Neurogenic muscle involvement in myasthenia gravis

A clinical and histopathological study

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SUMMARY An investigation was made into the occurrence of muscular atrophy and muscular pathology in a series of 170 patients with myasthenia gravis. The results can be summarized as follows: (1) Of the 148 patients with generalized myasthenia gravis, 14 showed local muscular atrophies. Of 10 biopsies from atrophic muscles, eight showed neurogenic changes, with or without lymphocytic infiltrations. One biopsy showed lymphocytic infiltrations only, and one showed type II-fibre atrophy (Table 1). No relationship was demonstrable between the presence of clinical muscular atrophy and age, sex, duration of the disease, severity of the disease, presence of a thymoma, or drug resistant ophthalmoplegia. (2) In this group of patients 61 biopsies were examined from 46 individuals; 40 of these biopsies were taken from the quadriceps muscle. A thymoma was present in 17 patients. Examination disclosed neurogenic changes in 17 biopsies, lymphocytic infiltrates in 21, and myositis in one biopsy (Table 2). A distinct correlation was established between the presence of a thymoma and lymphocytic infiltrates, but none was demonstrable between thymoma and neurogenic changes (Table 3). (3) An enzyme-histochemical study was carried out in 35 cases, including 14 with neurogenic changes. A normal differentiation of type I- and type II-fibres was observed in eight instances, type grouping of type II-fibres in three, and type II-fibre atrophy in two cases. (4) In 21 patients and 19 controls, the smallest mean diameter was determined in the quadriceps muscle. Both type I- and type II-fibres proved to have a smaller mean diameter in the female patients than in the controls. In the male patients this could not be proven. (5) Of the eight patients who had died without disorders of ventilation, 90 muscle specimens were examined postmortem. Four of these patients had a thymoma. Lymphocytic infiltrations, found in 32 biopsy specimens, were mostly observed in the presence of a thymoma. Neurogenic changes were apparently unrelated to the presence of a thymoma (Tables 5 and 6). The post mortem examination included the spinal cord in five, and peripheral nerves in three cases. No abnormalities were found. (6) The muscular atrophy found in patients with myasthenia is not a myopathy but an affection of the lower motor neurone. Neurogenic changes were regularly found in the muscles of patients with myasthenia, even without muscular atrophy. The finding of these changes is no reason to reject the diagnosis. It is postulated that denervation occurs at the neuromuscular junction as a result of permanent absence of acetylcholine.

Muscular atrophy is an unusual finding in patients with myasthenia gravis. Historically, absence of muscular atrophy in myasthenic bulbar paralysis had been one of the criteria by which this disease was differentiated from other forms of bulbar paralysis (Goldflam, 1893). Oppenheim (1901) mentioned in his monograph that he found muscular atrophy in a number of his patients, along with greatly diminished

electric excitability or a partial electric disintegration reaction.

Campbell and Bramwell (1900) and Montet and Skop (1908) also mentioned atrophy of the limb muscles in some patients. Pel (1904) described a patient with bilateral lingual atrophy. But in a number of subsequent publications the occurrence of muscular atrophy proved to be a controversial subject, and patients in this

category were therefore described as suffering from: myasthenic syndrome with pseudo-myopathy (Alajouanine, Lemaire, and Bourginon, 1954); myasthenic syndrome with progressive muscular dystrophy (Strüppler, 1955); myasthenic syndrome with associated neuropathy (Steidl, Oswald, and Kottke, 1962); myasthenic syndrome with polymyositis (Jesel, Stoeber, Zenglin, and Isch, 1969); ophthalmoplegia and myasthenic syndrome (Bonduelle, Bouygues, and Puech, 1954); myopathy with myasthenia gravis (Griffin, Natrass, and Posk, 1956); myasthenia gravis with myopathic atrophy (Hosotte, 1951); descending dystrophy or myasthenia gravis (Hausmanova-Petrusewicz, Falciewiczowa, Jedrzejewska, Kaimieniecka, and Fidianska, 1965). Some publications on polymyositis (Christensen and Levison, 1950; Coers, 1956, case 6) seem to refer to patients with myasthenia gravis. Osserman (1958) placed his patients with muscular atrophy (5%) in a separate group. He stated that 'The histologic changes in the biopsied muscle are indistinguishable from those seen in polymyositis or muscular dystrophy'.

In their paper on 'The classification, natural history and treatment of the myopathies', Walton and Natrass (1954) mentioned the 'myasthenic myopathies'. This designation has also been included in the Classification of Neuromuscular Disorders (1968).

Fenichel and Shy (1963) described neurogenic histopathological changes in 11 out of 37 patients with myasthenia, but presented no data on clinical muscular atrophy. Neurogenic features in biopsies were also mentioned by Oosterhuis (1964), Engel and McFarlin (1966), Fenichel (1966), and Oosterhuis, Bethlem, and Feltkamp (1968).

Patients with neurogenic muscular atrophy in association with myasthenia were described by Garçin, Fardeau, and Godet-Guillain (1965), Lapresle and Fardeau (1965), and Hopf and Ludin (1968).

After a review of these case histories it remains uncertain whether they represent an incidental combination of myasthenia with another disease, or a myopathy with intermittent muscular weakness reminiscent of myasthenia, or a phenomenon which, although rare, exceeds the incidental level and must therefore be

regarded as a symptom of the disease in question. Moreover, the aetiology of muscular atrophy in patients with myasthenia remains obscure. An explanation based solely on inactivity is generally considered unacceptable.

The following investigations report on personal observations in 170 patients with myasthenia gravis.

METHODS

PATIENTS One hundred and seventy patients were examined, in 22 of whom (15 males and seven females) the disease was confined to the eye muscles. In 148 patients (41 males and 109 females), the myasthenia was generalized. All patients fulfilled the following criteria: there were intermittent pareses of striated muscles; the disease involved the extrinsic eye muscles and/or the levator muscles of the eyelids and/or bulbar muscles; there was a favourable response either to cholinesterase inhibitors or after rest; or an unfavourable effect to a minimal dose of d-tubocurarine. There were no other neurological affections and no tumours other than a thymoma. There were no diseases of the thyroid. The diagnosis did not depend on electromyographic or muscle biopsy findings. Only one patient had also been referred because of muscular atrophy.

ASSESSMENT OF MUSCULAR ATROPHY A clinical assessment was made, taking account of physiological variations and right-left differences. In some patients the subcutaneous adipose tissue made it impossible to assess the muscle volume.

OPHTHALMOPLÉGIA This term denotes a drug-resistant and not spontaneously varying paralysis of the extrinsic eye muscles and/or the levator muscle of the upper eyelid. This condition was encountered in 23 of 137 patients with generalized myasthenia.

THYMOMA The presence of a thymoma was verified histologically in 20 patients. Typical radiological features were observed in three patients who, moreover, had antibodies against striated muscle tissue in a dilution of >1:10.

ELECTROMYOGRAPHY In 13 patients with muscular atrophy, an electromyographic examination (EMG) of the affected muscle was carried out. Whenever possible, the conduction velocity of the afferent nerve of the atrophic muscle was determined. Neurogenic abnormalities were assumed to exist in the presence of fibrillations or positive denervation potentials. Myogenic abnormalities were assumed to

TABLE 1
MUSCLE ATROPHY IN 14 PATIENTS WITH MYASTHENIA GRAVIS

Patient no.	Sex	Age at onset (yr)	Age at first examination (yr)	Type myasthenia	Bilateral affected muscles	Biopsy	EMG	Ophthalmoplegia	Thymoma
1	M	47	50	2B	Triceps	N	N	-	-
2	M	76	77	2B	Quadriceps	N	N	-	-
3	F	60	65	4	Tongue; facial	N	O	-	-
4	F	34	41	2B	Tibialis anterior; extensors of forearms	N	N	-	-
5	F	58	62	2A	Quadriceps femoris	N	N	-	-
6	F	12	29	2B	Quadriceps femoris and shoulder girdle	N + L	N + M	+	+
7	F	23	51	2B	Shoulder girdle	N	M	+	+
8	F	12	25	2B	Deltoid, triceps, and supraspinatus	N	M	+	+
9	F	53	55	2B	Shoulder girdle, upper arm, and masticatory	L	M	+	+
10	F	37	49	2B	Facial, masticatory, and deltoid			+	+
11	F	42	62	2B	Biceps and triceps			+	+
12	F	27	55	2B	Quadriceps, facial*, and masticatory	L†	O	-	-
13	F	45	57	2B	Quadriceps, tibialis anterior, and extensor digitorum communis	N + L	N	+	+
14	F	52	62	4	Erector trunci, supraspinatus, and trapezius	N + L	M	-	-

N = neurogenic. M = myogenic. L = lymphocytic infiltrations. O = normal. - = absent. + = present.

Type myasthenia (Osserman, 1958): 2A, mild; 2B, moderate fluctuating course; 4, severe with ventilatory crises.

* EMG: single pattern.

† type II fibre atrophy.

exist whenever the mean duration of 15–20 action potentials equalled or was less than 70% of the normal value (according to Buchthal). In the absence of these abnormalities the EMG was rated 'normal'.

MUSCLE BIOPSY In 46 patients a total of 61 biopsies was examined (Table 2). In 10 of these patients a biopsy was taken from an atrophic muscle. This muscle is listed first in Table 1. From all biopsies longitudinal and transverse paraffin sections were stained with haematoxylin-eosin and by Gomori's trichrome stain. In 35 biopsies, a histochemical examination was carried out. In 21 patients and 19 controls of the same age and sex distribution, the method of Brooke and Engel (1969a) was used to determine the mean minimal diameter of 200–400 fibres (134 fibres in one patient) in the quadriceps muscle, stained in transverse sections for myofibrillar ATP-ase activity. The study included all successive patients with myasthenia who had yielded technically measurable specimens showing more than 200 fibres with a normal distribution of type I and type II fibres. As controls, patients were used in whom clinical examination, EMG, and histological and enzyme-histochemical examination of the biopsy specimen excluded the probability of neurological disease.

The criteria of neurogenic abnormality were groups of angular fibres with a small diameter, with or without an increase of hyperchromatic nuclei, with or without the presence of target fibres.

Large collections of round cells located between the muscle fibres were regarded as lymphocytic infiltrations.

BIOCHEMICAL STUDY In all patients with muscular atrophy the following studies were carried out: 24-hour urinary creatine excretion, serum protein electrophoresis, creatine phosphokinase and aldolase activity.

NECROPSY FINDINGS In 12 cases necropsy was performed. The brain-stem and the spinal cord were examined in seven cases, the peripheral nerves in six, several skeletal muscles in all. Several levels of the cervical, thoracic, lumbar, and sacral parts of the spinal cord were examined. CNS sections were stained with haematoxylin-eosin and according to Nissl and Klüver-Barrera. Longitudinal and transverse sections were cut from the peripheral nerve specimens, embedded in paraffin, and stained with haematoxylin-eosin and according to Klüver-Barrera. Frozen sections were also obtained and stained with Sudan and according to Bielschowsky. Longitudinal and transverse sections of the skeletal

muscles were stained with haematoxylin-eosin and by Gomori's trichrome stain.

STATISTICAL METHODS The possible relation of several features was tested by way of 2×2 tables. A positive relation was assumed if $P < 0.05$. It was taken into account that these features belonged to the same population of patients.

The duration of the disease is indicated by the median (P_{50}). The median duration of the group with atrophy ($n=14$) and of the group without atrophy ($n=134$) is compared by application of the test of Wilcoxon.

As the ages of both groups of patients had a normal distribution, they were described by their means and standard deviations.

The mean values of the smallest diameter of the muscle fibres (see Table 4) were compared by Student's t test for two groups.

RESULTS

CLINICAL FINDINGS In 14 of the 148 patients with generalized myasthenia, muscular atrophy was established clinically in one of several

FIG. 1. Patient 12; woman aged 55 years. Bilateral facial weakness with Bell's phenomenon. Atrophy of facial muscles and masticatory muscles.

FIG. 2. Patient 9; woman aged 55 years. Atrophy of shoulder girdle and upper arm muscles.

groups of muscles (Table 1). Four other patients developed generalized muscular atrophy in the course of their 3–12 months of respiratory infections and artificial respiration (see Table 7). This group of four patients will be discussed separately.

Examples of muscular atrophy are presented in Figs 1, 2, and 3. Proximal muscles were relatively often involved, but other sites were the extensor muscles of the forearms and legs (patients 4 and 13), the facial muscles (patients 3, 10, and 12), and masseter muscles (patients 9, 10, 12); one female patient (no. 3) showed atrophy of the central part of the tongue (Fig. 3). The affected muscles showed no or a decidedly inadequate response to anticholinesterases.

Neurogenic changes were found in eight of the 10 biopsies taken from clinically atrophic muscles. The post mortem findings in patient 13 indicated the presence of neurogenic changes in all muscles. This female patient had always been

ambulant until she died from an intracerebral haemorrhage after fulminating pancytopenia. The necropsy disclosed no other cause of the neurogenic changes; peripheral nerves and spinal cord were normal.

The electromyogram and the biopsy were not always consistent. In three cases the EMG showed a pattern interpreted as myogenic,

atrophy, a follow-up had been made over a period of at least three years. These follow-ups had failed to disclose other diseases which might explain the muscular atrophy.

Sex Local muscular atrophy was diagnosed in two of 41 men and in 12 of 109 women with generalized myasthenia. This is not conclusive of a male or female predominance ($\chi^2=2.32$; $P>0.10$).

Age The age range of patients without muscular atrophy was 9–86 years ($\bar{X}=45.6$, $s=17.2$, $n=134$). That of patients with muscular atrophy was 29–77 years ($\bar{X}=52.9$, $s=13.8$, $n=14$). The difference is not significant ($t=-1.65$; $0.05<P<0.10$).

Duration of the disease The median (P_{50}) duration was six to eight years for the group without atrophy, and 11 years for the 14 patients with muscular atrophy. The test of Wilcoxon did not show a difference. The latter group included six patients whose illness had existed five years or less, and four with a history encompassing 17–28 years. In view of these findings, the duration of the disease does not seem a reliable factor in the aetiology of muscular atrophy.

FIG. 3. Patient 3; woman aged 65 years. Atrophy of the tongue: triple furrowed tongue.

whereas the biopsy from the same muscle showed neurogenic changes. In two cases the EMG was normal whereas the biopsy showed neurogenic changes.

The biochemical study disclosed no abnormalities other than an increased concentration of serum gamma-globulin (in patient 5). This woman developed a pure red-cell anaemia a few years after muscular atrophy was diagnosed; the anaemia responded well to therapy.

A moderately severe form of rheumatoid arthritis was found in a female patient with atrophy of the humeroscapular muscles: she was capable of virtually unlimited movement of the arms on the shoulders, and the rheumatoid arthritis therefore could not explain the muscular atrophy. In all patients with muscular

TABLE 2
MUSCLE BIOPSY FINDINGS IN 46 PATIENTS WITH MYASTHENIA GRAVIS

17 patients with thymoma 29 biopsies		29 patients without thymoma 32 biopsies	
Site of biopsy		Site of biopsy	
M. quadriceps	17	M. quadriceps	23
M. deltoideus	3	M. deltoideus	2
M. triceps	1	M. triceps	1
M. pectoralis	2	M. pectoralis	1
M. intercostalis	4	M. intercostalis	1
M. tibialis anterior	1	M. tibialis anterior	2
M. gastrocnemius	1	M. gastrocnemius	1
		M. erector trunci	1
Histopathology		Histopathology	
Normal	10	Normal	21
Lymphocytic infiltrations	10	Lymphocytic infiltrations	5
Neurogenic changes	3	Neurogenic changes	1
Neurogenic changes + lymphocytic infiltrations	5	Neurogenic changes + lymphocytic infiltrations	4
Myositis	1	Type II fibre atrophy	1

FIG. 4. Type II fibre grouping. Only a few type I fibres (darkly stained) are seen. NADH-tetrazolium oxidoreductase, $\times 150$.

FIG. 5. Type II fibre atrophy. Darkly stained type II fibres have a small diameter. Myofibrillar ATP-ase, $\times 150$.

Severity of the disease Muscular atrophy was found in 12 of 133 patients with a mild or moderate course and in two of 15 patients with respiratory difficulties. No relation could be proved.

Thymomas Muscular atrophy was present in three of 23 patients with a thymoma and in 11 of 125 patients without a thymoma. No relation could be proved ($\chi^2 = 1.48$; $P > 0.20$).

Ophthalmoplegia Muscular atrophy was present in four of 21 patients with ophthalmoplegia and in 10 of 114 patients without ophthalmoplegia. No relation follows ($\chi^2 = 1.06$; $P > 0.25$).

BIOPSIES Neurogenic changes were observed in 17 of the 61 biopsies examined. Twelve of these specimens were also submitted to enzyme-histochemical examination. A normal differentiation into type I and type II fibres was seen in

TABLE 3

RELATION THYMOMA, LYMPHOCYTIC INFILTRATIONS AND NEUROGENIC CHANGES

Lymphocytic infiltrations			Neurogenic changes		
+	-	Total	Total	+	-
9	8	17	Thymoma	17	6
4	25	29	No thymoma	29	9
13	33	46*		46†	15

* Significant: $\chi^2 = 6.28$; $P < 0.01$.

† Not significant.

eight biopsies. Type grouping of type II-fibres (Fig. 4) was found in three cases. In one biopsy, the majority of small angular fibres proved to be of type II (Fig. 5).

In only one of the 61 biopsies were the histo-

TABLE 4

MEAN VALUES OF THE SMALLEST DIAMETER OF QUADRICEPS MUSCLE FIBRES

		$\bar{x}$	s	n	Significance	A
Females						
with MG	type I	47.4	14.4	14	$P < 0.01$	7
controls	type I	59.0	6.9	12		0
Females						
with MG	type II	40.4	11.5	14	$P < 0.01$	9
controls	type II	47.3	7.4	12		1
Males						
with MG	type I	50.0	8.2	7	NS	4
controls	type I	52.9	5.4	7		2
Males						
with MG	type II	47.3	7.4	7	NS	5
controls	type II	56.0	7.9	7		3

 $\bar{x}$ = mean value of the smallest diameter in μ . s = standard deviation. n = number of patients examined. A = number of patients in whom $> 5\%$ of the fibres had a smallest diameter of $\leq 20 \mu$ (women) or $\leq 30 \mu$ (men).

MG = myasthenia gravis.

TABLE 5

NECROPSY FINDINGS IN PATIENTS WITH MYASTHENIA GRAVIS

Patient no.:	13	14	15	16	17	18	19	20
Sex:	F	F	M	M	F	M	F	F
Age:	62	62	58	35	63	66	72	32
Duration myasthenia in years:	13	19	1½	5	1	2	2	2
Thymoma:	+	-	+	+	+	-	-	-
Number of muscles examined:	8	25	14	13	4	15	18	5
M. quadriceps femoris		0/0	L	N+L/L			L/0	
M. iliopsoas	L	0/0	0	0	N	0	N/0	
M. gastrocnemius		0/L	L					
M. tibialis anterior				0				
M. peroneus		L		0				
M. deltoideus		0/0	L	L		0		
M. biceps brachii				0			0/0	
M. triceps brachii							0/0	
M. supraspinatus		N						
M. infraspinatus		N/N+L		L				
M. pectoralis	N	0/0	0/L	L	0	0	0/0	0
M. trapezius	N+L	N+L						
M. sternocleidomastoideus	N+L	0/N				0		0
M. sternohyoideus			L			0		0
M. masseter			0					
M. intercostalis	N+L	N	L	L	0	L/0	0/0	0
diaphragm	N	0	0		L	0	0/0	0/0
M. erector trunci		N+L/N+L	L	N+L				
M. erector nuchae				N+L		0		
M. obliquus abdominis	N+L		L			L	0/0	
M. rectus oculi superior		0/0	L			0	0	
M. obliquus oculi superior		0/0	0	0		0/L	0	
Spinal cord	0	0	0	0			0	
Peripheral nerves	0	0			0			

0 = normal.

0/0 = both sides normal.

N = neurogenic changes.

L = lymphocytic infiltrations.

N+L = neurogenic changes and lymphocytic infiltrations.

- = absent.

+ = present.

pathological features of myositis found. The necrotic fibres were often located at the margins of the fasciculi. Signs of phagocytosis were observed in these fibres. Extensive round-cell infiltrations were found in the interstitium. Another specimen showed marked variation of the muscle fibre diameter, all fibres showing a round form in the transverse sections. The fibres of small diameter were found nearly always to be of type II (type II fibre atrophy). There was no increase of internal nuclei.

Patient 4, with a 10 year history of muscular atrophy, yielded a biopsy from an atrophic muscle which showed a 'myopathic pattern'. There was marked variation of the muscle fibre diameter, the fibres showed a round form in the transverse section. There was a marked increase of internal nuclei, and marked proliferation of endomysial adipose tissue and connective tissue. The other histopathological findings and their relation to the presence of a thymoma are presented in Tables 2 and 3. As more than one biopsy was taken in six patients with a thymoma and in three patients without a thymoma, statistics were applied only on the data of the first biopsy of the patients of each group. A relation is shown between the presence of lymphocytic infiltrations and that of a thymoma (Table 3). It is also apparent that neurogenic changes were not more frequently seen in the presence than in

TABLE 6
RELATION BETWEEN THYMOMA, LYMPHOCYTIC INFILTRATIONS, AND NEUROGENIC CHANGES: ANALYSIS OF DATA OF TABLE 5 (EYE MUSCLES EXCLUDED)

<i>Lymphocytic infiltrations</i>				<i>Neurogenic changes</i>		
+	—	<i>Total</i>		<i>Total</i>	+	—
21	14	35	Thymoma	35	9	26
11	44	55	No thymoma	55	9	46
32	58	90*		90†	18	72

Numbers represent number of muscles examined.

* Significant: $\chi^2 = 13.2$; $P < 0.01$.

† Not significant: $\chi^2 = 0.65$.

the absence of a thymoma (Table 3). Normal findings in muscle biopsies were seen in 17 of 29 mild and moderate cases and in nine of 17 patients with respiratory difficulties. From this it is improbable that muscle pathology is related to the severity of the disease ($\chi^2 = 0.004$).

Table 4 presents the results of measurements of the smallest muscle fibre diameter. This Table shows that, in 14 women with myasthenia, the smallest mean diameter of type I as well as type II fibres was smaller than that in controls. Moreover, the number of biopsy specimens containing more than 5% fibres with a smallest diameter of less than 20 μ was significantly

TABLE 7
NECROPSY FINDINGS IN PATIENTS WITH MYASTHENIA GRAVIS: DEATH AFTER LONG-TERM CONTROLLED RESPIRATION AND/OR INTERCURRENT DISEASE

	Patient no.			
	21	22	23	24
Sex:	M	F	F	F
Age at necropsy:	35	38	45	51
Duration myasthenia (yr):	1	9	4	19/12
Duration controlled respiration (yr):	11/12	2/12	1	5/12
Thymoma:	+	-	+	+
Histopathology muscles				
number of muscles examined	8	25	5	24
normal	—	7	—	—
lymphocytic infiltrations only	—	1	1	7
neurogenic changes	—	4	—	—
neurogenic changes + lymphocytic infiltrations	8	13	4	17
Histopathology spinal cord				
peripheral nerves	Normal Segmental demyelination	Normal		Normal Segmental demyelination

larger in the myasthenia patients. This was true both for the type I and type II fibres. There would seem to be a systematic shift to the left. The seven men with myasthenia did not differ definitely from the control group. The mean diameter of type II fibres was smaller than that of the control group but the 5% level is not reached, possibly due to the low number of patients.

NECROPSY FINDINGS The post mortem findings obtained in 12 patients are summarized in Tables 5, 6, and 7. The findings are divided into those in a group of eight patients without artificial respiration and without chronic deterioration (Tables 5 and 6), and those in four patients who had needed continuous artificial respiration for three to 12 months before death (Table 7).

Table 5 shows that the changes were distributed over all muscles without any predilection. So far as could be established with the staining techniques used, the spinal cord, brainstem, and peripheral nerves showed no abnormalities. Table 6 reveals the same relation between lymphocytic infiltrations and the presence of a thymoma as that shown in Table 3; and again the data fail to show the likelihood of a correlation between thymoma and neurogenic changes.

Table 7 shows that all patients with severe myasthenia and respiratory disturbances have marked pathological changes in their muscles, largely of a neurogenic type. In patients 21 and 24, segmental demyelination was found in the peripheral nerves which might be held responsible for the neurogenic atrophy. These patients were in very poor condition before death, and infections and deficiencies may therefore have played a role. The four patients of Table 7 all had generalized muscular atrophy.

Patients 21 and 24 had developed total external ophthalmoplegia, and the eye muscles of these patients were examined. In patient 21 they were found to have been almost completely replaced by adipose and connective tissue. In patient 24 they showed neurogenic changes, the oculomotor nerve being intact. In patient 22, the presence of lymphocytic infiltrations in nearly all muscles was an exception to the rule that these occur in particular in the presence of a thymoma.

DISCUSSION

In our material, muscular atrophy proved to be present in approximately 10% of patients with generalized myasthenia gravis. Histopathologically, the atrophic muscles were nearly always found to show neurogenic changes. Even in the absence of clinical muscular atrophy, neurogenic changes were histopathologically demonstrable in 17 (28%) of 61 biopsy specimens (Table 2), and in 18 (20%) of 90 muscles examined at random at necropsy in eight cases (Table 5).

Muscular atrophy in patients with myasthenia gravis might be caused by: (1) inactivity; (2) the incidental presence of another primary affection of the lower motor neurone; (3) a paraneoplastic affection associated with a thymoma; (4) poor general condition—that is, recurrent infections, artificial respiration, nutritional deficiency—giving rise to cachexia and/or a polyneuropathy; (5) permanent denervation of a number of muscle fibres at the level of the motor end-plate.

re (1) Our 14 patients with muscular atrophy were all walking patients, capable of executing some degree of movement with the limbs in which the atrophic muscles were localized. The same applies to the facial and masseter muscles. In any case, the often very local atrophy did not develop during bed rest or immobilization of joints in the vicinity of the atrophic muscles. In view of these facts, inactivity seems an unlikely cause of the muscular atrophy. The only findings in which inactivity may have played a certain role, is the diminished muscle fibre diameter (Table 4) which in most patients showed a general 'shift to the left'. Brooke and Engel (1969b) carried out fibre measurements and as a rule found type II fibre atrophy with, in one-third of patients, type I fibre atrophy in addition. They interpreted this as an indication of denervation.

re (2) The findings on neurological examination—that is, normal sensibility and reflexes—the absence of biochemical changes, the non-familial occurrence, and the normal conduction velocity of the motor nerves (if examined) do not support any suspicion of another primary neurological disease. Moreover, a percentage of nearly 10 is too large to be accidental.

re (3) The occurrence of muscular atrophy was found to be unrelated to the presence or absence of a thymoma.

re (4) The 14 patients with clinical muscular atrophy were all in good general condition. The same applies to the eight patients whose muscles were examined at necropsy (Table 5). Only patients 21, 22, 23, and 24 (Table 7) were in poor general condition because of chronic infections and long-term artificial respiration. This probably explains the segmental demyelination found in the peripheral nerves in two of these patients. The generalized muscular atrophy observed in these patients, therefore, cannot be directly related to the myasthenia. Similar cases have been described by Steidl *et al.* (1962) and Lowenberg-Scharenberg (1962), who did not, however, present detailed post mortem findings in the spinal cord and peripheral nerves.

re (5) It is virtually certain that acetylcholine, besides transmitting the impulse, exerts a trophic influence on the muscle. Total acetylcholine depletion at the peripheral nerve endings, as observed in experimental botulism (Duchen and Strich, 1968), gives rise to paralysis and atrophy. During recovery from experimental botulism (Duchen, 1970), motor end-plate changes occur which resemble the changes at the end-plates described in myasthenia by Coërs and Desmedt (1959) and McDermot (1960). We do not know whether these end-plate changes represent a primary abnormality or one that is secondary to disturbed acetylcholine metabolism or to anticholinergic therapy. Since myasthenic muscular weakness occurs in all degrees of severity, complete, partial, or fibre-linked atrophy of the muscle is quite readily conceivable on the basis of a permanent local acetylcholine deficiency. The non-functioning of atrophic muscles after administration of cholinesterase inhibitors is likewise explained by lack of acetylcholine. Resistance to anticholinesterase medication can be established in a proportion of the muscles of a proportion of the patients. Specifically the extrinsic eye muscles are often partly resistant, so that diplopia can often not be controlled with the aid of anticholinesterase. The relation between muscular atrophy and drug resistant ophthalmoplegia could not be estab-

lished. The clinical data, however, suggest that the eye muscles, too, are sometimes totally or partially denervated. This was demonstrated at necropsy in one case.

The localization of lymphocytic infiltrations in the end-plate zone, with destruction of peripheral nerve endings, might also explain the neurogenic changes. A similar situation has been described in one patient by Wiesendanger and D'Allesandri (1963), but seems an exception rather than the rule. In any case, our study has failed to demonstrate a relation between lymphocytic infiltrations and neurogenic changes, although both occurred in the same muscle in some cases.

A 'myopathic pattern' of the kind observed in some cases of chronic denervation—that is, benign infantile spinal muscular atrophy, peroneal muscular atrophy—was observed in only one biopsy. We therefore believe that the term 'myasthenic myopathy' should be avoided.

Our study has established that muscular atrophy, as it may occur in patients with myasthenia gravis, results from an affection of the lower motor neurone. We regarded it as most likely that this muscular atrophy is caused by denervation as a result of chronic acetylcholine depletion at the motor end-plates involved.

The authors wish to thank Dr. W. J. M. Hootsmans for his help with the electromyographic measurements, Dr. A. E. F. H. Meyer for his help with the histochemical studies, and Professor Dr. J. Strackee for his statistical advice. This study was supported by a grant from the Prinses Beatrix Fonds.

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