Thyroid Neoplasms in the Rat: A Comparison of Naturally Occurring and $^{131}I$-induced Tumors*

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The widespread use of $^{131}I$ in the diagnosis and treatment of thyroid disease in man has focused attention on the effects of this radioactive isotope in experimental animals. In 1951, Goldberg and Chaikoff described the development of benign and malignant thyroid tumors in Long-Evans rats 1.5–2 years after the animals had received single injections of 400 $\mu$C. $^{131}I$ (7, 8). Doniach also found benign and malignant thyroid neoplasms in rats treated with $^{131}I$ alone or in combination with methyl thiouracil and acetylaminofluorene (3, 4). In a recent report (6), on the other hand, neoplasms were not observed in rats that had been given injections of $^{131}I$.

An extensive study of benign and malignant thyroid tumors induced, in the rat, with radioiodine is presented here. This report is based on examination of 198 Long-Evans rats, 1.5–3 years following a single injection of $^{131}I$. One hundred fifty-six rats of the same age served as controls. The production of malignant thyroid tumors in the Long-Evans rat by means of $^{131}I$ injections is confirmed. A high incidence of spontaneous carcinoma of the thyroid gland was noted, but these naturally occurring lesions are cytologically and histologically unlike the malignant lesions induced by $^{131}I$.

MATERIALS AND METHODS

A total of 550 Long-Evans rats, age 6–12 weeks, and raised in this laboratory, was given injections of varying amounts of carrier-free $^{131}I$; 385 served as controls. Two diets were used in these experiments, Purina Laboratory Chow and diet No. 1 (8). Of the total, 354 rats survived for 18–36 months after the $^{131}I$ injection. The remainder died of chronic respiratory disease. The surviving rats were anesthetized with ether or nembutal, and exsanguinated. The thyroid glands were removed with the tracheae and adjacent tissues and were fixed in 10 per cent neutral formalin for histological examination. A number of the thyroid glands and attached tracheae were sectioned serially at 7 $\mu$. Others were separated from the trachea after fixation, and representative sections were made. All sections were stained with hematoxylin and eosin. Selected sections were treated with the Laidlaw and Van Gieson connective tissue stains. Representative samples of other tissues were sectioned and stained in a similar manner.

RESULTS

GROSS DESCRIPTION

The irradiated thyroid glands were, as a rule, smaller than those of the control group. The smallest were found in rats that had received 200 $\mu$C. $^{131}I$. No thyroid tissue was visible grossly in most of the animals that had received 400 $\mu$C. Diffuse or nodular enlargement of one or both thyroid lobes was observed in a number of animals. The enlarged lobes often had lobulated surfaces and were deep pink and congested. Some were firm and pale, and a few glands adhered to the tracheae and surrounding muscle (Figs. 1–8).

MICROSCOPIC DESCRIPTION

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served. Some nuclei were large, vacuolated, and appeared degenerated, and the cytoplasm was often vacuolated (Fig. 4). Mitoses were absent. Residual thyroid tissue was not found in 46 of the 146 animals that had received 400 $\mu$c. Fibrinoid degeneration and perivascular inflammation of medium-sized and large thyroid vessels were the only vascular lesions observed, and these were found in animals injected with 400 $\mu$c. $^{131}I$. Minimal cellular atrophy and fibrosis were noted in the parathyroid glands of animals that had been given injections of larger doses of $^{131}I$. A chief cell parathyroid adenoma was found in one rat given injections of 100 $\mu$c. $^{131}I$.

**Occurrence of alveolar carcinomas in thyroid glands of normal and $^{131}I$-injected rats.**—The thyroid glands of 59 of the 354 rats that survived had neoplastic lesions designated here as alveolar carcinomas. The incidence of these carcinomas was approximately the same in both the control rats and those that received 10 or 25 $\mu$c. $^{131}I$ (Table 1). The thyroid glands of two rats given injections of 200 $\mu$c., which contained alveolar carcinomas, showed only minimal evidences of radiation injury. A gland of the 400-$\mu$c. group, which contained an alveolar carcinoma, displayed radiation injury comparable to that of the 100-$\mu$c. group.

The earliest lesions consisted of neoplastic epithelial cells that filled either a single follicle or a small, localized group of thyroid follicles. These follicles were devoid of colloid, and the normal lining epithelial cells were absent. The neoplastic cells were large and stellate and had a loose reticular arrangement (Fig. 5). The nuclei were pleomorphic and, as a rule, contained prominent nucleoli and a coarse chromatin network. The cytoplasm was granular, eosinophilic, and vacuolated. Some nuclei were condensed and hyperchromatic, but in the earliest lesions mitoses were not observed. These neoplasms were usually single, but in a few glands multiple lesions, apparently of multicentric origin, were found in one or both lobes. The majority of the neoplasms were at some distance from the ultimibranchial bodies within these thyroid glands, although some were found immediately adjacent to these structures (Fig. 6).

As those neoplasms enlarged peripherally, contiguous thyroid follicles became filled with neoplastic cells (Fig. 7) that, while smaller and more compactly arranged, still displayed a mild degree of pleomorphism. They had oval or elongated nuclei within which nucleoli and coarse chromatin particles were observed (Fig. 8). At this stage in

**TABLE 1**  
**INCIDENCE OF THYROID NEOPLASMS IN NORMAL LONG-EVANS RATS AND IN THOSE GIVEN INJECTIONS OF $^{131}I$**

<table>
<thead>
<tr>
<th>$^{131}I$ Injected ((\mu)c.)</th>
<th>Sex</th>
<th>Diet</th>
<th>No. Rats</th>
<th>Age When Sacrificed (months)</th>
<th>Alaevolar Carcinoma</th>
<th>Follicular Carcinoma</th>
<th>Papillifer Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Control)</td>
<td>F</td>
<td>Purina</td>
<td>9</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>M</td>
<td></td>
<td>31</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>M</td>
<td>Diet I</td>
<td>116</td>
<td>24-29</td>
<td>1*</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>Purina</td>
<td>6</td>
<td>32</td>
<td>5</td>
<td>52</td>
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<td>M</td>
<td></td>
<td>20</td>
<td>28</td>
<td>9</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>100</td>
<td>F</td>
<td></td>
<td>10</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>200</td>
<td>M</td>
<td></td>
<td>12</td>
<td>32</td>
<td>4</td>
<td>1†</td>
<td>8</td>
</tr>
<tr>
<td>300</td>
<td>M</td>
<td></td>
<td>5</td>
<td>32</td>
<td>0</td>
<td>1†</td>
<td>25</td>
</tr>
<tr>
<td>400</td>
<td>M</td>
<td>Diet I</td>
<td>121</td>
<td>24-29</td>
<td>2</td>
<td>1†</td>
<td>1</td>
</tr>
</tbody>
</table>

* Associated with ultimibranchial body.
† These glands showed minimal radiation damage.
‡ The gland of this rat had the same appearance as that of rats that had received 100 $\mu$c. $^{131}I$.

the development of the lesion, the original follicular walls were still intact. At the periphery of the lesions, however, perforations of follicular walls, with extension of the neoplastic cells into contiguous follicles, had occurred.

With further enlargement of the neoplasm, the original alveolar pattern was obliterated except at the periphery of the lesions where additional follicles were still being invaded. Some thyroid follicles in the central portions of the neoplasms escaped neoplastic invasion, and these follicles remained isolated in the surrounding neoplastic cells. In some neoplasms, a mild desmoplastic reaction appeared near a few follicles that were filled with neoplastic cells. In a few instances, invasion of neoplastic cells between thyroid follicles had occurred, but intrafollicular growth was the predominant feature.

Eventually, this neoplastic tissue almost completely replaced the thyroid parenchyma of one
lobe. Extensive bilateral lesions of this sort were rarely observed. Even though the neoplasm became large in later stages, it remained circumscribed and usually unencapsulated. In some cases stromal condensation limited growth. Growth was invariably limited either by the thyroid capsule or by the parathyroid capsule, although the residual peripheral thyroid parenchyma and parathyroid glands might be severely compressed. Even in the large, extensive lesions, the neoplastic cells were only mildly pleomorphic, and mitoses were rarely observed in them. In a number of moderate-sized or large neoplasms of this type, the neoplastic cells formed small thyroid follicles, some of which accumulated colloid. These follicles were easily distinguishable from the original thyroid follicles which had been isolated in the neoplasm (Fig. 9). Not a single instance of extrathyroid invasion or metastasis by this type of neoplasm has been observed.

**Occurrence of adenomas in the thyroid glands of I¹³¹-injected rats.**—Benign, circumscribed or unencapsulated nodules or adenomas were found in the thyroid glands of twenty of the irradiated animals (Table 1). These adenomas either occurred singly or were, in some instances, multiple in one or both lobes (Figs. 10–12). The earliest lesions consisted of one or more enlarged follicles lined, as a rule, by flattened, cuboidal, thyroid epithelial cells and filled with pale, vacuolated colloid (Fig. 13). As the nodules enlarged, epithelial hypertrophy occurred, followed by hyperplasia and some papillary infolding of the epithelium. These epithelial cells were uniform in size, and their oval nuclei lay near the adjacent basement membrane (Fig. 14). Further epithelial growth within the developing adenomas proceeded by means of follicular budding leading to the development of macrofollicular, microfollicular, or trabecular patterns (Figs. 15, 16). The smaller follicles in the adenomas contained little or no colloid, but the macrofollicles generally had a high colloid content. Some nodules, particularly those with a predominant macrofollicular pattern, contained large colloid cysts, some of which showed evidence of old and recent hemorrhage. When multiple nodules were present in one or both lobes their patterns varied, but a follicular pattern was predominant (Fig. 15).

The connective tissue stroma supporting the neoplastic epithelium was extremely delicate and revealed little vascularity. The interfollicular tissue of some follicular nodules was edematous. Continued growth of these adenomas in some instances finally obliterated the entire thyroid parenchyma, leaving narrow, compressed segments of thyroid tissue at either pole of the involved lobe (Fig. 11). The condensed stroma of the compressed thyroid parenchyma formed delicate connective tissue capsules about the enlarging nodules. When several nodules occupied most of one lobe, the residual parenchyma was sparse, compressed, and distorted (Fig. 15).

The cells comprising these benign follicular adenomas were uniformly distributed and varied from low cuboidal to high columnar. In some encapsulated nodules, particularly those having a trabecular pattern, the nuclei were mildly hyperchromatic, although the chromatin was delicate and particulate (Fig. 16). Occasional mitotic figures were observed. The amounts of cytoplasm varied in these benign neoplastic cells. It was most abundant, and often vacuolated, in adenomas with microfollicular or trabecular patterns (Fig. 16).

**Occurrence of follicular and papillary carcinomas in the thyroid glands of rats injected with I¹³¹.**—Malignant thyroid epithelial neoplasms were observed in five rats that had been given injections of I¹³¹ (Table 1). Four neoplasms were classified as follicular carcinomas, and one as a papillary adenocarcinoma (6). In a rat that had received 10 μc. I¹³¹, one thyroid lobe was enlarged and almost entirely replaced by a follicular adenoma (macrofollicular and microfollicular, Fig. 17). The other lobe was many times larger and contained a similar, but unencapsulated, follicular adenoma in its outer lateral portion (Fig. 17). The remainder of this lobe consisted of malignant thyroid epithelium with a trabecular and alveolar pattern, differentiated in some areas to form microfollicles containing small amounts of colloid (Fig. 18). These neoplastic cells were moderately pleomorphic and had large nuclei with coarse chromatin granules and large nucleoli. A moderate number of mitoses were present. The supporting stroma was delicate and was moderately infiltrated with lymphocytes and plasma cells. This malignant epithelium was continuous with that of the partially encapsulated, lateral nodule in the same lobe (Fig. 17), suggesting that the malignant process had originated from a benign adenoma. For the most part, the malignant epithelium was continuous with the thyroid capsule or was separated from the residual thyroid parenchyma by a thin, fibrous capsule (Fig. 18); but extraglandular invasion into adjacent cervical muscles had also occurred. Several large veins adjacent to the thyroid capsule were invaded by malignant thyroid epithelium (Fig. 19).

The glands of three of the twenty rats in the group given injections of 25 μc. I¹³¹ contained malignant thyroid neoplasms. In one animal, approximately two-thirds of one lobe was occupied
by a circumscribed, encapsulated, follicular adenoma (Fig. 20). Some follicles showed evidence of both old and recent hemorrhage. The majority were hyperplastic, with uniform, low columnar cells. The remaining parenchyma showed follicular atrophy (radiation injury) comparable in degree with that observed in other rats of this group. The opposite lobe in this same animal was greatly enlarged (Fig. 20). Part of the tissue of this lobe consisted of enlarged, hyperplastic, benign follicles similar to those seen in the nodule in the opposite lobe. However, most of the lobe consisted of neoplastic thyroid epithelium arranged in groups or large sheets. The epithelial cells were extremely pleomorphic and contained relatively large nuclei with macronucleoli that merged with the nuclear chromatin. The cytoplasm was sparse. A moderate number of mitotic figures were present in these more cellular portions of the thyroid tissue. Small thyroid follicles had formed in some areas. Some of these follicles contained pale colloid, whereas others were filled with fibrillary basophilic secretion (Fig. 21). The neoplastic tissue of this lobe was confined by the thyroid capsule, but, at one pole, neoplastic tissue had extended through the capsule into the adjacent areolar and adipose tissues. A large vein adjacent to the opposite lobe was filled with pleomorphic, neoplastic epithelial cells.

Both thyroid lobes of a second rat of the 25-μc. group were almost completely replaced by a neoplasm composed of thyroid epithelium with a trabecular and alveolar pattern showing widespread formation of small follicles which contained colloid. In a few small areas, a papillary pattern was observed. The neoplastic cells had large, pleomorphic nuclei with dense nuclear borders and coarse chromatin networks (Fig. 22). Mitotic figures were numerous. Although circumscribed and partially limited by the lateral thyroid capsule, the neoplasm had extended into the residual, compressed thyroid parenchyma (Fig. 23) at each pole, and into adjacent muscle. No vascular invasion was detected.

In the third animal of the 25-μc. group, one thyroid lobe was atrophied and consisted of small follicles (Fig. 24). The other lobe was greatly enlarged and, except for compressed residual parenchyma at one pole, was composed of a partially encapsulated nodule (Fig. 24). The peripheral portion of the nodule consisted of colloid-filled macrofollicles lined with uniform, flat epithelial cells. The bulk of the central portion of the nodule was composed of malignant thyroid epithelium having a distinct papillary arrangement (Fig. 25). Follicular spaces were largely filled by papillary epithelium, although small amounts of colloid were present in some follicles. In the papillary portion of the neoplasm, the nuclei were moderately pleomorphic, oval or round, and had an opaque, ground-glass appearance with indistinct nuclear chromatin; the cytoplasm was relatively scanty (Fig. 25). Peripherally, the neoplasm had extended through its capsule and was infiltrating the residual thyroid parenchyma, the adjacent areolar and adipose tissues, and cervical muscle (Fig. 26). In these extraglandular extensions the neoplasm was anaplastic, and the cells were arranged in large sheets with only minimal follicular differentiation. Mitotic figures were present in moderate numbers in this papillary portion, but they were much more numerous in extrathyroidal, anaplastic portions of the neoplasm. Vascular invasion had not occurred.

In a single animal of the 100-μc. group, one thyroid lobe was almost completely replaced by neoplastic thyroid epithelium. The cells lay in sheets, and only the peripheral portions showed minimal follicular differentiation. While the colloid was sparse in some of these peripheral follicles, the majority were filled with basophilic secretion. The cells were small, with oval or round nuclei containing delicate chromatin. The cytoplasm was scanty, and mitotic figures were rare. The neoplasm was partly limited by the thyroid capsule, but at one pole the neoplastic cells had extended through the capsule and were invading the adjacent areolar and adipose tissue. There a large vein was almost completely filled with neoplastic epithelial cells displaying formation of thyroid follicles.

No malignant neoplasms were found in the thyroid glands of animals given injections of 200 or 400 μc. I131.

Other neoplasms found in I131-injected and control rats.—Neoplasms, other than thyroid tumors, observed in the rats of this study are listed in Table 2. Descriptions of the pituitary glands will be reported separately. Although the incidence of adenomas of the breast was generally higher in the irradiated rats than in the controls, the incidence in rats given injections of 400 μc. of I131 was less than that in the controls. The incidence of malignant mediastinal lymphoma in the 400-μc. group was approximately 4 times that in the controls.

DISCUSSION

The pathologic lesions observed here in the thyroid parenchyma of rats irradiated with I131 are similar to those reported previously in this species (9) and in the human being (11). Mitoses were few or absent, indicating inability of the irradiated...
gland to respond to normal stimulation by thyrotropic hormone. Doniach and Logothetopoulos (5) found irradiated rat thyroids incapable of responding in a normal fashion to the administration of goitrogens. A depressed capacity of the I\textsuperscript{131} irradiated thyroid gland to respond to thyrotropic hormone as well as to goitrogens has also been observed in this laboratory (14).

An instructive finding of the present study is the high incidence of naturally occurring thyroid carcinomas both in the control rats and in rats given injections of 10 and 25 \( \mu \text{c.} \) I\textsuperscript{131}. Schlumberger (17) and Morris (13) have reported that the incidence of naturally occurring thyroid neoplasms in the rat is extremely low. In Long-Evans rats, the strain used here, Moon (cited by Goldberg and Chaikoff [9]) found six small adenomas in fourteen aged animals. In the previous study by Goldberg and Chaikoff (9), three of the nine carcinomas prevented the growth of this low-grade, naturally occurring carcinoma.

The naturally occurring carcinomas observed here both in the control and the I\textsuperscript{131}-irradiated rats bear little or no resemblance to the neoplasms induced by I\textsuperscript{131} or goitrogens. Their multicentric origin, their tendency to invade mainly thyroid follicles, their alveolar pattern, their relative cellular uniformity and lack of extrathyroidal invasion easily differentiate these low-grade neoplasms from those induced by I\textsuperscript{131}.

Benign neoplasms that developed in irradiated thyroid glands originated either as single thyroid follicles or as groups of follicles that had undergone hypertrophy and hyperplasia. These follicles were several times the size of the surrounding atrophied follicles and usually contained abundant colloid. Once formed, these nodules or adenomas increased in size by hyperplasia of the lining epithelium and

<table>
<thead>
<tr>
<th>TYPE OF NEOPLASM</th>
<th>FOUND IN RATS INJECTED WITH</th>
<th>TOTAL NO. OF RATS EXAMINED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 ( \mu \text{c.} )</td>
<td>25 ( \mu \text{c.} )</td>
</tr>
<tr>
<td>Adenofibroma of breast</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fibroma of mesentery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Primary carcinoma of liver</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adenoma of parotid gland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoma of subcutaneous tissue</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma of mediastinum</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malignant lymphoma of mesentery</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fibrosarcoma of skin</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Adenoma of parathyroid</td>
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</tbody>
</table>

Observed in Long-Evans rats were of the same type. The incidence was identical with that observed in the present study. However, examination of 1,000 normal rats up to 2\( \frac{1}{2} \) years of age, by Chaikoff and Goldberg (8), did not reveal this naturally occurring lesion. This type of thyroid carcinoma was described, in a Wistar rat that had received thiouracil, by Van Dyke (18), who regarded these particular lesions as arising by metaplasia from the ultimibranchial bodies. The incidence of this type of neoplasm in Long-Evans rats is presumably higher than in other strains of rats.

It is of interest that, although the incidence of these naturally occurring tumors was identical in the control rats and in rats that received 10 or 25 \( \mu \text{c.} \) of I\textsuperscript{131}, none was found in the animals given injections of 100 \( \mu \text{c.} \), and only three were found in 182 rats given injections of 200 or 400 \( \mu \text{c.} \) of I\textsuperscript{131}; presumably these three rats had lower I\textsuperscript{131} uptakes. These findings suggest that radiation injury to the thyroid glands of rats injected with larger doses of I\textsuperscript{131} (100–400 \( \mu \text{c.} \)) pre-
appeared that these malignant neoplasms had originated from benign nodules which presented microfollicular and macrofollicular patterns similar to those seen in the other benign adenomas of the irradiated animals. As a rule, the invasive portions were less well differentiated. The peripheral parts of the neoplastic tissue, which were infiltrating extrathyroidal tissues, had microfollicular or completely anaplastic patterns. This finding is common in human thyroid carcinoma. Intravascular invasion was demonstrable in three of the five malignant neoplasms.

These five neoplasms were designated carcinomas because of their aggressive tendencies and their invasion of residual thyroid parenchyma, extrathyroidal tissues, and blood vessels. Although no metastases from these malignant thyroid lesions were observed, their histologic patterns suggest that they would be capable of metastasizing. Whether such metastases would be dependent upon continued thyrotropic stimulation remains to be seen. A review of the microscopic sections of the metastases from thyroid neoplasms described by Goldberg and Chaikoff (8) revealed a number of primary tumors of various types, not thought to be of thyroid origin.

The benign and malignant follicular and papillary neoplasms observed in these irradiated rats were similar to those previously described in animals that received goitrogens or that suffered from chronic iodine deficiency (1, 2, 10, 12, 15, 16). It seems likely that these neoplasms, which were often multiple, resulted from long-standing, thyrotropic hormone stimulation of focal areas of the thyroid gland still capable of being stimulated after injury by internal irradiation. It also appears that the majority of malignant follicular and papillary neoplasms of the thyroid gland originated in benign thyroid adenomas which, after continued thyrotropic stimulation, eventually became malignant. These benign and malignant tumors, being similar to those resulting from goitrogen administration, should be considered as examples of hormonal carcinogenesis rather than as neoplasms resulting from irradiation per se.

The incidence of both benign and malignant follicular and papillary thyroid tumors was higher in rats given injections of the lower doses of I^{131}. This suggests that the less the gland is injured by internal irradiation, the greater is its capacity to respond to stimulation by thyrotropic hormone. Apparently, when larger doses of I^{131} are administered, the gland is so severely injured that a proliferative response can no longer occur (5, 14). This histological evidence of severe injury to the thyroid glands and the high incidence of thyroid tumors (both benign and malignant) reported earlier by Goldberg and Chaikoff (7, 8) in rats given injections of 400 µc. I^{131} suggest that the I^{131} uptakes by the thyroid glands of those rats must have been much less than the uptakes by the thyroids of the rats used in the present study.

**SUMMARY**

1. Radiation injury of the thyroid glands of 198 Long-Evans rats, 1.5–3 years following single injections of 10–400 µc. I^{131}, is described.

2. The degree of follicular atrophy and of cellular and nuclear pleomorphism of the thyroid parenchyma varied with the dose of I^{131}.

3. Single or multiple benign thyroid adenomas were found in twenty internally irradiated glands. The highest incidence of these adenomas was found in rats injected with 10 and 25 µc. I^{131}.

4. Follicular and papillary carcinomas were observed in five of the irradiated animals injected with 10, 25, and 100 µc. I^{131}.

5. The benign and malignant thyroid neoplasms found in I^{131}-irradiated rats originated as foci of nodular regeneration and hyperplasia.

6. The follicular and papillary thyroid carcinomas in the irradiated rats appeared to have...
Fig. 8.—Alveolar carcinoma (control) composed of mildly pleomorphic cells. Few mitoses are observed. Hematoxylin and eosin. ×565. Age of rat, 27 months.

Fig. 9.—Alveolar carcinoma (control), involving most of one lobe. The smaller follicles are composed of neoplastic cells. Hematoxylin and eosin. ×125. Age of rat, 38 months.

Fig. 10.—Follicular adenomas 26 months after I\(^{131}\) injection (25 \(\mu\)c.). Three nodules are present in one lobe. Hematoxylin and eosin. ×12. Age of rat, 28 months.

Fig. 11.—Follicular adenoma 30 months after I\(^{131}\) injection (200 \(\mu\)c.). Single nodule, involving most of one lobe, shown in Figure 2. Compressed segments of atrophic parenchyma are seen at each pole. Hematoxylin and eosin. ×30. Age of rat, 32 months.

Fig. 12.—Follicular adenomas 26 months after I\(^{131}\) injection (25 \(\mu\)c.). Multiple nodules in various stages of development are present. Hematoxylin and eosin. ×10. Age of rat, 28 months.

Fig. 13.—Early adenoma 26 months after I\(^{131}\) injection (25 \(\mu\)c.), consisting of hypertrophied follicles containing colloid. Hematoxylin and eosin. ×250. Age of rat, 28 months.

Fig. 14.—Follicular adenoma 26 months after I\(^{131}\) injection (25 \(\mu\)c.). The nodule has a macrofollicular pattern, and the surrounding parenchyma shows radiation damage. Hematoxylin and eosin. ×125. Age of rat, 32 months.
Fig. 15.—Follicular adenomas 36 months after I\textsuperscript{31} injection (25 μc.). Margins of adenomas with variable patterns. Note residual atrophic and compressed parenchyma. Hematoxylin and eosin. ×145. Age of rat, 28 months.

Fig. 16.—Trabecular adenoma 30 months after I\textsuperscript{31} injection (200 μc.). No follicular differentiation has occurred. There is mild cellular pleomorphism, and a few mitotic figures are present. Hematoxylin and eosin. ×250. Age of rat, 28 months.

Fig. 17.—Follicular carcinoma and follicular adenomas 31 months after I\textsuperscript{31} injection (10 μc.). The smaller lobe consists of a follicular adenoma. Laterally, in the larger lobe, there is a similar adenoma. The remainder of the larger lobe is composed of malignant epithelium which has invaded striated muscle at the superior pole. Hematoxylin and eosin. ×11. Age of rat, 28 months.

Fig. 18.—Higher power of Figure 17. In this area the pattern is follicular, and the neoplasm is separated from the residual parenchyma by a thin, fibrous capsule. Hematoxylin and eosin. ×145.

Fig. 19.—Higher power of Figure 17. Invasion of superior thyroidal vein. Hematoxylin and eosin. ×250.

Fig. 20.—Follicular carcinoma and follicular adenoma 26 months after I\textsuperscript{31} injection (25 μc.). The smaller lobe contains a follicular adenoma. The larger lobe is extensively invaded by malignant epithelium which extends through the thyroid capsule at the inferior pole. Hematoxylin and eosin. ×8. Age of rat, 28 months.
FIG. 21.—Higher power of Figure 20. The pattern is mainly microfollicular. Most follicles contain basophilic mucoid rather than colloid secretion. Hematoxylin and eosin. X125.

FIG. 22.—Follicular carcinoma 26 months after ¹³¹I injection (25 μc.). The microfollicles contain sparse colloid. The nuclei are pleomorphic, and mitoses are numerous. Hematoxylin and eosin. X565. Age of rat, 28 months.

FIG. 23.—Margin of neoplasm shown in Figure 22, with invasion of thyroid parenchyma. Hematoxylin and eosin. X250.

FIG. 24.—Papillary carcinoma 28 months after ¹³¹I injection (25 μc.). The large nodule has a follicular pattern peripherally. The central tissue is papillary. Note anaplastic, extrathyroidal extension at upper pole. Hematoxylin and eosin. X111. Age of rat, 28 months.

FIG. 25.—Higher power of Figure 24. The nuclei of the papillary neoplasm have the same clear appearance as papillary carcinomas in man. Hematoxylin and eosin. X250.

FIG. 26.—Extrathyroidal invasion of neoplasm shown in Figures 24 and 25. The invasive tissue is anaplastic. Hematoxylin and eosin. X125.
developed in most instances in previously benign adenomas. Parenchymal, capsular, and vascular invasion occurred in these malignant neoplasms, but regional or distant metastases were not demonstrable.

7. Naturally occurring alveolar carcinomas had an incidence of 30–35 per cent in normal, control Long-Evans rats. The incidence was the same in rats given injections of the lower doses of I¹³¹ (10–25 µc.), but was considerably lower in rats that received the higher doses (100–400 µc.) of radioiodine. These spontaneous carcinomas are unlike those resulting from irradiation with I¹³¹ and are characterized by an alveolar pattern and a low degree of malignancy.

ACKNOWLEDGMENTS

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Thyroid Neoplasms in the Rat: A Comparison of Naturally Occurring and $^{131}$-induced Tumors

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