Retrospective evaluation of subtotal and total thyroidectomy in Graves’ disease with and without endocrine ophthalmopathy

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A retrospective analysis was performed in 173 consecutive patients with Graves’ disease (GD) with the principal aim of evaluating the influences of subtotal (N = 157) and total (N = 19) thyroidectomy on postoperative recurrence rates, endocrine ophthalmopathy (EO) and thyrotropin receptor antibody (TSH-R-ab) titres. Postoperatively recurrent disease, identified by increased thyroid hormone levels, occurred in 32 patients (20%) who underwent subtotal resection. These recurrences were associated with over-representation of preoperative EO (p < 0.001) as well as high TSH-R-ab levels postoperatively (p < 0.05–0.01). Subtotal and total resections were followed by an aggravation of preoperative EO in nine (16%) and one (6%), and by a development of EO in two and none of the patients, respectively. Persistently elevated TSH-R-ab titers during thyrostatic therapy became close to normalized in seven (32%) and 15 (88%) of the patients undergoing subtotal or total thyroidectomies, respectively, which illustrates a thyroid tissue dependency of the autoantibody production. Among the total material of 173 patients, altogether 75 cases exhibited persistent or progressive EO and/or TSH-R-ab elevation after more than 1 year of preoperative thyrostatic treatment. In this group, recurrent GD or aggravated EO occurred in 23 (39%) of those operated with subtotal resection and in one (6%) of those undergoing total thyroidectomy (p < 0.05). The results thus indicate that EO, particularly at the time of surgery, and prevailing TSH-R-ab titers are associated with an increased risk of recurrent GD and suggest that patients exhibiting these characteristics should benefit from total rather than subtotal thyroidectomy.

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The surgical treatment of Graves’ disease (GD) characteristically comprises bilateral thyroid resection, whereby a variety of factors such as young age and remnant size, as well as microsomal antibody titers, have shown an inconsistent correlation to postoperatively recurrent GD (1–5). Recurrences may be troublesome to manage, especially in patients with histories of endocrine ophthalmopathy (EO), because the immunological activation at recurrence may concomitantly aggravate the eye involvement (6, 7). Provided that this activation is thyroid-tissue dependent, the reported variable influences of thyroid resection on EO and therapy-resistant GD (8–13) may be improved hypothetically by more radical operative procedures.

Thyrotropin receptor antibodies (TSH-R-ab) are generally regarded as mediators of thyroid stimulation in GD (14, 15). The TSH-R-ab titers characteristically decrease in cases of successful thyrostatic drug treatment (16, 17). In addition to goiter size, thyroid hormone levels and age at diagnosis (18), elevated TSH-R-ab values at the end of medical treatment have been shown to correlate to recurrent GD (19–21). The TSH-R-ab titers usually are elevated in patients suffering from EO but fail to correlate to the severity of the eye involvement (22). Subtotal thyroid resection has been associated with temporary antibody elevations, which generally tend to decline during the first postoperative year (5, 23–26). The preoperative TSH-R-ab level has not proved to be an accurate predictor of postoperative outcome (25, 27). Persistently elevated levels after surgery, however, seem to increase the risk of recurrent GD (5, 25).

The aim of the present study was to examine the outcome of surgery in GD. An analysis of subtotal resection and total thyroidectomy was performed, with particular attention to EO and TSH-R-ab levels.

Patients and methods

A retrospective evaluation was performed in 178 consecutive patients with GD who underwent thyroidec- tomy at our surgical department during 1980–1992. Preoperatively, 158 of the patients had been treated at our medical department, while the others were admitted from regional hospitals. Five patients were lost to follow-up, whereby 173 patients have been assessed in total. The diagnosis of GD was based on
clinical symptoms and signs, elevated thyroid hormone values or suppressed TSH levels, as well as histological examination of surgical specimens. Moreover, the 110 individuals examined with thyroid scintigraphy displayed a diffuse uptake and 64 had elevated TSH-R-ab levels. All patients with normal (N = 5) or unanalysed (N = 104) TSH-R-ab titers exhibited EO or diffuse uptake on thyroid scintigraphy.

The appraisal of hospital records substantiated that the patients were admitted for thyroid surgery mainly due to recurrent GD during (N = 20) or after (N = 41) cessation of thyrrostatics, after radioiodine therapy (N = 4) or subtotal thyroidectomy (N = 6); severe EO (N = 34); considerably elevated thyroid hormone levels combined with large goiter and young age at diagnosis (N = 57); necessity of maintained thyrostatic treatment for > 2 years (N = 5); adverse reactions to thyrostatics (N = 5); and cytological suspicion of malignancy (N = 1). Altogether, 157 patients underwent subtotal thyroidectomy (Table 1), which in five cases was a repeat procedure. Total thyroidectomy was performed in 19 patients, of whom three had been subjected previously to subtotal resection within the study. Total thyroidectomy invariably was performed by senior endocrine surgeons, while subtotal resection was performed by a substantially larger number of colleagues. All patients were followed routinely at our medical department during a median of 35 months (range 15–151 months) after subtotal resection and 28 months (range 12–144 months) after total thyroidectomy.

### Table 1. Characteristics of 173 patients subjected to subtotal or total thyroidectomy.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subtotal resection (N = 157)</th>
<th>Total thyroidectomy (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male)</td>
<td>137/20</td>
<td>17/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32</td>
<td>40</td>
</tr>
<tr>
<td>TSH-R-ab elevation</td>
<td>7.8</td>
<td>6.7</td>
</tr>
<tr>
<td>At diagnosis (N = 69)</td>
<td>91%</td>
<td>100%</td>
</tr>
<tr>
<td>At operation (N = 83)</td>
<td>74%</td>
<td>100%</td>
</tr>
<tr>
<td>EO (N = 173)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>58</td>
<td>13</td>
</tr>
<tr>
<td>Grade 1</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Grade 2</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>At surgery</td>
<td>58</td>
<td>15</td>
</tr>
<tr>
<td>Grade 1</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>Postop thyrostatics (N = 173)</td>
<td>19 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Postop follow-up (N = 173)</td>
<td>35 months</td>
<td>28 months</td>
</tr>
</tbody>
</table>

* Three patients underwent both subtotal and total thyroidectomy within the study.
  * Median values.
  * At time of diagnosis.
  * TSH-R-ab: thyrotropin receptor antibody.
  * EO: endocrine ophthalmopathy.

### Table 2. Operative findings and complications in 173 patients with Graves' disease.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Subtotal resection (N = 157)</th>
<th>Total thyroidectomy (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight of resected tissue (N = 158)*</td>
<td>22 g (7–220 g)</td>
<td>15 g (2–72 g)</td>
</tr>
<tr>
<td>Weight of thyroid remnant (N = 161)*</td>
<td>4 g (1–9 g)</td>
<td>–</td>
</tr>
<tr>
<td>Recurrent nerve palsy (N = 152)</td>
<td>5 patients</td>
<td>1 patient</td>
</tr>
<tr>
<td>Hypocalcemia (N = 152)</td>
<td>35 patients</td>
<td>5 patients</td>
</tr>
</tbody>
</table>

* Median and range.

### Subtotal resection

Preoperatively, 153 of the patients subjected to subtotal resection had been treated with thyrostatic drugs during a median of 17 months (range 5–160 months) together with thyroxine, while the others received only beta blockers or corticosteroids. Another two patients underwent additional radiiodine treatment. The median time from the recorded onset of GD to subtotal resection was 20 months (range 5–175 months).

The subtotal resection involved a bilateral exploration with the identification of the recurrent laryngeal nerve in all patients and macroscopic recognition of at least three parathyroid glands in 141 individuals. The wet weight of the excised thyroid tissue ranged from 7 to 220 g in the primary operations and 11–16 g at the re-resections. The estimated weight of the thyroid remnant was 1–9 g (Table 2) and located unilaterally in nine patients. Postoperatively, 45 of the subtotally resected patients were maintained on thyrostatic drug treatment for a median of 19 months (range 7–46 months), owing mainly to preoperatively active eye disease or prevailing TSH-R-ab levels (Table 1). After the subtotal resections, a majority (N = 108) of the patients received thyroxine substitution without consistent attempts to discontinue.

Truncal ligation of the inferior thyroid artery was not performed during subtotal or total thyroidectomy. Serum calcium values were assessed daily during the first 3–10 postoperative days and all patients underwent indirect laryngoscopy prior to and after operation. Postoperative vocal cord paralysis and vitamin D therapy persisting for more than 9 months were considered permanent.

### Total thyroidectomy

All 19 patients subjected to total thyroidectomy were treated preoperatively with thyrostatics in combination with thyroxine during a median of 12 months (range 1–56 months). Two individuals were also administered
corticosteroids, in one case together with azathioprin. Another two patients had been treated with radioactive iodine prior to inclusion in the study. The median duration from recorded onset of GD to total thyroidectomy was 15 months (range 1–276 months).

Total thyroidectomy encompassed macroscopically complete removal of the isthmus and residual thyroid lobes. The number of macroscopically identified para-thyroid glands was two in all unilateral and ≥3 in 15 of the bilateral explorations. The weight of the excised thyroid tissue varied between 6 and 72 g in the primary total thyroidectomies and between 2 and 15 g in the reoperations (Table 2). All these patients received thyroxine substitution, which was combined with thyrostatics for a median of 12 months (range 2–56 months) in 16 cases (Table 1).

Recurrent disease
Postoperatively recurrent GD was defined as consistently increasing serum triiodothyronine (T3) and thyroxine levels, even within the upper reference limit, provided that serum TSH values were suppressed and further that the thyroxine therapy was maintained at a constant dosage. This criterion was thus used also in patients with continuous postoperative thyrostatic and thyroxine medications.

Endocrine ophthalmopathy
Clinical symptoms and signs of EO were graded pre- and post-operatively: grade 1 (increased tearfulness and irritability, lid retraction or periorbital swelling) and grade 2 (proptosis, pain, impaired motility or optic nerve affection). Fifty-eight (37%) patients subsequently subjected to subtotal resection had EO at the time of diagnosis, and another 19 developed EO prior to the operation (Table 1). The ophthalmopathy required treatment with corticosteroids in a total of 21 cases. As EO grade 1 disappeared during preoperative therapy in 19 patients, a total of 58 patients demonstrated EO at the time of subtotal resection. In the total thyroidectomy group there were 13 patients (68%) with EO at diagnosis. Another three patients developed eye disease, while one patient’s EO disappeared prior to surgery. Thus, 15 of these individuals had EO at the time of surgery, which was grade 2 in all patients and necessitated corticosteroid therapy in 11 of them.

Biochemistry
Thyrotoprin receptor antibodies were determined by a radiorecepcor binding assay (reference range < 7 U/l, Henning Berlin, Berlin, Germany). These determinations were employed increasingly during the study, whereby data were available in 69 cases at diagnosis (57 subtotal and 12 total thyroidectomies) and in 94 cases at late follow-up (77 subtotal and 17 total thyroidectomies). The TSH-R-ab titers were measured repeatedly (>4 values per patient) before operation up to a minimum of 1 year after surgery in 46 patients undergoing subtotal and in 17 subjected to total thyroidectomy.

Triiodothyronine (reference range 1.2–2.8 nmol/l) and thyroxine levels were measured by solid-phase radioimmunoassays. Thyroxine-binding proteins were estimated as T3U by the “Phadebas T3U Test” (Pharmacia, Uppsala, Sweden) and TSH was measured by a radioimmunosorbert technique (reference range < 5 mU/l). Serum calcium was estimated by atomic absorption.

Statistics
Chi-square analysis, Student’s unpaired t-test (two-tailed) and the Mann–Whitney U-test were used to study differences between groups, whereby p < 0.05 was considered to be statistically significant. Scew distributions of variables were normalized by logarithmic transformation prior to statistical analysis. Odds ratios (OR) with 95% confidence intervals (CI) were used as a measure of relative risks.

Results
Recurrent GD
During postoperative follow-up after subtotal thyroidectomy, 32 patients (20%) had a recurrent GD after a median of 26 months (range 2–276 months). These recurrences occurred in 17 patients who had terminated and in 15 who were still in postoperative thyrostatic therapy. None of the patients subjected to total thyroidectomy demonstrated postoperatively recurrent GD. The 32 patients with recurrent GD were compared with the 125 individuals in remission after subtotal resection (Table 3). This evaluation showed that the patients with recurrent disease displayed a lower estimated weight of thyroid remnants (p < 0.01) and more prevalent EO during the period preceding operation (OR = 3.9 and 95% CI = 1.7–7.9). A separate analysis of patients with EO at the actual time of surgery showed an even stronger association with postoperative recurrence (OR = 6.4 and 95% CI = 2.9–14.3). Further, the patients with recurrent GD tended to have higher levels of TSH-R-ab, at diagnosis as well as at surgery, and this difference was statistically significant at 6 months and 1 year postoperatively.

Endocrine ophthalmopathy
When all patients with preoperative EO (N = 92) were compared with those lacking eye involvement at any time prior to surgery (N = 81), EO was associated with the following characteristics: a higher age at diagnosis
and operation of GD (p < 0.01), a lower size of estimated thyroid remnants (p < 0.001), higher (p < 0.05–0.01) levels of TSH-R-ab 6 months and 1 year after the operation and postoperatively recurrent GD (p < 0.01; Table 4). These differences persisted also when only the patients with EO grade 2 were investigated (data now shown). After subtotal resection, two patients developed EO together with recurrence of GD. Another nine patients suffered a postoperative deterioration in their EO, associated with recurrent GD in all cases. After total thyroidectomy one patient experienced a slight deterioration in EO.

**Thyrotropin receptor antibody**

Repeated TSH-R-ab measurements revealed five individuals with completely normalized levels and another 17 who responded to the preoperative medication with lowered but not normalized titers at the time of subtotal resection. Sixteen of these 22 patients ("TRAb responsive") had histories of EO prior to surgery and 13 received postoperative thyrostatic therapy. Three of them developed recurrent GD, which was accompanied by recurrent TSH-R-ab elevations and EO deterioration. In the remaining patients, the postoperative outcome was uneventful and the preoperative decrease in TSH-R-ab continued in those with incompletely normalized titers at operation. The thyroidectomy in itself, however, did not seem to have any major influence on the dynamics of the antibody levels in these cases.

In another group of 22 patients ("TRAb resistant"), the TSH-R-ab levels were still greatly elevated at the time of the subtotal resection. Seventeen of them suffered from preoperative EO and 15 received postoperative thyrostatic therapy. Thirteen of these patients, 10 of whom were administered postoperative thyrostatic therapy, all experienced recurrent GD with increasing TSH-R-ab levels and six of them an aggravated EO. Of the remaining nine patients, seven exhibited normalized TSH-R-ab titers up to 4 years postoperatively, while the antibody levels remained almost unchanged in two patients on thyrostatic therapy. Figure 1 contains the TSH-R-ab data from the "responsive" and "resistant" groups, arranged into two groups, presenting the different cases experiencing remission and recurrent GD following surgery, respectively.

All 15 patients with serial TSH-R-ab titer measurements subjected to total thyroidectomy received thyrostatic therapy postoperatively. Eleven of them demonstrated completely normalized antibody levels 1–2 years postoperatively and the others showed gradually decreasing levels close to normal 1 year after surgery (Fig. 2).

Four patients received radiiodine treatment prior to subtotal resection (N = 2) or total thyroidectomy (N = 2). Two of them had EO at the time of diagnosis and the others developed severe EO after radiiodine administration. All of them exhibited high levels of TSH-R-ab preoperatively, which remained largely unaffected by surgery and pre- and postoperative thyrostatic treatment (Fig. 3).

Patients characterized by persistent or worsening EO and/or highly elevated TSH-R-ab levels in spite of

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Table 3. Characteristics of patients with recurrent Graves' disease compared with patients in remission after subtotal resection.

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (N = 32)</th>
<th>Remission (N = 125)</th>
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<tbody>
<tr>
<td>Age (years) (^a)^</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Preop thyrostats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(months; N = 157) (^b)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>EO (N = 157) (^c)</td>
<td>15</td>
<td>43</td>
</tr>
<tr>
<td>Prior to surgery</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>At surgery</td>
<td>23</td>
<td>35</td>
</tr>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH-R-ab levels (^d) (U/l) (^e)</td>
<td>6.9</td>
<td>7.3</td>
</tr>
<tr>
<td>Resected thyroid tissue</td>
<td>(g; N = 141) (^f)</td>
<td>26</td>
</tr>
<tr>
<td>Thyroid remnant (g; N = 143) (^g)</td>
<td>3.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Postop thyrostats</td>
<td>(months; N = 157) (^h)</td>
<td>28</td>
</tr>
</tbody>
</table>

\(^a\) Mean values.  
\(^b\) At time of diagnosis.  
\(^c\) Median values.  
\(^d\) EO: endocrine ophthalmopathy.  
\(^e\) Geometric mean values.  
\(^f\) TSH-R-ab: thyrostatic receptor antibody.  

Table 4. Characteristics of patients with (N = 92) or without (N = 81) histories of pre-operative endocrine ophthalmopathy (EO).

<table>
<thead>
<tr>
<th></th>
<th>EO Without EO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (^a)</td>
<td></td>
</tr>
<tr>
<td>At diagnosis (^a)</td>
<td>39.8</td>
</tr>
<tr>
<td>At surgery (^a)</td>
<td>41.1</td>
</tr>
<tr>
<td>TSH-R-ab (^b)</td>
<td>7.9</td>
</tr>
<tr>
<td>Preop thyrostats</td>
<td></td>
</tr>
<tr>
<td>(months; N = 173) (^c)</td>
<td>16</td>
</tr>
<tr>
<td>TSH-R-ab levels (^d) (U/l) (^e)</td>
<td>19</td>
</tr>
<tr>
<td>Resected thyroid tissue</td>
<td>(g; N = 148) (^f)</td>
</tr>
<tr>
<td>Thyroid remnant (g; N = 161) (^g)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

\(^a\) Mean values.  
\(^b\) Geometric mean values.  
\(^c\) At time of diagnosis.  
\(^d\) Median values.  
\(^e\) TSH-R-ab: thyrostatic receptor antibody.  
\(^f\) GD: Graves' disease.
The antibodies were assessed at the time of diagnosis (I), 1–3 months after initiation of thyrostatic drug treatment (II), within 2 months prior to surgery (III), at 3–6 months (IV) and at 12–24 months after surgery (V). Upper reference range is indicated by the horizontal line.

thyrostatic treatment for more than 1 year (“bad responders”) were identified. This group contained 75 out of the total 173 cases. Among the individuals undergoing subtotal resection, 23 patients (39%) experienced recurrent GD and 11 (19%) a deterioration in or development of EO, whereas only one patient (6%) subjected to total thyroidectomy developed slightly progressive EO (p < 0.05). In comparison, an analysis of 24 patients subjected to subtotal resection without EO at the time of surgery and with preoperatively normalized TSH-R-ab levels (“good responders”) revealed that 96% stayed in remission and none developed EO during the follow-up.

Operative complications
Permanent hypoparathyroidism or unilateral vocal cord paresis were seen after surgery in 1.3% and 0.7% of the patients, respectively (Table 2). These complications occurred in individuals subjected to subtotal resection, one of whom underwent a re-operation. Transient hypocalcemia requiring oral calcium supplementation, or unilaterally reduced vocal cord motility were seen in a total of 40 (26%) patients, and one of these underwent subtotal re-resection. In addition,
re-operation due to hemorrhaging was performed after one subtotal resection.

Discussion

The present study of surgical therapy in GD disclosed that persistent or progressive EO and/or TSH-R-ab elevation were predictors for relapse after subtotal thyroid resection. The material included cases referred to operation because of active thyroid disease with recurrences during and after thyrostatic treatment and a high incidence of eye disease. All but four of the 173 individuals were subjected to preoperative thyrostatic therapy for at least 5 months in combination with thyroxine. Those responding unsatisfactorily to this treatment were generally subjected to operation if age and other factors permitted (33). Some consistent temporal variation became apparent during the retrospective evaluation. Thus, TSH-R-ab analyses were used increasingly during the later parts of the study in order to define GD and, in addition to age, goiter size and serum T₃ levels (18), to monitor the efficiency of thyrostatic drug responses. Further, an increasing number of individuals have been subjected to postoperative thyrostatic therapy and T₄ substitution in an attempt to improve the surgical outcome. Finally, owing to therapeutic difficulties associated particularly with the eye involvement of GD, total thyroidectomy was introduced in 1987 and applied to an increasing proportion of individuals with active thyroid-associated ophthalmic disease.

In the present study, the rate of recurrent GD after subtotal resection, identified by increased thyroid hormone levels, was 20%. This seemingly high figure reflects upon the strategy of selection of cases for surgery. In previous studies, a poor relationship between as well as great variations in the rates of postoperative recurrence and hypothyroidism (1–4, 28–32) have been reported. Remnant sizes of < 3–4 g seemed to be associated with hypothyroidism and sizes of > 10 g were correlated to recurrence. Most likely also other factors, such as iodine intake and the intensity of the disease, are of importance to the surgical outcome. In corroboration with certain previous studies (1, 2, 4) but not others (3, 5), we found no greater estimated weight of thyroid remnants among individuals with postoperatively recurrent GD. On the contrary, the group of cases with recurrent GD exhibited smaller thyroid remnants than that in remission. This paradoxical finding indicates that the activity of the disease process within the thyroid tissue is a stronger determinant of postoperative outcome than merely the amount (size) of the tissue itself.

Serial measurements of TSH-R-ab revealed that the effect of surgery differed depending on the characteristics of the disease and the extent of the operation. In cases with a benign course of the disease, i.e. without severe eye signs or relapse following surgery, the TSH-R-ab levels showed a continuous decline following the start of thyrostatic drug treatment and subtotal thyroid resection had minor detectable effects on these titer. Persistently elevated TSH-R-ab levels during drug treatment, however, increased or remained elevated after subtotal thyroid resection in more than half of the patients. Those with such therapy-resistant antibody levels also had a high incidence of EO (19/24), which, together with the elevated TSH-R-ab levels, can be seen as signs of high disease activity. Following total thyroidectomy, TSH-R-ab levels became undetectable or almost normal in 15 of the 17 evaluated cases. Only two of these patients displayed persistently elevated antibody levels (both had been given radioiodine), whereas the corresponding number for the subtotal resected patients was 19 out of 46. This indicates that TSH-R-ab production is stimulated by an antigen located in the thyroid and that, in cases with active disease, extensive thyroid surgery is required to achieve an immunosuppressive effect.

Of the 75 identified ‘bad responders’ with persistent or progressing EO or TSH-R-ab levels during at least 12 months of preoperative thyrostatic therapy, a biochemical relapse or aggravated EO occurred in 23 of 59 patients undergoing subtotal resection but in only one of 16 subjected to total thyroidectomy. Admittedly, although this difference was statistically significant, the two patient groups may differ in ways difficult to ascertain retrospectively. In conjunction with the absence of severe complications after total thyroidectomy, this finding nevertheless suggests that total thyroidectomy should be evaluated further in the treatment of complicated GD.

The present investigation indicates that the outcome of surgery is influenced by the extent of the thyroid resection and further by the severity of the underlying disease. In cases with an active disease process, as reflected in developing or progressive ophthalmopathy signs and prevailing TSH-R-ab titers, extensive thyroid surgery appears preferable, whereas in cases responding to thyrostatics with a reduction in EO signs and falling TSH-R-ab titers, subtotal resections may be sufficient. Prospective studies are needed to substantiate further such a differentiated management of patients with GD.

Acknowledgments. This work was supported by grants from the Medical Research Council. We wish to thank Majstín Wik-Lundberg and Margareta Ericson for excellent technical assistance.

References


Received June 22nd, 1994
Accepted November 29th, 1994