Induction of Neoplasms in the Thyroid Gland of the Rat by X-Irradiation of the Gland*

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SUMMARY

The development of benign and malignant neoplasms was studied in thyroid glands of Long-Evans rats 2 years after either both lobes of the glands had been irradiated with 500, 1000, or 2000 r, or the right lobe alone had been irradiated with 1000 r.

The degree of follicular atrophy and of nuclear pleomorphism observed in these irradiated glands varied with the dose of x-rays.

Benign nodules or adenomas were observed in 30 of the 74 irradiated rats that survived. These lesions appeared to have originated as foci of nodular regeneration and hyperplasia. Papillary and follicular thyroid carcinomas were found in nine of the irradiated rats. Two of the six papillary carcinomas appeared to have originated in previously benign adenomas. Naturally occurring alveolar or lobular carcinomas had an incidence of 33 per cent in normal control rats and of 22—45 per cent in rats whose thyroids were irradiated with x-rays. These naturally occurring carcinomas were of low-grade malignancy and were unlike those induced by irradiation. Parathyroid hyperplasia and adenomas were observed frequently in control as well as in irradiated rats.

Irradiation has been implicated in the development of benign and malignant thyroid neoplasms, both in the rat and in the human being (3–8, 11–13, 17, 22, 25–27). Goldberg and Chaikoff described the development of benign and malignant thyroid tumors in Long-Evans rats 1.5–2 years after single injections of 400 µc. of I¹³¹ (12, 13). Later, Doniach induced benign and malignant thyroid neoplasms mainly by combining the feeding of methylthiouracil with either the administration of I¹³¹ or the application of external irradiation to the thyroid gland (4–7). Lindsay et al. (19), in 1957, and Potter et al. (22), in 1960, reported that the highest incidence of I¹³¹-induced thyroid neoplasms occurred in Long-Evans rats that had received low doses of I¹³¹—either single injections of 25 µc. of radiiodine or four separate injections of 10 µc. each. Papillary and follicular carcinomas were found in twelve of the I¹³¹-injected rats (22). According to these investigators (19, 22), the I¹³¹-induced thyroid neoplasms differed from the naturally occurring thyroid tumors that appear with high frequency in old Long-Evans rats.

Frantz et al. (11) found four follicular and papillary thyroid carcinomas in 45 Long-Evans rats in which thyroid glands had been x-irradiated. Their failure, as well as that of Starr and his associates (9, 10), to induce thyroid carcinomas in Long-Evans rats by means of radioiodine is readily explained by the large doses of I¹³¹ used. In most cases, these completely (or nearly so) destroyed the thyroid glands. We have pointed out that the highest incidence of benign and malignant neoplasms was induced in rats with low doses of I¹³¹ (19, 22).

It is shown in the present report that benign and malignant neoplasms can be made to appear in thyroid glands of rats by subjecting those glands to irradiation by x-rays.

MATERIALS AND METHODS

Four hundred and fifty male Long-Evans rats, 8–12 weeks of age, were divided into five groups. All animals were anesthetized by intraperitoneal injections of sodium pentobarbital. Nothing fur-
Gross Description

The irradiated glands were, as a rule, smaller than those of control animals, and the decrease in size was proportional to the dose of x-rays administered. Only one of the control animals showed an enlarged left lobe—twice the size of the right lobe—the result of a naturally occurring thyroid carcinoma.

Diffuse enlargement of both lobes was observed in a thyroid gland that had been treated with 500 r. This gland was twice normal size and contained multiple follicular adenomas.

Unilateral nodular enlargement of the thyroid gland was observed in six rats of the group in which both lobes had been irradiated with 1000 r. The enlarged glands contained nodules which were either red and soft or firm and pale, and which measured 5–10 mm. in diameter. In two rats nodular enlargement was bilateral. The enlargement of the lobes in this 1000-r treated group resulted from infiltration by malignant thyroid neoplasms in four animals and from the presence of benign follicular adenomas in two animals.

In the group in which 1000 r were administered to the right thyroid lobe, two rats showed nodular enlargement of the irradiated lobe. This was due, in one case, to the presence of a follicular carcinoma and in the other to an alveolar or lobular carcinoma. In a third animal of this group the right lobe was approximately 4 times normal size and contained multiple follicular adenomas.

Nodules were not observed in any of the animals in which both thyroid lobes had been treated with 2000 r.

Two of the animals in which either 500 r had been administered to both lobes or 1000 r to the right lobe displayed hemorrhagic cystic enlargement of the pituitary glands. Descriptions of these pituitary glands will be reported separately.

Microscopic Description

1. The Thyroid Parenchyma

The thyroid follicles varied in size and location. The larger were at the periphery of the lobes, and the smaller occupied a central position. The peripheral follicles were lined by flattened cuboidal epithelium; the central follicles had taller cuboidal epithelial cells. The nuclei were uniform and contained delicate chromatin; some were vesicular. The cytoplasm was eosinophilic and granular. No mitoses were observed. The colloid was pale and vacuolated in most follicles and appeared granular in a few of the smaller ones. The interfollicular connective tissue was normal, and no vascular lesions were observed (Fig. 1).

2. Both lobes irradiated with 500 r.—As in the control group, the peripheral follicles were larger than the central ones. The irradiated glands, however, contained more smaller follicles than did the normal glands. The epithelium of these irradiated thyroid glands was cuboidal but tended to be flatter than that of normal tissues. The nuclei were mildly pleomorphic, and the chromatin appeared condensed; crenation of the nuclear margins was observed. The cytoplasm appeared normal. Mitotic figures were not found. The colloid was generally pale and vacuolated and, in a few smaller follicles, granular and eosinophilic. The
interstitial tissues and blood vessels appeared normal.

3. Both lobes irradiated with 1000 r.—In these glands there were a few large, peripheral follicles, but most follicles were smaller than normal. The follicles contained granular eosinophilic colloid. The cells were cuboidal, and their nuclei were slightly more pleomorphic and hyperchromatic than those of the 500-r group. The cytoplasm was more vesicular, eosinophilic, and abundant than that of control rats and of the 500-r rats. No mitotic figures were observed. The connective tissue and blood vessels of these glands were normal.

4. Right lobe irradiated with 1000 r.—In this group the irradiated right lobes closely resembled those of rats in which both lobes had been irradiated with 1000 r. In eighteen of the 26 rats the follicles were small and contained granular colloid. The thyroid nuclei were pleomorphic, and many were hyperchromatic. The cytoplasm generally was abundant, vacuolated, and eosinophilic. In three of the animals, portions of some thyroid lobules were hyperplastic; here the follicles were larger than those of the rest of the gland and were lined by cuboidal or low columnar, uniform epithelial cells. These follicles contained pale but otherwise normal colloid (Fig. 2). In four of the 26 animals of this group the irradiated right lobes were diffusely hyperplastic. In one animal the irradiated lobe was completely replaced by an extensive malignant epithelial neoplasm.

In six of the 26 animals, the left lobes, which were shielded during the irradiation, were normal, and were identical in appearance with those of the control groups. In seven there was focal hyperplasia involving segments of thyroid lobules, and in twelve animals the entire left lobe was mildly hyperplastic (Fig. 3). In one animal the parenchyma of the entire left lobe had been replaced by a large follicular adenoma and an alveolar or lobular carcinoma. In three animals the left lobe was largely replaced by multiple follicular adenomas.

5. Both lobes irradiated with 2000 r.—The glands of the animals of this group were composed of follicles significantly smaller than those of animals that received lower doses of irradiation. Moderate nuclear pleomorphism and hyperchromatism with nuclear irregularity were present; the cytoplasm was extremely abundant, granular, and eosinophilic. No mitoses were observed. The colloid was sparse and granular (Fig. 4). The interstitial tissue was normal.

Vasculitis of large thyroid arteries was observed in two animals treated with 2000 r. This lesion was characterized by endothelial swelling and fibrinoid degeneration of all layers and by a chronic inflammatory infiltration, especially of the adventitia (Fig. 5).

II. Thyroid Neoplasms

1. Adenomas.—A small, macrofollicular adenoma was observed in only one of the thyroid glands of the control group. Such thyroid nodules or adenomas were, however, found in many of the irradiated animals (Table 1). The smallest and earliest lesions observed consisted of a group of enlarged thyroid follicles that appeared to arise in a segment of a thyroid lobule. The enlarged follicles were lined by cuboidal epithelium, and contained pale, vacuolated colloid. In larger nodules, epithelial hyperplasia with papillary infolding was observed (Fig. 6). Further enlargement seemed to result from epithelial growth by follicular budding, leading to the development of macrofollicular or microfollicular patterns. As a rule the smaller follicles contained little colloid, whereas the macrofollicles generally were well filled with this substance. Evidences of old and recent hemorrhage were frequently found, particularly in those nodules with a macrofollicular pattern. The thyroid epithelium in these nodules was uniform, with round or oval nuclei. When the epithelium was columnar, the nuclei were near the basement membranes. Mitotic figures were not found in these lesions.

As the nodules enlarged, they tended to compress the surrounding parenchyma from which they were sharply demarcated by intact fibrous capsules. These adenomas occurred singly, but in many instances were multiple in one or both lobes (Fig. 7). In some cases, these enlarging macrofollicular nodules had entirely replaced the original thyroid parenchyma and thus caused enlargement and distention of an entire lobe (Fig. 8).

One benign adenoma had a trabecular pattern and contained only a few microfollicles devoid of colloid. The cells of this nodule were uniform and had oval to round nuclei with delicate chromatin and small discrete nucleoli. The cytoplasm was sparse, and mitoses were not observed. The thyroid epithelium was supported by sparse connective-tissue stroma (Fig. 9).

Two macrofollicular nodules were designated as papillary adenomas. These were cystic and encapsulated, and were composed of large follicles lined by thyroid epithelium that displayed many delicate papillary folds or fronds. The thyroid epithelium consisted of uniform, low-columnar cells with oval, or round, compact hyperchromatic
nuclei and sparse eosinophilic cytoplasm. No mitoses were present in these papillary adenomas.

2. Alveolar carcinomas.—The incidence of these naturally occurring carcinomas was high in both control and irradiated groups (Table 1). The earliest lesions observed consisted of neoplastic thyroid epithelial cells that filled single follicles or small groups of contiguous follicles in which they replaced the colloid and the normal lining epithelial cells. These neoplastic cells were larger than normal thyroid cells and had oval, or round, pale, vesicular, mildly pleomorphic nuclei and moderately abundant eosinophilic vacuolated cytoplasm. Many cells appeared stellate and lay in loosely arranged groups. The stroma was sparse or absent. Mitotic figures were rarely observed.

These neoplasms seemed to extend by invasion of adjacent and contiguous follicles. The filling of the follicles by neoplastic cells gave the neoplasm an alveolar or lobular pattern. The growth of the neoplastic cells also isolated thyroid follicles. In some instances, particularly in the more extensive neoplasms, small follicles were formed by neoplastic cells (Fig. 10).

In the large neoplasms the cells were smaller and were present in compact groups or sheets within follicular spaces. The nuclei were uniform, and the cytoplasm was moderately abundant and eosinophilic (Fig. 10).

Despite extensive involvement of the lobes, the lesions remained circumscribed and unencap-

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**TABLE 1**

**INCIDENCE OF NEOPLASMS IN NORMAL MALE LONG-EVANS RATS AND IN MALE RATS IN WHICH THYROID GLANDS WERE IRRADIATED**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Treatment of rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None, controls (31)</td>
</tr>
<tr>
<td>Thyroid adenomas</td>
<td></td>
</tr>
<tr>
<td>R. lobe</td>
<td>1</td>
</tr>
<tr>
<td>L. lobe</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
</tr>
<tr>
<td>Per cent</td>
<td>3</td>
</tr>
<tr>
<td>Thyroid papillary carcinomas (P)</td>
<td></td>
</tr>
<tr>
<td>R. lobe</td>
<td>0</td>
</tr>
<tr>
<td>L. lobe</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid follicular carcinomas (F)</td>
<td></td>
</tr>
<tr>
<td>R. lobe</td>
<td>0</td>
</tr>
<tr>
<td>L. lobe</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
</tr>
<tr>
<td>P+P, per cent</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid alveolar carcinomas</td>
<td></td>
</tr>
<tr>
<td>R. lobe</td>
<td>5</td>
</tr>
<tr>
<td>L. lobe</td>
<td>6</td>
</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
</tr>
<tr>
<td>Per cent</td>
<td>33</td>
</tr>
<tr>
<td>Parathyroid adenomas</td>
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<td>R. lobe</td>
<td>3</td>
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<tr>
<td>L. lobe</td>
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</tr>
<tr>
<td>Bilateral</td>
<td>0</td>
</tr>
<tr>
<td>Parathyroid hyperplasia</td>
<td></td>
</tr>
<tr>
<td>R. lobe</td>
<td>6</td>
</tr>
<tr>
<td>L. lobe</td>
<td>5</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3</td>
</tr>
<tr>
<td>Other neoplasms</td>
<td></td>
</tr>
<tr>
<td>Lipoma of abdominal wall</td>
<td>Fibroma of breast</td>
</tr>
<tr>
<td>Epidermoid carcinoma of thorax</td>
<td></td>
</tr>
</tbody>
</table>

* Studied 2 years after irradiation.
† Numbers in parentheses indicate number of rats studied.
3. Papillary carcinomas.—Malignant papillary neoplasms were not observed in the glands of the control group, but six were found in the irradiated thyroid glands, one in a gland that had been treated with 500 r and five in glands that had been irradiated with 1000 r (Table 1).

Both lobes of a thyroid gland that had been treated with 500 r were enlarged and almost completely replaced by neoplastic thyroid tissue; at the periphery of the neoplasm a few compressed segments of residual parenchyma were found. The central portions of the neoplasm in each lobe were macrofollicular, with many distinct papillary processes extending into cystic follicular spaces (Fig. 12); the colloid here was pale and sparse. Closer to the periphery the pattern became microfollicular (Fig. 13), and the outer portions trabecular or completely undifferentiated. The neoplastic cells were similar in all portions of the neoplasm. They were moderately pleomorphic, and their nuclei were oval or round and appeared opaque. Little nuclear chromatin was visible. Cytoplasm was sparse. In the less differentiated peripheral portion, the cells tended to be larger, and there moderate numbers of mitoses and hyperchromatic condensed nuclei were observed. Throughout the neoplasm the thyroid cells were supported by delicate, sparse stroma. At the margins of the neoplasm, the neoplastic tissue had infiltrated the compressed residual parenchyma and the adjacent cervical striated muscles. Neoplastic tissue had invaded the lumen of a small peripheral vein.

The left lobe of a thyroid gland that had been treated with 1000 r was almost entirely occupied by a circumscribed nodule surrounded by a narrow segment of compressed residual parenchyma. The neoplasm consisted of follicles of varying size (normal to microfollicular) which were composed of mildly pleomorphic, cuboidal or flattened epithelial cells. These follicles contained vacuolated, pale colloid; no mitoses were observed in this portion of the nodule. The pattern of this portion of the nodule was identical with those of the benign follicular adenomas observed in many of the animals. Approximately one-third of the large nodule was occupied by malignant neoplastic tissue that had a distinctly different histologic and cytologic pattern. The follicular and papillary structures were composed of moderately pleomorphic cells with pale, vesicular, opaque nuclei, characteristic of those of papillary carcinoma. The cytoplasm was sparse; a few mitoses were present. This papillary and follicular neoplastic tissue had infiltrated the benign nodule in which it appeared to have arisen and had penetrated the narrow rim of residual parenchyma to the thyroid capsule (Fig. 14). In the stroma of the cystic portion of the malignant neoplasm were many pigment-filled macrophages, the result of previous hemorrhage. No vascular or lymphatic invasion was demonstrable in this neoplasm.

In a second animal of the 1000-r group, the entire right lobe was occupied by a malignant neoplasm, surrounded in part by a thick connective tissue capsule. In one area the neoplastic tissue was in contact with and infiltrating adjacent adherent muscle. The pattern of the neoplasm was mainly macrofollicular, with many papillary structures extending into large follicular spaces (Fig. 15). Some follicles were cystic and filled with colloid. The cells were mildly pleomorphic and contained round, pale, opaque nuclei in which little chromatin was visible; the cytoplasm was sparse; few mitoses were present. At one margin of the neoplasm, neoplastic cells had invaded the lumen of a large vein.

A third animal in the 1000-r group had an enlarged right thyroid lobe occupied by a macrofollicular nodule that contained abundant colloid. Between the macrofollicles were a few follicles of normal size and smaller. This nodule consisted of uniform cuboidal epithelial cells; no mitoses were found. Approximately one-third of this nodule had been replaced by malignant thyroid neoplastic tissue that had infiltrated the pre-existing macrofollicular nodule as well as the adjacent rim of residual parenchyma. The neoplastic cells were arranged in sheets and groups and in many areas had produced microfollicles that contained colloid. Some centrally placed, larger follicles had poorly defined papillary structures. The cells were large; their nuclei were oval or round, vesicular and pale, with a ground-glass appearance. These nuclei contained prominent nucleoli. The cytoplasm was sparse and eosinophilic. Mitoses were numerous. No vascular or lymphatic invasion was demonstrable in this neoplasm.

In a fourth rat of the 1000-r group, a large neoplasm occupied the entire right lobe. The neoplastic tissue was surrounded in part by a narrow rim of thyroid parenchyma. This neoplasm had infiltrated widely and extended through the thyroid capsule. Many extraglandular satellite nodules were found, and invasion between tracheal cartilages had occurred. Several veins in the periph-
eral portion of the neoplasm were invaded by neoplastic thyroid epithelium.

The pattern of the neoplasm in this fourth rat was mainly undifferentiated. It contained a few microfollicles, some with colloid. A few poorly defined papillary structures were found in the central portion of the neoplasm. Large zones of scarring with evidences of old and recent hemorrhage were present. The cells were mildly pleomorphic. The nuclei were oval or round and contained little chromatin; they were opaque, with the appearance of ground glass. The cytoplasm was sparse, and few mitoses were present.

The thyroid gland of a fifth animal in the 1000-r group also contained a large neoplasm that occupied almost the entire left lobe. This neoplasm was largely encapsulated and was surrounded in part by a narrow segment of residual thyroid parenchyma. Neoplastic tissue, however, had invaded beyond the capsule, and several veins at the periphery of the neoplasm were infiltrated with neoplastic cells. The pattern varied from macrofollicular to microfollicular but also contained large sheets with an undifferentiated pattern (Fig. 16). A few papillary structures were present in the central portion of the neoplasm. The cells comprising this tumor were mildly pleomorphic; their cytoplasm was sparse, and their nuclei were oval, pale, and had a ground-glass appearance (Fig. 16). Few mitoses were present.

4. Follicular carcinomas.—Malignant follicular neoplasms were not found in the thyroid glands of the control group nor in those of rats treated with 500 or 1000 r. Two such carcinomas were, however, observed in the right lobes of two rats that received 1000 r to the right lobe, and one was found in the thyroid gland of a rat that had received 2000 r.

In a rat in which the right lobe had been irradiated with 1000 r, that lobe was almost entirely occupied by a large neoplasm. This had infiltrated a portion of the residual thyroid parenchyma locally but elsewhere was limited in its growth by a thickened, fibrous capsule. At the periphery of the neoplasm several veins had been invaded by neoplastic tissue (Fig. 17). The pattern of the neoplasm was mainly lobular, and few microfollicles were present. Some of these follicles contained colloid. The cells were moderately pleomorphic, with oval, or round, compact nuclei containing abundant, coarse chromatin particles and prominent eosinophilic nucleoli. In some areas elongated, spindle-shaped cells with a distinct perivascular arrangement were observed (Fig. 18). The cytoplasm was sparse, granular, and eosinophilic. Many mitotic figures were present in most portions of the neoplasm. Little connective tissue stroma was present. The histologic and cytologic patterns of this neoplasm were distinctly different from those of the papillary carcinomas observed in the irradiated thyroid glands.

A second animal of the group in which the right lobe was irradiated with 1000 r revealed a circumscribed but not entirely encapsulated nodule in the central portion of the right lobe (Fig. 19). This neoplasm had locally infiltrated the adjacent parenchyma and had invaded the lumen of a large thyroid vein. The pattern of this tumor was mainly microfollicular, but a few larger follicles, some containing fresh blood, were present. Many of the follicles contained pale, vacuolated colloid. The cells were mildly pleomorphic, with oval or round vesicular nuclei and abundant vacuolated cytoplasm. Few mitoses were present.

The left thyroid lobe of one rat of the 2000-r group was enlarged and was almost entirely replaced by a neoplasm that showed minimal invasion of the residual surrounding thyroid parenchyma (Fig. 20). One thyroid vein had been invaded by the neoplasm. The pattern of this neoplasm was mainly microfollicular, but many normal-sized follicles had been formed by the neoplastic cells. The follicles contained pale, vacuolated colloid. Most of the cells were columnar. The nuclei were oval or round, mildly pleomorphic, and rich in chromatin. They were generally located adjacent to the basement membranes. The cytoplasm was abundant and eosinophilic; few mitoses were present (Fig. 21).

III. Parathyroid Lesions

Proliferative lesions of the parathyroid glands were observed in many of the control and irradiated rats (Table 1). In some animals the lesions were bilateral. Some were characterized by diffuse or focal, hyperplastic foci of chief or clear cells (Fig. 22). These cells were generally slightly larger than normal parathyroid cells. Mitoses were absent. These hyperplastic parathyroid cells were supported by sparse stroma.

In other instances the proliferative foci were single and appeared as circumscribed and encapsulated nodules consisting of either chief or clear cells (Figs. 23 and 24). In these lesions, the cells were uniform, slightly larger than normal parathyroid cells, and devoid of mitotic figures. Narrow, compressed segments of residual parathyroid parenchyma surrounded some of these nodules or adenomas (Fig. 24). None of the parathyroid lesions appeared malignant.
IV. Miscellaneous Neoplasms

Neoplasms other than those of the thyroid and parathyroid glands are listed in Table 1. No significant difference in their incidence was observed between the control and the irradiated groups. An epidermoid carcinoma of the trachea, found in one animal that received 2000 r, is of interest. This neoplasm arose at the level of the thyroid gland, at the site of irradiation. It consisted of groups and cords of neoplastic squamous cells that infiltrated the tracheal submucosa and extended between and beyond tracheal and laryngeal cartilages to invade adjacent striated muscle. The neoplastic squamous cells were mildly pleomorphic and showed distinct keratin and pearl formation. A few mitoses were present. A moderate desmoplastic reaction had occurred (Fig. 25).

DISCUSSION

The pathologic lesions observed in the parenchyma of rat thyroid glands irradiated with x-rays closely resembled those observed previously in rat thyroids internally irradiated with I$^{131}$ (14, 19, 22) and those found in human thyroid glands (18) subjected to various forms of irradiation. The severity of the lesions in the rat thyroid glands was proportional to the dose of irradiation (from 500 to 2000 r) administered. Mitotic figures were absent in the glands that showed radiation injury, indicating a depressed capacity of the externally irradiated gland to respond in a normal fashion to thyrotropic hormone. The degree of radiation injury found resembled that seen previously in rats that received less than 400 μc of radioiodine (19).

When the right lobe alone was x-irradiated, the resulting changes closely resembled those seen when both lobes were irradiated with 1000 r, but in seven instances the irradiated right lobe displayed focal or even diffuse hyperplasia, an effect which probably resulted from thyrotropic hormone stimulation.

In the rats in which 1000 r had been administered to the right lobe only, nineteen of the 26 nonirradiated left lobes were characterized by focal or diffuse hyperplasia which also undoubtedly resulted from thyrotropic hormone stimulation. The incidence and histologic patterns of the benign nodules found in the right and left lobes were similar even in rats in which only the right lobe was irradiated with 1000 r.

Nine thyroid neoplasms found in the irradiated rats were designated carcinomas because of their local and extraglandular invasiveness and because of their extension into lumens of the thyroid veins. Regional or distant metastases, however, were not found. Six were classified as papillary carcinoma and three as follicular carcinoma. It is of interest to note that the relative frequency of these two forms of thyroid carcinoma in the irradiated rat was approximately the same as that observed in the human being (17). The histologic and cytologic patterns of these rat neoplasms are also similar to those seen in human beings (17).

Two of the papillary carcinomas observed in the irradiated thyroid glands appeared to have originated in pre-existing, benign macrofollicular adenomas, an origin not believed common in the human being (17). In one of two previous studies of thyroid neoplasms induced in rats with I$^{131}$, four out of five malignant thyroid neoplasms appeared to have developed in pre-existing, benign thyroid nodules or adenomas (19). In the second study, such an origin of the malignant neoplasms from benign ones was also suspected because of the similarity in the patterns of the benign and malignant tumors (22). This sequence from benign to malignant was probably more frequent in the x-irradiation-induced neoplasms of the rat. However, by the time large malignant neoplasms were examined, the benign neoplastic tissue had been overgrown and replaced by the malignant.

Both the benign and malignant papillary and follicular carcinomas observed in this study closely resembled those described previously in animals that received goitrogens or that had been subjected to chronic iodine deficiency (2, 21, 23, 24). It seems probable that the benign neoplasms found in these externally irradiated thyroid glands resulted from prolonged stimulation, by thyrotropic hormone, of focal areas of the gland still able to respond by proliferation despite injury by irradiation. The sequence from focal hyperplasia to benign nodule formation in these glands seems clearly demonstrated. That thyrotropic stimulation rather than irradiation was important in the development of these benign nodules was suggested by the appearance of identical benign nodules in the irradiated right lobes and in the non-irradiated left lobes. Whether the carcinogenesis was the result of continued thyrotropic stimulation of benign nodules or whether radiation primarily induced the malignant thyroid neoplasms cannot be decided on the basis of the present data. Most of the thyroid carcinomas were found in glands that received irradiation to both lobes, whereas only two were found in the singly irradiated right lobe. Further experiments to determine the relative importance of irradiation and thyrotropic hormone stimulation in initiation and
promotion of thyroid carcinoma in the rat are in progress in this laboratory.

The present study again revealed a high incidence of naturally occurring thyroid carcinomas (1, 11, 16) in both the control and irradiated rats. We had previously designated these lesions as alveolar or lobular carcinoma to distinguish them from malignant epithelial neoplasms induced by irradiation with \(^{131}I\) (19, 22). In this and in previous studies (19, 22), the incidence of alveolar or lobular carcinoma was the same in control and irradiated rats except that none was found in animals receiving the highest doses of \(^{131}I\) (400 \(\mu\)c). This indicates either that their development was prevented by irradiation or that they had been destroyed by the larger doses of \(^{131}I\) (19). The very high doses of \(^{131}I\) employed by Starr and his associates undoubtedly account for their failure to demonstrate alveolar carcinomas in their Long-Evans rats (9, 10).

The high incidence of proliferative parathyroid lesions in the animals of the present study, both controls and irradiated, is of considerable interest. No degenerative or fibrotic reactions like those observed in animals irradiated with \(^{131}I\) were found (19). Malcom et al. described similar proliferative lesions in rats that received thiouacil (20).

The extrathyroidal neoplasms found in these rats are comparable with those described previously in the Long-Evans strain (19). The single tracheal epidermoid carcinoma found in an irradiated rat was probably induced by radiation (15).

ACKNOWLEDGMENTS

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REFERENCES

5. ———. Effect of Radioactive Iodine Alone and in Combination with Methylthiouracil upon Tumor Production in the Rat’s Thyroid Gland. Ibid., 7:181-92, 1955.
24. ———. Studies on Experimental Goitre: VIII. Thyroid Tumors in Rats Treated with Thiouacil. Ibid., 28:40-63, 1947.
FIG. 1.—Normal thyroid gland of control rat. X250.

FIG. 2.—Hyperplasia of right lobe in thyroid gland irradiated with 1000 r. X250. The follicular cells are cuboidal, and a few mitoses are present.

FIG. 3.—Hyperplastic left thyroid lobe after right lobe was irradiated with 1000 r. X125. The cells are cuboidal or low columnar, and abundant pale colloid is present.

FIG. 4.—Thyroid gland irradiated with 2000 r. X250. Follicular atrophy and nuclear pleomorphism are present.

FIG. 5.—Large thyroid artery in gland irradiated with 2000 r. X125. Fibrinoid degeneration and inflammation are seen in the vascular wall.

FIG. 6.—Follicular adenoma in thyroid gland of rat irradiated with 500 r. X30. The epithelium is hyperplastic, and colloid cysts are present.

FIG. 7.—Follicular adenomas in thyroid gland of rat irradiated with 1000 r. X100. Margins of two hyperplastic macrofollicular nodules are seen. Compressed thyroid parenchyma is present on the right.

FIG. 8.—Follicular adenoma in thyroid gland of rat irradiated with 1000 r. X12. This large macrofollicular nodule occupies the entire left lobe.

FIG. 9.—Trabecular adenoma in thyroid gland of rat irradiated with 1000 r. X350. Note few microfollicles.

FIG. 10.—Alveolar or lobular carcinoma in thyroid gland of rat irradiated with 1000 r to the right lobe. X250.

FIG. 11.—Alveolar or lobular carcinoma in thyroid gland of rat irradiated with 500 r. X60. This neoplasm has replaced about one-third of the thyroid lobe but is limited by the thyroid capsule below.

FIG. 12.—Papillary carcinoma in thyroid gland of rat irradiated with 500 r. X250. This field shows the central portion of the neoplasm where most of the pattern is papillary. A few microfollicles are present.

FIG. 13.—Papillary carcinoma in thyroid gland of rat irradiated with 500 r. X250. This field is a more peripheral portion of the papillary neoplasm shown in Fig. 12. The pattern is still slightly papillary, but a few microfollicles are present.
Fig. 14.—Papillary carcinoma in thyroid gland of rat irradiated with 1000 r, X250. A small neoplastic nodule is invading the parenchyma above.

Fig. 15.—Papillary carcinoma in thyroid gland of rat irradiated with 1000 r, X250. A few papillary structures are present. Note pale nuclei.

Fig. 16.—Papillary carcinoma in thyroid gland of rat irradiated with 1000 r, X250. Note pale nuclei and predominant follicular pattern. A few papillary structures were present in this neoplasm.

Fig. 17.—Follicular carcinoma in right lobe of the thyroid gland of rat irradiated with 1000 r to the right lobe. X125. Two large capsular veins are extensively invaded by the follicular neoplasm.

Fig. 18.—Follicular carcinoma in the right lobe of thyroid gland of rat irradiated with 1000 r to the right lobe. X250. This neoplasm had a few microfollicles. Here the cells are spindle-shaped and have a perivascular arrangement.

Fig. 19.—Follicular carcinoma in right lobe of thyroid gland of rat irradiated with 1000 r to the right lobe. X125. The pattern is microfollicular, and invasion of the parenchyma is seen above.
FIG. 20.—Follicular carcinoma in thyroid gland of rat irradiated with 2000 r. X125. Minimal, early invasion of the parenchyma is seen above.

Fig. 21.—Follicular carcinoma in thyroid gland of rat irradiated with 2000 r. X250. Mild cellular pleomorphism and a microfollicular pattern are noted.

FIG. 22.—Chief-cell parathyroid hyperplasia in rat irradiated with 1000 r. X250. The proliferative process is diffuse, and the hyperplastic cells are larger than normal.

Fig. 23.—Clear-cell parathyroid adenoma in rat irradiated with 500 r. X125.

FIG. 24.—Chief-cell parathyroid adenoma in left parathyroid gland in rat irradiated with 1000 r to the right thyroid lobe. X60. Note compressed rim of residual parathyroid parenchyma.

FIG. 25.—Epidermoid carcinoma of trachea of rat irradiated with 3000 r. X125. The neoplasm is well differentiated and is invading the tracheal submucosa. Tracheal cartilage is seen below.
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