THE FUNCTION OF THE THYROID
IN EUTHYROID PATIENTS WITH EXOPHTHALMOS

By

Thorkild Friis and Earle M. Chapman

In the presence of severe exophthalmos it has been known that the basal metabolic rate, serum concentration of protein-bound iodine, and radioiodine uptake may be normal or compatible with either hypo- or hyperthyroidism. These findings have defied the clinician to relate exophthalmos directly to thyroid function. However, in a recent study of ten clinically euthyroid patients, Werner (1955) found all tests of function normal except for suppression of uptake by administration of triiodothyronine; here the patients with exophthalmos responded like thyrotoxic patients in that their uptake was not suppressed.

In an attempt to elucidate further the function of the thyroid gland in clinically euthyroid patients with exophthalmos, eight such patients have been studied. Measurements included basal metabolic rates, serum concentration of protein-bound iodide (PBI), uptake of I\(^{131}\) by the thyroid, and the conversion ratio of I\(^{131}\) in serum (PBI\(^{131}\)). Paper chromatographic analyses were made of the serum at varying times after the oral administration of radioactive iodine.

The clinical data are shown in Table 1. All except patients No. 7 and No. 8 had severe exophthalmos. The patients were otherwise clinically euthyroid. Six had been treated previously for thyrotoxicosis by sub-total thyroidectomy or with I\(^{131}\).

1. This work has been carried out in part with financial support from the Egmont H. Petersen Foundation, Copenhagen, Denmark.
2. Present address: Københavns Amts Sygehus (The County Hospital of Copenhagen), Hellerup, Copenhagen.
### Table 1.
Clinical data of 8 euthyroid patients with exophthalmos.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Nervousness</th>
<th>Tremor</th>
<th>Tachycardia</th>
<th>Loss of weight</th>
<th>Fatigue</th>
<th>Diarrhoea</th>
<th>Struma</th>
<th>Eye symptoms</th>
<th>Duration</th>
<th>Previous treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>♀</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
<td>Exophthalmos</td>
<td>1 yr.</td>
<td>Subtotal thyroidectomy 1954</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>♀</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Bilateral exophthalmos</td>
<td>5 yrs.</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>♀</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Bilateral exophthalmos</td>
<td>3 yrs.</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>♂</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Exophthalmos</td>
<td>6 yrs.</td>
<td>Subtotal thyroidectomy 1947</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>♂</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Exophthalmos</td>
<td>1 yr.</td>
<td>I^{131} 1953</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>♀</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Exophthalmos</td>
<td>3 yrs.</td>
<td>I^{131} 1955</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>♀</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td>Moderate exophthalmos (Improving)</td>
<td>4 yrs.</td>
<td>I^{131} 1955</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>♂</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td></td>
<td>Moderate exophthalmos (Improving)</td>
<td>5 yrs.</td>
<td>I^{131} 1953</td>
</tr>
</tbody>
</table>

**METHODS**

The doses of I^{131} employed as tracers without added carrier iodide were 20–40 microcuries except in those patients whose sera were chromatographed, and then 200–300 microcuries were administered.

The uptake of I^{131} by the thyroid was determined by three scintillation detectors
placed equidistant in a circle around the neck of the patient at a distance of 40 cm. from the thyroid. The uptake of $^{131}\text{I}$ was determined 24 hours after oral administration of the isotope. The normal value is 20–52 $\%$ of the dose administered.

The conversion ratio (Charkoff et al., 1947, Clark et al., 1949) was determined 24 hours after administration of $^{131}\text{I}$. Labeled iodine in 2 ml. of serum was measured in a well-type scintillation crystal detector. The proteins in this 2 ml. of serum were precipitated with 4 ml. 10 $\%$ trichloracetic acid, the precipitate washed twice with 4 ml. 2.5 $\%$ trichloracetic acid, once with 4 ml. water, and then the measurement repeated. The labeled iodine was expressed as per cent of dose per liter of serum. The PBI$^{131}$ value was then divided by the total $^{131}\text{I}$ value and multiplied by 100 to give the conversion ratio.

The protein-bound iodine in serum was determined after the method of Barker (1948). The normal values are 3.5–8 $\mu$g. $\%$.

The technique of paper chromatography was similar to the technique of Stanbury et al. (1955) with the exception that the ascending technique (Friis & Hall, 1957) was used. Analyses were in a butanol-dioxane-ammonia solvent system on 3 ml. of sera taken from the patients 2, 4, 6, 24 and 48 hours after the administration of $^{131}\text{I}$. In one patient (No. 3) it was also done in the butanol-acetic acid system.

**RESULTS**

The results of the studies are shown in Tables 2 and 3 and in Figs. 1 and 2. It will be seen from Table 2 that the basal metabolism determination, 24-hour uptake of $^{131}\text{I}$, and PBI values were normal in all cases except No. 3 where the basal metabolism was slightly increased, No. 7 where the protein-bound iodine was increased, and No. 1 where the protein-bound iodine was found to be low, and No. 5 where the 24-hour uptake was above normal. The conversion ratio was increased in all cases ($> 50 \%$), and the PBI$^{131}$ was elevated in half the patients.

The euthyroid treated patients without exophthalmos all had conversion ratios below 40 $\%$ except two, where it was slightly elevated (Table 3). In no case was the PBI$^{131}$ elevated. Previously, several observers (Bloom & Terpestra, 1953; Larsson, 1955; Lindeboom, 1955; Paley et al., 1955) have reported that such values may be increased after treatment with $^{131}\text{I}$ or after sub-total thyroidectomy.

Fig. 1 shows representative chromatograms from patient No. 1. Two and 4 hours after administration of $^{131}\text{I}$ only radioactive iodide could be found in the serum; after 6 hours activity corresponding to the thyroxine zone began to appear; 24 hours afterwards there was only radioactive thyroxine in the serum, and 48 hours after administration of $^{131}\text{I}$ both radioactive thyroxine and radioactive triiodothyronine could be found. Chromatograms of patient No. 2 were similar.

3. The sensitivity of this detector was 700,000 counts per minute (cpm) per micro-curie; background, 150 cpm.
Table 2.
Experimental results in 8 euthyroid patients with exophthalmos.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Previous treatment</th>
<th>Basal metabolism normal: 90–110%</th>
<th>Protein-bound iodine normal: 30–80%</th>
<th>Uptake of $\text{I}^{131}$ in 24 hours</th>
<th>Total $\text{I}^{131}$ in serum after 24 hours (% per litre)</th>
<th>PBI $\text{I}^{131}$ in serum after 24 hours normal: &lt;0.4 % per litre</th>
<th>Conversion ratio after 24 hours normal: 15–40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1954</td>
<td>93</td>
<td>1.6</td>
<td>33.8</td>
<td>2.02</td>
<td>1.98</td>
<td>98.0%</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>♀</td>
<td>None</td>
<td>89</td>
<td>5.0</td>
<td>49.1</td>
<td>0.87</td>
<td>0.79</td>
<td>90.8%</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>♀</td>
<td>None</td>
<td>123</td>
<td>4.6</td>
<td>50.3</td>
<td>0.32</td>
<td>0.29</td>
<td>90.6%</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>☢</td>
<td>Subtotal thyroidectomy 1947</td>
<td>95</td>
<td>6.1</td>
<td>35.7</td>
<td>0.50</td>
<td>0.36</td>
<td>72.0%</td>
</tr>
<tr>
<td>5</td>
<td>61</td>
<td>☢</td>
<td>$\text{I}^{131}$ 1953</td>
<td>91</td>
<td>6.6</td>
<td>55.8</td>
<td>0.31</td>
<td>0.26</td>
<td>83.9%</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>♀</td>
<td>$\text{I}^{131}$ 1955</td>
<td>103</td>
<td>6.4</td>
<td>45.0</td>
<td>1.24</td>
<td>1.04</td>
<td>84.0%</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>♀</td>
<td>$\text{I}^{131}$ 1955</td>
<td>84</td>
<td>10.2</td>
<td>49.6</td>
<td>0.46</td>
<td>0.24</td>
<td>52.5%</td>
</tr>
<tr>
<td>8</td>
<td>65</td>
<td>☢</td>
<td>$\text{I}^{131}$ 1952</td>
<td>90</td>
<td>5.5</td>
<td>34.2</td>
<td>0.75</td>
<td>0.45</td>
<td>60.0%</td>
</tr>
</tbody>
</table>

Chromatograms from patient No. 3 showed a zone of labeled iodine corresponding to the monoiodotyrosine zone both in the butanol-dioxane-ammonia system and the butanol acetic acid system (Fig. 2). In this case it was not possible to demonstrate radioactive triiodothyronine until 48 hours after administration of $\text{I}^{131}$. In the other patients, only radioactive iodide and thyroxine could be demonstrated.

Fig. 1 a–c.

a. Result of paper chromatography (butanol-dioxane-ammonia system) from patient No. 1 four hours after administration of $\text{I}^{131}$. – Abscissa: cm. from line on which the solution was applied. – Ordinate: net counts per minute. – D = Diiodotyrosine; M = Monoiodotyrosine; T$_4$ = Thyroxine; T$_3$ = Triiodothyronine.

b. Result of paper chromatography (butanol-dioxane-ammonia system) from patient No. 1 six hours after administration of $\text{I}^{131}$. – Abscissa: cm. from line on which the solution was applied. – Ordinate: net counts per minute.

c. Result of paper chromatography (butanol-dioxane-ammonia system) from patient No. 1 forty-eight hours after administration of $\text{I}^{131}$. – Abscissa: cm. from line on which the solution was applied. – Ordinate: net counts per minute.
Table 3.
Experimental results in 13 euthyroid patients previously strumectomized or treated with $^{131}$I.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age</th>
<th>Sex</th>
<th>Previous treatment</th>
<th>Basal metabolism normal: 90-110%</th>
<th>Protein-bound iodine normal: 3/5-8 μg/g</th>
<th>Uptake of I131 in 24 hours</th>
<th>Total I131 in serum after 24 hours (% per litre)</th>
<th>PBI I131 in serum after 24 hours normal: &lt;0.4 % per litre</th>
<th>Conversion ratio after 24 hours normal: 15-40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1931</td>
<td>81</td>
<td>2.2</td>
<td>27.5</td>
<td>0.77</td>
<td>0.38</td>
<td>49.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1931 1954</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1954</td>
<td>93</td>
<td>–</td>
<td>33.0</td>
<td>1.42</td>
<td>0.19</td>
<td>13.5%</td>
</tr>
<tr>
<td>3</td>
<td>73</td>
<td>♀</td>
<td>$^{131}$I 1954</td>
<td>95</td>
<td>–</td>
<td>43.3</td>
<td>0.94</td>
<td>0.21</td>
<td>22.3%</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>♀</td>
<td>$^{131}$I 1954</td>
<td>101</td>
<td>–</td>
<td>36.4</td>
<td>0.79</td>
<td>0.17</td>
<td>21.5%</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1955</td>
<td>92</td>
<td>–</td>
<td>22.4</td>
<td>0.29</td>
<td>0.03</td>
<td>10.3%</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>♀</td>
<td>$^{131}$I 1954</td>
<td>85</td>
<td>–</td>
<td>27.2</td>
<td>0.84</td>
<td>0.18</td>
<td>21.4%</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>♀</td>
<td>$^{131}$I 1954</td>
<td>93</td>
<td>–</td>
<td>32.0</td>
<td>1.23</td>
<td>0.25</td>
<td>20.3%</td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1953</td>
<td>93</td>
<td>–</td>
<td>26.1</td>
<td>0.64</td>
<td>0.06</td>
<td>9.5%</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1954</td>
<td>98</td>
<td>6.0</td>
<td>21.3</td>
<td>0.41</td>
<td>$&lt;$0.01</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1940</td>
<td>100</td>
<td>–</td>
<td>27.8</td>
<td>0.56</td>
<td>0.10</td>
<td>17.9%</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1949</td>
<td>106</td>
<td>5.7</td>
<td>20.2</td>
<td>0.36</td>
<td>0.07</td>
<td>19.8%</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1945</td>
<td>92</td>
<td>3.5</td>
<td>54.2</td>
<td>0.39</td>
<td>0.18</td>
<td>45.3%</td>
</tr>
<tr>
<td>13</td>
<td>68</td>
<td>♀</td>
<td>Subtotal thyroidectomy 1919</td>
<td>–</td>
<td>–</td>
<td>43.7</td>
<td>0.54</td>
<td>0.10</td>
<td>18.0%</td>
</tr>
</tbody>
</table>

212
DISCUSSION

In the present study the conversion of I\textsuperscript{131} was increased above normal in all of eight euthyroid patients with exophthalmos. Two of these eight had been thyroidectomized previously, and four had received radioactive iodine therapy one to three years previously. Concomitant studies on thirteen similar euthyroid
patients without exophthalmos showed a slightly increased conversion ratio in only two.

It is evident that the thyroid tissue present or remaining in patients with exophthalmos is overactive and that it is producing a normal amount of hormone. Implicit in these findings is a lowered storage of iodinated substances in the gland. Although the suspicion had been raised that the hastily produced hormone might be incompletely formed or abnormal in nature, the results indicated that, except in one case, only normally iodinated thyronines were secreted by these glands. The finding of small amounts of monoiodothyrosine in the serum of one patient is unexplained. In normal persons and patients with thyrotoxicosis only iodide, thyroxine, and triiodothyronine are found in serum after administration of I\textsuperscript{131} (Dingledine et al., 1955; Gross et al., 1950; Gross & Pitt-Rivers, 1952).

Triiodothyronine appeared in the serum of three patients and appeared later than thyroxine. This observation is contrary to that of Benua et al. (1955) who found that triiodothyronine appeared as early as one hour after the administration of larger doses of I\textsuperscript{131}. From this they concluded that triiodothyronine is released directly into the circulation. Our results are more in accord with those reported by Dingledine et al. (1955).

**SUMMARY**

In eight euthyroid patients with exophthalmos who had been previously treated with I\textsuperscript{131} or had a sub-total thyroidectomy, we found a marked increase in the conversion ratio of I\textsuperscript{131}. At the same time we found the conversion ratio normal in eleven of thirteen similar euthyroid patients who did not have exophthalmos. Paper chromatographic examinations revealed radioactive iodide and thyroxine in the sera of all exophthalmic patients; in only three patients was it possible to demonstrate radioactive triiodothyronine and in these it appeared later than thyroxine.

**ACKNOWLEDGMENT**

The authors wish to express their gratitude to Dr. John B. Stanbury for his advice and help.

**REFERENCES**


