an abrupt decline of the blood sugar level which is followed within 20 to 45 minutes by a sharp rise. This is accompanied by a significant rise of the eosinophil level which is thought to be mediated by the same mechanisms as is responsible for the rise of the blood sugar level. 2. The adreno-demedullated animal shows normal hypoglycemia responsiveness in the insulin tolerance test and an accompanying rise of the eosinophil level similar to that of the intact animal. This indicates that the medullary secretion is unnecessary for either of these phenomena. 3. In the adrenalectomized and hypophysectomized animals a rise of the eosinophil level similar to that of the normal was demonstrated after insulin, even though the blood sugar changes showed no evidence of hypoglycemia responsiveness. This is interpreted to signify that the mechanism for hypoglycemia responsiveness in the hypophysectomized and adrenalectomized animal is intact but is not apparent, due to depletion of liver glycogen in the absence of the anterior-pituitary and adreno-cortical secretions.

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## Autonomous Transplantable Pituitary Tumors Arising in Growths Dependent on Absence of the Thyroid Gland.* (19501)

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"Invasive," "autonomous," "unrestrained" are adjectives commonly used to characterize cancerous growth. The study now to be described indicates the uncertainty of these terms in relation to neoplastic growth. Autonomy may be only apparent or partial, can never be certified to be absolute, and metastases may occur with conditioned neoplasms. Destruction of the thyroid by $I^{131}$ (250-300 $\mu$c) is followed by the development of pituitary growths 10 to 14 months later(1). These growths can be grafted readily in the muscle of mice similarly radio-thyroidectomized but not in normal mice(2). They grow progressively in the former until the death of the host and almost invariably metastasize to the draining lymph nodes. In over 100 such tumor-bearing mice not a single spontaneous regression was noted.

The procedures of inducing and transplanting the pituitary tumors have been described (2). All studies have been made in C-57 black mice. Seven transplantable strains were established thus far in radio-thyroidectomized

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TABLE I. Transplantation of Original $I^{131}$ Induced Pituitary Growths.

| Original Mouse No. | $I^{131}$, $\mu$c subcut. | Days from inj. to death | Recipients: $I^{131}$ pretreated No. + / No. inj. | Recipients: $I^{131}$ pretreated Latency, days | Recipients: Normal No. + / No. inj. |
|---|---|---|---|---|---|
| B 3 | 265 | 536 | 7/7 | (61-158) 117 | — |
| 19 | 198 | 516 | 2/2 | (157-175) 166 | 0/3* |
| 77 | 275 | 476 | 3/10 | (156-232) 188 | — |
| 163 | ±400 | 501 | 7/9 | (183-251) 220 | 0/10 |
| 124 | ±400 | 474 | 3/4 | (117-283) 161 | 0/5† |
| 101 | ±400 | 474 | 12/12 | (111-275) 153 | 0/2 |
| 82 | 278 | 564 | 2/5 | (176-359) 268 | 0/7 |
| | | Total | 36/49 | | 0/27 |

* Gonadectomized. † Two of these were gonadectomized.

TABLE II. Origin and Passages of an Autonomous Pituitary Tumor Line (B3).

| Passage | Sex | Mice: $I^{131}$ pretreated | Mice: Normal | Latency period (days): $I^{131}$ pretreated Range | $I^{131}$ pretreated Avg | Normal Range | Normal Avg |
|---|---|---|---|---|---|---|---|
| I a | ♀ | 13/14* | 8/8* | 80–173 | 96 | 179–239 | 208 |
| IIa | ♂ | 3/4 | 8/8 | 59–76 | 68 | 38–60 | 45 |
| b | ♂ | 3/4 | 9/10 | 45–53 | 50 | 45–63 | 49 |
| | ♀ | — | 10/10 | — | — | 29–63 | 41 |
| c | ♂ | 0/15 | 6/9 | — | — | 47–67 | 54 |
| | ♀ | — | 3/4 | — | — | 67 | 67 |
| d | ♂ | 0/4 | 5/5 | — | — | 46–56 | 51 |

* Number of mice with "takes" over number inj.

hosts (Table I). From 474 to 564 days elapsed after injection of $I^{131}$ until a marked loss of weight, humped posture, ruffled fur, and cachexia suggested the presence of a pituitary growth. The animals were killed and fragments of the pituitary growths were grafted into the muscle of 49 radio-thyroidectomized mice, in 36 of these with success. Grafts attempted simultaneously in 27 normal mice were uniformly unsuccessful. The period of latency of the growth in the primary grafts was usually long, averaging 117 to 268 days in these 7 strains (Table I). The first generation grafts grew very slowly and measured but 1 to 2 cm across after 2 to 4 months of manifest growth when the animals were sacrificed to make further subpassages. Several of these $I^{131}$ pretreated recipients had their own primary pituitary tumors at death. In the 2 strains in which primary grafts were made only in radio-thyroidectomized mice, subpassages were also made in normal mice thus far without success.

In one subpassage of the first strain (B3) so established in $I^{131}$ pretreated mice, the grafts grew also in normal mice (Tables II and III), but appeared after a longer latency period; this averaged 96 days in radio-thy-

TABLE III. Transplantation of Pituitary Growths of Strain B3 Dependent Line and Origin of an Autonomous Line in Passage Ia.

| Passage | $I^{131}$ pretreated hosts: No. + / No. inj. | $I^{131}$ pretreated hosts: Latency period, days* Range | $I^{131}$ pretreated hosts: Latency period, days* Avg | Normal hosts: No. + / No. inj. | Normal hosts: Observ. period, days |
|---|---|---|---|---|---|
| Original | 7/7 | 61-158 | 117 | | |
| I a | 13/14 | 81-172 | 95 | 8/8† | 319 |
| b | 10/10 | 95-104 | 96 | 0/11 | 240 |
| c | 11/11 | 96-190 | 116 | 0/11 | 246 |
| d | 6/6 | 77-96 | 87 | 0/6 | 210 |
| II a | 7/7 | 93-139 | 125 | 0/7 | 225 |
| b | 6/6 | 93-139 | 118 | 0/7 | 225 |
| c | 6/6 | 65-75 | 73 | 0/5 | 197 |
| d | 6/6 | 74-100 | 85 | 0/4 | 188 |
| e | 15/15 | 61-126 | 89 | — | — |
| f | 4/4 | 90-112 | 98 | 0/4 | 159 |
| g | 5/5 | 72-99 | 82 | 0/11 | 126 |
| h | 5/5 | 77-91 | 83 | 0/5‡ | 113 |
| IIIa | 10/10 | 60-76 | 68 | 0/16 | 88 |

* In $I^{131}$ pretreated hosts.
† Origin of the autonomous line.
‡ Received 25 $\mu$c of $I^{131}$ that does not destroy the thyroid gland.

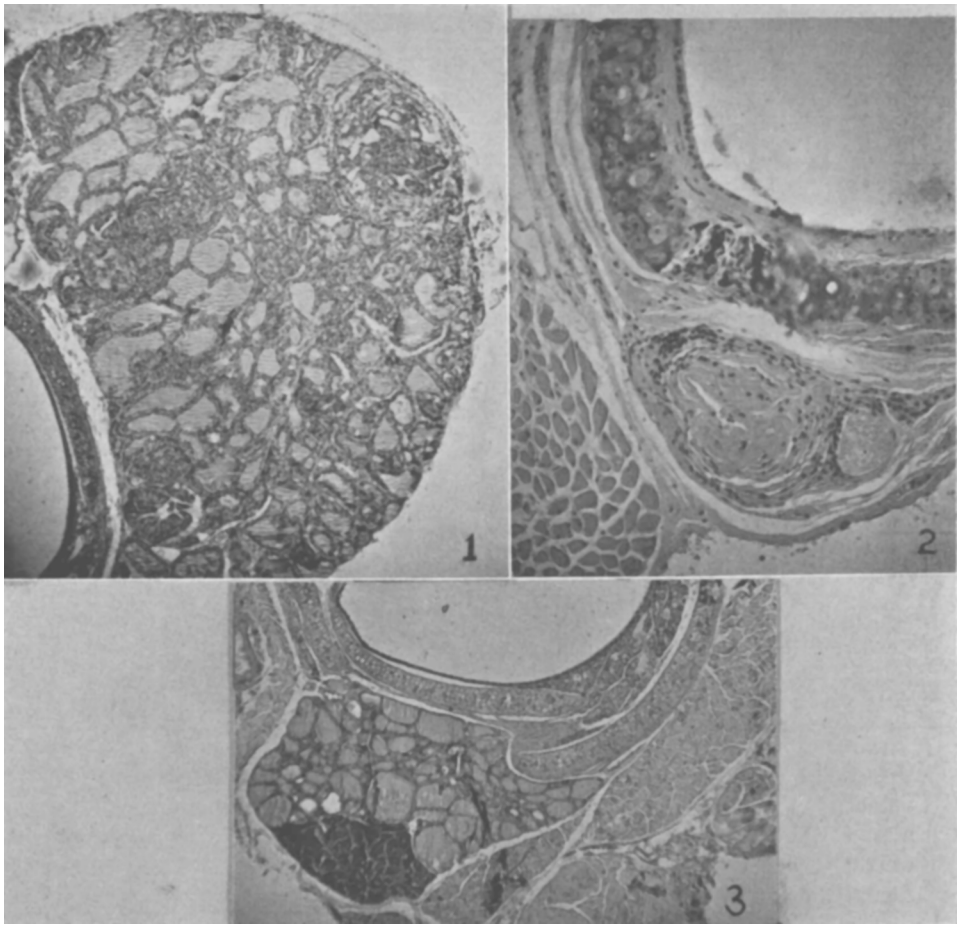


FIG. 1. Thyroid with numerous nodular areas of hyperplasia (adenomas). Mouse carried a pituitary tumor of the autonomous line. × 40.

FIG. 2. The site of a thyroid destroyed by $I^{131}$, marked by "radiation arteritis." Mouse carried a grafted pituitary tumor of the dependent line. × 100.

FIG. 3. Normal thyroid gland of a mouse with parathyroid gland. × 40.

roidectomized mice and 208 days in normal mice. Similarly, the tumors grew at a much slower rate in normal mice than in those receiving thyroid destructive doses of radio-iodine. In further subpassages of this autonomous line the tumor grafts took even more readily in normal mice than in radio-thyroidectomized mice as indicated in Table II. Passage IId includes 4 additional mice (not listed in Table II) pretreated with thiouracil beginning 13 days before grafting. In 2 of these mice tumors appeared after 45 days.

Table II indicates the readiness with which the pituitary tumor that gained autonomy can be passed to normal mice. In contrast, other passages of strain B3 in which this autonomous line originated remained dependent on the absence of the thyroid gland as indicated in Table III during the period of observation.

*Discussion.* It is remarkable that transformation should occur in the first subpassage and not again during the next 11 subpassages involving 87 normal mice receiving tumor fragments.‡ In contrast all 91 radio-thyroidec-

‡ After the observation period indicated, several months after death of the $I^{131}$ pretreated mice with large tumors, some of the normal mice have developed small slowly growing tumors. This phenomenon is being studied.

tomized mice that had been injected with the same material developed tumors and almost all metastasized to the regional lymph nodes. The passages were made with tumor fragments. It is possible that some pituitary cells in lymph nodes did acquire some autonomy.

The salient characteristic features of this autonomous in contrast to the dependent growth† are as follows: Hosts bearing autonomous growths have tremendously stimulated thyroids (Fig. 1). In $I^{131}$ pretreated hosts of the dependent line the thyroids are absent (Fig. 2) or atrophic, non-responsive to TSH. The thyroid in the former mice is several times larger than in normals (Fig. 3); the colloid tends to disappear and numerous adenoma-like nodules replace the normal gland (Fig. 1).

There is morphologic evidence of stimulation of the gonads in mice of both sexes with both FSH and LSH in both autonomous and dependent lines. This stimulation is, however, less intense in the autonomous line.

Hyperplasia with cystic dilatation of the extrahepatic ducts has not been seen in mice with autonomous pituitary tumors thus far autopsied. This endocrine effect occurred in most radio-thyroidectomized mice bearing large tumors(3). Most autonomous tumors thus far studied were, however, smaller than the dependent tumors, but many of them equaled in size the dependent tumors which were associated with common duct cysts. Further observations are needed to ascertain if the absence of stimulation of the common duct is related to the tumor size, lack of the thyroid gland of the hosts or differences in the tumor cells.

The adrenals in both lines are smaller than normal or approximately normal. There are retrogressive changes in the reticular zone of the adrenal cortex in both tumor lines. In the autonomous line the cells of the reticular zone characteristically contain large (presumably fat) vacuoles. Although in radio-thyroidectomized mice the thymus glands were characteristically atrophic, in normal mice with autonomous growths they were frequently present and approximately normal in size. These morphological observations suggest lack of ACTH production by these tumors. The pituitaries of these mice have thus far not been adequately studied. In the radio-thyroidectomized tumor-bearing mice, they are enlarged and show either the well-known changes of thyroidectomy or hyperplasia with adenoma-like nodules as described by Gorbman(1). The pituitaries of normal tumor-bearing animals appear of normal size and contain the normal type of cells.

*Summary.* 1. All of 7 pituitary growths induced by thyroid destructive doses of $I^{131}$ proved transplantable to mice similarly pretreated but not to normal mice. In a subpassage of one strain (B3) a tumor acquired the ability to grow in normal mice giving origin to a pituitary tumor line which can be grafted as readily if not better in normal mice than in radio-thyroidectomized mice. 2. In normal hosts of this autonomous tumor there is a tremendous hyperplasia of the thyroid gland with multiple adenoma-like nodules. There is also some gonadal stimulation of the hosts but no evidence of ACTH secretion by these tumors. Thus a gain in autonomy occurred with retention of the ability of these pituitary tumor cells to secrete thyroid and gonad stimulating hormones. 3. These studies indicate the uncertainty and relativity of the term "autonomy" in relation to neoplastic growth. Regional metastases do not indicate "autonomy" as they occur also with conditioned neoplasms.

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† These terms are retained for didactic purposes only.

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