Partial end organ resistance to thyroid hormone in congenital hypothyroidism

JOHN M. C. CONNELL*
M.B., M.R.C.P.

E. H. McLAREN†
B.Sc., F.R.C.P.

Departments of Medicine, *Western Infirmary, Glasgow G21 1GT, and †Stobhill General Hospital, Glasgow G21 3UW

Summary
End organ resistance to thyroid hormone has been described for a number of years: the defect may be partial or generalized. A case of partial end organ resistance to thyroid hormone in congenital hypothyroidism is described, with evidence of an alteration in TSH threshold to feedback inhibition by thyroid hormone. The implications of this factor in the management of hypothyroidism are discussed.

Introduction
A number of cases of end organ resistance to the action of thyroid hormone have been reported over the past few years (Bode, Danon and Weintrub, 1973; Elevant, Mussche and Vermenten, 1976). In some cases the defect appears to lie only at pituitary level, with inappropriately elevated levels of thyroid stimulating hormone for thyroid hormone levels at or above the upper end of the normal range, and clinical features of thyrotoxicosis (Gershengorn and Weintrub, 1975). Other cases have been described with a more generalized end organ resistance, with clinical features including deaf mutism, goitre and stippled bony epiphyses (Refetoff, De Wind and De Groot, 1967). Recent evidence suggests that in some cases there is reduced affinity of nuclear receptors for T₃ (Daubresse et al., 1980). These previously reported cases with normal thyroid gland function, however, responded to chronically elevated thyroid-stimulating hormone (TSH) concentrations with goitre formation. Reports have also been made of an elevation in the threshold for TSH suppression by thyroid hormone in congenital hypothyroidism, which may be regarded as a partial end organ resistance phenomenon (Schultz, Glassman and MacGillivray, 1980; Sato et al., 1977). The authors describe a case of pituitary end organ resistance to thyroid hormone in a child with congenital hypothyroidism which, they believe, differs from previously reported cases.

Case report
A female infant was born in September 1970 and congenital agogoitrous hypothyroidism was diagnosed on clinical and biochemical grounds shortly after birth (serum PBI < 1.8 µg/dl). She was started on L-thyroxine 0.03 mg daily. Initial progress was satisfactory. In July 1971, on 0.04 mg thyroxine daily, her bone age was normal, and no developmental delay was detected. Over the next few years her clinical progress was satisfactory, and the dose of thyroxine was gradually increased to 0.1 mg daily. In August 1978, while on that dose, total T₄ was 242 nmol/l, and T₃ was 2.9 nmol/l (Table 1). She was clinically euthyroid and the growth velocity was normal. Bone age, however, was retarded at 6 years. Because of the biochemical evidence of over-replacement, the dose of thyroxine was reduced to 0.075 mg/day.

At review one year later, she was thought to be clinically euthyroid. Intellectual development was normal, and growth velocity had been maintained, with height and weight above 25th and below 40th centiles. T₄ at that time was again elevated at 161 nmol/l, with a high T₃ at 3.1 nmol/l; TSH was also elevated at >60 µmu/l. Because of the discrepancy between non-suppression of thyroid stimulating hormone despite the clearly adequate levels of T₄ and T₃, she was admitted to hospital for supervision of therapy.

During admission, she was maintained on 0.075 mg of thyroxine daily. T₄ and T₃ levels were consistently at the upper end of the normal range, and elevated TSH levels were confirmed (Table 1). Free T₄ and thyroid-binding globulin were within the normal range. A thyrotrophin-releasing hormone (TRH) test was compatible with 'hypothyroidism', showing an exaggerated increment following the i.v. injection of 200 µg of TRH. Serum cholesterol was normal. In an effort to gauge the tissue response to circulating thyroid hormone, left ventricular contractility was assessed by measuring systolic time intervals, using the method described by Parisi et al. (1974). This suggested that the child was euthyroid. The pituitary fossa was normal radiologically and no goitre was palpable.
The thyroxine dose was then increased to 0.1 mg/day and thyroid function tests were repeated several weeks as an out-patient. Total T₄ and T₃ levels were now clearly outside the normal range, and free T₄ was also elevated (Table 1). TSH was, however, now suppressed at 2.6 μu/l. Clinical assessment at this time was consistent with marginal over-replacement of thyroxine, and systolic time intervals were also consistent with this finding. In view of the retarded bone age, however, the dose of thyroxine was maintained at 0.1 mg/day. At the latest review she was well, and clinical progress was thought to be satisfactory. Persistent elevation of total T₄ and T₃ was confirmed, as was suppression of TSH to within the normal range. Regular review of this dose will be carried out and skeletal, intellectual and motor development closely monitored.

**Discussion**

This case is thought to be unusual: the finding of chronically elevated TSH levels with clinical, biochemical, metabolic and physiological evidence of euthyroidism, and suppression of TSH secretion only when free T₄ rose into the 'thyrotoxic' range, with associated clinical and physiological evidence of thyroid over-replacement is, the authors think, evidence of an alteration in end-organ sensitivity to thyroid hormone negative feedback effects at hypothalamic/pituitary level.

Correlation between free T₄ levels and systolic time intervals suggests that myocardial end organ response to thyroid hormone is normal; it is possible that the persistently retarded bone age is evidence of an end organ defect affecting other tissues.

Previous reports of an elevation in the threshold for TSH suppression in congenital hypothyroidism have described similar observations to the present ones, with elevation in TSH levels despite 'adequate' thyroxine replacement doses judged by clinical criteria (Schultz et al., 1980; Sato et al., 1977). Schultz et al. (1980) postulated that this phenomenon may be a consequence of failure of development of sufficient numbers of receptors for thyroid hormone in the fetal hypothalamic/pituitary regulatory centres, owing to sub-normal fetal concentrations of the hormone. Thus, in both of the previous reports, the abnormalities in TSH suppressibility were noted at the initiation of therapy; the total duration of therapy observed was not more than 24 months in any case. It was postulated that the threshold for thyrotropin suppression is initially high, but that the pituitary/hypothalamic centres become increasingly sensitive to thyroid hormone negative feedback effects with prolonged therapy. Thus higher doses of thyroxine replacement therapy may be necessary to suppress TSH in infancy than in later childhood (Sato et al., 1977).

In the present case, however, the abnormality in TSH suppressibility was only detected after 8 years of thyroxine therapy, in doses which were clinically and biochemically (in terms of PBI and total T₄) adequate. This does not accord with the hypothesis of Sato et al. stated above, and suggests that, in some children at least, the elevated threshold for TSH suppression may be a more prolonged, or even a permanent feature.

In current management of children with hypothyroidism, attainment of T₃ and T₄ levels in the 'normal' range, and the suppression of an elevated TSH level are taken as guides to the adequacy of therapy (Rezvani and Di George, 1977). The authors would, however, extend the caveat expressed

**Table 1.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Daily thyroxine replacement dose</th>
<th>Total T₄ (nmol/l)</th>
<th>T₃ (nmol/l)</th>
<th>TSH (μu/l)</th>
<th>Free T₄ (pmol/l)</th>
<th>Thyroid binding globulin (mg/l)</th>
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<td></td>
<td></td>
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<tr>
<td>February</td>
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<td>179</td>
<td>4.1</td>
<td>2.4</td>
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<td></td>
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<td>1979</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>242</td>
<td>2.9</td>
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<tr>
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<td>161</td>
<td>3.1</td>
<td>60</td>
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<tr>
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<td>139</td>
<td>2.8</td>
<td>32.8</td>
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<td>144</td>
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<td>33.6*</td>
<td>25</td>
<td>29</td>
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<tr>
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<td>3.3</td>
<td>2.6</td>
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<td>38</td>
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<tr>
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</tr>
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</table>

*TRH test: 200 μg (TRH given i.v.); TSH concentrations at 0, 20 and 60 min.
Normal values: T₄=55–144 nmol/l; T₃=0.9–2.8 nmol/l; TSH=8 μu/l; Free T₄=10–30 pmol/l; Thyroid binding globulin =12–30 mg/l.
T₄, T₃ and TSH measured by radioimmunoassay using a double antibody method. Free T₄ and thyroid binding globulin measured using a Corning medical systems assay kit.
by Schultz et al. that ‘alteration of the dose of thyroid hormone to attain TSH suppression places
the infant at risk for overtreatment’ to embrace all
children (and perhaps even adults) with congenital
hypothyroidism. Clearly, where there is a change
in the relationship between peripheral levels of
thyroid hormone and TSH secretion, the concept of
‘euthyroidism’ becomes harder to define, and re-
peated careful clinical assessment of the patient is of
paramount importance in the control of therapy.
Other indices of peripheral thyroid hormone status,
such as the systolic time-interval measurement and
serum cholesterol, can provide useful, reproducible ancillary aids to management.

Acknowledgment
We would like to acknowledge the help of Dr Stuart Hillis
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References
target resistance to thyroid hormone. Journal of Clinical
Investigation, 52, 776.
Daubresse, J.C., Dozin-Van Roye, B., De Nayer, P. &
Visscher, M. (1980) Partial resistance to thyroid hormones:
reduced affinity of lymphocyte nuclear receptors for T3
in two siblings. (Abstract) VIIIth International Thyroid
Familial partial target organ resistance to thyroid hormone.
induced hyperthyroidism caused by selective pituitary resistance to thyroid hormone. Journal of Clinical Inves-
tigation, 56, 633.
to thyrotoxicosis. Circulation, 48, 900.
Familial syndrome combining deaf mutism, stippled
epiphyses, goiter and abnormally high PBI: possible
target organ refractoriness to thyroid hormone. Journal of
Clinical Endocrinology and Metabolism, 27, 279.
Rezvani, I. & Di George, A.M. (1977) Reassessment of the
daily dose of oral thyroxine for replacement therapy in
Sato, T., Suzuki, Y., Taketani, T., Ishiguro, K. &
Nakajima, H. (1977) Age-related change in pituitary
threshold for TSH release during thyroxine replacement
therapy for cretinism. Journal of Clinical Endocrinology,
44, 553.
Schultz, R.M., Glassman, M.S. & MacGillivray, M.H.
(1980) Elevated threshold for thyrotopin suppression in
congenital hypothyroidism. American Journal of Diseases
of Children, 134, 19.