Autonomous Mammotropic Pituitary Tumors in Mice
Their Somatotropic Features and Responsiveness to Estrogens*

JACOB FURTH, EVELYN L. GADSDEN, KELLY H. CLIFTON,† AND EVELYN ANDERSON

(Children's Cancer Research Foundation, Departments of Pathology, Harvard Medical School, and The Children's Medical Center, Boston, Mass., and National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.)

The development of transplantable mammotropic pituitary tumor strains, now reported in detail, was mentioned briefly at recent conferences (7, 8, 10). It has made possible a study of functional interrelationship of gonads, pituitary, and mammary glands, yielded a new model for the induction of conditioned or autonomous neoplasms through disturbances of a feed-back mechanism, and made mammotropic cells available for morphologic, physiologic, and chemical studies.

Autonomous mammotropic tumors were induced in mice by total-body ionizing irradiation, and dependent mammotropic tumors in mice and rats by large doses of estrogens. Of nine tumors induced by total-body ionizing irradiation from an atomic detonation (17) that were assayed by transplantation in normal hosts, three were adrenotropic, one predominantly somatotropic, and five were of the type here described. The common basic features of these tumors are: ability to stimulate the mammary gland, lack of overtly detectable stimulation of other endocrine organs, some dependence on estrogens, associated somatotropic effects, and, frequently, the presence of coarse acidophilic granules in the cytoplasm of tumor cells. The differences among these mammotropic strains appear to be quantitative, and therefore only one (Strain 4) which has been most extensively studied will be fully described.

It has long been known that estrogens induce pituitary tumors, but little is known about the character of these tumors. Evidence is presented in the accompanying paper (9) that rat pituitary tumors induced by estrogens are also mammotropic. Dunning et al. (6) found that such tumors could be successfully transplanted only to animals treated with estrogens. Thus, they appear to be dependent variants which arise from the same pituitary cell types as the mammotropic tumors of mice. From a consideration of all facts detailed in this and the accompanying article, the conclusion is reached that the basic mechanism of induction of mammotropic tumors by administration of estrogens or by total-body ionizing irradiation is essentially the same.

Nomenclature

The mammary gland-stimulating cells of the pituitary and those of the tumors here described will be referred to as mammotropes (Mt), the tumors as mammotropic tumors (MtT), their hormone mammotropin (MtH, syn. prolactin). These terms are used merely to simplify presentation; we are aware of the dispute as to the dual action of this hormone (on both ovary and mammary gland), the differences in the mechanism of stimulating growth and secretion of the mammary gland, and between ductal and alveolar growth of this organ. In the animals under study tubular and alveolar growth and secretion in the mammary gland were present in varying proportions.

Correspondingly, the other types of pituitary tumor cells studied will be spoken of as adrenotropes (At), thyrotropes (Tt), and somatotropes (St); their hormones as AtH, TtH, and StH; and their tumors as AtT, TtT, and StT, respectively. The insertion of “t” is proposed in these symbols to distinguish “tropic” hormones and tumors of the pituitary from those of its target organs; e.g., adrenal tumors will be referred to as AT, adrenotropic tumor of the pituitary as AtT.

MATERIALS AND METHODS

Transplantations.—All experiments were carried out in LAP1 mice in which the tumor arose. Almost all these mice were obtained from the Jackson Memorial Laboratory. For routine transfers mice 6–12 weeks of age were grafted intra-
muscularly in the right thigh with tumor particles suspended in 0.05-0.1 ml. chilled saline.

Operative technic.—Hypophysectomies were made by two of the authors, one (E.G.) using the technic of Speirs,1 the other (E.A.) a technic of her own. Gonadectomies were performed by standard methods.

Hormonal maintenance of gonadectomized animals.—Estriol dipropionate (Ciba), dissolved in sesame oil, was given by standard methods in 0.05-0.1 ml. chilled saline. Progesterone (Pfizer)2 in sesame oil was administered subcutaneously in a dose of 0.2 mg. daily for 7 days, then S times weekly for 11 weeks, and twice weekly thereafter.

RESULTS

Transplantation of Strain 4.—The salient transplantation data of Strain 4, shown in Table 1, are characteristic of radiation-induced pituitary tumors of this type, and the results and conclusions are, in general, applicable to other mammotropic pituitary tumor strains.

The latency period, i.e., the time required for microscopic study of a large part of the gland.

The pituitary gland was fixed with the underlying sella and stained with trichrome as described by Gude (13). This preparation yields some information on invasiveness of the tumor and, incidentally, samples the bone and bone marrow of the sella.

Table 1: Transplantation Data of Mammotropic Tumor Strain 4

<table>
<thead>
<tr>
<th>Passage</th>
<th>No. inj.</th>
<th>No. +</th>
<th>Latency (day)</th>
<th>Duration (day)</th>
<th>Av. (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1/2</td>
<td>182</td>
<td>282</td>
<td>105-185</td>
<td>154-244</td>
</tr>
<tr>
<td>IIa</td>
<td>2/5</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIb</td>
<td>1/5</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIIa</td>
<td>2/6</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIIb</td>
<td>1/6</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIIc</td>
<td>2/6</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIId</td>
<td>1/6</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
<tr>
<td>IIIe</td>
<td>2/6</td>
<td>281</td>
<td>234</td>
<td>155-244</td>
<td>195-244</td>
</tr>
</tbody>
</table>

1 We are indebted to Dr. Robert Speirs for his instruction.
2 Kindly supplied by Dr. Joseph T. Velardo.
3 Data on radiation-induced primary pituitary tumors are cited with permission of Dr. A. C. Upton.

the grafted tumors to become palpable, was very long at first and became shorter in the course of passages. The first-generation grafts caused large tumors in 281–431 days in contrast to 87–91 days of a line of third-generation grafts.

Anatomic characteristics of MtT.—The tumors were soft, usually pink or grey-red, containing many sinusoidal or cavernous blood vessels. Hemorrhages and necrosis were common in large tumors; fibrous stroma was scant.

The tumor cells of Strain 4 had two distinct features: coarse acidophilic granules in the cytoplasm (Fig. 3) and a tendency to line up along cavernous spaces forming ductlike structures (Figs. 1, 2) with the nuclei located away from the sinuses. The granules were not seen in the usual hematoxylin-eosin-stained preparations but were marked with the Mallory-Martin stain (13). The tumor cells were uniformly uniform in size and shape, and giant forms were few. Mitotic figures were present in moderate numbers. Frequently, erythrocytes filled the lumina of spaces lined with tumor cells. This is a characteristic feature of...
many spontaneous, induced, and grafted pituitary tumors and explained their hemorrhagic appearance. The tumor cells failed to give the periodic acid-Schiff and aldehyde-fuchsin reactions.

The pituitaries of mice bearing grafted MtT showed no distinct change other than a decrease in eosinophils. This may be expected to occur with acidophilic tumors but has also been noted in the presence of TtT and therefore cannot be considered a specific change.

Mammary gland.—Gland stimulation was either predominantly ductal (Figs. 6, 8) or alveolar (Figs. 6, 9); usually both were present in varying degrees. Stimulated ducts distended with secretion were recognized grossly as thick linear structures radiating from the nipples (Fig. 6). When alveolar hyperplasia was marked, it resembled that of pregnancy. Fat stains showed acini and ducts distended with lipid-laden cells and lipid-rich cell debris.

The mammary glands of tumor-bearing males contained collapsed rudimentary ducts only, but those of castrated males bearing ovarian grafts were similar to those of females on both gross and microscopic examination.

Mammary tumors were not seen in these glands even though the tumor-bearing periods were very long (Table 1). Spontaneous MT is rare in mice of this strain.

Sex organs.—The ovaries were characteristically smaller than normal (Figs. 10—12). The granulosa follicles were small without evidence of maturation; there was an unexpected lack or scarcity of luteinized follicles, and often there was a marked stromal luteinization (Figs. 11, 12).

The uterine horns were slightly but invariably thinner than those of paired normal controls (Fig. 6). The vaginal epithelium was mucinuous.

The testes were of about normal size. Spermatogenesis was maintained, the Leydig cells were normal or hypertrophied. The seminal vesicles were usually large.

Figure 13 illustrates an ovarian graft in a castrated male and shows numerous "healthy" granulosa follicles. Estrogens, the main stimulants of Mt secretion, are probably the product of these granulosa cells.

Somatotropic effects.—Chart 1 indicates a marked increase in total body weight and that of certain organ weights in MtT-bearing animals. The organ weights are shown in terms of per cent of body weight. The gain in body weight was much beyond that accounted for by tumor weight; e.g., mouse 2964 weighed 22.1 gm. more than the controls, and the tumor weighed only 10.7 gm. In males there was a marked somatotropic effect without mammary gland stimulation. Enlargement of liver and kidneys was conspicuous at autopsy in tumor hosts of both sexes (Fig. 6).

Liver.—The microscopic appearance of the liver was highly characteristic: in the centers of the lobules were areas of greatly enlarged liver cells with large, frequently hyperchromatic nuclei and abundant cytoplasm, alternating with peripheral
areas of normal liver cells (Figs. 14, 15). Mitotic figures were common. PAS-positive material seemed more abundant in the hyperplastic than in the normal cells. Sudanophilic fat was usually absent.

Spleen.—There was enlargement of this organ due to extensive myelopoiesis, both granulocytic and erythropoietic with megakaryocytes.

Kidney.—This organ was frequently enlarged, but the cause of the enlargement was not immediately evident. Frequently, the surface was very finely granular, and the microscopic examination indicated marked nephrotic changes with tubular degeneration or necrosis. Distention of the tubules with hyaline material similar to that noted in rats with dependent or autonomous grafted estrogen-induced MtT was common (Fig. 16).

TABLE 2

<table>
<thead>
<tr>
<th>TUMOR-INDUCING HOSTS</th>
<th>DAYS AFTER TUMOR GRAFT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>110</td>
</tr>
<tr>
<td>Females:</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>5 (6)*</td>
</tr>
<tr>
<td>Ovariectomy</td>
<td>0 (7)</td>
</tr>
<tr>
<td>Ovariectomy-estrogen</td>
<td>0 (8)</td>
</tr>
<tr>
<td>Ovariectomy-progesterone</td>
<td>0 (7)</td>
</tr>
<tr>
<td>Ovariectomy-estrogen-progesterone</td>
<td>0 (8)</td>
</tr>
<tr>
<td>Males:</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>0 (8)</td>
</tr>
<tr>
<td>Castrate</td>
<td>0 (8)</td>
</tr>
<tr>
<td>Castrate-ovarian graft</td>
<td>0 (7)</td>
</tr>
</tbody>
</table>

* The figures indicate the mean tumor diameter in mm., those in parentheses, the number of mice in the group.

Relation of gonads to tumor growth.—Table 1 indicates that the transplanted tumors appeared sooner and grew faster in females than in males. Mammary gland hyperplasia occurred only in females. The growth rate of the tumors markedly increased in the third successive generations, but the preferential growth in females persisted.

Strain 5 was studied almost as extensively as Strain 4 but will not be detailed because it appeared hormonally less active. The mean latent period in the original grafts was 248 days in females; in the first sub-transplant generation, 82 and 117 days in females and 102 and 899 days in males; in the second generation, 50, 110, 125, and 136 days in females and 155 days in males. Thus, responsiveness to female gonadal hormone was evident in spite of greater dedifferentiation. Strain 8, which is presently under investigation, likewise exhibits a marked preferential growth in females.

In order to elucidate this sex influence the experiments shown in Table 2 were undertaken.

Ovariectomy not only abolished mammary gland stimulation in females (as might have been expected), but also greatly retarded the growth of these mammatropic pituitary tumor cells. Thus, in spite of marked autonomy, Strain 4 was still dependent to a considerable extent on gonadal hormones. The same was found to be true of the even more dedifferentiated Strain 3 in which the latent period of tumor growth in normal females (passage IIb) was 50 days and in ovariectomized females 97 days.

Following up these observations showing that ovariectomy markedly delayed the growth of MtT, an experiment was performed in which ovariectomized mice were given small doses of estrogen, progesterone, or ovarian grafts. Growth of MtT was greatly promoted by estrogen in castrated females or ovarian grafts in castrated males.

Growth on hypophysectomized hosts.—Dependence of these neoplastic mammatropic tumor cells on ovarian hormones is clearly indicated by extraordinary retardation of their proliferation by hypophysectomy. Tumor grafts of Strain 4 (passage II) were not palpable in hypophysectomized mice before 500 days, while all normal siblings had tumors of about 2—3 cm. in diameter 85—130 days after grafting.

In passage II of Strain 4, tumors were not detected in two hypophysectomized females which died 161 and 174 days after receiving tumor grafts and in one autopsied at 302 days. In normal female mice grafted at the same time, tumors appeared within 59—140 days, and these mice died with large tumors after 121—216 days.

In Strain 8 (passage II) all normal females developed tumors after a latency period of 74—129 days, while all three hypophysectomized mice were still alive at 220 days without tumors. In one operated animal in which the tumor grew as well as in normal mice a small pituitary remnant was present.

In passage IIb of Strain 8, normal females developed tumors after latency periods of 51—97 days and died or were killed with large tumors after 110 and 125 days. Two hypophysectomized mice
grafted at the same time with the same material developed tumors at 191 and 205 days. One died with a 2-cm tumor at 230 days, while the other is alive at 250 days.

Changes in a mouse 17 months after hypophysectomy.—In one animal grafted 3 months after hypophysectomy, the graft was first palpated at 349 days. The animal died 485 days after graft and 17 months after hypophysectomy, at 638 days of age. Because of lack of information on late changes in hypophysectomized mice, the findings in this animal will be detailed. Pituitary tissue was not identified. At autopsy the tumor measured 2 cm. in average diameter. The appearance of the tumor cells is shown in Figures 4 and 5. Superficially, the individual cells resembled liver cells without any definite structural organization. The thyroid was enlarged but on microscopic examination was found to be atrophic with deposition of much interstitial "hyalin" (Fig. 19) causing the increase in size. Much of the parenchyma of the parathyroid was similarly replaced by this hyalin (Fig. 20). The ovaries were atrophic, mature follicles and corpora lutea were absent, and the uterine horn was very thin. Microscopic examination of the mammary gland showed atrophy with a few scattered ducts and much fibrous interstitial tissue. Blood vessel walls were thickened, and the interstitium contained many mast cells. The significance of these changes is not clear. The advanced atrophy of the adrenal is shown in Figures 17 and 18. Only two types of cells were present in the very thin cortex: small atrophic subcapsular cells, probably at the site of the glomerulosa zone, and large cells with bulky eosinophilic cytoplasm at the site of the fascicular zone. A few ceroid cells marked the site of the reticular zone. There was slight lymphocytic hyperplasia of spleen and lymph nodes with perivascular lymphoid infiltration in scattered organs. A small cavernous hemangioma was found under the skin. The bone marrow of the sella showed hyperplasia of normal marrow elements, mainly granulocytes and megakaryocytes.

Atypical sub-line of Strain 4 characterized by mammotropie and adrenotropic features.—In passage IIb (transfer from a male) the grafts grew equally well in both males and females. The latency period was about 73–97 days, in contrast to the donor line in which the latent period was 225–505 days in males. The tumors grew rapidly, and the hosts became obese. Typical MtT strains cause weight gain but only slight or no obesity. Adrenalectomy abolished obesity in four of six mice. Although the tumors grew as well in males as in females, a typical MtT grows better in females. The mammotropic character of the tumor cells was indicated by the extensive alveolar stimulation of the breast in all six tumor-bearing female mice. AtT does not stimulate the mammary gland. Leukopenia, characteristic of AtT-bearing animals, was absent. The thymus was, however, atrophic in all nonadrenalectomized tumor-bearing hosts. AtT causes involution of the thymus while the tumor is small and the animal is in excellent health. Hypophysectomy retarded the growth of these tumors, the latency period in three animals being 151, 151, and 199 days, in contrast to 97–130 days in normal males. Gain in body weight with obesity and splanchnemegaly was evident in hypophysectomized mice. At 202 days after tumor graft two mice with tumors of about 1 cm. weighed 88 and 42 gm., an estimated gain in weight of over 15 gm. The thymuses of the hypophysectomized mice were atrophic, the adrenals were normal or slightly enlarged. The testes and seminal vesicles were markedly atrophic, and the thyroids were small-normal.

Thus, in spite of the increased growth vigor of the tumors, their characteristic somatomotropie and mammotropie features persisted; but it seems that this line had also some adrenotropie properties.

This atypical line presents a puzzle to us. Earlier, we noted the sudden development of a highly malignant nonsecretory line in an adrenotropic tumor strain. It is possible that a modification of hormone secretion occurred in the course of transplantations, or that the strain contained a few adrenotropes which overgrew the mammotropes in a host favoring their growth.

DISCUSSION

A tumor is usually the result of unrestrained proliferation of one cell type of the organ in which it arises. Therefore, it should be possible to develop functioning pituitary tumors of as many cell types as the organ possesses; e.g., functioning thyrotropic pituitary tumors have been induced by destroying the thyroid gland or blocking its function (4); adrenotropic tumors have been induced by total-body ionizing irradiation (17). Neither of these exhibits mammotropie properties in normal hosts. The specificity of these tumors is well shown in hypophysectomized hosts; e.g., hypophysectomized hosts with adrenotropic tumors died with overactivity of the adrenals, while other target endocrinies of the hypophysis remained atrophic. Mammotropie tumors are unknown in man. Acromegaly is sometimes associated with lactation. Mammary gland hyperplasia in mice with pituitary tumors has been mentioned by several

*J. Furth, E. Anderson, and E. L. Gadsden, unpublished data.*
investigators, but transplantable mammatropic tumors have not been described in any species. The mammatropic tumors here described were autonomous, though they retained responsiveness to estrogens.

MtH is generally considered to have a dual action: stimulation of secretion by corpora lutea and a direct effect on the mammary tissue causing secretion (16). The lutein hormones are thought to prepare the mammary gland for the direct action of MtH. The present findings do not indicate excessive gonadal stimulation in transplanted MtT of MtH. The ovaries and uterine horns were not enlarged, as they would be when hyperstimulated. Corpora lutea were often absent in ovaries of mice bearing MtT. Nevertheless, in mice the ovarian hormones seem necessary for mammary gland stimulation by MtT, since mammary growth was not found in male MtT hosts. It was, however, seen in rats bearing similar tumors (9). In this species the estrogenic hormones may not be necessary for growth of the mammary gland or may have been supplied by the adrenals. Furthermore, physiologic quantities of estrogen act as a driving force of the Mt, i.e., estrogen increases the rate of proliferation of Mt. These results emphasize the need for more information on the interrelationship of MtH and ovarian hormones, both as to effects of each on secretion of the other and as to their combined action on the mammary gland.

Transplantation.—Most variations in the latency period were probably due to inadequate standardization of number of cells grafted and age of recipients. The shortening of the latency period with successive generations is best explained by the natural selection of more rapidly growing variants. Because of a diminution in hormone production with the acquisition of growth vigor, transfers were made from slowly growing lines whenever feasible, and rapidly growing lines were closed out.

While occasional failures in takes in earlier passages could be attributed to technical errors, the more numerous failures in later passages may have another explanation. It is probable that many cells of the primary radiation-induced tumors were not fully autonomous or histocompatible and that some natural selection of more malignant variants adapted to normal LAF1 mice occurred in the course of subpassages. The LAF1 mice were irradiated in 1951. The original tumors were detected and the primary grafts made in 1953; subsequently, both host mice and tumor cells may have undergone independent modifications. The occurrence of modifications in tumor cells during successive transplantations is well known.

The usual change in the course of transplantation is loss of secretion and increase in virulence and rate of proliferation. With radiation-induced tumors an apparent change in character may occur. A specific hormonal disturbance induces a specific type of pituitary tumor, while radiation induces several types of tumors. It is natural, therefore, that some radiation-induced tumors are composed of mixed-cell populations, and one cell type may outgrow others in the course of subpassages. The radiation-induced pituitary tumors assayed were usually adrenotropic or mammatropic; one was somatotropic. It is conceivable that the predominantly mammatotropic tumors initially contained adrenotropes in small numbers and that hosts used acted as selectors: e.g., a female host would select Mt at the expense of At, and passage in male hosts would result in relative loss of Mt. Excessive estrogen stimulation would act as a selector of Mt, and adrenal depression as a selector of At. It is of interest in this connection that primary radiation-induced ovarian tumors were usually complex, and it has been possible to isolate by transplantations from a single tumorous ovary three different types of ovarian neoplasms (secretory granulosa and lutein-celled tumors and an adenomatous growth [1]). These considerations may serve as leads to experiments designed to better characterize the radiation-induced (and other) pituitary tumors as to autonomy and hormonal secretion, and to isolate pure cell strains.

Secondary changes.—The somatotropic effects of mammatropes, first indicated by the work of Bates et al. (2), are discussed in the accompanying paper (9). The secondary changes noted in mice bearing different types of autonomous pituitary tumors thus far studied are surveyed in Table 3.

The somatotropic action of grafted MtT on the liver is similar but not as extensive as that noted earlier in mice bearing transplants of a radiation-induced tumor which was predominantly somatotropic (7, 8). Autonomous MtT in mice caused focal, predominantly central hyperplasia of liver cells, while autonomous StT in mice caused a more marked hyperplasia involving the entire organ. Enlargement and hyperchromatophilia of liver cell nuclei and increased basophilia of the cytoplasm suggest stimulation of synthesis or "storage" of DNA and RNA by both StH and MtH. In contrast, the gain in body weight in AtT hosts is due to obesity which is absent with StT and is slight with MtT. Stimulation of lipid and carbohydrate metabolism with AtT (Ath) of mice is indicated by studies of Mayer et al. (14). MtT hosts (in contrast to StT hosts) are usually slightly obese. Apparently, several pituitary hormones have

J. Mayer, personal communication.
some general growth-promoting effects. Earlier, we noted the gain in weight of normal mice bearing autonomous thyrotropic pituitary tumors but have overlooked the general growth-promoting effect of TtH. To fill this gap, body and organ weights of groups of three normal mice bearing such tumors were determined with those of well matched controls.

Table 4 indicates that autonomous TtT in normal hosts has some growth-promoting effect. It is probable that TtH causes these changes by stimulation of the thyroid gland.

Specificity of mammary gland stimulation.—Primary pituitary tumors induced in mice and rats by different procedures are frequently associated with mammary gland hyperplasia. These procedures are: administration of large quantities of estrogen (3, 15, 19), ovariectomy (5), thyroidectomy (4, 12), and whole-body ionizing irradiation (17). The mere presence of mammary gland hyperplasia in a tumor-bearing host does not indicate that the tumor secretes MtH. A slight mammary gland hyperplasia is common in old female mice, and a moderate hyperplasia may be induced by indirect mechanisms—as seems to be the case with pituitary tumors induced by thyroidectomy. Assays of such tumors performed by Bates indicate the presence of large quantities of TSH but no MtH. When such TtT are grown on normal hosts they fail to stimulate the mammary gland but cause a tremendous enlargement of the thyroid. Therefore, bioassays for MtH and other hormones will be essential to define precisely the character of these tumors. Hormonal aspects of mammary gland stimulation are discussed in the accompanying paper (9).

Relation between estrogen- and radiation-induced

R. W. Bates, personal communication.

TABLE 3

<table>
<thead>
<tr>
<th>Scheme of Changes Noted in Mice Bearing Transplanted Autonomic Pituitary Tumors of Several Types Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Mammary gland in females</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Adrenal</td>
</tr>
<tr>
<td>Thymus</td>
</tr>
<tr>
<td>Changes in hypophysectomized mice</td>
</tr>
</tbody>
</table>

* Statements made from study of a single strain. Of the other types, three or more strains were studied.
† Depending on the size of the tumor; decrease may be due to nonspecific stress.
‡ Probably dependent on the degree of autonomy of the tumor. Ovarian hormones may be essential for growth of fully dependent mammaryotropic tumors. Similar considerations apply to the other types of tumors.

TABLE 4

<table>
<thead>
<tr>
<th>Gain in Body and Organ Weights in Mice Bearing Autonomous TtT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mice</strong></td>
</tr>
<tr>
<td><strong>Weights</strong></td>
</tr>
<tr>
<td>(gm.)</td>
</tr>
<tr>
<td>Body</td>
</tr>
<tr>
<td>Tumor</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Kidney</td>
</tr>
<tr>
<td>Heart</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
</tbody>
</table>

All figures are from mice bearing mammatropic tumors or from controls. All sections were stained with hematoxylin and eosin with the exception of Figure 5 showing the acidophilic granules, which was stained with trichrome (18).

Fig. 1.—Tumor (Strain 4) grown in normal male; note ductlike growth. X200.

Fig. 2.—Same as Figure 1, with higher magnification; orientation of tumor cells about sinusoidal capillaries. X680.

Fig. 3.—Tumor (Strain 8) showing acidophilic granules in cytoplasm characteristic of mammatropic cells. X2000.

Fig. 4.—Tumor (Strain 4) grown in a hypophysectomised mouse. X800.

Fig. 5.—Same as Figure 4. X680.
Fig. 6.—(A) Mouse with grafted MtT of Strain 4: Note tumor (T), marked alveolar hyperplasia of the mammary gland (arrows), enlargement of liver, kidneys, and spleen (compare size of these organs with those of control B), and lack of enlargement of ovaries and uterine horns. (B) Control animal: Arrows point to atrophic, slightly fatty mammary gland. (C) Marked ductal hyperplasia of the mammary gland (arrows) of a mouse bearing MtT, Strain 4.
FIG. 7.—Mammary gland of a young adult normal female mouse. X95.

FIG. 8.—Microscopic appearance of the greatly distended mammary ducts of the tumor-bearing mouse, shown in lower left field of Figure 6. X95.

FIG. 9.—Microscopic appearance of the mammary gland of the tumor-bearing mouse, showing predominantly alveolar stimulation as shown in upper field of Figure 6. X95.
Fig. 10.—Ovary of an 8-month-old normal mouse. ×40.

Fig. 11.—Ovary of a 9-month-old mouse with a large mammotropc tumor (Strain 3); atrophy with stromal luteinization. ×40.

Fig. 12.—Same ovary as in Figure 13. ×105.

Fig. 13.—Ovarian graft in castrated male with a large tumor (Strain 4); well preserved granulosa follicles, some of which have ova, corpora lutea, and interstitial luteinization; some lutein cells appear degenerated. ×105.

Fig. 14.—Normal liver. ×200.

Fig. 15.—Liver of a mouse with a large tumor (Strain 4); foci of greatly enlarged liver cells and one mitotic figure. ×200.
Fig. 16.—Kidney of a 10-month-old female mouse with a large tumor (Strain 4); hyalin and cellular casts distending many tubules. X 150.

Fig. 17.—Adrenal cortex of a female mouse hypophysectomized 17 months earlier; the animal had a large, very slowly growing tumor (Strain 4); advanced atrophy. X 40.

Fig. 18.—Same as Figure 17 with higher magnification. The cortex is represented by two layers: a markedly atrophic subcapsular layer and a thin layer of hypertrophied cells with abundant eosinophilic cytoplasm. The epicapsular fat cells are atrophic.

Fig. 19.—Atrophy with marked interstitial hyalinization which caused enlargement of the thyroid in the same hypophysectomized mouse. X 204.

Fig. 20.—Atrophy with interstitial hyalinization of parathyroid in the same mouse. X 204.
gen-induced MtT in rats (9) and radiation-induced MtT in mice are striking. Both tumors have somatotropic and mammotropic properties, both respond to estrogens, and both bear acidophilic granules in many cells. Most common ovarian tumors induced by radiation are of the granulosa-cell type (11), and such tumors result in hyperestrogenization (1). These considerations lead to the conclusion that estrogen-induced and radiation-induced MtT are predominantly composed of the same functional cell type, and it seems most probable that they are induced by the same basic mechanism, i.e., prolonged and continuous stimulation by estrogens. According to this postulate, radiation-induced MtT may be secondary to a primary ovarian and/or adrenal dysfunction related to hyperestrogenization. If this is correct, ovariectomy should prevent MtT induced by radiation.

**SUMMARY AND CONCLUSIONS**

Two types of transplantable pituitary tumors were commonly found in female mice following massive whole-body ionizing irradiation: adrenotropic and mammotropic. The former appeared earlier, but the latter was more common.

Mammary gland hyperplasia is distinct only in female mice bearing mammotropic tumors.

The mammotrophic tumor also exerts some somatotropic effects, and this occurs in animals of both sexes. Proliferation of mammotropes appears to be dependent on stimulation by gonadal hormones, mainly estrogens. The neoplastic mammotropes of mice, although autonomous, retained responsiveness to estrogens.

Most mammotropes have coarse acidophilic granules. These radiation-induced mammotrophic tumors appear similar to those induced by large doses of estrogen.

The working hypotheses are advanced (a) that estrogen is the physiologic growth stimulant of the mammotropes and (b) that the mechanism by which two known procedures (total-body irradiation and large doses of estrogens) induce mammotrophic pituitary tumors is continuous hyperestrogenization.

An incidental observation recorded is a marked somatotrophic effect of autonomous thyrotropic tumors grown in normal hosts. It is suggested that several pituitary hormones possess general somatotropic properties probably exerted by different mechanisms.

**ACKNOWLEDGMENTS**

The excellent technical assistance of Mrs. Lena Zompetti is acknowledged.

All photographs were taken by Mr. John Carabittes.

**REFERENCES**

Autonomous Mammotrophic Pituitary Tumors in Mice: Their Somatotropic Features and Responsiveness to Estrogens

Jacob Furth, Evelyn L. Gadsden, Kelly H. Clifton, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/16/7/600

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cancerres.aacrjournals.org/content/16/7/600.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.