Aims and Methods: Thyroid function tests were initially carried out on 122 children with Down's syndrome aged 6–14 years and then repeated four to six years later in 103 adolescents (85% of the group of 122) when they were aged 10–20 years (median 14.4 years). At the second test two were hypothyroid and two with isolated raised thyroid stimulating hormone (IR-TSH) were receiving thyroxine.

Results: At the first test there were 98 (80%) euthyroid children; 83 were retested and four (5%) had IR-TSH. At the first test 24 had IR-TSH: 20 were retested and 14 (70%) had become normal. Seventeen with IR-TSH on initial testing had a thyrotrophin releasing hormone test within three months; TSH had become normal in eight (47%) of these children. There was no association between reported clinical symptoms and IR-TSH, but there were clear symptoms in one of the two with definite hypothyroidism.

Conclusions: The likelihood ratio for a positive result on second testing when raised TSH and positive antibody status on first testing are combined is 20. This suggests initial testing results could be used as a basis to select a subgroup for further testing at say five yearly intervals unless new symptoms emerge in the interim. It also suggests that yearly screening (as recommended by the American Academy of Pediatrics, 2001) is probably not justified in the first 20 years of life.

The association between thyroid dysfunction and Down's syndrome is well recognised, but the natural history of this dysfunction is not known. To date published results are presented as cumulative incidence or prevalence rather than incidence data. This serves to over emphasise the frequency of abnormality and has led many paediatricians to check thyroid function in those with Down's syndrome on an annual basis in childhood and adolescence.

We report a longitudinal cohort study. The design has allowed us to define the properties of thyroid function tests carried out late in the first decade and to what extent they predict subsequent abnormality in the second decade. This enables a rational approach in decision making analysis to define target groups for subsequent testing.

Prasher cites 30 case reports of hypothyroidism and 19 of hyperthyroidism. Smith was probably the first to report the use of thyroid extract in a person with Down's syndrome. A number of cross-sectional studies of thyroid function in individuals with Down's syndrome have shown an increased prevalence of both congenital hypothyroidism and acquired thyroid dysfunction. More recently, larger studies have defined the pattern of abnormality in more detail, though study design has varied. The studies of Toledo and colleagues, Gruneiro de Papendieck and colleagues, and Noble and colleagues were cross-sectional studies, while those of Rubello and colleagues, Ivarsson and colleagues, Rooney and Walsh, Karlsson and colleagues, and Tuysuz and Beker were all longitudinal. The research of Toledo and colleagues and Rubello and colleagues was hospital based, whereas the work of Prasher, Rooney and Walsh, Karlsson and colleagues, Ivarsson and colleagues, and Noble and colleagues was community based. Prasher studied adults, Rooney and Walsh and Rubello and colleagues studied individuals from childhood to the sixth decade, and the others mainly studied children and adolescents.

All reported a significantly raised frequency of thyroid abnormality, which Rubello and colleagues and Rooney and Walsh showed rises with age, particularly after the age of 10 years.

Figure 1 Study population.
40. Thyroid autoantibodies were shown to be commonly raised where they were measured.8–11

One pattern of thyroid abnormality in Down’s syndrome is isolated raised thyroid stimulating hormone (IR-TSH). Other terminology used for this pattern of abnormality includes isolated hyperthyrotrophinaemia, compensated hypothyroidism, and subclinical hypothyroidism.13–14 There are no absolute thresholds between hypothyroidism, IR-TSH, and euthyroidism. The study of van Trotsenburg and colleagues15 of neonates with Down’s syndrome indicates that the Gaussian distribution of thyroxine and TSH values are skewed to the left and right respectively, and that there may be a Down’s syndrome specific thyroid (regulation) disorder. Variability in definitions as well as laboratory techniques and population identification in part explain the wide range in quoted rates of thyroid dysfunction in Down’s syndrome.

**METHODS**

Between 1973 and 1980, Cunningham,16 working at the Hester Adrian Research Centre, University of Manchester, recruited a population based cohort of 180 children with Down’s syndrome in Manchester, England. These children and their families were studied prospectively in detail. Study population details are described by Selby and colleagues17 and summarised in fig 1.

Blood was first collected from 122 of this cohort when they were aged 6–14 years (median 9.8 years). Blood samples were analysed for thyroid stimulating hormone (thyrotrophin, TSH), thyroid binding globulin, total thyroxine (T4) (quoted according to thyroid binding globulin), and the two autoantibodies thyroglobulin and thyroid microsomal antibody. The more specific anti-thyroperoxidase assay was not available at first testing and was not pursued at second testing.

The investigating team usually performed blood sampling and analysis. Occasionally blood had already been taken by the local paediatric team; in these cases results were collated from the participating hospital.

At the time of the initial sampling, clinical data were collected on hair, appetite, bowel function, height, weight, and family history of autoimmune disease.

For the purposes of this study the following definitions are used:

- **Hypothyroidism**: low thyroxine and TSH of 6 μu/ml or more
- **Isolated raised TSH (IR-TSH)**: normal thyroxine and TSH of 6 μu/ml or more
- **Euthyroid**: normal thyroxine and TSH less than 6 μu/ml
- **Positive autoantibodies**: titre greater than 1:64.

We assessed whether testing aspects of thyroid function in the first decade (“first testing” in table 1) was predictive of hypothyroidism in the second decade. We express results in terms of the following functions to help guide clinical decision making.

The properties of tests are defined as follows:

<table>
<thead>
<tr>
<th>Table 1 Testing of thyroid function in the first decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism, 2nd test (aged 10–20)</td>
</tr>
<tr>
<td>Present</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>First testing Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
</tbody>
</table>
predicts normal thyroid function aged 10–20, \[ \frac{c/(a+c)}{d/(b+d)} \].

Likelihood ratios can be used in clinical practice to influence management decisions. Referring to Fagan’s nomogram (fig 2) it can be seen that a likelihood ratio of unity makes the probability of a positive or negative result aged 10–20 the same as the pretest probability. Likelihood ratios greater than unity magnify the probability of a like result on testing aged 10–20. Likelihood ratios less than unity diminish the probability of a like result on testing aged 10–20.

RESULTS
In 1986–87, of 122 children, one child had been commenced on thyroxine by a local paediatrician prior to the first test. We reviewed this 13 year old’s data: TSH 9.2 mu/l, T4 93 nmol/l, thyroid binding globulin 26.3 mg/l. We identified this as a case of IR-TSH.

Ninety-eight of the remaining 121 children had normal thyroid function and 23 had IR-TSH. Between first sampling and resampling in 1990–93, 18 cases were lost to follow up, and the individual on thyroxine was excluded from further analysis because she remained on thyroxine (fig 1). Of the group of 103 individuals resampled, 91 had normal thyroid function, 10 had IR-TSH (one of whom had been commenced, in our view unnecessarily on thyroxine by her local paediatrician), and two cases of definite hypothyroidism were identified. Treatment was commenced on the two newly identified cases (one from the 1986–87 normal thyroid function group and one from the IR-TSH group).

Table 2 compares thyroid function on second testing with thyroid function on first testing. Fourteen who remained untreated with initial IR-TSH showed normal results on second testing. Table 3 combines the euthyroid and IR-TSH groups aged 10–20 as “normal”.

Table 4 shows the autoantibody status at first and second testing. Data are available on 101 at initial testing (data missing on two of the 103, one of whom developed hypothyroidism) and eight were positive (all eight for antimicrosomal antibody and two of these additionally for antithyroglobulin antibody). Between first and second testing three became normal, and two initially negative became positive. For the eight with positive autoantibodies on first testing, five were still positive on second testing, three retained IR-TSH, and one developed hypothyroidism. The association between positive autoantibodies on first testing and a second abnormal test (combining hypothyroidism, IR-TSH, and positive antibodies) was significant (Fisher’s exact \( p < 0.05 \)), but not with hypothyroidism on its own (Fisher’s exact \( p < 0.5 \)). There was no significant sex difference in autoantibody status.

Table 5 shows the results of 101 children with available results at 10–20 years and their combined thyroid function and antibody status at initial testing.

### Table 2

<table>
<thead>
<tr>
<th>Thyroid function, 2nd test</th>
<th>Hypothyroidism</th>
<th>Isolated raised TSH</th>
<th>Euthyroid</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid function, 1st test</td>
<td>Hypothyroidism</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Isolated raised TSH</td>
<td>1</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Euthyroid</td>
<td>2</td>
<td>4</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3</td>
<td>9</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>103</td>
</tr>
</tbody>
</table>
There is no association between reported clinical symptoms and IR-TSH. There were clear symptoms in one of the two with definite hypothyroidism. Clinicians should pay particular attention to symptoms explainable on the basis of hypothyroidism when parents or the young people with Down’s syndrome themselves report these, remembering some of these symptoms can at times be features of Down’s syndrome.

We therefore propose that a decision on retesting is based on the initial test results. In our first decade group of 122, regular retesting could have been confined to 25. This would have been cost effective and minimised inconvenience and distress for the majority. Our results challenge the validity of population based screening programmes for thyroid dysfunction in Down’s syndrome. The vast majority of those young people with thyroid dysfunction were shown to have a self-limiting condition and those with definite hypothyroidism in our series had definite symptomatology.

### Conclusions

Hypothyroidism in Down’s syndrome should not be over-diagnosed. Knowledge of IR-TSH and its frequent self-limiting natural history needs dissemination. Treatment and frequent retesting of IR-TSH is not indicated. Our data suggest that early positive results for autoantibodies or data suggest that early positive results for autoantibodies or

### Table 3 Results of 103 children with available results for outcome aged 10–20 years

<table>
<thead>
<tr>
<th>Thyroid function, 1st test</th>
<th>Hypothyroidism</th>
<th>“Normal”</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated raised TSH</td>
<td>1</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Euthyroid</td>
<td>2</td>
<td>81</td>
<td>83</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>100</td>
<td>103</td>
</tr>
</tbody>
</table>

The children are defined at age 10–20 years as having hypothyroidism or “normal” (IR-TSH is included as “normal”, meaning not having hypothyroidism, and not needing therapy). Sensitivity 50% (95% CI 40–60%); specificity 82% (95% CI 74–90%). Positive predictive value 5%; negative predictive value 99%. Likelihood ratio for positive test result 2.7; likelihood ratio for negative test result 0.62.

### Table 4 Results of 101 children with available results at 10–20 years and their antibody status at first testing

<table>
<thead>
<tr>
<th>Thyroid antibody, 1st test</th>
<th>Hypothyroidism</th>
<th>“Normal”</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive antibody</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Negative antibody</td>
<td>0</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100</td>
<td>101</td>
</tr>
</tbody>
</table>

The children are defined at age 10–20 years as having hypothyroidism or “normal” (IR-TSH is included as “normal”, meaning not having hypothyroidism, and not needing therapy). Unfortunately the antibody status of one child with hypothyroidism was unavailable. Sensitivity 100%; specificity 93% (95% CI 82–99%). Positive predictive value 13%; negative predictive value 100%. Likelihood ratio for positive test result 14; likelihood ratio for negative test result very small (0.001).
IR-TSH can be used as a basis to select a subgroup for further testing at, say, five yearly intervals unless new symptoms emerge in the interim. They also suggest yearly screening as recommended by the American Academy of Pediatrics,24 is probably not justified in the first 20 years of life.

**Table 5.** Results of 101 children with available results at 10–20 years and their combined thyroid function and antibody status at first testing

<table>
<thead>
<tr>
<th>Thyroid disease (hypothyroidism), 2nd test</th>
<th>Hypothyroism</th>
<th>“Normal”</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid antibody and isolated raised TSH, 1st test</td>
<td>Positive for both</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Negative for one or both</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>100</td>
<td>101</td>
</tr>
</tbody>
</table>

The children are defined at age 10–20 years as having hypothyroidism or “normal” (IR-TSH is included as “normal” meaning not having hypothyroidism, and not needing therapy). Unfortunately the antibody status of one child with hypothyroidism was unavailable.

Sensitivity 100%, specificity 95% (95% CI 91–99%).

Positive predictive value 17%; negative predictive value 100%.

Likelihood ratio for positive test result 20; likelihood ratio for negative test result very small (<0.001).

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**REFERENCES**


