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Evaluation of Results of Thymectomy in Myasthenia Gravis*

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Summary. The results of thymectomy carried out in 150 cases of myasthenia gravis are discussed. In a group of 123 cases followed for 1 to 5 years after the operation, full remission was observed in 24.4% of cases, significant improvement in 36.6%, slight improvement in 24.4% and no improvement in 8.1%, while deterioration occurred in 1.6% of patients. No correlation was found between the result of the operation and the age and sex of patients, but better results were achieved in those treated surgically rather soon after the onset of symptoms. This correlation was particularly evident in the group with full remissions. The results obtained in the cases without thymic tumors were better than in the cases with tumors. No correlation was noted between the results of the operation and the histological characteristics of the thymus in the group with thymic hyperplasia and in the group with thymic atrophy. The surgically treated group (150 cases), compared with the conservatively treated group (75 cases), showed the superiority of the surgical method (lower rate of death and deterioration, higher rate of improvement and remission).

In discussing the indications for surgical treatment the authors emphasize that advances in anaesthesiology in recent years have reduced the risk of operation. It is suggested that the indications for surgical treatment should be expanded and operations should be performed as early as possible after the onset of clinical manifestations without regard to the age and sex of the patient. Operation should not be considered in cases belonging to group 1, 2a (sometimes 2b) only, with duration of the disease over 8—10 years and with little or no progression of the process, if the presence of a thymic tumor has been excluded.

Key words: Myasthenia — Thymectomy.

Zusammenfassung. Es werden die Ergebnisse der Thymektomie bei 150 Myastheniefällen besprochen. Unter 123 Patienten, die zwischen 1 und 5 Jahre nach dem Eingriff kontrolliert werden konnten, fanden sich folgende Ergebnisse: vollständige Remission in 24,4% der Fälle, nennenswerte Besserung in 36,6%, leichte Besserung in 24,4% und keine Besserung in 8,1%. Bei 1,6% der Patienten trat eine Verschlechterung auf. Es fand sich keine Korrelation zwischen der Qualität der Ergebnisse des Eingriffes und dem Alter und dem Geschlecht der Patienten, jedoch waren die Ergebnisse um so besser, je früher nach Beginn der Symptome der Eingriff erfolgte. Diese Korrelation war besonders eindrücklich in der Gruppe mit vollständiger Remission. Bei den Fällen ohne Thymustumor waren die Ergebnisse besser als in jenen mit Tumor. Es fand sich keine Korrelation zwischen den Ergebnissen des Eingriffes und den histologischen Charakteristika der entnommenen Thymus in der Gruppe mit Thymushyperplasie und in jener mit einer Thymusatrophie. Die 150 chirurgisch behandelten Fälle wurden mit 75 konservativ behandelten verglichen. Hierbei zeigte sich die Überlegenheit des chirurgischen Vorgehens: geringere Mortalität und geringerer Grad an Verschlechterung und größere Zahl von Besserungen und vollständigen Remissionen.

Bei der Diskussion der Operationsindikation wird hervorgehoben, daß in den letzten Jahren durch die Fortschritte der Anaesthesiologie das Operationsrisiko gesenkt werden konnte. Es wird empfohlen, die Indikation zum chirurgischen Vorgehen auszudehnen, und gefolgert,

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daß der Eingriff so früh als möglich nach Beginn der klinischen Symptome, unabhängig vom Alter und Geschlecht der Patienten, durchgeführt werden sollte. Auf die Operation darf wohl verzichtet werden in Fällen, die zur Gruppe 1, 2a (manchmal auch 2b) gehören, wenn die Dauer der Erkrankung mehr als 8—10 Jahre beträgt und keine oder praktisch keine Progression der Symptome vorhanden ist, sofern ein Thymustumor ausgeschlossen worden ist.

Introduction

Although many decades have passed since thymectomy for the treatment of myasthenia was introduced, opinions about its effectiveness and, consequently, about acceptance of more strict criteria of patient selection for this treatment, are still at issue. The milestones in this time period were the works of Keynes [17, 18] based on a large material, the paper of Ross [35], the early Americal analysis of the material from John Hopkins University published by Blalock [3], the reports of Harvey [15] and Grob [13], the cases from the Massachusetts General Hospital described by Viets [43, 44], and Schwab and Leland [37, 38], and the Mayo Clinic material published by Eaton and Clagett [7]. The results of thymectomy varied considerably in the reports quoted. It depended in some instances, either on differences in the material analyzed, especially when the surgical results were compared with those in a conservatively treated group, or to differences in the length of the postoperative follow-up, or to many other factors, e.g., differences in the proportion of tumors in the material studied [7]. A survey of these papers as well as of those published later by Simpson [41], Henson [16], Kuzin [22], Perlo and Poskanzer [32], or of the recent reports of Papatestas *et al.* [31], Levasseur [27], LeBrigand *et al.* [24—26] shows, however, that most authors are convinced about the effectiveness of thymectomy, especially in certain selected groups of patients.

More exact indications for thymectomy however, still remain in dispute: some authors suggest that wider indications should be established for this operation [21, 30, 31], while others believe that they should be limited by such factors as duration of the disease [7, 16, 33, 41], clinical forms [8, 11, 32], sensitivity of the patient to drugs [4, 16, 24], or the age and sex of the patient [16, 31, 33]. Still others have stressed the progressive reduction of surgical risk with improvement of the operative and anaesthesiological methods, and the modern preoperative and postoperative management of patients, as additional arguments in favour of wider indications for the operation [2, 19, 22, 26, 36, 39].

This paper reports and analyzes the group of patients treated in the Warsaw Department of Neurology in the last 10 years.

Material and Method

The material included 225 cases of myasthenia observed at the Warsaw Department of Neurology, and its Outpatient Clinic for Muscular Diseases from 1963 to 1973; 150 patients were treated surgically by thymectomy and 75 were treated exclusively with cholinesterase inhibitors. The characteristic features of the material with regard to the sex and the age of onset of the disease are shown in Table 1.

The material was divided into groups depending on the clinical manifestations using the classification of Osserman [30] with the modification of Perlo *et al.* [32]. In accordance with this classification the following groups were isolated: group I = with exclusively ocular manifestations, group 2a = mild generalized myasthenia with ocular symptoms, group 2b =

Table 1. Material (225 cases)

Group	Sex		Age of onset of the disease					
	M	F	10	11—20	21—30	31—40	41—50	50
Surgically treated (150)	30	120	8	46	47	26	15	8
Conservatively treated (75)	23	52	6	17	18	14	12	8

Table 2. Clinical type of myasthenia

	Group			
	1	2a	2b	3
Surgically treated	3 2.0%	26 17.3%	87 58.0%	34 22.7%
Conservatively treated	5 6.7%	49 65.3%	17 22.7%	4 5.3%

moderately severe, generalized, with ocular symptoms and slight bulbar signs, group 3 = acute, severe, with significant bulbar signs, group 4 = late developing from group 1, 2a and 2b, group 5 = complete remission.

Table 2 characterizes our material of patients with regard to the clinical form. In the group of surgically treated patients, fairly severe clinical forms prevailed in 58.0% of cases belonging to group 2b, and 22.7% included in group 3. Respiratory disturbances were present in 36 cases. Myasthenic crises occurred in 20 cases, sometimes even several times, and tracheostomy was done in 12 patients. This selection of cases was due to the fact that, in the beginning, almost only severe, conservatively incontrollable cases were referred for thymectomy. We were unable therefore to gather a conservatively treated group, properly matching the group of thymectomized patients, as regards the intensity of symptoms. Table 2 shows that cases from group 2a outnumbered (65.3%) all patients not operated upon.

In agreement with others [16, 17, 22, 41], the following criteria for evaluation of therapy have been accepted: group A = full remission, group B = significant improvement (reduction of the dosage of cholinergic drugs by one half at least, with simultaneous increase in patients activity), group C = slight improvement (slight reduction of drug dosage or improvement with the same doses of drugs as previously), group D = no improvement, group E = deterioration.

The basis for assessment of the results of surgical treatment, or the course of the disease in the conservatively treated group, was a systematic follow-up of cases in the Outpatient Clinic for Muscular Diseases and inquiries sent to the patients.

The duration of follow-up in the surgical groups averaged about 3 years after operation, but in 27 cases it was slightly less than 1 year, and in 45 cases it exceeded 5 years. The longest follow-up was 23 years. In the group treated conservatively, the duration of follow-up ranged from 2 to 6 years, 3 years on the average.

Results

The results of surgical treatment[1] are presented in Table 3, arranged according to the time interval from the operation to the last examination. The results

[1] Thymectomy was carried out in the Department of Thoracosurgery in Zakopane (Prof. W. Rzepecki, M.D.), Department of Surgery, Warsaw Medical School (Prof. J. Nielubowicz, M.D.), Department of Paediatric Surgery, Warsaw Medical School (J. Kamiński, M.D.), and Institute of Tuberculosis in Warsaw (Assoc. Prof. T. Otto, M.D.).

Table 3. Results of thymectomy

Group	Time of observation after thymectomy			
	3 mos (150 cases)	3—12 mos (135 cases)	1—5 yrs (123 cases)	> 5 yrs (45 cases)
A	6.7% (10)	17.0% (23)	24.4% (30)	24.4% (11)
B	34.4% (51)	43.7% (59)	37.4% (46)	37.8% (17)
C	33.3% (50)	23.0% (31)	24.4% (30)	22.2% (10)
D	18.0% (27)	14.1% (19)	8.1% (10)	8.9% (4)
E	3.3% (5)	0.7% (1)	1.6% (2)	4.4% (2)
Death	4.7% (7)	1.5% (2)	4.1% (5)	2.2% (1)

changed with progressing duration of observation, e.g., the proportion of cases with full remission (group A) was only 6.7% within a period up to 3 months after thymectomy, but it rose later to 17% in the period from 3 to 12 months after operation, and in groups observed longer (1—5 years or more) it was stabilized at the level of $\pm 24\%$. The proportion of cases belonging to group B (significant improvement) remained at a similar level in all periods selected by us for assessment of results, about 34—38%. The proportion in group D (no improvement) showed a decreasing tendency from about 18% in the first 3-month period to about 8—9% in later periods. The proportion in the group of slight improvement (group C) decreased somewhat during the first several months. In group E (deterioration), which was relatively small, no consistent changes could be found. It may be stated, after a careful analysis of all cases in this group, that deterioration within the first months after thymectomy was connected, in the beginning, with postoperative complications with a simultaneous increase in the intensity of myasthenic symptoms; later it happened less frequently, sometimes as relapses of myasthenia, even after a fairly long asymptomatic period.

Deaths deserve a separate analysis. In the first 3 months after thymectomy the mortality rate was 4.7% and death was connected sometimes directly with the operation, sometimes with late complications after surgical and anaesthesiological procedures. Attention is called to the fact that all patients who died in the postoperative period belonged to group 3 (severe cases), operations having been performed sometimes in critical conditions, after prolonged controlled respiration because of a myasthenic crisis. Death occurring long after the operation was sometimes connected directly with myasthenia (myasthenic crisis, growth of an infiltrative thymic tumor) and sometimes only indirect by (e.g., death after cholecystectomy performed under general anaesthesia, myocardial infarction, etc.).

It seems that the group of 132 patients presented in Table 4 with follow-up of 1 to 5 years is most suitable for drawing more reliable conclusions about the results of treatment.

Improvement (group A + B + C) was achieved in 80.2% of cases, with significant improvement (group A + B) in 57.5%. Table 4 indicates that these results are not significantly different from those obtained by other authors, who used similar criteria for assessment.

Table 4. Results of surgical treatment of myasthenia

Group	Simpson, 1958		Henson, 1965		Kuzin, 1968		Papatestas, 1971		LeBrigand, 1972		Our material, 1974	
	cases	%	cases	%	cases	%	cases	%	cases	%	cases	%
A	55	21.3	15	50.0	35	20.4	28	25.2	8	10.0	30	22.7
B	32	12.4	4	13.3	78	45.3	56	50.4	49	59.0	46	34.8
C	60	23.3	1	3.3	29	16.9					30	22.7
D	47	18.2	5	16.7	20	11.6	12	10.8	12	13.0	12	9.1
Death	47	18.2	5	16.7	10	5.8	15	13.5	15	17.0	14	10.6
No. inform.	17	6.6	—	—	—	—	—	—	—	—	—	—
Total	258	100	30	100	172	100	111	100	84	100	132[a]	100
A + B + C		57.0		66.6		82.7		75.6		69.0		80.2

[a] Our material of 132 cases includes patients observed 1 to 5 years after operation and patients who died soon after operation.

Table 5. Results of thymectomy in patients observed 1 to 5 years after operation

Group	Without thymic tumor		With thymic tumor	
	number of cases	%	number of cases	%
A	26	23.2	4	20
B	41	36.6	5	25
C	29	25.9	1	5
D	5	4.4	5	25
E	1	0.9	1	5
Death	10	8.9	4	20
Total	112		20	

The most common opinion in the literature is that surgical results are much better in cases of myasthenia in which thymic tumor was not found at operation than in cases with thymic tumors. This problem was analyzed in the present material of 20 cases with thymic tumors. The group is small in relation to the comparable group of 112 cases without tumor and the comparison is regarded by us as preliminary.

Table 5 demonstrates, however, that improvements rated as A, B, C are more numerous in patients without thymic tumors; the percentage classified as D and E and the death rate are higher in the patients with thymic tumors.

The thymic tumors were not uniform, being encapsulated as well as infiltrating tumors with a prevalence of epithelial cells resembling carcinomas.

Table 6 demonstrates that surgical results are significantly better with encapsulated thymomas and poor with infiltrating tumors. In the present material the results in the group of encapsulated tumors were not significantly different from those in the group of myasthenia without thymic tumors. The clinical material in this group is, however, too small to draw more definite conclusions.

Table 6. Results of thymectomy in patients with thymic tumor

	A	B	C	D	E	Death
Encapsulated thymoma (12)	4	5	1	2	—	—
Infiltrating tumours (8)	—	—	—	3	1	4

Table 7. Results of thymectomy versus histopathological picture of thymus

Thymus	No	A	B	C	D	E	Death
Thymoma	12[a]	4	5	1	2	—	—
Infiltrating tumors	8	—	—	—	3	1	4
Hyperplasia	72	17	32	10	9	—	4
Residual thymic tissue	34	5	17	7	2	1	2
Fatty tissue	4	1	1	1	—	1	—
Total	130						

[a] In view of the fact that the groups compared differ considerably as to size (some very scarce), data are expressed in absolute numbers and not in percent.

An attempt was also made to determine whether there was any relationship between the results of the operation and the histological findings in the thymus. In the present material thymic tumors were found in 15.3% of cases, thymic hyperplasia in 56.4% thymus persistens without evidence of hyperplasia in 26.1%, and only in 3.2% of cases was no thymic tissue disclosed at the typical site in the mediastinum.

The problem of surgical results in the group of myasthenia with thymic tumor in relation to the group without tumor has already been discussed. We thought it worthwhile to compare the results of treatment in the group with thymic hyperplasia and in the group with residual thymus (Table 7).

It might seem that the results were somewhat better in the group with hyperplasia: full remissions (A) were found in 23.6% of cases in this group, but in the group with residual thymic tissue in only 14.7%. If, however, the percentage of improvements is compared jointly in groups A and B, it is evident that in the cases with hyperplasia this proportion is 66.7% and in those with residual thymus 65.7%, the difference being insignificant. It seems, therefore, that the histological findings in the thymus are not prognostic.

The assessment of therapeutic results in myasthenia is particularly difficult in view of the fairly changeable course of this disease, with spontaneous remissions and exacerbations. The question arises now, what would be the course of the disease had the patients studied by us not been treated surgically. For this reason we tried to compare the surgically treated group with those treated conservatively with classical cholinergic drugs, the follow-up period being similarly long (from 2 to 5 or more years). Comparisons of this type are subject to criticism because it is difficult to select clinically equivalent groups. It is true that the group of 75 cases treated conservatively comprises clinically less severe cases, as is demonstrated in Table 2, at the beginning of observation. Despite this, the

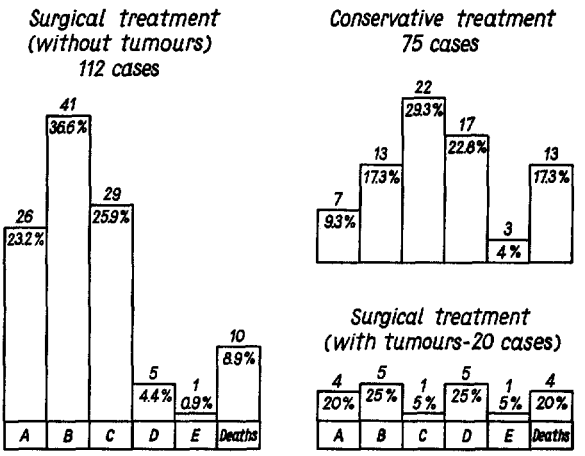

Fig. 1

Table 8. The effect of thymectomy versus duration of the disease

Duration in years	No	Results					
		A	B	C	D	E	Death
< ½	22	36.5% (8)	50.0% (11)	4.5% (1)	4.5% (1)	—	4.5% (1)
½—1	46	23.9% (11)	30.4% (14)	23.9% (11)	13.0% (6)	2.4% (1)	6.5% (3)
> 1—2	39	15.4% (6)	43.5% (17)	18.0% (7)	10.2% (4)	—	13.0% (5)
> 2—5	33	15.1% (5)	48.4% (16)	18.1% (6)	3.1% (1)	3.1% (1)	12.1% (4)
> 5	10	20.0% (2)	30.0% (3)	20.0% (2)	10.0% (1)	—	20.0% (2)
Total	150						

therapeutic results in both groups differed rather considerably (Fig. 1) in favor of the surgical group. During 4 years of follow-up there were 17.3% of deaths in the conservatively treated group while in the surgical group the mortality was 8.9% in the same period. Lack of improvement or deterioration occurred in only about 6% of surgical cases and in over 25% of the non-surgical cases. Similarly, full remissions and significant improvements were more frequent in the surgical group.

No correlation was found between the degree of improvement after the operation and the clinical form, age and sex of the patient. It seems, however, that we could establish a relationship between the result of the operation and the duration of the disease. Table 8 shows that the proportion of cases with full remissions in the group treated surgically within 6 months from the onset of the disease was 36.5% and in the group operated upon from 6 to 12 months after the onset 23.9%, while in the groups treated surgically later the proportion of full remissions fell to about 15%. Such evident correlation has not been observed in other groups.

Discussion

Every several years reports appear in the literature summing up experiences with new series of myasthenic patients treated by thymectomy. Unfortunately, it is not easy to compare the results obtained by various authors because of differences in the criteria for evaluation of therapeutic effects and in the clinical material observed. Many authors accept the clinical classification of Osserman [30] as a basis for evaluation. This classification has already been mentioned in the present work under Material and Method, since we have accepted it with the modification of Perlo *et al.* [32]. Even if one finds two series of clinical cases reported by different authors but similar in the clinical characteristics and clinical classification applied, the criteria accepted for assessment of therapeutic results differ usually. In the present work the criteria accepted were similar to those used by Simpson [41], Henson [16], Kuzin [22], and others.

Despite these reservations and the difficulties mentioned in comparing various clinical materials, the therapeutic results reported by different authors seem to be fairly similar. Some of them are presented in Table 4. Simpson [41] in his clinical material of 258 cases, found improvement and full remissions in 57.0%, Schwab [37] in a group of 130 cases found them in 61.0%, Ross [35] observed improvement in 87.0% of his group of 100 cases, LeBrigand *et al.* [24] noted full remissions in 10% and improvement in 59% of cases, Papatestas *et al.* [31] found improvement in 75.6% of cases including full remissions in 25.2%. In most of these reports, these results were obtained in cases of myasthenia without thymic tumor. In our material, improvement was achieved in 80.2% of cases, but the proportion of significant improvement (groups A + B) was 57.5% not differing significantly from the results of others [16—18, 22, 29, 40, 45]. It was stressed, as a rule, that the improvement after the operation was not immediate and sometimes developed months or even years after the operation. Goulon *et al.* [11] stated, for example, that in their material, followed-up for 5—6 years, significant improvement and full remission was observed in nearly all patients. Similarly Papatestas *et al.* [31] believed that the proportion of improvement, and particularly that of remissions, increased progressively parallel to the time after the operation, reaching a peak in the 7th year after operation. These observations are of considerable value from the standpoint of theoretical considerations concerning the mechanism of this delayed improvement [31] as well as prognosis in individual cases. They may explain differences between the results of various authors if they evaluate the therapeutic results at different periods after the operation. Our data presented in Table 3 are obtained from shorter periods but they confirm the view that the proportion and degree of improvement increase sometimes over a longer time following thymectomy. This is particularly evident in cases with full remissions. A similar observation was also made in our previous report [9]. But our material fails to support the opinion of these who believe that after an improvement recurrences are not observed [11]. Schwab, for example, found no recurrences in the group without thymic tumors [37]. In our material relapses were seen sometimes after 4—6 years of full remission in the groups with and without thymic tumors, independently of the age and sex of the patients.

A prevailing majority of authors consider that the surgical results are significantly worse in patients with thymic tumors than in cases without these tumors

and that these groups should be evaluated separately. This view was presented by Perlo *et al.* [37] on the basis of an analysis of 1355 cases of myasthenia, including 276 treated surgically. Kuzin [22] found that the proportion of improvement in a group without thymic tumor was 65.7% and in the group with thymic tumor only 24%. LeBrigand *et al.* [24—26] estimated that the proportion of favorable results was 69—79% in the group without tumors and 50% in those with thymic tumors; Buckberg [4] saw improvement in 63% of cases without tumors and in 47% of cases with tumors of the thymus. Similar conclusions have been reached by others [7, 29, 31, 41, 45].

Attention is also called in the literature to the fact that deterioration after thymectomy, postoperative deaths and recurrences are significantly more frequent in the group with thymic tumors.

In the present material the group with thymic tumors includes only 20 cases and the comparison of results can give only an approximate orientation to the problem. The data presented in Table 5 seem to support the generally accepted view that therapeutic results are worse in the cases with thymic tumors. We think, however, that grouping of all cases with thymic tumors together is unacceptable in view of their exceptional diversity on histological examination as well as on gross inspection. We believe that the opinion about poor prognosis in thymic tumors should be restricted to invasive, infiltrating tumors, while the prognosis is much better in histologically benign, encapsulated, non-invasive thymomas in which it is not significantly different from that in the group of myasthenia without tumor. It is true, however, that, e.g. the report of Fechner [10] on recurrences in cases of non-invasive thymomas does not support this opinion. As we have already mentioned, however, relapses were observed by us even in the group without tumors.

For a correct evaluation of the effectiveness of thymectomy, a comparison of the course of myasthenia in the group treated surgically and in another treated conservatively is necessary. Nearly all who reported larger clinical materials compared such groups, but nearly all of them also stressed the difficulties in selection of groups matched with respect to clinical features, age, sex, duration of the disease, etc. It is known [14, 30, 31] that spontaneous remissions occur in about 25% of cases of myasthenia, especially in ocular myasthenia, but they are usually transient and occur only in the first years of the disease. A careful comparison of surgically and conservatively treated groups was reported by Perlo *et al.* [32], who found a striking difference in favor of the surgically treated group, with improvement and remission in 89% of surgically treated females versus 32% in the conservatively treated group. In the group of surgically treated males, this proportion was 37 and 11% respectively. The survival rate after 20 years of follow-up was again higher in the surgical group of females than in the non-surgical group. Many authors have called attention to a much higher mortality in the conservatively treated group [17, 22, 29, 31, 32, 37, 45]. In our material, the mortality rate was considerably lower in the surgical group (cases of thymic tumors excluded) than in the conservatively treated one (8.9 and 17.3% respectively).

Fig. 1 shows the difference observed between the groups compared with regard to the percentage of remissions and improvements. These differences indicate

unquestionably the superiority of surgical treatment, although, as already mentioned, the group treated conservatively comprise clinically milder cases, and theoretically, the course of the disease should have been more favorable in this group.

The operative risk is another factor, often of essential importance, in establishing indications in addition to the effectiveness of surgical treatment. Death connected with the operation (that is occurring not only during the operation but also within 3—4 weeks after it due to various postoperative complications) is differently evaluated by various authors. It is unquestionable, however, that the operative risk has been reduced considerably by modern advances in surgery. Keynes in 1949 [17] evaluated the operative mortality rate at 4.2%, Eaton and Clagett in 1955 [7] at 6.6% (9.8% in the group with thymic tumors and 4.3% in the group without tumors), Schwab *et al.* [39] evaluated the operative mortality in the earlier part of their material in the 1950s at 7—10%, while in the cases treated surgically in the years 1960—1964, there were no operative deaths. Perlo [32] estimated that the operative mortality rate was 2%, and Rzepecki reported an identical rate [36]. Kuzin [22] had a mortality rate of 1.6% in a group of 250 surgical cases. Eckmann [8] estimated it at 0—3% on the basis of a survey of the literature and his own cases. Similar data were reported by others [19, 24, 26, 45]. In our material the intraoperative deaths and deaths in the first 3 months after the operation amounted to 4.7% of the whole material. It must be stressed, however, that all patients dying in connection with the operation belonged to group 3, with a severe course of the disease, bulbar signs and a rapid progression.

Surgical treatment of patients with very pronounced signs (sometimes treated for many days by controlled respiration) increases the surgical risk, as is evidenced by our material.

Another problem is the late mortality, which frequently is not due directly to myasthenia (increased growth of the tumor, myasthenic crisis) but sometimes to other causes. Operative, as well as late deaths are estimated jointly to amount to between 10 and 20% during a follow-up of many years [16, 24, 26, 31, 41]. In our material they amounted to 10.6%.

As other authors we tried to find various clinical features which might have been responsible for the results of surgical treatment, that is sex, and age of patients, clinical form of the disease and its duration up to the time of operation.

The opinion was expressed frequently that the best results were obtained in young females without thymic tumors [32, 38, 41].

Buckberg *et al.* [4] observed better results in females than in males independently of their age and also found better results in patients with shorter duration of the disease and without thymic tumors. LeBrigand [24] noted improvement in 77% of females and only in 47% of males, and the best results were obtained in the group of young females with the duration of the disease up to 5 years. Other authors [12, 18, 21, 31], failed to note any correlation with the sex or the age of the patients [31, 35, 45]. With regard to the clinical form, Kuzin [22] achieved better results in milder cases (76.2% of improvement) in relation to severe cases (52.6%). He also observed, as others, a relation between the duration of the disease and improvement: in a group with duration of myasthenia up to 5 years, improvement was achieved in 73% of cases, in a group with duration

over 5 years improvement was achieved in only 45% of cases. Better results obtained in cases with shorter duration of the disease were reported by most authors [16—18, 29, 35, 41]. In our material we failed to find any relation between the results of the operation and the sex and age of the patients, or the clinical form, but we believe that there is a correlation between the degree of improvement and the duration of the disease as illustrated by Table 8. Our material differed from some other reports because in many of our patients the operation was performed very early, even within several months from the onset of symptoms. In this group remissions, even full remissions in some cases, appeared rather early after the operation (even within several weeks) and amounted to 36.5%, while in patients operated upon later (over 2 years), they were observed in only 15.1% of cases.

We also tried to evaluate the relationship between the result of the operation and the histological examination of the thymus.

The proportion of tumors in the present material was 15.3% and was similar to that in the material of others. Keynes [17] found thymic tumors in 11.6% of his cases, Castleman [5] in 10%, Grashtchenkov and Perelman [12] in 16%, Kuzin [23] in 12.5%, Perlo *et al.* [32] in 9.5%. Only LeBrigand [24] reported a relatively high proportion of thymic tumors—39%.

The results of surgical treatment of thymic tumors has already been discussed above. Kornfeld *et al.* [20] found histological abnormalities in the thymus of 80% of myasthenic patients. Many authors have tried to answer whether surgical results were better in the group of patients with thymic hyperplasia and abundant germinal centers, or in cases without thymic hyperplasia. The views on this problem differ considerably: Castleman and Norris [6], and Reinglass *et al.* [34] noted no correlation between the type of thymic changes and the results of treatment, Mackay [28], on the other hand, believed that improvement was greater in cases of thymic hyperplasia; similar conclusions were reached also by Kuzin *et al.* [22]. On the other hand, Alpert, Papatestas *et al.* [1, 31] considered that better results were obtained in the group without hyperplasia, in cases of "atrophic" thymus. Simpson and Vetters [42] supported rather the opinion of Alpert *et al.* In the present material no correlation was observed between the histological appearance of the thymus and the results of surgical treatment. The proportion of improvement in the group with hyperplasia (group A + B) was 66.7%, in the group with residual thymic tissue 65.7%. It should be kept in mind, however, that in several cases of myasthenic recurrences (in the surgical group without thymic tumors), after several years of full remission, it was found that the histological pattern of thymus was consistent with thymic hyperplasia.

As other authors, we were unable to reach a definite opinion on the indications for the operation. We want to stress, however, that we support the policy of fairly extensive and early application of surgical treatment in myasthenia. We think that an apparently mild course of the disease and relatively good response to drugs should not deceive us, since a change for the worse may develop very rapidly and with longer duration of the disease the probability of good improvement after the operation decreases. Also, as already mentioned, we suppose that the surgical risk is lower when the operation is performed earlier, in a good clinical condition. Because of that, most of our patients from groups 2a, 2b and 3 with

a not excessively long duration of myasthenia are referred for surgical treatment. The age or sex of the patient are not important factors in establishing the indications. All cases with suspected thymic tumor are also referred for operation. Surgical treatment is not taken into consideration (after ruling out the presence of thymic tumor by means of pneumomediastinography) only in cases of mild ocular myasthenia, and sometimes in patiens from group 2a, and even 2b, if the duration of the disease is long (more than 8—10 years) and the disease shows no progression.

We believe that the decision of surgical treatment should be taken in every case after a through consideration of all factors discussed above.

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