changes had been aggravated by the administration of 131I (the number of thyrotropic cell adenomata in Groups II and III were not significantly different). On the other hand (Table 3), the absence of thyrotroph hyperplasia in the pituitaries of the irradiated unoperated rats is considered to prove that no thyroxine deficiency was present in these animals. The finding of 2 malignant thyroid neoplasms in rats treated with 1 μc of 131I (Groups VI and VIII) and showing no sign of pituitary thyrotropic cell stimulation lends support to the view that irradiation per se can be an exciting cause of carcinogenesis in the thyroid gland of the rat.

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Formation of Adenomata in Hypophyses of Rats Subjected to both Subtotal Thyroidectomy and Administration of $^{131}$I, and its Prevention by Feeding of Desiccated Thyroid

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