INFLUENCE OF OESTROGENS ON THYROID FUNCTION. I.

By

E. L. Noach

The effect of oestrogens on thyroid function has interested many investigators throughout the years. When reviewing the literature it appears that despite much work in this field, no unanimous conception has emerged: data on stimulation of the thyroid gland alternate with reports on inhibition, without there being any explanation for these discrepancies based on differences in animal species used or on experimental procedure. More accurate analysis of the data from the literature, however, suggests that oestrogens influence the thyroid gland in at least two counterbalancing ways: on the one hand via an inhibition of thyrotrophin (TSH) release by the pituitary gland, on the other, by a direct action on the thyroid gland, viz., a potentiation of TSH action. The total effect on the thyroid function then may be the algebraic sum of these two actions. In this way small quantitative differences in both aspects of action, e.g. caused by differences in experimental condition, might lead to the variable results found in the literature. The result of our investigations was that a sensitization of the thyroid for TSH under the influence of oestrogens, only suggested by the data in the literature, could actually be demonstrated.

LITERATURE

For a comprehensive review of the literature the reader is referred to Noach (1953). From this the following data are briefly given:

1. Influence of oestrogens on the thyrotrophic activity of the hypophysis.

It is generally found that treatment with oestrogens results in a decrease in TSH content of the hypophysis (Grumbrecht & Loeser, 1938; Simpson & Evans, 1941; Paesi & Hoogstra, 1954). However, since the TSH content of the hypophysis and its release into the blood, need not run parallel (Griesbach & Purves, 1943; Purves & Griesbach, 1946; d'Angelo, 1953), it is thus by no means certain that the quantity of TSH available for the thyroid is also decreased by treat-
ment with oestrogens. If this is really the case, then the stimulation of the thyroid by oestrogens, as found by some authors and to be discussed later, would have to be based on the sensitizing action of oestrogens as mentioned in the introduction. Experiments performed in order to determine TSH release by investigating the influence of oestrogens on the thiouracil-goitre – in which it is assumed that thiouracil causes maximal TSH release – by implication are based on a constant relationship between the quantity of TSH acting on the thyroid and its effect, whereas the results of our experiments to be discussed below, show that on the contrary the sensitivity of the thyroid gland to TSH is increased by oestrogens. Such experiments, in which, incidentally, no unanimous results were obtained (Chamorro, 1949; Gineste, 1949; Calapá, 1950; Lindner et al., 1950; Desclin et al., 1950), thus give no evidence for an alteration in TSH release.

2. Stimulating effect of oestrogens on the thyroid gland.

This has been demonstrated by De Amilibia et al. (1936) and by Desclin and collaborators (Desclin & Ermans, 1950, 1951; Desclin, 1952 a, b) in rats, by Morris (1952) in chickens, and by Engström et al. (1952) in man. It is possible that oestrogens, by hyperstimulation and subsequent exhaustion of the thyroid, cause a degeneration of the structure of this organ: this may be indicated by the histological findings of Alexiu (1939) and Morrell & Hart (1941). In accordance with the activating effect of oestrogens is the observation that the lack of oestrogens following castration may result in a decreased activity of the thyroid, again counteracted by treatment with oestrogens (Milco & Pitis, 1941).

3. Inhibition of thyroid function by oestrogens.

Heyl et al. (1934) found in rats that increasing dosages of oestrogen caused increasing inhibition of the histological activity of the thyroid gland. Similar results were obtained by Grumbrecht & Loeser (l. c.) in some of their numerous investigations on this subject; sometimes, however, they were able to demonstrate a stimulation. It is difficult, however, to review their data, because of the many variations in their experimental procedures and the lack of sufficient controls. Moreover, Gaarenstroom et al. (1942) were unable to confirm the observations on which Grumbrecht & Loeser base their conception of a transformation of oestrogens in the uterus, as a necessary condition for an influence on the thyroid; hence we will refrain from further discussion of this question.

Müller & Aeppli (1949) found a decreased uptake of I\(^{131}\) in the thyroid of oestrone-treated rats. The number of their animals was too small, however, for statistical evaluation, so that their results may at most be considered as complementary to those of Money et al. (1951).
4. **Thyroid inhibition or stimulation dependent on the dosage of oestrogens.**

The controversial results of the investigations discussed in the previous paragraphs, might possibly be reconciled by a number of observations concerning a qualitative difference between the effect of small and large doses of oestrogens: small doses caused activation, larger doses, a more or less distinct inhibition of the thyroid (Money et al., 1950; Wolterink et al., 1950; Mercier-Parot & Tuchmann-Duplessis, 1951). Previous results of Gustavson et al. (1941) might also be interpreted as showing similar differences. Possibly the lack of influence of oestrogens on thyroid function, as observed by Gaarenstroom et al. (I.c.), Paschiks et al. (1948) and Aron et al. (1951) may be interpreted as the result of a dosage critically placed between stimulation and inhibition. As well as different effects with various dosages of oestrogens, it has also been shown that the same dosage may have opposite effects according to the pre-treatment of the experimental animals: Lindner et al. (1950) found that implantation of a hexoestrol pellet in intact female rats resulted in a historical decrease of the activity of the thyroid, whereas a similar treatment in spayed female rats was actually followed by activation of the follicular epithelium. Desclin et al. (1950) arrived at similar results. Based on the above-mentioned data therefore the impression is obtained that the same dosage in intact females acts as a »large«, but in spayed rats as a »small« quantity of hormone. This again suggests a sensitivity for thyrotrophic influence on the thyroid, increased under the influence of small doses of oestrogens. An intrinsic »thyrotrophic« effect of oestrogens is less likely, since it is known that an increase of dosage mostly results in increasing thyroid inhibition. It cannot be denied, however, that other interpretations are possible.

5. **Influence of oestrogens on the basal metabolic rate.**

As Gessler (1936, 1937) and Sherwood (1941) were able to show that oestrogens may cause a decrease of BMR independently of their action on the thyroid, no value can be attributed to conclusions concerning the influence of oestrogens on thyroid activity, when obtained by this method. Consequently we think the mention of relevant literature unnecessary.

**Summarizing** it can be said that the possibility of a potentiation of TSH by oestrogens is repeatedly suggested by the literature, so far without such an effect having been demonstrated, in our opinion, by experiments on this problem.

**OWN INVESTIGATION**

**Methods**

The thyroid activity was determined by measuring the 24-hour-uptake in the thyroid gland, of a tracer dose of NaI^{131}. With the exception of one series of experiments male rats were always used, castrated one week prior to the commencement of the
treatment, in order to eliminate the influence of the endogenous sex hormones. Preference was given to male animals in order to avoid the possibility that the interpretation of the results might be complicated by possible differences in affinity for iodine between the uterus that had, and that had not been, influenced by oestrogens. For technical reasons, however, in one experiment, to be discussed later, females had to be used.

When hypophysectomized animals were used, hypophysectomy was performed 5 days previous to the commencement of the oestrogen treatment. The completeness of the hypophysectomy was confirmed at autopsy by inspection of the base of the skull, using a binocular dissecting microscope.

In all experiments paired feeding was used: oestrogens cause a decrease in appetite, thus making it possible that in feeding ad libitum the oestrogen treated animals the \( \text{I}^{131} \) might be less diluted by the iodine from the food than in the control rats. Therefore the control animals were offered the same quantity of food as the oestrogen treated animals had consumed in the previous 24-hour period. The rat food used (Bertels, Amsterdam), contained 40 µg. iodine per 100 gm. Drinking water was given ad libitum. Exogenous oestrogens were injected subcutaneously twice daily as oestradiol benzoate in olive oil (Dimenformon, Organon) in a volume of 0.1 ml. Controls were given an equal volume of olive oil. TSH (Ambinon, Organon) in physiological saline solution was injected into another region of the body, also subcutaneously. Control animals were given saline.

In one series of experiments instead of administering exogenous oestrogens, the production of endogenous oestrogens was enhanced. To obtain this, hypophysectomized female animals were treated with a daily dose of 10 I. U. of serum gonadotrophins (Gestyl, Organon) subcutaneously. The production of oestrogens was checked by means of the vaginal smear. As control animals in this experiment, identically treated, spayed, hypophysectomized female rats were used. The hormone treatment in all cases lasted one week. On the 6th day the animals were given an intraperitoneal injection of 1 ml of saline, in which approximately 1 µc. carrier-free Na\(^{131}\) had been diluted. Animals with intact pituitary gland were subsequently starved until autopsy. In order to prevent hypoglycemia, hypophysectomized animals were given 3 gm. of food, which as a rule was consumed. In both cases the animals were given water ad libitum. Twenty four hours after administration of the tracer dose, the animals were killed by a blow on the neck, after which the thyroid gland was rapidly dissected out, weighed on a torsion balance, and then dissolved in 10 ml. 2N NaOH in 1% KI in a water-bath at 38°. Dried samples of this solution were counted on aluminium dishes in a \( \beta \)-ray Geiger-Müller counter manufactured by Brul & Kjaer, type 6501. For comparison a standard of known radio-activity was used. The count values measured were corrected for physical decay and expressed as % uptake of the tracer dose per whole thyroid, and, as a standard for the avidity of the thyroid tissue for iodine, also calculated per mg. thyroid. (Full technical details cf. Noach, 1953). In the statistical evaluation of the material, Student's t-test was used.

**Experimental procedure**

1. In a first series the «over-all» effect of oestrogens on the thyroids of our rat strain was investigated. For this purpose different groups of castrated male rats were treated with 10, 20, 50, 100, 500 and 1000 µg. of oestradiol benzoate per day respec-

1. Determined by Dr. A. A. H. Kassenaar, Dept. for Clinical Endocrinology and Metabolism, Leiden.
tively, for one week. The thyroid weights and the I\textsuperscript{131} uptake in the thyroid was compared to that of paired fed oil-treated controls.

2. Subsequently experiments were performed to determine whether oestrogens have a direct thyrotrophic effect. Hypophysectomized animals were treated with 50 µg. oestradiol benzoate daily. The I\textsuperscript{131} uptake and thyroid weights were compared with those of oil-treated controls.

3. In a further series the effect of oestrogens on the activity of TSH was investigated. When it was found that treatment of hypophysectomized animals with 2 Heyl-Laqueur (1934) Units of TSH daily for one week caused a definite increase in thyroid function as measured from the I\textsuperscript{131} uptake, various doses of oestrogens were injected simultaneously with TSH into hypophysectomized animals, and the thyroid activity determined and compared with that of control animals given TSH and oil. The doses of oestrogens in this series had to be lower than in experiment 1, because of their toxicity for hypophysectomized animals. Three dosages were used: 50 and 20 µg. oestradiol benzoate, and as a lowest dosage the endogenous oestrogens produced in the previously discussed hypophysectomized gonadotrophin-treated female animals; from previous experience in our laboratory it may be assumed that the quantity of oestrogens, liberated from the ovary under the influence of a daily dose of 10 I. U. serum gonadotrophins, is less than the equivalent of 20 µg. oestradiol benzoate.

RESULTS

1. (Table 1). Oestradiol benzoate in a dosage range of 10-1000 µg. daily caused a significant increase in I\textsuperscript{131} uptake in the thyroid. The average thyroid weights were also increased, but the differences were not significant in all cases. The uptake per mg. thyroid tissue shows no clear-cut difference.

2. (Table 2). Oestradiol benzoate in a daily dosage of 50 µg., which caused in intact animals a clear increase in the I\textsuperscript{131} uptake in the thyroid, had no influence at all on the thyroid of otherwise untreated hypophysectomized animals. A direct «thyrotrophic» effect of oestrogens could therefore be excluded.

3. (Table 3). Oestrogens in different dosages cause an increase in I\textsuperscript{131} uptake per whole thyroid gland, as well as per mg. of thyroid gland, and of the thyroid weight of hypophysectomized rats on a constant maintenance dose of TSH. The dose of TSH was so chosen, that, although a marked effect was noted, thyroid function was not quite normalized (Table 4). Thus the possibility that thyroid function might approach a maximum, which could not be surpassed by the simultaneous action of oestrogens, was avoided.

DISCUSSION

The results of the first series of experiments were surprising in that oestrogens in a wide dosage range cause stimulation of the thyroid. Consequently we were unable to confirm either an inhibition, or the results indicated in the literature, namely that increase of dosage of oestrogens results in a reversed effect.
<table>
<thead>
<tr>
<th>Dose of oestradiol benzoate (µg/day)</th>
<th>Mean body weight start of treatment (g)</th>
<th>Mean body weight end of treatment (g)</th>
<th>Thyroid weight per 100 gms body weight (mg)</th>
<th>Uptake of 1³¹I per mg thyroid (as % of tracer dose) in 24 hours</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>112 (contr.)</td>
<td>121</td>
<td>17.3±0.66</td>
<td>58±2.4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>113</td>
<td>124</td>
<td>17.0±0.53</td>
<td>57±2.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>127</td>
<td>16.4±0.50</td>
<td>56±2.5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>131</td>
<td>15.8±0.45</td>
<td>56±2.5</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>104</td>
<td>116</td>
<td>14.9±0.96</td>
<td>66±1.5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>119</td>
<td>11.8±0.72</td>
<td>56±3.1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>117</td>
<td>11.2±0.05</td>
<td>41±3.9</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>117</td>
<td>9.3±0.05</td>
<td>22±2.6</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>104</td>
<td>116</td>
<td>14.1±0.05</td>
<td>60±3.1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>117</td>
<td>11.2±0.05</td>
<td>41±3.9</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>107</td>
<td>117</td>
<td>9.3±0.05</td>
<td>22±2.6</td>
<td>12</td>
</tr>
<tr>
<td>100</td>
<td>139</td>
<td>151</td>
<td>12.4±0.07</td>
<td>61±2.2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>151</td>
<td>12.4±0.07</td>
<td>61±2.2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>151</td>
<td>12.4±0.07</td>
<td>61±2.2</td>
<td>10</td>
</tr>
<tr>
<td>500</td>
<td>142</td>
<td>156</td>
<td>15.5±1.02</td>
<td>64±3.3</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>142</td>
<td>156</td>
<td>15.5±1.02</td>
<td>64±3.3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>142</td>
<td>156</td>
<td>15.5±1.02</td>
<td>64±3.3</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 1. Influence of oestradiol benzoate on thyroids of castrated male rats.
Table 2.
Influence of 50 µg. oestradiol benzoate/day on uptake of tracer dose of I¹³¹ by thyroids of hypophysectomized castrated male rats.

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Treatment</th>
<th>Thyroid weight (mg./100 gm. body weight)</th>
<th>% uptake tracer dose I¹³¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>oestr. benz.</td>
<td>9.9</td>
<td>3.7</td>
</tr>
<tr>
<td>7</td>
<td>olive oil</td>
<td>9.1</td>
<td>3.9</td>
</tr>
</tbody>
</table>

This, however, is not in contradiction to our working-hypothesis that oestrogens influence the thyroid in more ways than one: as discussed previously, if this hypothesis is correct, small quantitative differences, determined by factors such as species, strain, experimental conditions, may then result in what appears at first sight to be qualitative discrepancies found with other investigations. In this connection it is remarkable that the successive series of oestradiol benzoate dosages do not show a «trend» in the results: when we express the results of the oestradiol benzoate treated groups as a percentage of the corresponding values of the relevant control groups (Table 5), then it appears that no common tendency in the sense of increase or decrease of effect on the different aspects of thyroid function is observable. The most plausible explanation for the absence of an increase in effect is, that with the lowest oestradiol benzoate dosage (10 µg.) a peak is reached that cannot be surpassed, although it is remarkable that the effect on I¹³¹ uptake with the dosage of 50 µg. is even greater, and in the other dosages, smaller. The absence of a decrease in effect with increase of dosage, as expected from previously discussed data in the literature, cannot, however, be explained in this way. In considering other possible explanations, however, the results in animals without hypophysis may provide the key to the problem. For it appears that, although oestradiol benzoate has no thyrotrophic effect (Table 2) with the dosage that causes the greatest increase in uptake in intact animals, oestrogens in various dosages bring about an increase in the effect of a constant dose of TSH. Hence when the values of oestrogen-treated animals are expressed in a corresponding way as in Table 5, as a percentage of the value in the control animals (Table 6), then it appears that in the animal deprived of its hypophysis, an increase in dosage of oestrogenic substance results in an increase in the effect, as regards the total uptake as well as the uptake per mg. and the thyroid weight. A possible explanation for the absence of such a tendency in intact animals with the corresponding range of dosage (10–50 µg. oestradiol benzoate) is that in these animals the oestrogens cause not only a sensitization of the thyroid to TSH, but also an increasing inhibition of TSH release with increasing dosage, so that the algebraic sum of both ac-
Table 3.
Influence of oestrogens on thyroid of hypophysectomized castrated male rats on a maintenance dose of TSH (2 Heyl-Laqueur-units/day).

<table>
<thead>
<tr>
<th>Dose of oestrogens/day</th>
<th>Mean body weight start of treatment</th>
<th>Thyroid weight per 100 gm. body weight</th>
<th>Uptake of I$^{131}$ (% of tracer dose) in 24 hours</th>
<th>Uptake of I$^{131}$ per mg. thyroid (% of tracer dose)</th>
<th>Number of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 I. U. serum gonadotrophin contr.</td>
<td>124 112</td>
<td>11.0 ± 0.28 p = 0.05</td>
<td>22 ± 1.3</td>
<td>1.8 ± 0.10</td>
<td>49</td>
</tr>
<tr>
<td>20 μg. oestr. benz. contr.</td>
<td>122 108</td>
<td>10.8 ± 0.44 p &lt; 0.02</td>
<td>24 ± 2.2</td>
<td>2.0 ± 0.20</td>
<td>26</td>
</tr>
<tr>
<td>50 μg. oestr. benz. contr.</td>
<td>109 99</td>
<td>9.8 ± 0.50 p &lt; 0.01</td>
<td>25 ± 3.3</td>
<td>2.5 ± 0.25</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>105 97</td>
<td>7.6 ± 0.30 p &lt; 0.01</td>
<td>13 ± 1.5</td>
<td>1.7 ± 0.18</td>
<td>9</td>
</tr>
</tbody>
</table>
**Table 4.**
Influence of 2 Heyl-Laquer-Units of TSH per day on uptake of tracer dose I\(^{131}\) by thyroids of hypophysectomized male rats.

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Treatment</th>
<th>Thyroid weight (mg./100 gm. body weight)</th>
<th>% uptake tracer dose I(^{131})</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>TSH</td>
<td>12.2</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>saline</td>
<td>10.4</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 5.**
Increase of thyroid weight and radio-iodide uptake of oestrogen treated castrated male rats as compared with control animals (100%).

<table>
<thead>
<tr>
<th>Oestr. benz. ((\mu g./day))</th>
<th>Thyroid weight (% of controls)</th>
<th>Uptake of I(^{131}) (% of controls)</th>
<th>Uptake of I(^{131}) per mg. thyroid (% of controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>157*</td>
<td>157*</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>126*</td>
<td>118*</td>
<td>97</td>
</tr>
<tr>
<td>50</td>
<td>121*</td>
<td>186*</td>
<td>164*</td>
</tr>
<tr>
<td>100</td>
<td>114</td>
<td>125*</td>
<td>112</td>
</tr>
<tr>
<td>500</td>
<td>117*</td>
<td>133*</td>
<td>122</td>
</tr>
<tr>
<td>1000</td>
<td>122*</td>
<td>123*</td>
<td>106</td>
</tr>
</tbody>
</table>

* Statistically significant (\(p < 0.05\)) increase.

**Table 6.**
Increase of thyroid weight and radio-iodide uptake of oestrogen treated hypophysectomized rats as compared with control animals (100%).

<table>
<thead>
<tr>
<th>Dose/day</th>
<th>Thyroid weight (% of controls)</th>
<th>Uptake of I(^{131}) per thyroid (% of controls)</th>
<th>Uptake of I(^{131}) per mg. thyroid (% of controls)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 I. U. serum gonadotrophin</td>
<td>108*</td>
<td>122*</td>
<td>112</td>
</tr>
<tr>
<td>20 (\mu g). oestradiol benzoate</td>
<td>113*</td>
<td>160*</td>
<td>143*</td>
</tr>
<tr>
<td>50 (\mu g). oestradiol benzoate</td>
<td>129*</td>
<td>193*</td>
<td>147*</td>
</tr>
</tbody>
</table>

* Statistically significant (\(p < 0.05\)) increase.
tions as measured by the thyroid activity, shows no clear trend. An indication for the decrease in quantity of available TSH is the fact that the percentage increase in the thyroid weight becomes smaller and smaller between 10 and 100 µg. in intact animals. In that case one would have to assume that the influence of the growth-promoting and iodine uptake aspects of TSH action may be influenced by oestrogens in various ways. This might lead to an acceptance of the point of view of Greer (1952) on the existence of two separate thyrotrophic factors. However, this is not in agreement with the finding that the figures from Table 6, not only do not support this point of view but rather indicate that the measurements of the I\(^{131}\) uptake is a more sensitive method for the determination of the thyroid function than is the thyroid weight.

Changes in sensitivity of the thyroid to TSH have also been found under the influence of other substances: Cortell & Rawson (1944) found that administration of thyroxin to hypophysectomized rats decreased the sensitivity to TSH. Rawson & Money (1949) observed that thiouracil in the hypophysectomized animal causes an increase of the (histological) effect of exogenous TSH. This observation has since repeatedly been confirmed (a. o. Gassner et al., 1950, Wessels et al., 1950).

A decrease in sensitivity of the thyroid to TSH appeared to be also caused by the glucocorticosteroids of the adrenal cortex (Woodbury et al., 1951). Although others have denied such an inhibition (Halmi, 1952) one has to take into account the finding that oestrogens are able to cause an enlargement of the adrenal (Korenchevsky & Dennison, 1934, 1935) and also to activate adrenal function (Skelton et al., 1949) by increasing corticotrophin release. Hence it still remains possible that besides the sensitization of the thyroid by oestrogens, there is no inhibition of TSH release but an activation of the adrenal cortex, thus causing a desensitization by adrenal steroids, which competes with the direct sensitization of the thyroid, thus complicating the picture even more. However, in a further paper we will present evidence to demonstrate that at least in the relevant range of dosages, no appreciable influence of the adrenal can have been present.

We can only speculate as to the finer mechanism of the sensitization process. On the one hand there is the possibility that oestrogens sensitize the thyroid to TSH. Perhaps this is based on the fact that the circulating TSH can penetrate better into the thyroid owing to the well-known vasodilating action of oestrogens: at autopsy of the animals it was evident that the thyroid glands of the oestrogen-treated animals were very hyperaemic. On the other hand, however, it cannot be excluded that oestrogens do not act on the thyroid cells but on the circulating TSH, as is known from other substances: Albert et al. (1947) were able to increase the effect of TSH by incubating it in vitro with small quantities of thiouracil. Experimental data are not yet available which allow a conclusion as to whether such a mechanism is the basis for the action of oestrogen.
In a further paper we will describe a number of experiments, which were performed to exclude other possible explanations of the above results.

SUMMARY

1. Oestrogens, administered in daily dosages of 10–1000 µg. oestradiol benzoate for a week, in male castrated albino rats cause an increase in the 24-hour uptake of NaI\textsuperscript{131} and of the thyroid weight as compared with paired fed, oil-treated controls. However, there is no distinct relationship between dosage and effect.

2. In hypophysectomized castrated male rats, 20 and 50 µg. oestradiol benzoate administered daily for a week, cause an increase of the effect of simultaneously injected TSH (2 Heyl-Laquer Units daily), both on thyroid weight and I\textsuperscript{131} uptake. A qualitatively similar effect was produced by the administration of 10 I. U. serum gonadotrophins to TSH-treated hypophysectomized female rats, compared with paired fed hypophysectomized spayed female rats, treated in the same manner. In the hypophysectomized animals, increase of the dosage of oestrogens resulted in an increase of the effect.

3. In the hypophysectomized animal, oestrogens have no thyrotrophic effect.

4. On the basis of these data it is probable that oestrogens influence the thyroid gland in two ways, viz., by decreasing TSH release by the hypophysis, and by intensifying the action of TSH on the thyroid gland.

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Angelo, S. A. d': Endocrinology 52, 331, 1953.