Influence of Oestrogens on Thyroid Function. II.

By

E. L. Noach

In a previous report arguments were presented in support of the conception that oestrogens have a dual action on the thyroid gland: on the one hand an intensification of the action of TSH on the thyroid, on the other an inhibiting effect, very likely but not with certainty due to a decrease in release of thyrotrophin (TSH). This conception was arrived at by experiments in which the $^{131}$I uptake by rat thyroids was determined. However, since these experimental results were open to other interpretations, we performed further series of experiments in order to clarify doubtful points. Unless otherwise stated, references to previous results are to our preceding paper in this field (Noach, 1955).

A. $^{131}$I Uptake by Thyroid Glands of Castrated Male Adrenalectomized Rats

The results of our above-mentioned experiments, in which castrated animals were given oestradiol benzoate in doses of 10–1000 $\mu$g., showed that oestrogens increase the uptake of $^{131}$I, but that there is no distinct relation between the dose of oestradiol benzoate and the extent of the effect. On the basis of experiments in hypophysectomized, oestrogen-treated animals on a constant maintenance dose of TSH and in which an increasing effect was observed after increasing the dose of oestrogen the assumption was made that as well as the «activation» of TSH in the intact animal (with hypophysis), there is at the same time an inhibiting effect that also increases when the dose of oestrogens is increased, thus counterbalancing the sensitization. Although the data in the literature indicate that a decreased TSH release by the pituitary gland is the most likely cause of this inhibition, we were unable to disprove the possibility
that oestrogens decrease the sensitivity of the thyroid to TSH via an increased corticotrophin release and subsequent release of glucocorticosteroids (Woodbury, 1951). The »dual mechanism« of oestrogen action on the thyroid in that case would be localized exclusively in this organ, on the one hand with, on the other without mediation by the hypophysis. From the experiments to be discussed below it has appeared, however, that oestrogens in doses corresponding to those on which our previous findings are based, do not influence the adrenal in such a way as to explain the inhibiting influence.

**Material and methods**

Male rats between 120 and 140 gm. were castrated; two days later the adrenals were removed. Starting with the day following adrenalectomy, the animals were treated for 5 days with daily doses of 10, 20 and 50 µg. of oestradiol benzoate in olive oil, or olive oil only respectively, administered subcutaneously. On the 5th day of treatment a tracer dose of approximately 1 µc. carrier-free NaI131 was injected intraperitoneally. Twenty four hours later the animals were sacrificed and the thyroid weights and I131 uptake determined according to the method previously described. During treatment, paired feeding with the usual rat food was applied, and the animals were also given 1 ½ % NaCl as drinking fluid.

**Results**

Table 1. All three doses of oestradiol benzoate appear to increase significantly the uptake of I131 by the thyroid glands, but the increase is practically the same in all cases. The thyroid weight increased significantly only in the lowest dosage group.

**Table 1.**

Influence of oestradiol benzoate on thyroids of adrenalectomized castrated male rats.

<table>
<thead>
<tr>
<th>Dose of oestradiol benzoate (µg./day)</th>
<th>Mean body weight (gm.) at start of treatment</th>
<th>Thyroid weight (mg.)</th>
<th>Uptake of I131 (% of tracer dose/24 h.)</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>131</td>
<td>16.1 ± 1.0</td>
<td>30 ± 3.4</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>136</td>
<td>20.2 ± 0.9*</td>
<td>41 ± 3.1*</td>
<td>17</td>
</tr>
<tr>
<td>20</td>
<td>134</td>
<td>17.0 ± 1.0</td>
<td>44 ± 2.5*</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>133</td>
<td>16.8 ± 1.1</td>
<td>42 ± 2.5*</td>
<td>20</td>
</tr>
</tbody>
</table>

* Statistical significant difference (p < 0.05) with controls.
Discussion

In adrenalectomized animals with hypophysis we observed the same phenomenon as in intact animals, namely that oestrogens in various doses cause an activation of the thyroid gland without any correlation between dose and effect. Consideration has already been given to this lack of relationship in intact animals and its presence in hypophysectomized animals as evidence for the existence of an inhibiting influence of oestrogens, mediated via the hypophysis. We are of the opinion that these results in adrenalectomized animals show that this hypophysial influence is not mediated via an activation of the adrenal by increased ACTH release (Skelton et al., 1949). An inhibition of the sensitivity of the thyroid to TSH by glucocorticoids in our case can therefore be excluded. Hence the only remaining possibility of an inhibition of the thyroid, mediated by the hypophysis, would be a decreased TSH release.

B. INFLUENCE OF OESTRADIOL BENZOATE ON THE EXCRETION OF I\textsuperscript{131} IN THE URINE

Our conception that oestrogenic substances may stimulate thyroid function is based on the observation that in various experimental conditions oestrogens may increase the uptake of I\textsuperscript{131} in the thyroid gland. It is not strictly permissible, however, to draw conclusions about the thyroid function exclusively from changes in thyroid I\textsuperscript{131} uptake unless the distribution of the iodine in the body has been taken into account. In this respect, the renal function with regard to the excretion of iodine compounds is of special importance since the kidney is the principal competitor of the thyroid with respect to iodide withdrawal from the blood: primary changes in the excretion of this ion may result in a changed blood level, possibly resulting in turn in different values of thyroid uptake. In the literature we found no data concerning the influence of oestrogens on the excretion of iodides. The only indication regarding renal function changed by oestrogens with regard to halogens, is found in the observation of Thorn et al. (Thorn, Nelson & Thorn, 1938; Thorn & Engel, 1938), that oestradiol causes a retention of a. o. Na\textsuperscript{+} and Cl\textsuperscript{-} in dogs, therefore an action similar to that produced by DCA. Since the measurement of the renal and thyroid clearance of iodide (Pochin, 1950) in small laboratory animals is not very accurate, we attempted to obtain an impression of the excretion of I\textsuperscript{131} in castrated male thyroidectomized rats on a maintenance dose of thyroxine either treated with oestradiol benzoate or not: the binding of I\textsuperscript{131} in the thyroid gland is thus eliminated, without changing drastically the metabolism of the experimental animals. It appeared that oestradiol benzoate produced a slight retention of radioactive iodine compounds in the body.
Material and methods

Castrated male rats, fed ad libitum, in which thyroidectomy had been performed approximately two weeks prior to the commencement of the experiment, were treated with 10 µg. dl-thyroxine (Roche) and 50 µg. oestradiol benzoate in oil, daily for 9 days. The control animals, pre-treated operatively in the same way, were given thyroxine and oil. All these injections were given subcutaneously. In order to eliminate differences in I uptake with the food, the animals, in addition to a tracer dose of approximately 1 µc. NaI131, were also given 10 µg. KI in 0.5 ml. saline intraperitoneally, 24 hours before the end of the experiment. Subsequently the animals were put into metabolism cages and the urine collected for 24 hours, i.e. for the same period in which in previous experiments the thyroid uptake was determined. At the end of this period the cages were carefully rinsed with a known quantity of approximately 75 ml. of 10 % KI solution in order to collect any I131 possibly adherent to the metal of the cage. The radioactivity of the KI-urine mixture was measured in dry samples in the usual way and calculated in percentage of the administered dose of I131, excreted in a 24-hour period. The completeness of the thyroidectomy was confirmed by measuring the radioactivity of the entire trachea and larynx inclusive, after autopsy of the animals. When the radioactivity of the trachea preparation gave a higher count value than twice the background activity, the presence of a thyroid remnant was assumed and the experimental result of the relevant animal discarded.

Results and discussion

Table 2 shows that treatment with oestradiol benzoate results in a decreased excretion of I131. Hence it can be said that there is no proof that the increase in thyroid uptake as found in earlier experiments is caused by an increased activity of the thyroid with regard to iodine uptake following treatment with oestrogens: for, if the excretion of iodine has been decreased by oestradiol benzoate, more of this substance is available for the thyroid gland, and consequently, the uptake of the same percentage in the thyroid will be expressed by a larger absolute quantity, and it is the latter that we measured in previous experiments. At the other hand, we cannot, without further investigation, conclude that such a «pseudo-activation» occurs, and for the following reasons:

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Treatment</th>
<th>Body weight (gm.)</th>
<th>% excretion of tracer dose I131</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>10 µg. thyroxine plus 50 µg. oestr. benz./day</td>
<td>105</td>
<td>76 ± 1.6 p = 0.05</td>
</tr>
<tr>
<td>40</td>
<td>10 µg. thyroxine plus olive oil</td>
<td>111</td>
<td>80 ± 1.2</td>
</tr>
</tbody>
</table>

Table 2.
Urinary 24-hour excretion of I131 in castrated thyroidectomized male rats.
firstly the possibility is not excluded that treatment with oestradiol benzoate caused a lag in urine excretion in our experimental animals, which is a well-known effect of oestrogens. It is true that this cannot have been an absolute retention, since the animals actually were micturating, but it is nevertheless possible that the excretion by the kidneys, and hence the elimination from the blood, was only apparently inhibited. In that case the result of the experiments would not be significant for the I\textsuperscript{131} uptake by the thyroid. However, it can also not be excluded that oestradiol benzoate actually causes a decrease in elimination of iodides, not only the radioactive, but also those derived from the food. Increases thus occurring in the level of the non-radioactive iodides in the blood might then cause an interfering dilution of the I\textsuperscript{131} added only once, which perhaps had not been buffered completely by the carrier dose of 10 µg. KI given simultaneously. If this were the case, then the increase observed in thyroid uptake would merely reflect an avidity, in reality even greater, of the «oestrogen thyroid gland» for iodine, and thus would not alter our previous conclusions concerning an increase of activity.

Finally it is remarkable that the differences found in I\textsuperscript{131} excretion, although statistically nearly significant, are considerably less than the differences in thyroid uptake, so that one might assume that in spite of the possible I retention, an increased thyroid function has nevertheless been demonstrated. In this assumption, however, one has to consider that the administered thyroxine causes only an approximately normal metabolic rate. Presumably the dose was too large in view of the decrease in weight, also observed in control animals fed ad libitum. The values in excretion experiments and in uptake experiments therefore can not be compared without further consideration. From the preceding discussion it appears that some other method is necessary to determine whether the increased thyroid uptake of I\textsuperscript{131} is based on a retention of iodides in the blood, or is an independent phenomenon. With this in view the following group of experiments was performed.

C. INFLUENCE OF OESTRADIOL BENZOATE ON THE UPTAKE OF I\textsuperscript{131} BY THYROID GLANDS IN VITRO

By using a method in which the I\textsuperscript{131} uptake in vitro by isolated thyroid glands is measured, possible complications caused by differences in blood level of non-radioactive iodide are avoided. We were able to establish that the in vivo treatment of the experimental animals with oestradiol benzoate results in an increased uptake of I\textsuperscript{131} by the isolated thyroid gland in vitro.

Material and methods

Castrated male rats of 100–150 gm. body weight were treated for one week with daily doses of 50 or 300 µg. oestradiol benzoate subcutaneously. Paired fed control animals
were given oil injections. The animals were killed by a blow on the neck; the thyroid glands were rapidly dissected out and weighed. Subsequently the I\textsuperscript{131} uptake in vitro was determined according to Hamolsky et al. (1951): each thyroid gland was put into an oxygen-saturated medium, consisting of 2 ml. Krebs-Ringer-phosphate to which approximately 2 µc. NaI\textsuperscript{131} in 1 ml. saline had been added. After shaking for 1 hour at 38\(^\circ\) in a Warburg apparatus the glands were twice rinsed for half a minute in KI solution in order to remove adsorbed I\textsuperscript{131} from the surface of the organ. Subsequently the radioactivity was measured in the usual manner.

**Results**

Table 3. With both doses of oestradiol benzoate the thyroid glands of the oestradiol-treated animals accumulate more I\textsuperscript{131} than those of the control animals. Whereas in the group of 50 µg. the increase in uptake is proportional to the increase in thyroid weight, in the group of 300 µg. an increase in uptake per mg. thyroid tissue was also observed.

**Discussion**

Since it now appears that the uptake of I\textsuperscript{131} by thyroid glands in vitro following pre-treatment with oestradiol benzoate is increased, one must rather assume that the results of previous experiments demonstrate an actual thyroid stimulation and are not based on an apparent increase in thyroid activity resulting from an altered distribution of the iodide in the body. In contrast to the experiments in which the I\textsuperscript{131} uptake was determined in vivo in intact animals, in these in vitro experiments the I\textsuperscript{131} uptake per mg. thyroid tissue does not appear to be increased with an oestradiol benzoate dosage of 50 µg. but is apparently increased with a dosage of 300 µg. It is of little use, however, to draw conclusions from this as the experimental conditions in both types of experiments differ so much that a quantitative comparison of the results is not justifiable.

**D. THE CONVERSION OF RADIOACTIVE IODIDE ACCUMULATED IN THE THYROID GLAND INTO ORGANIC COMPOUNDS UNDER THE INFLUENCE OF OESTROGENS**

An increased avidity of the thyroid for iodide need not result in an increased secretory function, as long as the possibility that the conversion of the iodide into organically bound iodine has decreased has not been excluded. The literature provides examples of this: Rawson et al. (1944) found that thyroid glands of KCNS-treated animals, notwithstanding a lack of hormone synthesis, accumulate more I\textsuperscript{131} than those of control animals. Vanderlaan & Vanderlaan (1947) made similar observations following treatment of their experimental animals.
Table 3.
In vitro uptake of I^{131} by isolated thyroids of oestrogen treated castrated male rats.

<table>
<thead>
<tr>
<th>Dose of oestradiol benzoate (µg./day)</th>
<th>Mean body weight (gm.) at start end of experiment</th>
<th>Thyroid weight (mg./100 gm. body weight)</th>
<th>Uptake of I^{131} (% of tracer dose)</th>
<th>Uptake of I^{131} per mg. thyroid</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 controls</td>
<td>148 146</td>
<td>18.7 ± 0.89 13.3 ± 0.71 p &lt; 0.01</td>
<td>25 ± 3.2 17 ± 1.8 p &lt; 0.05</td>
<td>0.92 ± 0.10 0.89 ± 0.09 p &gt; 0.8</td>
<td>11 10</td>
</tr>
<tr>
<td>controls</td>
<td>151 149</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 controls</td>
<td>119 99</td>
<td>14.6 ± 0.9 12.5 ± 0.4 p = 0.05</td>
<td>14 ± 0.6 10 ± 1.5 p &lt; 0.05</td>
<td>1.01 ± 0.07 0.77 ± 0.08 p &lt; 0.05</td>
<td>7 9</td>
</tr>
<tr>
<td>controls</td>
<td>115 97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
with propylthiouracil. We were therefore interested to see whether oestrogens also have this property in common with goitrogenics, together with their sensitizing action to TSH. We found, however, that the organic binding of the iodide by oestrogens is not inhibited so that an increased hormone production in the thyroid gland is probable.

Material and methods

Castrated male rats were treated with 50 µg oestradiol benzoate daily for a week, given subcutaneously. Paired fed control animals were injected with oil. On the last day of treatment the animals were given approximately 2 µc NaI\(^{131}\) intraperitoneally. 24 hours later autopsy was performed, the thyroid glands of 3 to 5 animals from each group were collected, and according to the method of Albert & Lorentz (1951) the iodine compounds present were separated into fractions either soluble or insoluble in trichloroacetic acid. The precipitate, containing organic iodine compounds, was counted in dry samples, and the result was calculated in % uptake of the administered dose. The acid-soluble fraction, containing inorganic iodides, was counted in a liquid counter (model Veall, 1948) and in view of the low radioactivity, expressed in counts per minute after correction for physical decay.

Results and discussion

Table 4. The liquid counters used give a counting rate of approximately 25,000 c. p. m. for 2 µc. This means that in oestrogen-treated animals as well as in controls, 24 hours after administration of the tracer dose, only about 1 % of the radioactive iodine is still present in inorganic form. No significant difference was found between the results of the oestradiol benzoate treated animals and the controls, and there is consequently no indication of a significant inhibition of the conversion of iodides into organic iodine compounds. This is even more apparent from the fact that the radioactivity of the organic fraction

<table>
<thead>
<tr>
<th>Dose of oestradiol benzoate (µg./day)</th>
<th>Mean body weight (gm.) at start of experiment</th>
<th>Thyroid weight (mg.)</th>
<th>Thyroidal I(^{131})</th>
<th>Number of groups of 3–5 animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Organic (% of tracer dose)</td>
<td>Inorganic (counts/min.)</td>
</tr>
<tr>
<td>50</td>
<td>134</td>
<td>18.7 ± 1.4</td>
<td>45 ± 5.3</td>
<td>241 ± 39</td>
</tr>
<tr>
<td>0</td>
<td>132</td>
<td>16.7 ± 1.6</td>
<td>38 ± 5.5</td>
<td>233 ± 36</td>
</tr>
</tbody>
</table>

Table 4. Conversion of radioactive iodide into organic iodine compounds by oestrogen treated rats, 24 hours after administration of a tracer dose I\(^{131}\).
is of the same order of magnitude as that found in previous experiments for total radioactivity in the thyroid glands of oestrogen-treated experimental animals. It should be noted, however, that in these experiments the variation of the separate observations was considerable. The differences found therefore between oestrogen-treated animals and controls are not significant. Since, however, in numerous experimental conditions already mentioned we have found a clearly significantly increased thyroid uptake of $^{131}$I, we think it permissible to accept the increased average result of the oestradiol benzoate treated animals as an indication of increased thyroid function.

**E. THYROID HISTOLOGY**

Functional activation of the thyroid gland as a rule is accompanied by increased height of the follicular epithelium. Many of the conclusions concerning thyroid activity under the influence of oestrogens mentioned in the literature reviewed in our previous paper, are based on histological observations. We have investigated the histological findings in hypophysectomized animals on a constant maintenance dose of TSH, that were given a dose of oestrogen, which, although being small, in previous experiments had already caused a distinct increase in $^{131}$I uptake as compared with control animals. Notwithstanding this increase in function we found no histological changes.

*Material and methods*

Hypophysectomized female rats were treated with oestrogens by stimulating the endogenous oestrogen production with serum gonadotrophins in a way similar to that mentioned in our previous report: treatment for one week with 10 I. U. serum gonadotrophins and 2 Heyl-Laquer U. TSH. As control animals hypophysectomized female spayed rats were used, which were treated in the same way. The production of oestrogens was confirmed by taking vaginal smears. After killing the animals, thyroid sections of 3 $\mu$ thickness were prepared and stained with haematoxylin-eosin. In each thyroid preparation the height of 200 cells in transversely cut follicles that were not situated along the extreme periphery of the thyroid gland was measured with the help of an ocular micrometer at a linear magnification of 600 X.

*Results*

Table 5. The follicle cells usually showed a cuboid shape, and were very rarely cylindrical. The general morphological aspect of the thyroid gland was such that thyroids of oestrogen-treated animals and controls were indistinguishable from each other.

147
Table 5.
Follicular cell height in thyroids of hypophysectomized spayed and non spayed female rats treated with TSH (2 Heyl-Laquer-U./day) and serum gonadotrophins (10 I. U./day).

<table>
<thead>
<tr>
<th></th>
<th>Mean thyroid weight (mg.)</th>
<th>Mean cell height (micrometer units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spayed animals</td>
<td>12.9</td>
<td>2.95</td>
</tr>
<tr>
<td>Non spayed animals</td>
<td>14.5</td>
<td>2.75</td>
</tr>
</tbody>
</table>

Discussion

Treatment with gonadotrophins in a dosage that in previous experiments had caused a distinct increase in I$^{131}$ uptake, caused no increase in height of the follicular cells. This need not be in contradiction to the results of other authors, since the dosage of oestrogens used here is in all probability much smaller. The importance of our observation is that we have obtained histologically confirmation of a conclusion previously arrived at on the basis of alterations in thyroid weight following treatment with oestrogens, namely that functional changes in the thyroid need not run parallel with observable structural changes. Apart from the possibility that there is more than one thyrotrophic factor (Greer, 1952), the assumption remains that the increase in I$^{131}$ uptake has a lower threshold value than the morphological properties such as thyroid weight and follicle cell height.

FINAL CONSIDERATIONS

1. The experiments described above confirm the previous findings that oestrogens possess an inhibiting as well as a stimulating action on thyroid activity. The inhibition is mediated by the hypophysis and is not the result of activation of the adrenals. It is thus very likely that oestrogens inhibit the release of TSH from the hypophysis. The increased I$^{131}$ uptake in the thyroid is possibly also caused by a retention of iodides in the body, but is mainly due to a direct effect on the thyroid gland (for which, incidentally, the presence of TSH is necessary), since the thyroid in vitro also appears to possess an increased capacity for accumulating I$^{131}$. The conversion of iodide into organic iodine compounds is not appreciably inhibited by oestrogens. Finally it was possible to demonstrate that the increased thyroid activity need not necessarily be accompanied by histologically demonstrable activation of the thyroid tissue.
2. The increased sensitivity of the thyroid to TSH under the influence of oestrogens may possibly offer an explanation of the well-known clinical fact that hyperthyroidism occurs much more frequently in women than in men. Furthermore it may be a clue to the observation that therapy of hyperthyroidism with oestrogens (cf. e.g. Goldman et al., 1940) given in order to inhibit the release of TSH, could have but little success.

3. We have no data of our own concerning hormone release by the activated thyroid gland, but it is indeed very likely that the increased uptake and synthesis of organic I-compounds is also followed by an increased release of hormone into the blood. This is in fact in accordance with the previously cited observation of Engström et al. (1952), that in man treatment with oestrogens results in an increase of blood PBI. In view of this the question arises whether the assumed inhibition of TSH release by oestrogens might not take place by mediation of an increased release of thyroid hormone and its inhibiting action on the pituitary gland.

4. At present one can only speculate about the biological significance of the dual action of oestrogens on thyroid activity: it is known that hypo- as well as hyperthyroidism are disadvantageous to optimal ovarian function. Hypothyroidism is known as an important cause of sterility; furthermore it has been observed that the ovary in experimental animals degenerates following thyroid extirpation (De la Peña Regidor, 1941). The high iodine content of the ovary (Maurer & Dugue, 1928) might indicate the importance of thyroid hormone for this organ; further analysis of the origin and mode of action of ovarian iodine may clarify this point. Hyperthyroidism likewise is harmful to the ovary, presumably because this condition causes a decreased sensitivity of the gonads to gonadotrophins (Bischoff et al., 1941; Laqueur & Emge, 1941; Meites & Chandrashaker, 1949; Clavert, 1951). Thus if euthyroidism is a necessary condition for optimal ovarian function, there is also an increased need for thyroid hormone in cases of increased ovarian activity (e.g. during pregnancy).

5. It may be imagined that the ovary controls an adequate supply of thyroid hormone, varying with its various functional stages; it regulates the production of thyroid hormone since increased production of oestrogens results in an increased sensitivity of the thyroid to TSH and thereby to an increased thyroid hormone production. However, excessive hormone production is prevented by the inhibiting action of oestrogens on TSH release, while the increase of the basal metabolic rate is counteracted by the peripheral antagonism between thyroid hormone and oestrogens with regard to the metabolic level. The mechanism described therefore may include a dynamic equilibrium with adaptations to various functional conditions. Only extensive further investigation, however, will enlighten us as to whether a real significance can be attributed to the above-outlined hypothesis.
SUMMARY

1. In castrated adrenalectomized male rats, oestradiol benzoate in daily doses of 10, 20 and 50 µg, for one week, causes a similar increase in $^{131}$I uptake in the thyroid. Consequently there is no correlation between dosage and effect.

2. 50 µg. oestradiol benzoate daily for one week, in thyroidectomized castrated male rats on a maintenance dose of 10 µg. dl-thyroxine daily, causes a slight retention in the 24-hour excretion in the urine of a tracer dose of Na$^{131}$.

3. The in vitro uptake of $^{131}$I by thyroid glands of rats treated for one week with 50 or 300 µg. oestradiol benzoate daily, is larger than that of untreated control animals.

4. The conversion of iodide into organically bound iodine in the thyroid gland, is not inhibited by treatment with 50 µg. oestradiol benzoate daily for one week.

5. Endogenous oestrogens in a small dosage that, however, has a definite increasing effect on the action of TSH on the $^{131}$I uptake by the thyroid gland, does not cause changes in the histological structure of this organ.

6. The biological significance of the influence of oestrogens on the thyroid is discussed.

The author is greatly indebted to Prof. A. Querido, M. D., Leiden, for kindly providing him with the radioactive iodide used in this study.

REFERENCES