REMISSION OF FAMILIAL GOITROUS HYPOTHYROIDISM

By

Henry W. Gray, John A. Thomson and J. Stuart Kennedy

ABSTRACT

Three male siblings with familial goitrous hypothyroidism due to a defect of thyroidal iodide organification have been studied. Withdrawal of thyroxine therapy from 2 of the brothers led to a rapid return of clinical hypothyroidism in one but the other brother remained euthyroid for approximately 3 years off his thyroxine therapy despite continuing evidence of defective iodide organification in his thyroid. The phenomenon is contrasted with that produced by massive administration of thyroid hormones ("Stoss therapy"), but no satisfactory explanation for its occurrence can be given.

A well documented clinical and biochemical diagnosis of hypothyroidism is usually correctly accepted as indicating the need for life long thyroxine therapy. Until recently, the only valid exception to this has been where the patient has been receiving a thyroid blocking drug either intentionally as in the treatment of thyrotoxicosis or as a side-effect from a drug given for another reason. For example, goitrous hypothyroidism may be induced in asthmatic patients taking proprietary preparations which contain considerable quantities of iodine (Begg & Hall 1963). In these circumstances withdrawal of the offending drug results in remission of the hypothyroidism.

Recently 2 cases were reported from this unit in which patients with hypothyroidism on the basis of autoimmune thyroiditis later became thyrotoxic (Gavras & Thomson 1972).

In this paper we present another clinical situation, namely familial goitrous hypothyroidism, in which remission of clinical and biochemical hypothyroidism appears to have taken place for a period of 3 years.
CASE MATERIAL

Case 1 (G. B.)

(This patient has been previously briefly cited by Thomson & Wallace (1966), as brother of case 3 in that paper).

This young man presented aged 19 years in 1966 with a 4 month history of tiredness, coarse dry skin, paraesthesia of hands and feet, and general mental and physical sluggishness. He had also noted a goitre in the recent past and thought that his face had become puffy. There was no history of drug ingestion. He gave a family history of one brother (Case 2) being on treatment for hypothyroidism.

On examination his skin was pale, cold and very coarse; his face was puffy; the thyroid gland was enlarged to about twice normal size and was symmetrical.

Fig. 1.
Histology of thyroid in G. B. Case 1 (x 560). The follicular cells show evidence of TSH stimulation but thyroiditis is not present.
and smooth; there was no thrill or bruit. The pulse rate was 56 per min and the blood pressure 120/80 mmHg. General examination was negative except for a marked delay in the relaxation phase of the ankle jerks.

A confident clinical diagnosis of hypothyroidism was supported by a PB127I of 0.3 μg/100 ml and BMR 47% below standard. The serum cholesterol was 240 mg/100 ml and the ECG showed widespread T wave abnormalities consistent with hypothyroidism. Radioiodine studies following an oral dose of 25 μCi 131I showed a thyroid uptake at 4, 24 and 48 h of 17% dose, 15 and 12% dose respectively. The 48 h total plasma iodine (TP131I) was 0.18% dose/litre with a negligible 48 h PB131I. Following the administration of an intravenous dose of 131I, the initial thyroidal clearance of iodide from the plasma was elevated at 159 ml/min/1.73 m² (normal range 15–80 ml/min/1.73 m²). The salivary/plasma ratio of radioiodine was 16:1. A perchlorate discharge test performed during the thyroid clearance study in which 600 mg of potassium perchlorate (KClO4) was administered orally showed only 6.9% discharge (discharge of 10% on this test is taken as abnormal). The thyroid precipitin test was negative. A thyroid biopsy was carried out (Fig. 1) and this showed a hyperplastic gland without evidence of thyroiditis. This biopsy was performed 48 h after an oral dose of radioiodine and subsequent autoradiography confirmed that iodine had accumulated in the follicular colloid. A normal oral MIT test confirmed that the patient was able to deiodinate monoiodotyrosine to iodide.

A diagnosis of dyshormonogenetic goitre was made and although he did not fit into any of the typical defects, the overall impression was that he probably had some abnormality of iodide organification. He was started on replacement thyroxine therapy and the dose steadily increased until he was on 0.3 mg/day. On this therapy his signs of hypothyroidism disappeared and his thyroid gland diminished in size.

In 1970 we had developed in our unit a more refined test for defective organification of iodine in the thyroid and the patient agreed to discontinue his thyroxine therapy in May of that year in order to permit further study.

Subsequent investigations are shown in Table 1. The net clearance of 131I by the thyroid at varying intervals after an intravenous dose of radioiodine was estimated by the technique of Wayne et al. (1964) and consisted of measurement of the thyroidal uptake at the beginning and the end of the clearance period and the removal of a mid-point sample of blood, the clearance being subsequently estimated on conventional principles. We noticed that one month after stopping his thyroxine his early thyroidal clearance was elevated and showed a 30% fall in the 15–20 min period as compared to the 5–10 min period, this being consistent with the presence of a minor organification defect (Owen et al. 1960). He was re-assessed at 20 and 46 weeks after stopping thyroxine and on both occasions he was clinically and biochemically euthyroid.
Table 1.
Data on Case 1, G. B.

<table>
<thead>
<tr>
<th>Time after stopping thyroxine</th>
<th>PB&lt;sup&gt;127&lt;/sup&gt;I mg/100 ml</th>
<th>Net clearance of &lt;sup&gt;131&lt;/sup&gt;I by the thyroid (ml/min)</th>
<th>iv perchlorate discharge test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–5 (min) 5–10 (min) 10–15 (min) 15–20 (min)</td>
<td></td>
</tr>
<tr>
<td>4 weeks</td>
<td>–</td>
<td>– 150 103 97 –</td>
<td></td>
</tr>
<tr>
<td>20 weeks</td>
<td>5.8</td>
<td>– 64 25 29 –</td>
<td>1.6% dose 21% gland uptake</td>
</tr>
<tr>
<td>46 weeks</td>
<td>6.1</td>
<td>– 48 39 38</td>
<td></td>
</tr>
<tr>
<td>16 months</td>
<td>10.0</td>
<td>– – – –</td>
<td>1.5% dose 19% gland uptake</td>
</tr>
<tr>
<td>28 months</td>
<td>8.2</td>
<td>– – – –</td>
<td>1.8% dose 15% gland uptake</td>
</tr>
<tr>
<td>40 months</td>
<td>1.5</td>
<td>– – – –</td>
<td>4.9% dose 50% gland uptake</td>
</tr>
</tbody>
</table>

although the clearance studies still showed definite evidence of an iodide organification defect. At 46 weeks off his thyroxine he had, in addition, studies using a sensitive intravenous perchlorate discharge test (Gray et al. 1973) which confirmed the presence of a binding defect by revealing a 1.6% dose discharge (normal range 0–0.5). Similar results were found at 16 and 28 months after stopping his thyroxine, during which time he remained clinically euthyroid, the PB<sup>127</sup>I being at the upper end of our normal range at 8.2 mg/100 ml. His serum TSH, estimated at 28 months by courtesy of Professor Hall, was within the normal range at 2.1 μU/ml and repeat studies of his thyroid antibodies showed that he had a negative precipitin and tanned red cell agglutination titre of antibodies to thyroglobulin and that thyroid microsomal antibodies were negative.

He remained asymptomatic but when reviewed at 40 months after stopping thyroxine, the intravenous perchlorate test revealed an increased discharge of 4.9% administered dose. A total serum thyroxine of 2.6 μg/100 ml, serum triiodothyronine of 1.9 ng/ml and serum TSH of 33 μU/ml all measured by Dr. Ratcliffe, confirmed that a relapse of hypothyroidism was imminent.

Case 2 (W. B.)

(Previously cited by Thomson & Wallace (1966), as Case 3 in that paper).
This boy, the brother of Case 1, presented to the Victoria Infirmary, Glasgow, in 1959 when aged 11 years. At that time he had marked lethargy, cold in-
tolerance, a puffy face and a slightly enlarged smooth thyroid gland. The pulse rate was 60 per min and the ECG showed T wave changes consistent with hypothyroidism. The serum cholesterol was 273 mg/100 ml and the BMR was 34% below standard. Antibodies to thyroglobulin were negative as shown by the thyroid precipitin test as was the complement fixation test for antibodies to thyroid microsomes. A diagnosis of hypothyroidism was made and he was commenced on thyroxine therapy but this was inadvertently stopped the following year. When seen in 1965 he was clinically hypothyroid and had a PB¹²⁷I of 0.1 μg/100 ml. An oral KClO₄ discharge test showed slight but not significant discharge of accumulated radiiodine (6% of accumulated dose discharged). Thyroxine therapy was, therefore, restarted and he remained well. In 1970 he too agreed to further study and his thyroxine was discontinued in May 1970.

Subsequent investigations are shown in Table 2. One month after stopping thyroxine his net thyroid clearance of ¹³¹I was in the high normal range and showed little fall from 5–20 min. When seen 4 months later however, he had developed mild cold intolerance and his PB¹²⁷I was 3.0 μg/100 ml which was strongly suggestive of recurrent hypothyroidism. On this occasion his clearance studies showed clear evidence of an organification defect with a marked fall in his net thyroidal clearance of ¹³¹I over the period 5–20 min. The presence of an iodide organification defect at 20 weeks after stopping thyroxine was confirmed by an intravenous perchlorate discharge test which showed a discharge of 1.6% of the dose, amounting to 25% of the total glandular ¹³¹I at 10 min. Replacement therapy was withheld for a further 4 weeks but hypothyroidism became clinically very obvious and the biochemical evidence of the binding defect was more striking. Thyroxine therapy was therefore restarted.

### Table 2.
Data on Case 2, W. B.

<table>
<thead>
<tr>
<th>Time after stopping thyroxine</th>
<th>PB¹²⁷I μg/100 ml</th>
<th>Net clearance of ¹³¹I by the thyroid (ml/min)</th>
<th>iv perchlorate discharge test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–5 (min)</td>
<td>5–10 (min)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>–</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>20 weeks</td>
<td>3.0</td>
<td>–</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 weeks</td>
<td>1.0</td>
<td>111</td>
<td>27</td>
</tr>
</tbody>
</table>

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Table 3
Data on Case 3, R. B.

<table>
<thead>
<tr>
<th>Time</th>
<th>PB(^{127})I (\mu g/100) ml</th>
<th>Net clearance of (^{131})I by the thyroid (ml/min)</th>
<th>iv perchlorate discharge test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0–5 (min)</td>
<td>5–10 (min)</td>
</tr>
<tr>
<td>Before thyroxine therapy 1970</td>
<td>5.0</td>
<td>380</td>
<td>100</td>
</tr>
<tr>
<td>Thyroxine stopped for 6 weeks</td>
<td>6.5</td>
<td>180</td>
<td>170</td>
</tr>
<tr>
<td>17 months after starting therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Case 3 (R. B.)

This third brother, aged 17 years, was seen in April 1970 at the time of the review of Cases 1 and 2. He complained of fatigue, dry skin, cramps, paraesthesia and had a goitre on examination. Clinically he was hypothyroid with a smooth thyroid gland about twice normal size. There was delay in the relaxation phase of his tendon jerks and his pulse rate was 60 per min. Radioiodine studies showed a 24 h uptake of 18 % of dose, a 48 h TP\(^{131}\)I of 0.24 % of dose/litre and a PB\(^{131}\)I of 0.02 % of dose/litre. The PB\(^{127}\)I surprisingly was 5.0 \(\mu g/100\) ml but the serum cholesterol was 327 mg/100 ml. The thyroid precipitin test for antibodies against thyroglobulin was negative.

Detailed studies on this patient are shown on Table 3. The clearance studies before therapy was initiated showed the very classical pattern of an iodide organification defect with a very high initial value and subsequent fall. Because of his clinical status, thyroxine replacement therapy was commenced with dramatic clinical improvement and complete disappearance of the goitre. Seventeen months after commencing thyroxine, therapy was withheld for 6 weeks allow further assessment. At the time of study the PB\(^{127}\)I was 6.5 \(\mu g/100\) ml and a 30 % fall in the net thyroidal clearance of \(^{131}\)I over the period of 5–20 min was noted, indicating persistence of the biochemical defect. At this time the intravenous perchlorate discharge test showed a significant discharge of accumulated radiiodine from the gland. Although the patient was euthyroid 6 weeks off his therapy he informed us that he was contemplating emigration and because of uncertainty about his remaining in the Glasgow area, thyroxine therapy was recommenced.
**Fig. 2.**
Family history. Case 1 (G. B.) is sibling 3, Case 2 (W. B.) is sibling 4 and Case 3 (R. B.) is sibling 5.

*Other members of the family*

The family tree is shown in Fig. 2. There is no evidence of consanguinity as far as we can elicit. The parents had no clinical evidence of thyroid dysfunction nor do other sibs. There is no history of deafness in any members of the family and there is no previous history of thyroid disease in other relatives.

**DISCUSSION**

These 3 brothers appear to have a dyshormonogenetic goitre due entirely or in part to defective organification of iodide within the thyroid. It is of particular interest that conventional perchlorate tests failed to reveal the defect while the intravenous perchlorate test clearly demonstrated the abnormality.

Since the brothers had a similar biochemical defect, it is difficult to understand why they showed such variation in clinical response to cessation of thyroxine therapy. While it is easy to understand in Case 2 why discontinuing thyroxine resulted in the rapid restoration of hypothyroidism, the outcome in Case 1 could not have been predicted. He had been clinically and biochemically hypothyroid when first seen and had shown an excellent clinical response to thyroxine treatment. Stopping this treatment did not cause a relapse of hypothyroidism over a 3 year period despite continuance of the biochemical defect. Indeed his plasma TSH level at 28 months off thyroxine was in the normal range suggesting strongly that his thyroid was not under TSH stimulation which would have been expected if even mild hypothyroidism had been present (*Evered et al. 1973*). When hypothyroidism eventually re-appeared after 3 years, the biochemical defect became more obvious on testing and his plasma TSH rose.

Although no similar reports have appeared in the literature, *Zondek et al. (1960)* have documented a comparable phenomenon. These workers adminis-
tered large doses of thyroid hormones in the short term (a form of treatment referred to as "Stoss therapy") to 3 hypothyroid siblings, each with a defect of thyroidal iodide organization, and produced a protracted clinical remission of hypothyroidism for 6 months in 2 and 3½ years in the third. In contrast to our own findings, however, they were unable to produce the remission with standard thyroxine replacement therapy. Zondek’s postulate that “Stoss therapy” possibly activated dormant enzymatic pathways in the thyroid was criticised by Stanbury (1961) on the basis firstly that it was impossible to exclude such factors as the surreptitious administration of thyroxine and secondly, that Zondek had failed to exclude a dehalogenase defect which would have responded to the iodide given in “Stoss therapy”. We are satisfied that in our patients, there was no surreptitious intake of thyroxine and in Case 1, the persistent moderately elevated radioactive iodine clearance of the thyroid would be against any self-medication. In addition we have shown that the MIT test was normal in Case 1. It could also be argued that in 1965, the cause of hypothyroidism was the presence of severe iodine deficiency in conjunction with a subclinical defect of thyroidal iodide organization. This appears unlikely since Glasgow is not an iodine deficient area and our patients diets have not apparently varied over the last 7 years.

Although it can be shown that the defect of iodide organization in thyroid can vary in severity among affected patients with the disorder (Bax & Weiner 1967), it is difficult to understand why, in a single patient (Case 1), the expression of the defect should vary from time to time. One must postulate that something occurred during thyroxine treatment to increase the efficiency of endogenous thyroxine formation and secretion but whether this was in response to the physiological replacement of thyroxine or whether it indicates a real spontaneous variation in the disease is a matter for conjecture.

ACKNOWLEDGMENTS

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REFERENCES


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