Thymectomy in myasthenia with pure ocular symptoms

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SUMMARY Eighteen patients with exclusively ocular symptoms of myasthenia were thymectomised. Suspected thymoma, resistance to pyridostigmine therapy or relapse following immunosuppressive therapy were taken as indications for surgery. The mean preoperative observation period before operation was 40 months, and after operation was 26 months. There was no operative or postoperative morbidity or mortality. Histological thymic abnormalities were found in all patients (in one case, thymoma; in four, persistent thymus; in 13, thymic hyperplasia). The histological abnormalities were identical to those found in generalised myasthenia. This included the distribution of T-cell subtypes as identified by use of monoclonal antibodies. The severity of ocular symptoms was rated using a score developed for this purpose. The score progressively declined after surgery to an average of 70% of its initial amount in 80% of patients. Full remission occurred in three cases. No patient developed generalised myasthenia. Antibody titres against acetylcholine receptors if elevated preoperatively also dropped following surgery, with one exception. Clear criteria for the expected therapeutic success of thymectomy could not be identified. Based on our results, and on the assumed significance of the thymus gland for pathogenesis, thymectomy should be considered in patients with pure ocular symptoms.

Thymectomy is now widely accepted as a surgical treatment for myasthenia gravis in younger patients with generalised symptoms and in patients with associated thymoma.[1–12] In purely ocular myasthenia, in children, and in older patients without thymoma, the indications for thymectomy are controversial.[6 13] Thymectomy generally is not employed for ocular myasthenia, but the annoyance of double vision, possible side effects of drugs and later risk of generalisation may be compared to the likely therapeutic advantages and the low risks of the operation.[7 9 10 14 15] The efficacy of thymectomy in patients with pure ocular symptoms has not yet been evaluated over a long period and in a large sample of patients. Except for the occasional report of a thymectomised patient,[16] all available long term postoperative studies concern patients with generalised myasthenia.[1 3 5 10 16–20]

After two favourable experiences with thymectomy, in cases incorrectly suspected of thymoma based on the mediastinal CT-scan, we have thymectomised 18 out of 42 patients with ocular myasthenia since 1978. The results which we report here strongly suggest that surgical treatment is beneficial and leads to remissions or considerable improvement and prevents the possible generalisation of the disease.

Patients and methods

A total of 18 patients (13 men and five women) with a mean age of 39 and 32 years, respectively, underwent thymectomy. All patients had purely ocular symptoms and a positive edrophonium test without clinical or electrophysiological indications of a generalised neuromuscular block, tested in thenar and trapezius muscles.[21] In about 16 cases enlargement of the thymus gland was suspected prior to surgery based on the thoracic CT-scan. Nine had elevated titres of anti-acetylcholine receptor (ACHR) antibodies (more than 0·6 nmol/l bungarotoxin-binding sites) before surgical treatment.

The mean observation period before operation was 95 months (SD = ±128) for women and 17 months (SD = ±23) for men; five patients had symptoms for more than 2 years before operation; the mean observation period after

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Table 1 *Parameters for the assessment of the ocular myasthenia score*

I Symptoms of the external ocular muscles	Grade	II Ptosis
No paresis of the external ocular muscles	0	No ptosis after continued upward gaze for more than
No double vision		one min. (Simpson-Test)
Paresis observable in extreme position-of the eyes. Double vision in up to two gaze directions (more than 20° excentricity)	1	Simpson-Test positive prior to 60 s. (one or both sides)
Paresis observable in a gaze position more than 20° from the midline. Double vision in up to three gaze directions	2	Simpson-Test positive prior to 30 s. (one or both sides)
Paresis of more than three external ocular mucles. No double vision in the midline position.	3	slight spontaneous ptosis on one side
Nearly continuous double vision	4	slight spontaneous ptosis on both sides
Continuous double vision	5	marked ptosis with pupils visible
Marked paresis of three external ocular muscles	6	eyelid covers pupil on one side
Marked paresis of four external ocular muscles	7	eyelid covers pupil on both sides
Only very small eye movements	8	iris visible on both sides
One eye cannot be moved	9	iris visible on one side
Both eyes cannot be moved	10	both eyes closed

$$\frac{I + II}{2} = \text{Score}$$

operation was 27 months (SD = ±14) for women, 24 months (SD = ±15) for men.

A new score was developed to evaluate the degree of myasthenic ocular symptoms. The severity of eye muscle paresis and of ptosis was separately evaluated (table 1). The score for ocular symptoms was comprised of the parameters: paresis of the external ocular muscles (I) + paresis of the upper eyelid (II) ÷ 2 = score.

When there was no suspicion of thymoma, observation was continued for at least another 6 months to allow time for a possible spontaneous remission. Thymectomy was performed on patients with considerable disability due to double vision and/or ptosis who showed no satisfactory compensation under monotherapy with pyridostigmine and on patients whose symptomatology was resistant to prednisone or azathioprine or recurred after discontinuation of drugs.
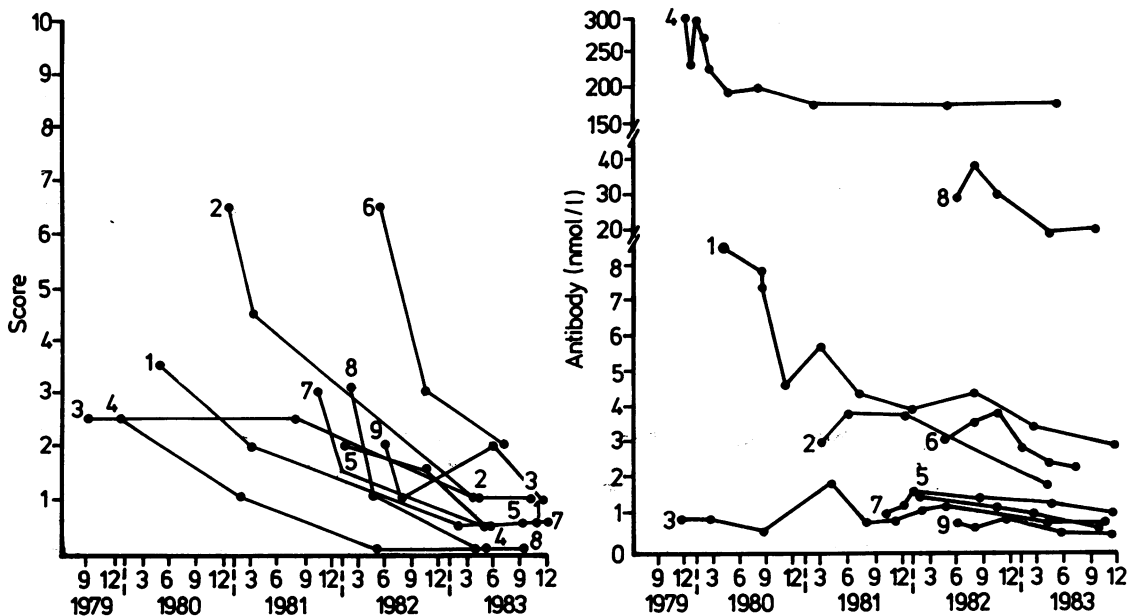
A median sternotomy was performed on all patients.

Fig 1 *Time-course of the score (a) and the anti-acetylcholin-receptor antibody titre (b) (nmol/l bungarotoxin binding sites) in patients with ocular myasthenia pre- and postoperatively. (First score and AB-titre 1–3 days before thymectomy.)*

Table 2 *Ocular myasthenia, anti-acetylcholine receptor antibodies and score before and after thymectomy (n = 18)*

Patient	Age (yr)	Sex	Time before thymectomy (months)	Histological finding	Antibodies before (nmol/l)	after	Score before	after	Follow-up in months after thymectomy
1	46	M	8	Hyperplasia	8·4	2·9	5·0	0·5	39
2†	41	M	2	Persistent thymus	3·0	1·8	6·5	1·0	27
3†‡	62	M	4	Thymoma	0·9	0·67	2·5	1·0	41
4†	20	W	4	Hyperplasia	299	170	2·5	0·0	46
5†‡	32	W	264	Hyperplasia	1·4	0·63	2·0	0·5	19
6	22	M	48	Hyperplasia	3·1	2·3	7·0	2·0	14
7	20	M	6	Hyperplasia	0·8	0·99	3·0	0·5	25
8	48	M	12	Hyperplasia	38·1	20·3	3·0	0·0	22
9	38	M	6	Hyperplasia	0·81	0·73	2·0	1·0	16
10†	22	M	3	Hyperplasia	0·4	0·7	3·5	0·5	12
11†	25	W	3	Hyperplasia	0·0	0·28	2·0	0·0	34
12*	32	M	84	Hyperplasia	0·11	0·3	2·5	0·5	36
13	39	M	6	Hyperplasia	—	0·36	3·0	0·5	60
14	40	W	204	Hyperplasia	0·59	0·8	4·0	2·0	17
15†	42	W	2	Hyperplasia	0·4	0·6	4·5	2·5	24
16†	45	M	3	Persistent thymus	0·37	0·4	3·5	0·5	20
17*	54	M	28	Persistent thymus	0	0	3·5	1·0	7
18	55	M	17	Persistent thymus	0·21	0·4	3·5	1·0	36

*Relapse after therapy with cortisone.
†Mediastinal CAT-scan, suspicion of thymoma.
‡Six months after surgery additional treatment with azathioprine and prednisone.

The thymus glands were studied by routine histological methods and stained histologically with monoclonal antibodies (Leu 1, 2a, 3a + b, 4, HLA-DR; Becton-Dickinson) in order to characterise the T-cell subtypes. Staining was performed by the sandwich technique with the Avidin-biotin-method. Antibodies of the Leu-series were used: Leu 1 demonstrating whole T-cells, Leu 2 mainly suppressor cells, Leu 3a + b helper cells, and Leu 4 supplied as a pan-T-cell-antibody.

Results

There was no operative or postoperative morbidity or mortality. All patients were transferred to the general thoracic surgery ward within 24 hours after surgery and to the neurological ward after 3 to 4 days.

Of the nine patients with elevated levels of anti-ACHR-antibodies, a successive decline in titre was found post-operatively in eight cases, in six patients by more than 40% (fig 1). The decline in titre after operation was most marked in patients whose anti-ACHR-levels were greatly elevated prior to surgery. In three patients whose antibody titres before operation were normal or only slightly elevated, the antibody titres increased somewhat after the operation (table 2).

The score of ocular symptoms decreased in all patients but one. Correspondingly, their subjective condition also improved. The scores were reduced by 0·5–5 units of measurement (an average 70% of the initial score). At the end of the observation period, nine of 18 patients still had slight ocular

symptoms with double vision and ptosis, one female patient still had marked ocular symptoms, and eight patients were free of any complaints. Three patients exhibited full remission also in the clinical test, two of them with elevated antibody titres (table 2). For almost all patients the pyridostigmine dosage was reduced (10/18) or discontinued (6/18). All patients returned to work.

Improvement almost always appeared during the first 6 months after surgery. In two patients who showed no clear remission of symptoms by that time, we started immunosuppressive therapy with prednisone and azathioprine. In these, improvement of symptoms occurred within a matter of weeks, and immunosuppressive therapy could be terminated after 24 months without relapse (observation period after treatment of 17 months and 3 months). In no patient did deterioration or generalisation of the myasthenic symptoms occur postoperatively.

Histologically, a lymphocytic thymoma was found in one patient, a persistent thymus in four, and thymic hyperplasia in 13. Thymic hyperplasia or "lymphoid hyperplasia"[22] was characterised by the appearance of a large number of secondary follicles. The cell pattern, represented by the T-cell-subtypes and B-lymphocytes in the secondary follicles, resembled the cell division in the follicles of lymph nodes: in the germinal centre and in the corona of mantle lymphocytes, HLA-DR positive cells (B-lymphocytes, mononuclear phagocytes, and possibly stimulated T-lymphocytes) was primarily demonstrated (see fig 2). These were surrounded by a broad
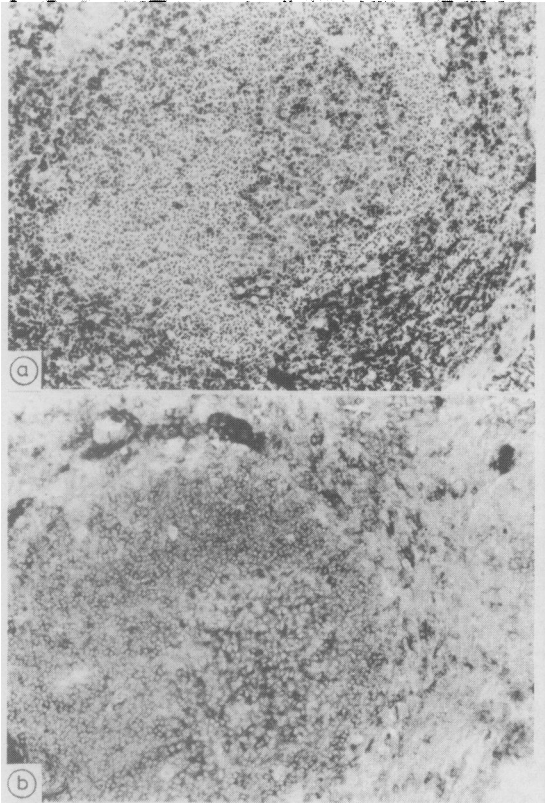
Fig 2 *Lymphoid follicle in thymic hyperplasia. Cells are stained with monoclonal antibodies by the Avidin-biotin-method (×90). (a) Demonstration of T-cells with anti Leu 4 (pan-T-cell). (b) Staining of HLA-DR positive cells (dendritic reticulum cells, mononuclear phagocytes, B-cells and some activated T-cells) is nearly exclusively observed in the follicle. Cells in the germinal centre are mainly cytoplasmatically positive, whereas in the mantle-cell layer the cell-membrane is stained.*

border of Leu 3a + b positive helper cells. The Leu 1 positive pan-T-cells from a border hemmed by dendritic reticulum cells, whereas the Leu 4 positive lymphocytes were spread over the entire cortex. The fraction of Leu 2a positive suppressor cells amounted to about 20% of the T-lymphocytes (fig 3). Individual secondary follicles with the same structure could be identified in non-tumour part of the thymoma as well. Here, the epithelial cells were not stained. The thymus histology especially the extent of follicle production showed no relation to the duration of the symptoms before operation, the antibody-titres and the postoperative outcome (table 2).

Statistics

t test for dependent samples with heterogenous variants yielded $t = 7.105$, df $= 34$, $p > 0.001$, for the comparison of symptom-scores pre- and postoperatively. Wilcoxon test, comparing the antibody titre prior to and after thymectomy (end of the observation period), showed no significant change ($T = +1$, n $= 9$).

Discussion

Thymectomy caused a beneficial effect in approximately 80% of patients with exclusively ocular symptoms of myasthenia. This compares favourably with the results in generalised myasthenia.[1 8 10 16 17] Only three patients had not improved considerably one year after surgery. Immunosuppression with steroids and azathioprine was necessary in two of them. With monotherapy using corticosteroids, relapse is frequent after reduction or withdrawal of prednisone.[23 24] It cannot be decided whether relapse was avoided here by the additional administration of azathioprine or by the preceding thymectomy. In any case, it seems probably that long term therapy with prednisone, with all its related problems, can be avoided by surgery in some patients. Generalisation of the neuromuscular block was never observed after thymectomy. Our results therefore suggest that generalisation, which occurs in almost 50% of cases with pure ocular symptoms of myasthenia not treated with immunosuppressants,[25] can be avoided by early surgery.

We did not find reliable parameters for predicting which patients could benefit most from the operation. The conditions seem to be the same as for the generalised form.[7 10] Patients who were diagnosed and thymectomised early seemed to respond to the operation most favourably. The initial level of antibody titre did not allow a prognostic statement. Patients with a high titre showed good postoperative remission of symptoms just as well as patients in whom antibodies could not be measured.

The fact that thymic histology was abnormal in every case (primarily thymic hyperplasia) suggests that the thymus gland is pathogenetically significant even for the exclusively ocular manifestation of myasthenia. The pathological features, in particular the specific B- and T-cell-subtype distribution of thymus hyperplasias and the thymoma in ocular myasthenia, did not differ in any way from those found in generalised myasthenia.[26 27] Thus, not only the purely morphological criteria, but also functional-cytologic characteristics of the pathological thymus are identical in the different forms of myasthenia. It seems plausible to assume that the mechanisms by which the disease is caused and sus-
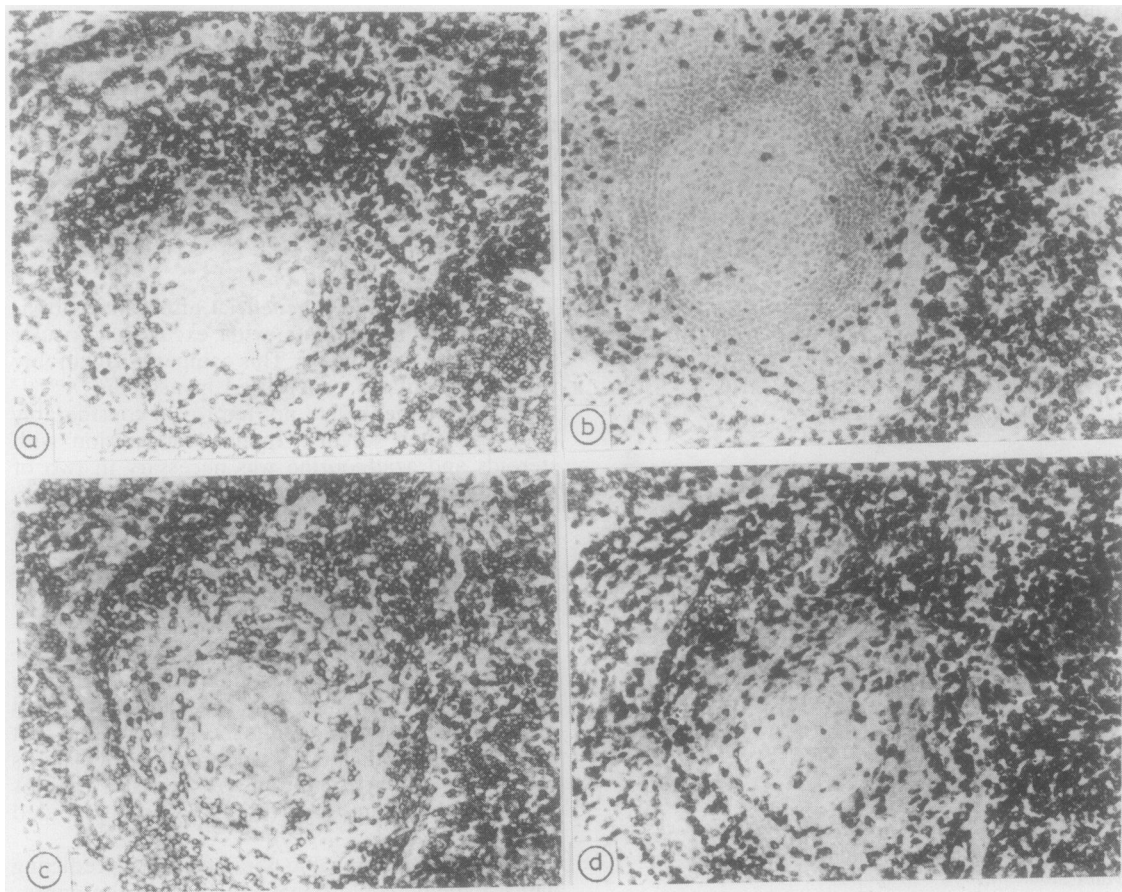
Fig 3 *Lymphoid follicle in thymic hyperplasia. T-cell subsets are stained with monoclonal antibodies by the Avidin-biotin-method (×120). (a) Anti Leu 1: Leu 1+ cells are distributed throughout the concentric layer of mantle-cells and spread into the cortex. A dense cap of positive cells can be identified sitting on the mantle-cell layer. (b) Anti Leu 2: Only very rare Leu 2+ suppressor-cells are seen in the follicle. The structure of that follicle with a germinal centre and mantle cells is demonstrated. (c) Anti-Leu 3a+b+ helper-cells are mainly localised on the rim between mantle-cells and cortex respectively medulla. (d) Anti Leu 4: Leu 4+ pan-T-cells are arranged in rows between germinal centre and mantle-cells and mantle-cells and cortex respectively medulla. The majority are confined to the cortex.*

tained are identical. On the basis of a special genetic disposition, lymphocytes may be sensitised within the thymus to acetylcholine receptor components and thus induce the autoimmune process and finally maintain it. Reduced functional availability of the receptors is caused by antibodies against acetylcholine receptors in the postsynaptic membrane.[13 28 29] Thymectomy appears to reduce the number of specially sensitised T-lymphocytes.[30] Similar thymic pathology in a few individuals with ocular myasthenia was also described by Tamaoki.[31]

As in generalised myasthenia,[32 33] the quantitative development of antibody titres, not necessarily its absolute amount, gives an estimate of the activity of the autoimmune process and thus represents a

measure for the efficacy of each of the treatments selected. In this study, the almost regular decline in titre (as in generalised myasthenia)[32] was demonstrated for the first time on a large sample of patients. It supports the assumption that the autoimmune process is weakened by thymectomy.[10]

Based on our experience of no operative morbidity or mortality we conclude that thymectomy should be considered for patients with exclusively ocular symptoms of myasthenia, if no satisfactory improvement occurs in response to therapy with cholinesterase inhibitors and when there is no spontaneous remission within a six-months period. It is likely that early surgery inhibits generalisation, which otherwise appears in about half the patients

within two years. In addition, it is frequently possible to avoid the risks of a long term therapy with prednisone and azathioprine.

References

1 Papatestas AE, Genkins G, Horowith SM, Kornfeld P. Thymectomy in myasthenia gravis: pathologic, clinical and electrophysiological correlations. *Ann NY Acad Sci* 1976;**274**:555–73

2 Emeryk B, Strugalska MH. Evaluation of results of thymectomy in myasthenia gravis. *J Neurol* 1976;**211**:155–68.

3 Keesey JC. Indications for thymectomy in myasthenia gravis. In: Dau PC, ed. *Plasmapheresis and the Immunobiology of Myasthenia Gravis.* Boston: Houghton 1979:124–36.

4 Mattila S, Pirskanen R. Thymectomy for myasthenia gravis. In: Dau PC, ed. *Plasmapheresis and the Immunobiology of Myasthenia Gravis.* Boston: Houghton 1979:137–43.

5 Scopetta C, Tonale P, Eroli A, Davis P, Crucitti F, Vaccario ML. Treatment of myasthenia gravis. *J Neurol* 1979;**222**:11–21.

6 Rowland CP. Controversies about the treatment of myasthenia gravis. *J Neurol Neurosurg Psychiatry* 1980;**43**:644–59.

7 Simpson JH. Myasthenia gravis and myasthenic syndromes. In: Walton J, ed. *Disorders of Voluntary muscles.* Edinburgh: Churchill Livingstone 1981:585–624.

8 Johns TR. Treatment of Myasthenia gravis by thymectomy. *Seminars in Neurology* 1982;**2**:217–2.

9 Engel WK, Dalakas M. Treatment of neuromuscular diseases. In: Wiederholt WC, ed. *Therapy for Neurological Disorders.* New York: J Wiley 1982:51–101.

10 Mulder DG, Herrmann C, Keesey J, Edwards H. Thymectomy for myasthenia gravis. *Am J Surg* 1983;**146**:61–6.

11 Howard JF, Sanders DB. The management of patients with Myasthenia gravis. In: Albuquerque EX, Eldefrawi AT, eds. *Myasthenia Gravis.* London: Chapman and Hall. 1983:457–89.

12 Rodriquez M, Gomez MR, Howard FM, Taylor WF. Myasthenia gravis in children: long term follow up. *Ann Neurol* 1983;**13**:504–10.

13 Seybold ME, Lindstrom JM. Immunopathology of acetylcholine receptors in myasthenia gravis. *Springer Seminars in Immunopath* 1982;**5**:389–412.

14 Mertens HG. Myasthenie und andere neuromuskuläre Übertragungsstörungen. In: Flügel KA, hg. *Neurologische und Psychiatrische Therapie.* Erlangen: Dr Straube 1978:26–35.

15 Havard CWH, Scadding GK. Myasthenia gravis—pathogenesis and current concepts in management. *Drugs* 1983;**26**:174–84.

16 Fraser K, Simpson JH, Crawford J. The place of surgery in the treatment of myasthenia gravis. *Br J Surg* 1978;**65**:301–4.

17 Simpson JH. An evaluation of thymectomy in myasthenia gravis. *Brain* 1958;**81**:122–44.

18 Genkins G, Papatestas AE, Horowith SH, Kornfeld P. Studies in myasthenia gravis: Early thymectomy. *Am J Med* 1975;**58**:517–24.

19 Buckingham JM, Howard FM, Bernatz PL, *et al.* The value of thymectomy in myasthenia gravis. *Ann Surg* 1976;**184**:453–7.

20 Kunze K. Thymectomy in the treatment of myasthenia. *Thorac Cradiovasc Surg* 1980;**28**:380–5.

21 Schumm F, Stöhr M. Accessory nerve stimulation in the assessment of Myasthenia gravis. *Muscle Nerve* 1984;**7**:147–51.

22 Rosai J, Levine GD. *Tumors of the Thymus.* Washington Atlas of Tumor Pathology Second Series Fac. 13, 1976.

23 Fischer KC, Schwartmann RJ. Oral corticosteroids in the treatment of ocular myasthenia gravis. *Ann NY Acad Sci* 1976;**274**:596–607.

24 Okamoto S, Takeyami T. Current concepts of steroid therapy in myasthenia gravis. In: Satoyoshi E, ed. *Myasthenia Gravis.* Tokyo: University of Tokyo Press 1981:383–97.

25 Bever CT. Aquino AV, Penn AS, Lovelace RA, Rowland LP. Prognosis in ocular myasthenia. *Neurology (Minneap)* 1980;**30**:387.

26 Fuji N, Itoyama Y, Tabira T, Kuroiwa Y. Subsets of lymphoid cells in blood and thymus in myasthenia gravis. Monoclonal antibody analysis. *J Neuroimmunol* 1983;**4**:151–9.

27 Thomas JA, Willox HNA, Newsom-Davis J. Immunohistological Studies of the Thymus in Myasthenia gravis. *J Neuroimmunol* 1982;**3**:319–35.

28 Wekerle H, Hohlfeld R, Ketelsen UP, Kalden JR, Kalies I. Thymic myogenesis, T-lymphocytes and the pathogenesis of myasthenia gravis. *Ann NY Acad Sci* 1981;**377**:455–75.

29 Vincent A, Newsom-Davis J. Acetylcholine receptor antibody characteristics in myasthenia gravis. I. Patients with generalized myasthenia or disease restricted to ocular muscles. *Clin Exp Immunol* 1982;**49**:257–65.

30 Conti-Tronconi BM, Scotti A, Sghirlanzoni A, Clementi F. Specific involvement of peripheral T lymphocytes against acetylcholine receptors in myasthenia gravis. *J Neurol Neurosurg Psychiatry* 1983;**46**:832–6.

31 Tamaoki N, Nakazato A, Tsuchiya M, Satoyoshi E. Thymuspathology and effects of thymectomy. In: Satoyoshi E, ed. *Myasthenia Gravis.* Tokyo: University of Tokyo Press 1981:269–81.

32 Schumm F. *Studien zum Nachweis von causalen und symptomatischen Therapieeffekten bei der Myasthenia gravis.* Tübingen: Habilitationsschrift 1982.

33 Besinger UA, Toyka KV, Heininger KT *et al.* Long-term correlation of clinical course and antibodies to acetylcholine receptors in patients with myasthenia gravis. *Ann NY Acad Sci* 1981;**377**:812–5.