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# The Influence of Estrogens on Thyroid Function as Measured by Uptake of Radio-active Iodine.

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The influence of ovarian hormones on thyroid function has been the subject of many studies. It is generally believed that castration is followed by increased output of thyroid hormone, and that administration of estrogens depresses thyroid function. These changes are believed to be mediated by release and suppression of secretion, respectively, of thyrotrophic hormone as a result of the "shot gun" action of estrogens upon the anterior pituitary. Previous methods of investigation have included studies of the histology of the thyroid gland, determination of B.M.R., and determination of iodine in the blood.

Inasmuch as the uptake of iodine by the thyroid gland is a sensitive measure of its function, or, more precisely, of one specific phase of thyroid function, it appeared of interest to investigate the influence of estrogen administration and of castration upon the process.

**Methods and materials.** 159 female rats, descendants of Wistar strain, were used in this study. One group was injected with  $\alpha$ -estradiol benzoate; a second group was spayed. In each experiment an equal number of animals served as controls.

Iodine uptake was determined by the use of a tracer dose of  $I^{131}$ . All rats, both experimental and control, were given an iodine-poor diet (Steenbock) and received 3.9  $\gamma$  potassium iodide in 100 ml double distilled drinking water, following a procedure used previously by one of us.<sup>1</sup> This slightly iodine-deficient regime insures a more uniform and higher iodine uptake than that of rats on a stock diet, in which the uptake in controls may be too low to determine significant decreases in treated groups.

<sup>1</sup> Rawson, R. W., Tannheimer, J. F., and Peacock, W. C., *Endocrinology*, 1944, **34**, 245.

TABLE I.  
Uptake of  $I^{131}$  by Thyroids of Ovariectomized Rats. Exp. 1.

|                                              | Spayed 50<br>days before | Controls        |
|----------------------------------------------|--------------------------|-----------------|
| No. of rats                                  | 21                       | 21              |
| Days on diet*                                | 14                       | 14              |
| Tracer dose of $I^{131}$                     | 3.75 $\mu$ C             | 3.75 $\mu$ C    |
| Uptake of $I^{131}$ by<br>thyroid in 4 hr: % | 18.4 $\pm$ 5.43%†        | 18.0 $\pm$ 7.8% |
| Thyroid wt mg                                | 11.5 $\pm$ 1.76          | 11.3 $\pm$ 2.37 |

\* Steenbock diet with 3.9  $\gamma$  % KI in drinking water.

† Standard deviation =  $\sqrt{\frac{S(X)^2}{n-1}}$

At the end of the experiment all rats received  $I^{131}$  as sodium iodide intraperitoneally. Four hours after the injection the animals were killed and the thyroids removed and dropped into 3 ml of 2% sodium hydroxide solution. Radioactivity was determined on aliquots of the macerate of the thyroid glands by a Geiger counter.

**Results.** The findings are summarized in Tables I and II. In Experiment 1, the iodine uptake by the thyroid of rats spayed 64 days previously was compared with that of normal female controls, both groups being maintained on the experimental diet for 14 days prior to the time of sacrifice. There was no difference in either thyroid weight or uptake of  $I^{131}$  in these groups.

In Experiments 2, 3, and 4 (Table II) there was no significant difference in uptake of  $I^{131}$  between normal intact rats and those receiving estradiol benzoate. Fifty  $\gamma$  of the latter was administered 3 times weekly for 4 weeks (Experiment 2), 3½ weeks (Experiment 3), and one week (Experiment 4) to different groups.

**Discussion.** The extensive literature on the influence of ovarian hormones on thyroid

TABLE II.  
Uptake of I<sup>131</sup> by Thyroids of Rats Treated with Estradiol Benzoate.

|                                                     | Exp. 2                          |              | Exp. 3                           |              | Exp. 4                        |               |
|-----------------------------------------------------|---------------------------------|--------------|----------------------------------|--------------|-------------------------------|---------------|
|                                                     | T                               | C            | T                                | C            | T                             | C             |
| No. of rats                                         | 23                              | 17           | 17                               | 17           | 22                            | 21            |
| Days on diet*                                       | 27                              | 27           | 24                               | 24           | 28                            | 28            |
| Estradiol benz.                                     | 12 × 50 γ<br>= 600 γ<br>(4 wks) | —            | 11 × 50 γ<br>= 550 γ<br>(3½ wks) | —            | 3 × 50 γ<br>= 150 γ<br>(1 wk) | —             |
| Tracer dose of I <sup>131</sup>                     | 3.78 μ C                        | 3.78 μ C     | 2 μ C                            | 2 μ C        | 2 μ C                         | 2 μ C         |
| Uptake of I <sup>131</sup> by<br>thyroid in 4 hr: % | 33.7<br>σ† = 2.24               | 36.8<br>7.25 | 34.2<br>8.65                     | 35.0<br>10.2 | 10.97<br>4.39                 | 14.95<br>6.60 |
| Thyroid wt mg                                       | 12.0<br>σ† = 2.24               | 13.1<br>2.75 |                                  |              |                               |               |

\* Steenbock diet, 3.9 γ % KI in drinking water.

† Standard deviation =  $\sqrt{\frac{\sum(X)^2}{n-1}}$

function and structure contains contradictory observations, reviewed by Salter<sup>2</sup> and Farbman.<sup>3</sup> The only general agreement appears to be that ovarian secretions exert some influence on the thyroid.

The data presented here indicate that there is no difference in the uptake of a tracer dose of I<sup>131</sup> in female rats 64 days after castration as compared with normal female controls. Moreover, injection of estradiol benzoate in quantities of 150 to 600 γ over 1 to 4 weeks failed to influence uptake of I<sup>131</sup>.

The uptake by the thyroid of a tracer dose of radioactive iodine is generally regarded as a measure of thyroid function; it has been shown that the uptake is increased in conditions of increased function and is decreased in conditions of hypofunction of the thyroid.

The following points should be borne in mind in interpreting these negative results and in comparing them with various reports in the literature.

The synthesis, storage, release and peripheral metabolic action of thyroid hormone constitute a complex chain of events. Uptake of iodide by the thyroid gland is the first link in this chain. Obviously, without adequate uptake of iodide there can be no adequate hormone synthesis, but equal uptake in two types

of experiments does not eliminate the possibility that differences may exist in the several further links of the chain. Thus it has been shown that iodine is taken up by the thyroid of thiouracil-treated rats but is not utilized for purposes of hormone synthesis. This evidently is not what is happening in the estrogen treated animals, but serves merely to indicate that study of one phase of thyroid functional activity does not permit final conclusions regarding other phases. Furthermore, there is good evidence that prolonged treatment with larger doses of estrogen, both natural and synthetic, do suppress the pituitary-thyroid "axis." The time factor may therefore play a significant role in this connection.

For reasons mentioned above the present studies were conducted under conditions of a slight iodine deficiency. This deficiency was not sufficiently severe to be goitrogenous as evidenced by the normal weight of the thyroids, but did make the glands more avid for iodine than those of rats kept on a stock diet. The uptake of tracer iodine was comparatively high, and the response to castration, or to the small amounts of estrogen employed in our experiments might be different at different levels of dietary iodine.

**Summary.** Uptake of tracer doses of I<sup>131</sup> by rats' thyroids was not influenced by ovariectomy or by administration of estrogenic hormone.

<sup>2</sup> Salter, W. T., *The Endocrine Function of Iodine*, 1940.

<sup>3</sup> Farbman, A. A., *J. Clin. Endocrin.*, 1944, 4, 17.