HYPOPHYSEAL TUMORS INDUCED BY ESTROGENIC HORMONE

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In previous papers (1 and 2) it has been shown that prolonged treatment with estrogenic hormone eliminates the growth and gonadotropic hormones of the anterior pituitary, while the thyrotropic and parathyrotropic hormones are uninfluenced. The result in experimental animals is retarded growth and arrested sexual development. Rats from four to six weeks old and weighing from 30 to 50 grams proved to be the most suitable experimental animals. For a period of three to four weeks both the injected and the control animals develop to a like degree, up to a weight of about 55 grams. With further treatment the weight of the injected rats rises slowly to 90 grams, where it becomes stationary, while that of the controls rises rapidly to 160 grams. To bring about this effect bi-weekly doses of 5000 units of estradiol benzoate are necessary. All of the 240 rats treated with this dosage showed the same retarded growth and arrested sexual development.

The pituitaries of the treated animals enlarge after some months of treatment and in the course of eight months tumors of the pituitary appear. This discovery was made independently in three laboratories. (a) Cramer and Horning in London (3) reported on hypophyseal tumors in mice on Feb. 1, 1936. They painted the skin of 12 mice twice weekly with a 0.01 per cent chloroform solution of estrin. Only one gland remained grossly normal, 8 were enlarged, and 3 animals had definite adenomatous tumors. (b) On April 4, 1936, McEuen, Selye and Collip in Montreal (4) reported that they had produced enlargement of the pituitary as well as several large cavernous adenomas by treating rats for several months with estrone. (c) On the very same day we described similar findings from Jerusalem (5). In the meantime we have succeeded in obtaining about a hundred enlarged pituitaries and 28 additional tumors of the pituitary in eunuchoid dwarfed rats.

Recently Burrows (6) in London reported that among 679 mice treated percutaneously with estrogenic hormone only one case of hypophyseal tumor was found after 483 days' treatment. In rats, on the other hand, it has been found that tumors can be produced regularly in from seven to nine months.

In the present communication the anatomical changes in the pituitaries of our eunuchoid dwarfed rats are to be described.

(A) The Pituitary after Four Months' Treatment with Estrogenic Hormone: Macroscopic changes in the pituitary are not observed until treatment has been carried out for four months. The changes observed after that period differ greatly in the two sexes. As previously reported (1), after sixteen weeks' treatment with a total of 232,000 units of estradiol benzoate the average weight of the pituitary of the male rats was 26.08 mg., while that of the...
controls was 9.7 mg. In another series of 14 male animals which had received 361,000 units over a period of eighteen weeks, the average weight of the gland was 22.5 mg. It must be emphasized, however, that this enlargement is not observed in every case. In one male rat which had received 180,000 units in a period of nineteen weeks the pituitary weighed 41.6 mg., while in another animal which had undergone similar treatment the weight was only 9 mg. Both rats were typical male eunuchoid dwarfs. The reason for this striking difference in the macroscopic appearance of the gland cannot be stated at present, but it is evident that the size of the gland is not correlated with the functional changes, for the effect on growth and sexual development was identical in the two animals.

In the female animals the pituitary did not react in the same way as in the males. While the average weight of the male pituitaries after four months' treatment was 26.08 mg., that of the females was only 11.7 mg. It was found, however, that pituitary enlargement could be brought about if adult females were used instead of infantile ones and were injected six times a week instead of bi-weekly.

(B) The Pituitary after Eight Months' Treatment with Estrogenic Hormone, Hypophyseal Tumors: After eight months' treatment with estrogenic hormone there is no longer any difference between the sexes in the macroscopic appearance of the pituitary. In all of the animals the glands were transformed into enormous hypophyseal tumors which caused death with symptoms of intracranial pressure. These tumors had an average weight of 149.3 mg. They were soft and friable, greenish yellow in color with brownish red areas representing vascular dilatation and hemorrhage. The larger tumors were adherent to the optic nerves (Fig. 1). In every instance the base of the brain showed a distinct impression due to the pressure of the tumor. In one tumor hemorrhage was absent. In another instance there was a hemorrhage-free thin-walled cyst, the clear fluid of which was aspirated and shown to be free of gonadotropic hormone. One animal had, besides the typical hypophyseal

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1 I am indebted to Dr. Marion Tausk of the "Organon" laboratories for generously supplying the dimenformon for these experiments.
tumor, a round, smooth, reddish tumor in the frontal lobe, 1 mm. in diameter (Fig. 2).

The histologic examination of these tumors was begun by the late Professor Erdheim of Vienna. He arrived at the conclusion that they were composed chiefly of chromophile cells, which is contradictory to the findings of other investigators (3 and 7). Unfortunately he was unable to complete the investigations on this material, and the complete histologic findings must be reported later.

(C) Influence of Duration of Treatment and Dosage: In these experiments 187 rats were used. The majority were killed from four to six months after the beginning of treatment. In 23 animals, 11 females and 12 males, the

![Fig. 2. Tumor of the Pituitary Gland of a Female Rat Which Received 53,000 Mouse Units of Estradiol Benzoate Percutaneously for Fifty-three Weeks Together with 32 mg. Benzpyrene](image)

Note the large pituitary tumor and the base of the brain (a), which shows a distinct impression due to the pressure of the tumor. In the right frontal lobe is another round smooth tumor (b) measuring about 1 mm. in diameter. \(\times 2\)

treatment was continued to an average of 39.2 weeks. In this group all of the females and 8 of the males developed large hypophyseal tumors with an average weight of 149.3 mg. Thus the tumors occurred in 19 animals or 82.6 per cent. In 3 cases, or 13 per cent, the pituitary was enlarged to 55, 62, and 65 mg. respectively, but did not have the macroscopic appearance of tumor. In one case, or 4.3 per cent, the gland showed no gross changes, weighing 15 mg. The average total dose of hormone in this group was 524,526 mouse units.

In another series of 4 animals, eight weeks of age and already sexually mature, a dose of 5000 mouse units of estradiol benzoate was given four times weekly in order to investigate the effect on more adult animals. After twenty-eight weeks 3 of the rats showed hypophyseal tumors with an average weight of 91.6 mg., while in one there was no tumor, but the pituitary was enlarged
to three times the normal size. It will be noted that in this more adult group the tumors were much smaller than in the younger group.

In order to confirm the importance of the time factor, another series of animals four weeks of age, 4 males and 7 females, were given 5000 mouse units of estradiol benzoate twice a week. In 2 of the male rats after twenty weeks the pituitary weighed 10 and 22 mg. The weight of the gland in the other two males after thirty-four weeks was 53 and 100 mg. In the females the gland was not enlarged after twenty weeks; after twenty-four weeks it weighed 30 mg., after thirty-four weeks, 190 mg., and after forty-two weeks, 300 mg.

While the duration of treatment is of primary importance in the production of hypophyseal tumors, the amount of hormone administered seems to play but a small part. For example, one rat which received 1,640,000 mouse units had a smaller tumor than one receiving 420,000 in the same period of time.

(D) Hypophyseal Tumors Following Percutaneous Application of Estrogenic Hormone: As was reported previously (8–10) the estrogenic hormone is also effective if applied percutaneously. Much smaller doses were used in this series. The animals were painted on the back twice a week with one drop of a benzol solution containing 500 mouse units of estradiol benzoate per drop. After twenty-eight weeks and forty-one weeks when the rats had received respectively 28,000 and 41,000 mouse units, the pituitary was only slightly enlarged. After fifty-three weeks, with a total dose of 53,000 mouse units, hypophyseal tumors weighing 250 and 300 mg. were observed in 2 animals. These animals were also painted three times a week with 0.2 mg. of benzpyrene in benzol solution. It is possible that the benzpyrene supported the effect of the estrogenic hormone.

(E) Clinical Symptoms of Hypophyseal Tumors: The hypophyseal tumors are always fatal and give rise to symptoms due to intracranial pressure. The animals move slowly, eat poorly, are ataxic, and show loss of orientation. In some there is a fine tremor of the whole body which is intensified by handling. Four animals turned continuously to the right or rolled around their axis. The most characteristic sign, however, is a fall in temperature. This may drop gradually from 37° to 34° C., remain at that level for some days, and then fall rapidly to 24° C., when death occurs, or there may be a gradual decline from 37° to 30° C., at which point death is imminent. This fall in temperature cannot be explained with certainty, but probably is to be ascribed to pressure on the third ventricle. In any event it indicates the formation of a tumor. It is not due to a hypoglycemia, since the blood sugar in 10 animals was found to be within normal limits.

Ophthalmological examination 2 of the fundus showed a marked contraction of the vessels, which does not seem to depend on the presence of a tumor, for it was seen in one case where the pituitary weighed only 16 mg. It would seem that this contraction of the vessels is the result of prolonged treatment with estrogenic hormone.

2 I am indebted to Dr. A. Feigenbaum, Chief of the Ophthalmological Department of the Rothschild-Hadassah Hospital, for these examinations.
Hormone Content of the Pituitary Gland: On observing the retarded growth and inhibited sexual development of these animals, it was assumed that growth and gonadotropic hormones were not being produced by the pituitary. To test this out, the gonadotropic hormone content was measured by a method previously described (11). Measurement of the growth hormone was not practicable, as too large quantities of the gland are required. The average amount of gonadotropic hormone present in the pituitaries of the control rats was 1 to 2 mouse units. The enlarged glands of the dwarf animals showed on the average the same amount of this hormone as did those of the controls. This seems to be an observation of fundamental importance, showing that with injections of estrogenic hormone it is not the production of gonadotropic hormone that is inhibited, but only its delivery to the blood stream or its utilization.

Summary

1. Treatment of 240 infantile rats either parenterally or percutaneously with estrogenic hormone caused eunuchoid dwarfing.
2. Such treatment for four months caused enlargement of the pituitary in the males, while in the females the gland remained grossly normal.
3. After continued treatment for eight months the pituitaries of both sexes were transformed into enormous hypophyseal tumors in 29 of 35 rats. These tumors caused the death of the animals.
4. The duration of treatment is of primary importance, no tumor having developed in less than seven months; the size of the dose of estrogenic hormone is of only secondary significance.
5. The tumors can be diagnosed by typical clinical symptoms, the most characteristic of which is a decrease in the body temperature. This was shown not to be due to hypoglycemia.
6. The enlarged pituitaries and the tumors contained the same amount of gonadotropic hormone as the normal pituitaries of control animals. It is, therefore, not the production but the utilization of the gonadotropic hormone that is inhibited in the eunuchoid dwarf animals, causing a functional deficiency.

References