Pituitary Tumors in Rodents Following Changes in Thyroid Function: A Review*

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It is the primary purpose of this review to examine the problem of the genesis of tumors of the pituitary gland following thyroid removal or destruction by radioiodine. Since this problem is now under active investigation, it is hoped that such a summation of the pertinent data may be helpful in evaluating what has been done and in orienting research that may follow. Radioiodine-induced hypophyseal growths are especially interesting, because they occur in response to a single experimental manipulation in such high incidence (almost 100 per cent) that they can be distinguished readily from normal or “spontaneous” tumorous growths in old animals. Furthermore, the high incidence of the tumors in response to the I\(^{131}\)-treatment suggests that a definite analyzable mechanism for atypical growth is triggered by the treatment. The frequency of the pituitary tumor permits the use of relatively small numbers of animals and thus facilitates analysis of the factors which precipitate tumorous growth. The fact that the tumorous organ is endocrine creates an especially valuable and interesting situation, since the physiologic properties and responsiveness of the atypical tissue can be subjected to study at any stage.

Before concentrating on the best studied situation, the experimental elicitation of hypophyseal tumors by radiothyroidectomy in C57BL mice, it would be well to consider, even briefly, the general problem of hypophyseal tumorigenesis in rodents. Within this context the more specific problem can be better evaluated. At least five different factors now have been reported as effective in rats and mice in bringing about tumorous hypophyseal enlargement: (a) old age, (b) hypothyroidism (with or without radiation), (c) gonadectomy, (d) chronic estrogen administration, and (e) whole-body radiation. Various methods have been used to produce the hypothyroid state: (a) low-iodine diets, (b) feeding of goitrogenic drugs, (c) surgical thyroidectomy, and (d) radiothyroidectomy (using I\(^{131}\)). There is no way of knowing, at this time, whether the mechanism underlying hypophyseal tumorigenesis after any or all of these various treatments is the same, or even whether parts of such mechanisms are shared by the different kinds of experiments. There is some variation in the cytology and in the secretary properties of the experimentally obtained tumors, suggesting that at least partially different mechanisms exist, resulting in different terminal species of pituitary growths.

The results of these various approaches are summarized in Table 1. Although hypophyseal tumors occur spontaneously very infrequently in mice (36), in rats, and especially in certain strains of rats, they occur to such an extent that evaluation of tumor-eliciting experiments is difficult (8, 33, 34, 38). Thus, there has been some question in this sense, in certain of the claims listed in Table 1, of the relation between experimental manipulations and subsequent hypophyseal tumors in aged rats.

It appears odd that both gonadectomy and continued estrogen treatment will induce pituitary tumors in mice. However, there is considerable variation in susceptibility in different strains. The C57BL strain, which is the most sensitive to estrogen tumorigenesis (19), will not develop pituitary tumors after gonadectomy (9, 24). In contrast, in the CE strain, in which estrogen will induce the tumor, castration will do the same (9). However, according to Dickie and Woolley (9), in this strain, as well as in F\(_1\) hybrids of this with C57’s and other strains, adrenal cortical adenomas precede the eventual pituitary adenomas.

Hypothyroidism, whether instituted by dietary means or by thyroid destruction or removal, seems to be in general one of the most potent factors in precipitating atypical hypophyseal growth.
Of the alternatives, administration of large doses of I^{131} to mice has been the most successful method of eliciting hypophyseal tumors. The role of the whole-body radiation in this phenomenon will be discussed in a later part of this review. At this point it should be noted that, although whole-body radiation in general has an injurious effect upon the pituitary of mice (review in [32]) in one type, the F_{1} hybrid of C57L (leaden) and A strains, whole-body radiation is a stimulus to formation of adenomas (37).

The first experimentally induced hypophyseal tumors in C57BL mice were those following repeated injections of crystalline estrogens in sesame oil (19). Relatively little research has followed which would further characterize the mechanism by which this tumor, considered to be "chromophobic," is caused to form. Work has been confined to transplantation attempts and measuring the antitumorigenic action of certain other steroid hormones.

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**TABLE 1**

**REPORTED METHODS OF OBTAINING PITUITARY TUMORS FROM RODENTS**

(Uncritical summary of literature)

1. By aging:
   - Rats, Yale strain and others (33, 34, 38).
2. By dietary regimen:
   - a) Low-iodine diets; rats, Sherman strain and others (1, 2, 4).
   - b) Feeding goitrogenic drugs; rats, several strains (4, 35); mice, A strain (30).
3. By thyroidectomy:
   - a) Surgical; mice, C57 strain (8).
4. By gonadectomy:
   - a) Gonadectomy alone; mice, CE and DBA strains, and F_{1} hybrids; CE×C57, CE×A, CE×C3H, CE×DBA, DBA×C57 (0).
   - b) Gonadectomy followed by 545 r x-ray; mice, C57 strain (11).
5. Chronic estrogen treatment:
   - a) Gamma radiation; mice, F_{1} hybrids C57L×A (87).
   - b) x-ray following radiothyroidectomy; mice, C57 strain (23, 26).
6. Nitrogen mustard injection:
   - Following radiothyroidectomy; mice, C57 strain (11).

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**TABLE 2**

**SUMMARY OF EXPERIMENTATION ON TUMORIGENESIS IN PITUITARY OF C57BL MOUSE**

1. Doses of I^{131} which elicit tumors in mice fed Purina Chow:
   - a) 10 μc.–80 μc.—no tumors (23, 24); 150 μc. or more—tumors (6, 12, 14, 21, 23, 24, 25).
   - b) 25 μc. in α') tumors (8, 16).
   - c) 50 μc. in α') tumors (8, 16).
2. Doses of I^{131} which elicit tumor in mice fed low-iodine diet:
   - a) 30 μc.—no tumors (11, 25); 200 μc.—tumors (25).
   - b) 30 μc.—tumors (8, 16).
3. Low-iodine diet, 30 μc. thyroidectomy followed by various treatments:
   - Followed by:
     - a) 179 μc. I^{131}—tumors (11).
     - b) 500 or 545 r x-ray to whole-body, to head alone, or to trunk alone—tumors (11, 12, 26).
     - c) 50 r whole-body x-ray—tumors (8).
     - d) 120 or 160 μc. Na^{24}—tumors (11).
     - e) 0.02 mg. nitrogen mustard—tumors (11).
4. Radiation alone:
   - a) 300 r x-ray—no tumors (11, 26).
   - b) 160 μc. Na^{24} or 0.02 mg. nitrogen mustard—no tumors (11).
5. Surgical thyroidectomy:
   - Followed by 5–9 μc. I^{131} to check completeness of thyroidectomy—tumors (8).
6. Chronic goitrogen treatment:
   - 0.1 per cent thiouracil up to 18 months—no tumors (22).
7. Chronic estrogenization:
   - By implantation of pellets or injection of oil solution—tumors (19).
8. Gonadectomy:
   - a) Gonadectomy alone—no tumors (11, 24).
   - b) Gonadectomy followed by 545 r whole body x-ray—tumors (11).
9. Prevention of pituitary tumor after radiothyroidectomy with 200 μc. I^{131}:
   - a) By implantation of fresh thyroid tissue (25).
   - b) By injections of thyroxine (21, 25).

Since it is difficult, if not impossible, to appraise accurately the general literature for insight into the mechanisms of hypophyseal tumorigenesis, the critical analysis of this question will be directed toward the C57BL mouse as much as possible. This "tumor-resistant" strain has received a major proportion of attention by experimenters. A discussion concentrating upon it has at least the advantage of avoiding the question of strain functional differences. This work is summarized in Table 2.

Induced hypophyseal tumors in some strains, are without such action in C57's. However, a combination of gonadectomy and x-radiation has been successful in the induction of such tumors in C57BL mice (11).

Radiothyroidectomy of young adult C57BL mice fed "normal" diets with doses of about 200 μc. of radioiodine (I^{131}) has been found by several laboratories a highly effective means of obtaining pituitary tumors (5, 13, 20, 23). Not all thyroid tissue needs to be destroyed, but that which re-
mains after extensive thyroidal destruction is morphologically atypical, reduced in functional capacity, and unable to regenerate (24). In an experiment in which large numbers of C57BL mice were maintained on antithyroid diets (thiourea, thiouracil) for periods of time comparable to that required after I\(^{31}\) for pituitary tumorigenesis, no pituitary growths were observed (22). In A strain mice, however, several pituitary tumors have been found after 17 months of feeding propyl thiouracil (30). Surgical removal of the thyroid was found (8) to lead to growth of pituitary tumors in C57BL mice. In this experiment 9 \(\mu\)c. of I\(^{31}\) was given to the thyroidectomized animals 3 months after their surgery.

The exact amount of I\(^{31}\) required to induce the pituitary tumor in C57's fed a "normal" diet is not a matter of agreement. Although the different published figures are not far apart, the precise appraisal of the question of radiation dose is dependent upon them. It is claimed by Gorbman (24) that mice fed the commercial Purina Laboratory Chow diet require 200 \(\mu\)c. of I\(^{31}\) for thyroid destruction and for a high proportion of pituitary tumors in a given experiment. Doses of 100–150 \(\mu\)c. gave variable lower proportions of tumors, and doses below 100 \(\mu\)c. yielded no tumors and relatively little harm to the thyroid. Furth (16) states that somewhat smaller doses, 25 \(\mu\)c. in female C57BL's fed Purina Laboratory Chow, will injure the thyroid severely and produce a fairly high proportion of tumors; males require 50 \(\mu\)c. If variations in the iodine content of the commercial diet over a period of several years cannot reconcile these differences, it is perhaps possible that different methods of assaying the radioactivity of the isotopic iodine might explain them. Certainly, if the biological end-point of thyroidal destruction is used, and if 50 \(\mu\)c. and 200 \(\mu\)c. in different laboratories both arrive at the same end-point, some such explanation as one of these must apply.

In C57BL's whose thyroids are destroyed by 200 \(\mu\)c. of I\(^{31}\), growth of pituitary tumors is prevented by the continued injection of thyroxine (18, 21, 25) or by the implantation of fresh thyroid tissue. It was this fact that led Goldberg and Chai-koff (14) and later, on the same and other grounds, Furth (12) and Dent et al. (8) to conclude that the lack of thyroid was the main, if not sole, inciting factor for the tumor.

Another type of radiothyroidectomy can be accomplished by giving relatively smaller amounts of I\(^{31}\) to mice fed a low-iodine diet, usually the Remington formula or a modification of it (25). In such cases the thyroidal uptake of iodine is about 60 per cent, in contrast to 7.5 per cent for Purina Chow fed C57BL mice (24). Thus, to achieve the same degree of thyroid destruction as by the 200 \(\mu\)c. dose in mice of both sexes fed "normal" diets, only 30 \(\mu\)c. is needed. Since the thyroid retains a large part of the 30 \(\mu\)c., it is obvious that, in the two types of radiothyroidectomy, a large difference exists in the whole-body radiation dose (calculated to be about 15-fold) due to extrathyroidal circulating I\(^{31}\). In several different experiments (25, 26) we found that radiothyroidectomy with 30 \(\mu\)c. of I\(^{31}\) in mice fed low-iodine diets, though it is just as destructive to the thyroid as 200 \(\mu\)c. given to normally fed C57BL's, is not followed by pituitary tumors. In contrast, Furth et al. (16) have noted such tumors in low iodine-fed C57BL mice given 30 \(\mu\)c. In our experiments, in which the 30-\(\mu\)c. dose, though thyroid-destructive, is not tumorigenic, the opportunity has been presented to do further experimental analytical work. The conclusion seems warranted, in our work, that thyroid destruction is necessary for subsequent pituitary tumorigenesis but that it is not capable by itself of inducing the tumorous growth. On this basis it appeared that one of the significant differences between the tumorigenic 200-\(\mu\)c. dose and the unharmful 50-\(\mu\)c. dose is the whole-body radiation delivered by the larger dose. Accordingly, we supplemented the 30-\(\mu\)c. (low-iodine diet) thyroidectomy by (a) additional I\(^{31}\), (b) 545 r x-ray (whole-body, to the head alone, or to the body alone) or 120–160 \(\mu\)c. of radiosodium (Na\(^{24}\), dose calculated to approximate the \(\beta\)-radiation of 200 \(\mu\)c. of I\(^{31}\)). Each of these supplemental methods of delivering radiation to the mouse succeeded in eliciting growth of pituitary tumors (26). It seems especially significant that, although the radiation must supplement the 30 \(\mu\)c. in order for the tumor to grow, it need not actually fall on the pituitary itself.

GENERAL DISCUSSION

It is now quite well established that the removal of pituitary target organs, like the gonads, thyroid, or adrenals, leads to hypersecretion by the pituitary. Virtually all the experimental procedures listed in Tables 1 and 2, excepting, perhaps, the whole-body radiation, involve the destruction or impaired function of hypophyseal target organs. An important question, which must be answered, inquires into the possibility that long-continued overactivity of a secretory organ can, by degrees, lead to disorganized hyperplasia and eventually to metaplasia and neoplasia. This question has been reviewed by others (12, 17, 18) and will be mentioned here without further elaboration. In regard to pituitary tumorigenesis, this might seem to apply to the growths in CE and DBA.

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mice after gonadectomy, but it has been shown in these strains by Dickie and Woolley (9) that adrenal changes of an unknown character precede those in the pituitary. This complicates the picture to the extent that further work is needed to clarify the role of the adrenal in the genesis of the eventual basophil tumor.

In the C57BL mouse it is quite clear that the stimulation, or removal of inhibition, caused by gonadectomy per se does not lead to pituitary tumorigenesis, and the same is true in a number of strains of mice other than CE and DBA. Thus, it is of some interest that supplementary x-radiation of castrated C57's will result in appearance of hypophyseal tumors. What is the aggravating or precipitating action of the whole-body radiation in this situation? Since a similar phenomenon has been found in thyroidectomized mice, this question will be considered in more detail in that context.

Although it might seem paradoxical, in a sense, that both gonadectomy and chronic estrogenization lead to growth of hypophyseal tumors, it has been adequately shown that estrogen is a pituitary stimulant for luteinizing hormone (LH) secretion (see review by Gardner [17, 18]). Though their modes of activating the pituitary differ, both of these experimental approaches share the common property of hypophyseal stimulation. The tendency to form pituitary tumors varies considerably among strains of estrogen-treated rats and mice (10, 19). It is possibly meaningful that the C57BL mouse, which is so sensitive to the estrogenization procedure, also readily yields pituitary tumors after radiothyroidectomy. The estrogen-induced tumor, like that after radiothyroidectomy, is chromophobic. However, as Halmi and others have pointed out (27), it probably is insufficient to designate these growths as chromophobic, since this does not indicate whether they may, in fact, have developed by degranulation of one of the normally chromophilic cell types.

The cytological and physiological stimulation of the pituitary after thyroidectomy is now well documented (citations in 12, 27). Thus, it is reasonable to assume that thyroidectomy, like gonadectomy, imposes some functional stress upon the pituitary. Whether the long continuation of such a stress is in itself sufficient to cause tumorous growth in the pituitary is not yet clear. Hypothyroidism induced by withholding iodine from the diet has been claimed (1, 2) to yield pituitary tumors in old animals. These were basophilic or consisted of chromophobes "presumed to be basophils." Long-term feeding of goitrogenic drugs to rats has been shown to produce slight hypophysoidal enlargement (30), and a few tumors have been found after 2 years of antithyroid treatment (35), and review by Bielschowsky [4]. Unfortunately, in the face of the relatively high spontaneous incidence of hypophyseal tumors in rats, it is difficult to accept unreservedly reports in which only a few tumors are described.

In mice, several large series of long-term goitrogen-feeding experiments have been reported in which slight enlargement, but no tumorous growth, of the pituitary was found in A, C, C57BL, C5H, and 1 strains, and in the F1 hybrids A × C5H, A × CBA (7, 22, 31). On the other hand, Moore et al. (30) have described chromophobic hypophyseal tumors in two of four A strain mice fed .8 per cent propylthiouracil for 534 days.

C57BL mice surgically thyroidectomized by Dent et al. (8) developed hypophyseal tumors. Uncomplicated evaluation of this experiment is made difficult by the fact that they treated the animals with up to 9 μc. of radioiodine several months after removal of the thyroid. In the same report, Dent states that 25 μc. of 131 is sufficient, in normally fed C57's, to destroy the thyroid. The 25-μc. dose of Dent is, therefore, equivalent to the 200 μc. dose which other investigators have found necessary for thyroidectomy. If such a comparison of dosages is justifiable, the 9 μc. (one-third of a thyroidectomizing dose) injected into a thyroidless mouse would seem enough to deliver an appreciable whole-body radiation. It is difficult, therefore, to agree with Dent on the basis of this experiment that the surgical thyroidectomy is the sole factor precipitating the hypophyseal tumors which resulted.

Radiothyroidectomy (with larger doses of 131) of several strains of mice, including C57's, has been the procedure yielding the highest proportion of hypophyseal tumors of any yet attempted. Any modifications of this procedure designed to test some aspect of it have, in our hands, yielded smaller proportions of tumors, even when successful. Because supplemental administration of thyroxine or fresh thyroid implants (21, 25) antagonized development of hypophyseal tumors, it has been concluded by Goldberg and Chaikoff (15) and by Furth et al. (16) that thyroidectomy alone is necessary for its stimulation. The growth of the tumors after goitrogen feeding of A strain mice (30) and surgical thyroidectomy (8) has been taken as additional support for this view. If this simplified view is adopted, then the absence of tumors in long-term goitrogen-fed C57BL mice (22) and in C57BL mice radiothyroidectomized with only 50 μc. of 131 still must be explained. It is possible that thyroidectomy and its immediate physiologi-
cal consequences may provide sufficient stimulus, under certain circumstances, for hypophyseal tumorigenesis. The nature of the circumstances which distinguish tumor-yielding from negative experiments must yet be determined.

The fact that under certain conditions radiothyroidectomy of C57BL mice with 30 μc., or less, of \( ^{131}I \) is not tumorigenic has permitted experimentation which may further elucidate the problem. The additional treatment of such mice with whole-body x-ray, \( \beta \)-radiation from Na\(^{24} \), or with nitrogen mustard, has yielded pituitary tu-

Since the x-radiation need not fall directly on the pituitary to exert its action, it is unnecessary to cite the direct tumorigenic action of ionizing radiation in explanation of the tumors following the double treatment. Such properties are evident in the post-radiation pituitary tumors in LAF1 mice (37) and in the ovaries of mice (13). Because the action of the radiation can be indirect, it is probably mediated by a humoral agent. Among the working hypotheses that can be offered at this point in explaining the pituitary tumors following target organ removal plus radiation is one invoking a “stress”-like stimulus, possibly involving the adrenal (as does castration in the CE and DBA mice). Such a theory was recently suggested by Edelmann (11). It is one that deserves experimental testing. A mechanism of this sort, represented graphically in Chart 1, could reconcile some of the apparent disagreement in regard to the genesis of pituitary tumors in C57BL and other mice. For example, according to this hypothesis, it is possible that the trauma of surgery, the loss and re-establishment of parathyroid function, and the 9 μc. of \( ^{131}I \) might supply the addi-

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**Chart 1.**—Hypophysial tumorigenic influences in mice. Graphic representation of hypothesis requiring that single stimuli (or removal of inhibitions) may not, but double stimuli, usually involving the adrenals, may induce tumorous enlargement.
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The absence of pituitary tumors in mice fed less toxic quantities of goitrogen could have been explained on the basis of a low level, or absence, of stress of the type imposed by the diet of Moore et al. The same approach possibly could be used in explanation of the tumor following chronic estrogenization in C57BL mice. Estrogens in high dosage are known to be toxic (19). The stress of the toxicity in addition to the direct stimulation of the pituitary by this steroid could be conceived to be working in a similar manner.

In summary, it appears that removal or impairment of function of either of two target organs of the pituitary will provide part, but not all, of the stimulus needed for its tumorous enlargement in the C57BL mouse. Addition of body stress factors, which in themselves have no discernible effect upon the pituitary, will precipitate the atypical type of growth. It may be seen that, according to the hypothesis represented in Chart 1, body stress is the one factor which is common to all pituitary tumor-yielding experiments. Is this because the pituitary of the stressed animal is called upon to secrete a second trophic hormone, ACTH, in addition to the gonadotrophin or thyrotrophin? Another possibility, also susceptible to experimental analysis, is that some humoral agent, part of the stress phenomenon, exerts a direct effect. A further possibility is the direct stimulation of the pituitary of susceptible mice by an adrenal steroid, analogous in its action to the estrogens. If the role of stress in pituitary tumorigenesis in C57BL mice is simply the secretory demand for ACTH, then it would seem that the size of the secretory load is the principal causative factor of eventual atypical growth. If the role of stress is the addition of some qualitatively different humoral agent to the circulation, the further analysis of the problem will be more difficult.

Given the differences in hormonal secretion, sensitivity, and balance in each species and genetic strain, the effectiveness of the respective stimuli for hypophyseal tumorigenesis must vary. For example, in the C57L × A mouse, gamma radiation (stress?) alone induces pituitary tumors, and these secrete ACTH (37). Furthermore, with the different experimental approaches toward tumorigenesis, it is probable that the functional properties and cellular composition of the pituitary tumors must also vary and, indeed, they appear to do so (16).

Even if it should eventually prove untenable, the two-factor hypothesis has the present virtues of reconciling some apparently opposed points of view on the genesis of hypophyseal tumors, and it provides the basis for logical experimental exploration of this problem in the immediate future.

**SUMMARY**

The different approaches to the experimental induction of pituitary tumors are reviewed. Such tumors have been found to follow whole-body radiation, castration, thyroidec-tomy, and estrogen administration. The particular conditions surrounding each of these approaches are analyzed. It is suggested that a common feature to all procedures yielding hypophyseal tumors is a double stimulation to the pituitary. One stimulus usually, but not always, is provided by removal of a hypophyseal target organ; the second is a humoral stimulus following stress to the animal involving, perhaps, the adrenal gland.

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