MEDICAL GRAND ROUNDS January 11, 1973

MYASTHENIA GRAVIS

[redacted]

This 23 year old [redacted] woman was first seen at [redacted] on [redacted]-68 when she was admitted in coma with typical meningococcal meningitis. She responded well to treatment with large doses of intravenous penicillin and was discharged asymptomatic except for frontal headaches which persisted for about two weeks. On [redacted]-68 she was re-admitted with a 1 week history of malaise and rhinorrhea followed by 4 days of fever, chills and sore throat. One day prior to admission she had developed a severe headache with nausea and vomiting. On arrival vital signs were normal except for a temperature of $100^4°$ and a tachycardia. She was found to have a stiff neck, palpable, tender right cervical nodes and a large peritonsillar abcess. The latter was drained and antibiotics were started after two spinal fluid examinations showed no evidence of recurrent meningitis. Clinical response was excellent.

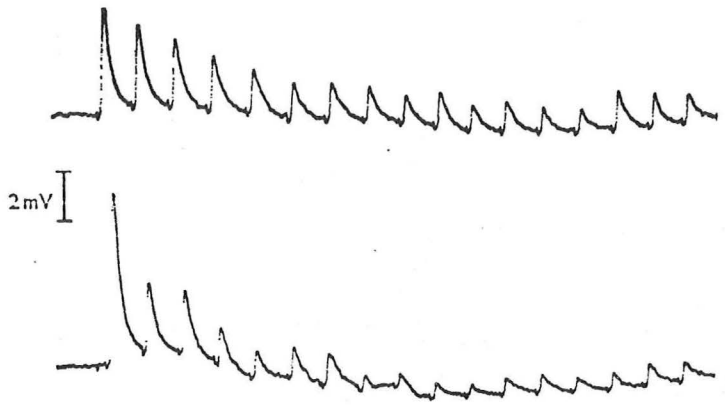
During the course of this admission the patient complained of afternoon weakness which had been present for about nine months, but which had not been mentioned in the first hospitalization. Emphasis was placed on difficulty in climbing stairs and sudden falls where she was unable to gain her feet. She had also noted difficulty in combing the hair, with fatigue developing promptly when the arms were raised over her head. Diplopia had been observed on several occasions. Because of these symptoms a Tensilon test was carried out and was interpreted as being unequivocally positive. She then had electromyographic studies which showed the classic fatigue phenomenon of myasthenia gravis.

Other laboratory tests were unremarkable. She had a PBI of 4.7 µGs%. X-rays of the skull, chest, and cervical spine were normal, as were laminograms of the anterior mediastinum. Immunoelectrophoresis was normal and no antibodies to skeletal muscle were found.

The patient was discharged on Mestinon therapy with some improvement of symptoms initially on a dosage schedule of 120 mgs in the morning and 60 mgs at noon and in the evening. By [redacted] of 1969 she had increased the dosage to 60 mgs 6 times daily and was still observed to have a right ptosis and proximal muscle weakness. Moderate side effects of increased salivation and sweating together with occasional nausea had developed, but were considered within acceptable limits. In [redacted] of 1970 she complained of persistent diplopia on 60 mgs of Mestinon 8 times daily. Over the next three months control became increasingly difficult to obtain, with side effects supervening at drug levels insufficient to manage the symptoms. For this reason she was readmitted on [redacted]-70.

On examination she had bilateral ptosis, diplopia in the direction of the gaze, nystagmus at the extremes of upward and lateral vision and decreasing strength of response on repetitive exercise of the upper extremities. (The neurological examination was otherwise normal.) She was also noted to have a nodule in the right lower lobe of the thyroid, but thyroid function tests were normal.

Following thoracic surgery consultation the decision was made to perform a thymectomy. Surgery was carried out on [redacted]-70 and sternal splitting was required when the thymus could not be delivered through a transverse cervical incision. She tolerated the procedure well. An elective tracheostomy was carried out before the patient was returned to the recovery room. The post-operative course was characterized by a mild episode of aspiration and a persistent induced respiratory alkalosis which led to hypokalemia, but the patient was at no time in serious difficulty. Pathologic examination of the thymus revealed lymphoid hyperplasia without tumor. She was discharged on [redacted]-70 with no medications prescribed. In the two years since surgery she has had only minimal symptoms while performing her household duties. She occasionally takes 30 mgs of Mestinon when she feels more fatigued than normal, but in general requires no drugs.



Myasthenia. Above is first part of conditioning tetanus of 10 sec duration.

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General review

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While this review is rather loose and personal in style, it probably is the best single article covering both a vast clinical experience and current concepts of myasthenia gravis.

The normal synaptic structure of skeletal muscle

2. Couteaux, R., and Taxi, J. Recherches histochimiques sur la distribution des activites cholinesterasiques au niveau de la synapse myoneurale. Arch. Anat. Micr. Morph. Exp. 41:352, 1952.
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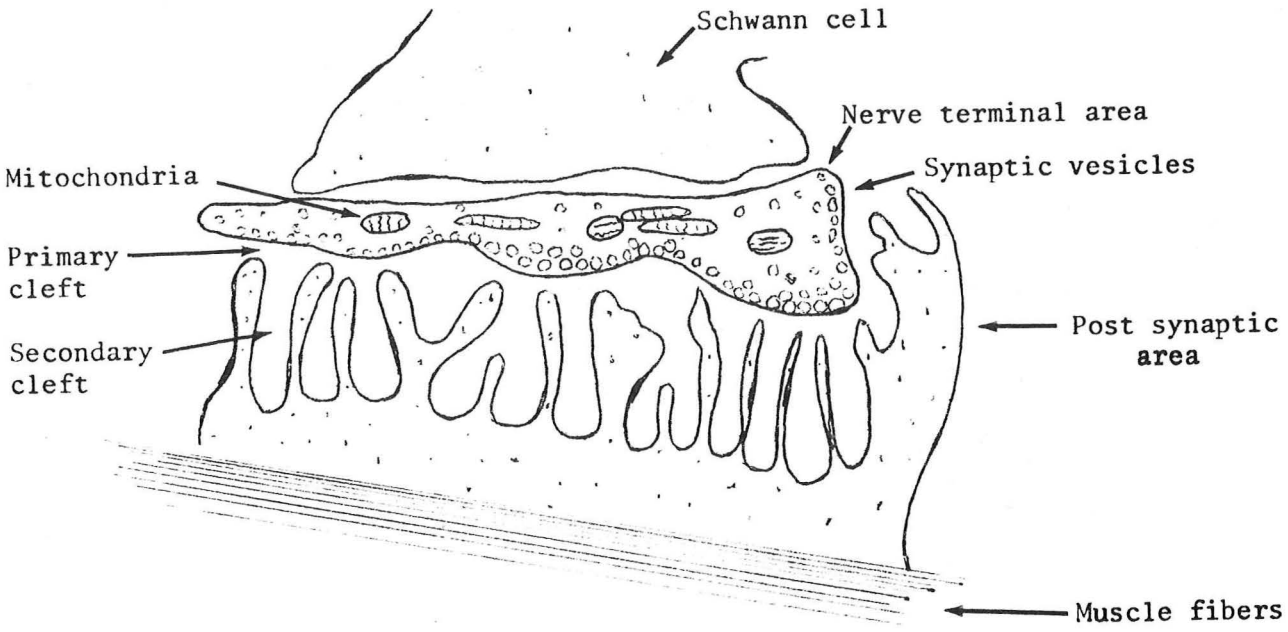

Fig 1

Schematic diagram of electronphotomicrograph of synaptic structure

As the motor nerve fiber approaches the muscle, it loses its myelin sheath, then terminates as a series of coils which, when viewed from above, has a pretzel-like appearance. The motor nerve terminal lies in a depression, known as the synaptic gutter, on the surface of the muscle fiber. There appears to be no organized cellular structure within the primary synaptic cleft. The end plate itself, a modification of the sarcoplasmic membrane, is folded into a complex series of invaginations on which the receptor sites are presumably located. The primary cleft is about 500 Å in width. Its edges at the surface of the muscle fiber appear to be covered by teloglial cells, derivatives of Schwann sheath cells, as is the upper surface of the axon terminal. Within the axonal terminal are dense concentrations of both synaptic vesicles and mitochondria. The synaptic vesicles represent packets or quanta of acetylcholine (approximately 1000 molecules per vesicle) while the mitochondria provide oxidative enzymes necessary for synthesis of the transmitter. The average area of the nerve terminal is close to 4 μ^2. The terminal contains 50-200 synaptic vesicles per μ^2 or up to about 1600 per μ^3. Mitochondria occupy about 18% of the total space. The postsynaptic area is 2 1/2 times greater than the pre-synaptic area and the post-synaptic membrane, because of the complicated folding, is 10 times longer than the pre-synaptic membrane.

Physiology of synaptic transmission

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8. Katz, B. Nerve, Muscle and Synapse. McGraw-Hill, New York, N. Y., 1965.
9. Del Castillo, J., and Katz, B. Local activity at a depolarized nerve-muscle junction. J. Physiol. 128:396, 1956.
10. Whittaker, V. P. Origin and function of synaptic vesicles. Ann. N. Y. Acad. Sci. 183:21, 1971.
11. Hubbard, J. I. Mechanism of transmitter release from nerve terminals. Ann. N. Y. Acad. Sci. 183:131, 1971.
12. Katz, B., and Miledi, R. The role of calcium in neuromuscular facilitation. J. Physiol. 195:481, 1968.

There is now a considerable body of evidence that acetylcholine is released at the motor end plate in uniform packets, presumably the equivalent of the synaptic vesicles seen by electron microscopy. Each packet (or quantum) has been estimated to contain 10^3 to 10^4 molecules of acetylcholine. In the absence of a nerve impulse single quanta are released at a rate of about 1 per second and generate what is called a miniature end plate potential (MEPP), generally near 1 mV in amplitude, far below the critical level of depolarization necessary to generate an action potential in the muscle. The release of transmitter is enormously but transiently increased by nerve impulses with some 100-200 packets being released as a result of depolarization. The end result is an end plate potential (EPP) of sufficient magnitude to generate an action potential in the end plate and initiate the events of the excitation-contraction sequence in the muscle.

Descriptions of the events accompanying excitatory nerve stimulation are well known. An applied depolarizing current causes a sudden selective increase in permeability of the axonal membrane with a rapid influx of

sodium ions such that the internal potential becomes positive. The downward sweep of the action potential is caused by an outward flux of potassium ions and subsequent self-propagation of the impulse to the terminal axon. The mechanism by which this impulse triggers release of vesicle contents is less well understood, but seems to be dependent on entry of calcium through the pre-synaptic membrane. One specific hypothesis is that Ca^{++} after entering the nerve terminal masks negative charges on the inner membrane thus allowing the negatively charged vesicles to approach and attach to the membrane releasing sites. After release acetylcholine in the synaptic clefts is removed primarily through the hydrolytic action of acetylcholinesterase.

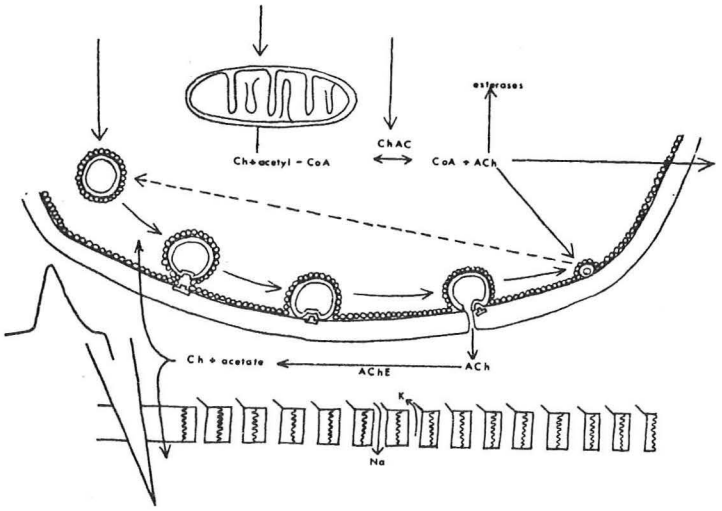


FIGURE 2. A schematic summary of the microphysiology of neuromuscular transmission. The nerve terminal above contains vesicles, mitochondria and enzymes, and the synthesis of ACh and its fate are schematically illustrated. The muscle membrane below is shown with independent channels for Na^+ and K^+ flow. AChE is depicted schematically by the wiggly line. It will be noted that Ch, formed by ACh hydrolysis, is taken up by muscle and nerve. A microelectrode is depicted to the left recording an e.p.p., set up by ACh action, from the junctional region. Further description in text.

It is important to recognize that acetylcholine is both stored and synthesized in the terminal axon. The latter process occurs in the cytoplasm under the influence of the enzyme choline acetylase utilizing acetyl CoA generated in the mitochondria and choline re-entering the axon after the splitting of acetylcholine in the synaptic cleft. There are at least two pools of acetylcholine, one rapidly turning over and the other less rapid, both probably existing in synaptic vesicles from geographically different locations. In analogy to insulin and the beta cell, initial acetylcholine release comes from a labile pool which is then dependent on continued synthesis for renewal. If synthesis is interrupted, as by interference with choline re-entry, continued stimulation results in the disappearance of vesicles, failure of transmitter release and ultimately a blockade of neuromuscular transmission.

Abnormalities of neuromuscular transmission and etiologic theories in myasthenia gravis

At the physiologic level the abnormalities which most characteristically describe the neuromuscular block operative at the nerve-end plate synapse may be listed as follows:

(1) There is a small but statistically significant decrease in the muscle action potential following a single supramaximal nerve stimulus.
(2) There is a normal muscle response to direct stimulation.
(3) There is an increase in the muscle action potential following a single supramaximal nerve stimulus after the administration of anticholinesterase drugs.
(4) There is a decrement in successive muscle action potentials following supramaximal nerve stimulation at 50 impulses per second.
(5) There is a repair of this decremental response to 50 per second stimulation with anticholinesterase drugs.

At the present there is no definitive answer to the question of the underlying etiology of the disease or the mechanism by which the above defects are produced. Three main theories can be identified:

1. Presynaptic theory
2. Post synaptic theory
3. Humoral theory

Presynaptic theory

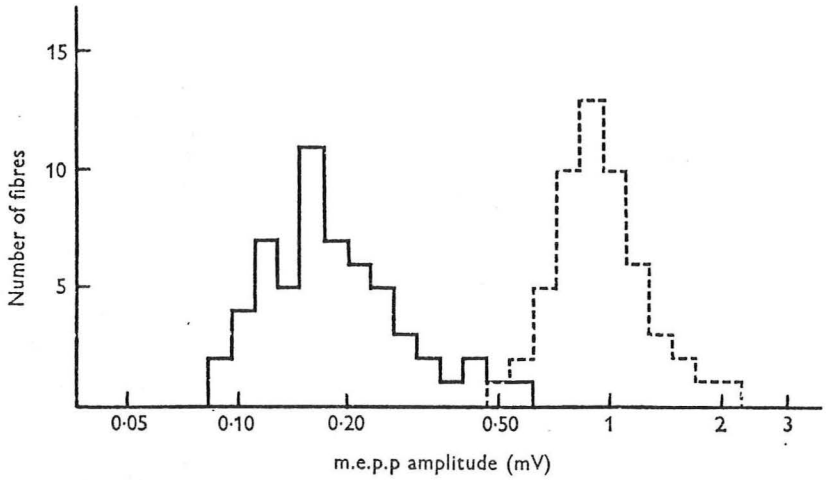
13. Elmqvist, D., Hofmann, W. W., Kugelberg, J., and Quastel, D. M. J. An electrophysiological investigation of neuromuscular transmission in myasthenia gravis. J. Physiol. 174:417, 1964.
14. Desmedt, J. E. Presynaptic mechanisms in myasthenia gravis. Ann. N. Y. Acad. Sci. 135:209, 1966.

Ref. 13 is the classic and widely quoted paper which indicates that quantum size is diminished in myasthenia gravis to about one-fifth that found in normal muscle. Tests were done in vitro utilizing a muscle-nerve preparation obtained by biopsy in the intercostal region. Results were as follows:

TABLE 1. Comparison of electrical properties and m.e.p.p. amplitudes at normal and myasthenic end-plates

	Normal	Myasthenic
Resting potential (mV)	81·7 ± 4·4 (129)	81·0 ± 3·9 (85)
Input resistance (MΩ)	0·57 ± 0·19 (28)	0·54 ± 0·07 (8)
Time constant (msec)	18·9 ± 3·2 (7)	18·2 ± 2·4 (8)
M.e.p.p. amplitude (mV)	0·98 ± 0·30 (54)	0·20 ± 0·11 (57)*

Arithmetric means ± S.D.; number of fibres in brackets.
* Sample biased, mean probably too high, see text.



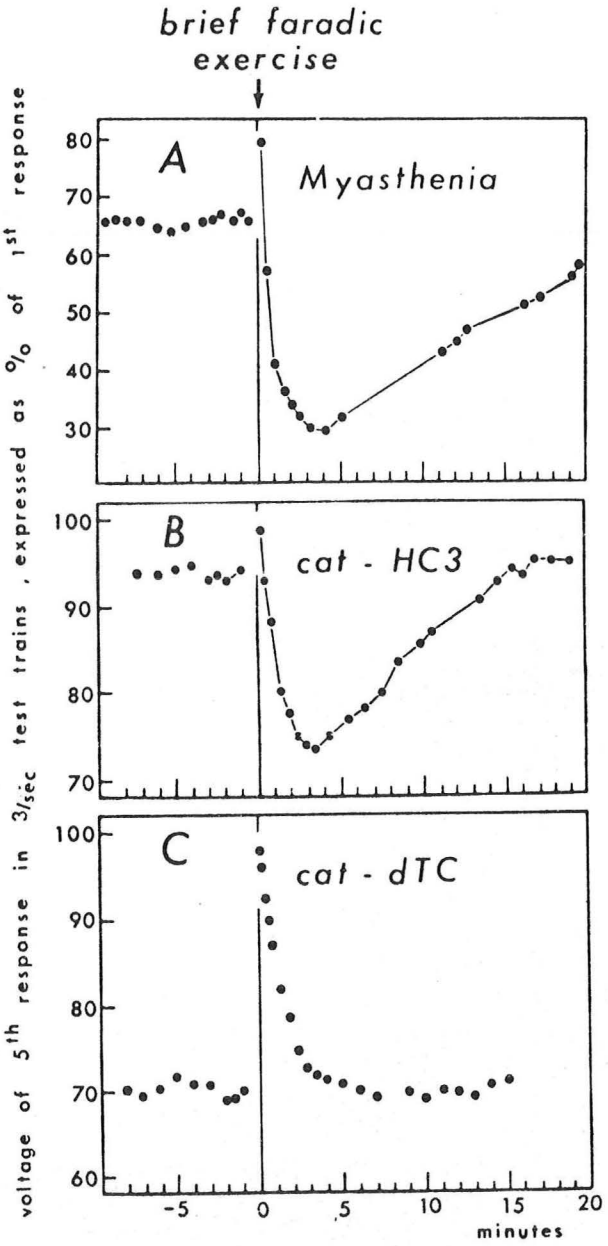
Distributions of mean m.e.p.p. amplitudes obtained from fifty-seven myasthenic and fifty-four normal fibres in normal bathing mediums. All amplitudes corrected to a membrane potential of 85 mV. Full line myasthenic fibres, broken line normal fibres. Noise level was usually 50–100 μV.

Fig 3

The number of quanta released per nerve impulse was normal. Decreased amplitude of the MEPP could be due to diminished size of the acetylcholine packet released or to diminished end plate response to a normal size quantum (post synaptic mechanism). Elmqvist, et al considered the latter possibility to be unlikely since input resistance was the same in normal and myasthenic muscle and since sensitivity to carbachol and decamethonium (depolarizing agents similar to acetylcholine) was normal. Moreover, anticholinesterase drugs, which restored muscle action potential to normal did not change the size of the quanta. One weakness in their argument was the claim that quantum size did not decrease with repetitive nerve stimulation. If true it would be difficult to account for the decremental response seen clinically in myasthenia, although initial weakness might be explained. The basic findings have now been confirmed in several laboratories.

Desmedt, in his carefully reasoned article, indicates that quantum size (or number) must decrease during repetitive stimulation in both normal and myasthenic terminals, though quantitatively the decrease is greater in the myasthenic. The decrement is usually expressed by giving the amplitude of the 5th end plate potential as a percentage of the 1st in a train of nerve stimulations administered at 3 per second intervals. In normals the decrement is essentially never greater than 10%, while in the myasthenia the figure is almost always greater than 20%. In normal muscle the "safety factor" of transmission is quite large; i.e., the amount of acetyl choline

released is in considerable excess of that required to evoke an action potential at the end plate. Thus the decrement occurring during repetitive stimulation would not result in transmission failure. Myasthenics, on the other hand, starting with a quantum size 1/5 of normal would have almost no margin of safety. Under these circumstances decremental depletion of quantum size (or number) during repetitive firing would be expected to yield progressive failure of motor response.



Comparison of the postactivation cycles in myasthenic muscle (A), in normal cat muscle treated by hemicholinium HC-3 plus transmitter depletion through activity (B) and in normal cat muscle in a steady state of partial curarization with *d*-tubocurarine (C). Abscissa, time in minutes with the zero corresponding to the faradization of the motor nerve at 50 per sec. for 2 to 10 seconds. Ordinate, percentage decrement of the fifth electrical response in 3 per sec. test trains. (From Desmedt, 1958*a*).

Fig 4

It is of interest to note that Desmedt postulates that the quantitatively greater decrement seen in myasthenia is due to a defect in acetylcholine synthesis. The drug hemicholinium HC-3 blocks choline re-entry through the pre-synaptic membrane and thereby inhibits the synthesis of transmitter. Nerves treated with this compound remarkably resemble myasthenic preparations and it is on this basis that Desmedt builds his hypothesis. (See Fig 4)

Post synaptic theory

15. Grob, D., and Johns, R. J. Further studies on the mechanism of the defect in neuromuscular transmission in myasthenia gravis with particular reference to the acetylcholine insensitive block. In Myasthenia Gravis, H. R. Viets, ed., p 127. Ch. Thomas, Springfield, Ill., 1961.
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Evidence in favor of a postsynaptic mechanism comes from both pharmacologic and structural studies. In regard to the former, in vitro evidence for induced end plate resistance (desensitization) to depolarization has now been universally discredited because of the extremely high concentrations of depolarizing agent and the long time intervals required (ref 18; see also ref 13). Grob and co-workers still hold to the view that acetylcholine or choline injected intraarterially in vivo has different effects in myasthenics than in normal and that in the former a postsynaptic block to depolarization exists.

19. Grob, D. Spontaneous end plate activity in normal subjects and in patients with myasthenia gravis. Ann. N. Y. Acad. Sci. 183:248, 1971.

More recently Grob has studied end plate activity in vivo in normal and myasthenic patients. Two important conclusions were drawn. First, he was unable to demonstrate decreased amplitude of miniature end plate potentials, a finding in direct contrast with that reported in ref 13. He implies that the latter were artifacts of the in vitro preparation. Secondly, he observed that both normal and myasthenic end plate potentials were increased by intraarterial injections of acetylcholine and neostigmine, but with both drugs the threshold was higher in myasthenia.

	Acetylcholine*		Neostigmine*
	initial	repeated	
Normal	.03	.07	.12
Myasthenic	.15	.61	1.02

* Smallest dose in mg required to increase EPP

He thus argues again that a postsynaptic lesion is likely to be the primary defect in myasthenia. To the present his studies have not been confirmed, but they have to be taken seriously. (One other point of interest in the study is that an average of 9 minutes was required to locate a suitable end plate in normal muscle while a mean of 111 minutes was necessary to identify end plates in the myasthenic. This implies a decrease in total end plates in the patient population.)

20. Woolf, A. L. Morphology of the myasthenic neuromuscular junction. Ann. N. Y. Acad. Sci. 135:35, 1966.
21. Santa, T., Engel, A. G., and Lambert, E. H. Histometric study of neuromuscular junction ultrastructure. Neurology 22:71, 1972.
22. Engel, A. G., and Santa, T. Histometric analysis of the ultrastructure of the neuromuscular junction in myasthenia gravis and in the myasthenic syndrome. Ann. N. Y. Acad. Sci. 183:46, 1971.

It is now clear that the motor end plates are abnormal in myasthenia gravis. The primary lesion appears to be marked simplification of the postsynaptic folding ordinarily seen. The result is a widening of the primary and secondary synaptic clefts which would be expected to dilute the acetylcholine released and facilitate its diffusion away from receptor sites. Moreover the total number of receptor sites is likely be decreased. Both of these findings would be compatible with a postsynaptic mechanism for the physiologic abnormalities of myasthenia. The best indicator of the abnormality is the membrane profile concentration (the ratio of postsynaptic membrane length to end plate area). The results of Santa, Engel and Lambert's studies are shown in Tables 2 and 3 and Fig 5.

TABLE 2

HISTOMETRIC ANALYSIS OF NERVE TERMINALS*

	Area, μ^2	Mitochondrial Area (%)	Vesicles per μ^2	Vesicle Diameter (Å)
Control	3.92 ± 0.4 (n = 63)	18.1 ± 1.5 (n = 51)	50.3 ± 3.6 (n = 59)	560.8 ± 2.8 (n = 1133)
Myasthenia gravis	2.28 ± 0.2† (n = 112)	16.6 ± 1.3 (n = 100)	46.3 ± 2.8 (n = 104)	568.2 ± 4.9 (n = 1420)
Myasthenic syndrome	4.12 ± 0.5 (n = 79)	13.1 ± 1.1† (n = 77)	53.4 ± 3.6 (n = 80)	537.3 ± 6.6† (n = 1260)

* Values indicate Mean ± S.E.

† Indicates significant difference from control value ($p < 0.05$); n indicates number of nerve terminals analyzed, except in last column where it refers to number of vesicle diameters. More than one nerve terminal can be found in an end plate.

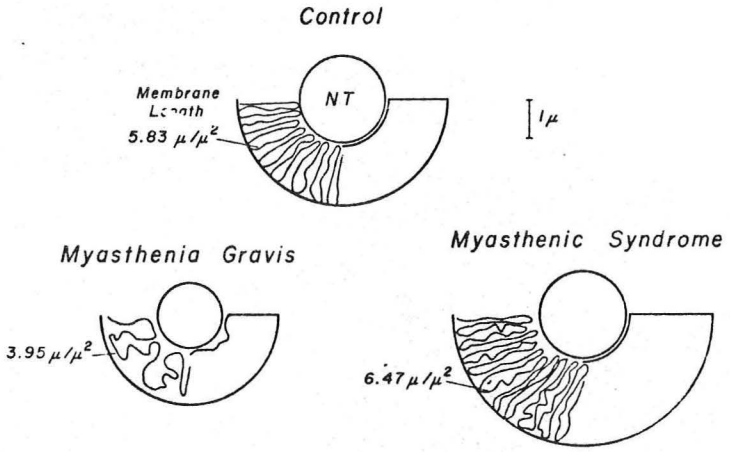
HISTOMETRIC ANALYSIS OF POSTSYNAPTIC REGION*

	Area per Nerve Terminal, μ^2	Membrane Profile Concentration μ/μ^2	Postsynaptic Membrane Length / Presynaptic Membrane Length
Control	10.58 ± 0.79 (n = 54)	5.83 ± 0.25 (n = 47)	10.10 ± 0.75 (n = 39)
Myasthenia gravis	6.55 ± 0.36† (n = 1 8)	3.95 ± 0.21† (n = 87)	8.04 ± 0.72 (n = 85)
Myasthenic syndrome	16.20 ± 1.81† (n = 64)	6.47 ± 0.21 (n = 59)	17.10 ± 2.03† (n = 54)

* Values indicate Mean ± S.E.

† Indicates significant difference from control value ($p < 0.05$). Postsynaptic region here refers to area of folds and clefts per nerve terminal. More than one such region can be found in an end plate. n indicates number of regions analyzed.

Table 3



Schematized control, myasthenia gravis and myasthenic syndrome end plates drawn to the scale of the mean figures. Schwann cells and junctional sarcoplasm are not shown.

Fig 5

The question of course is whether the changes are primary or secondary (see section on muscle atrophy).

Humoral theory

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25. Goldstein, G., and Whittingham, S. Experimental autoimmune thymitis. An animal model of human myasthenia gravis. Lancet 2:315, 1966.
26. Goldstein, G., and Whittingham, S. Histological and serological features of experimental autoimmune thymitis in guinea pigs. Clin. Exp. Immunol. 2:257, 1967.
27. Goldstein, G., and Manganaro, A. Thymin: a thymic polypeptide causing the neuromuscular block of myasthenia gravis. Ann. N. Y. Acad. Sci. 183: 230, 1971.
28. Kalden, J. R., Williamson, W. G., Johnston, R. J., and Irvine, W. J. Studies on experimental autoimmune thymitis in guinea pigs. Clin. Exp. Immunol. 5:318, 1969.

It has long been known that a syndrome of transient myasthenia gravis can exist in infants born to mothers with myasthenia gravis. Because the syndrome lasts only about 6 weeks and because the children subsequently are completely normal, it has been postulated that a circulating myasthenic factor passed through the placenta from the mother to cause the illness. Goldstein and coworkers claim to have discovered such a factor and have named it Thymin. Their experiments began with the injection of thymus extracts in complete Freund adjuvant. Within two weeks these animals had antibodies to thymus and muscle and evidence of thymitis histologically. They subsequently developed a neuromuscular block which was similar to that seen in myasthenia gravis. The authors next isolated and partially purified the thymin molecule from bovine thymus and showed it to be a polypeptide which has a molecular weight of 7000. When injected subcutaneously thymin produced a defect in neuromuscular transmission after 5 days which had characteristics resembling myasthenia gravis. The neural block was sustained for a week to 10 days and then disappeared. As noted in ref 27, animals with the transmission defect showed decreased sensitivity of the end plate to depolarization with acetylcholine under circumstances where acetylcholine production and cholinesterase activity were normal. These findings are, of course, those of an acquired postsynaptic lesion. Injection of antigen in thymectomized animals did not produce a myasthenia like syndrome. The thesis they propose is that an autoimmune thymitis causes the release of thymin which in turn results in the neuromuscular block.

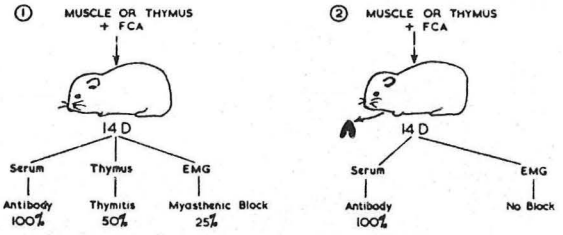

Diagram illustrating experimental "autoallergic thymitis" in guinea-pigs. (1) Guinea-pigs were injected with muscle in Freund's complete adjuvant (F.C.A.). After 14 days the serum contained myoid antibody and, in a proportion of animals, the thymus showed thymitis and neuromuscular block was demonstrable. (2) With thymectomy before immunization, antibody was still demonstrable, but not neuromuscular block

Fig 6

29. Vetters, J. M., Simpson, J. A., and Folkarde, A. Experimental myasthenia gravis. Lancet 2:28, 1969.
30. Kaufman, B. M., Rushworth, G., and Wright, R. Experimental studies related to autoimmunity in myasthenia gravis. J. Neurol. Neurosurg. Psychiat. 32:281, 1969.
31. Jones, S. F., Brennan, J. L., and McLeod, J. G. An investigation of experimental myasthenia gravis. J. Neurol. Neurosurg. Psychiat. 34:399, 1971.
32. Simpson, J. A. A morphological explanation of the transmission defect in myasthenia gravis. Ann. N. Y. Acad. Sci. 183:241, 1971.

The humoral theory is extremely attractive and the initial reports of Goldstein, et al, were received with enthusiasm. One laboratory (ref 28) confirmed the findings, but subsequently three laboratories have been unable to reproduce the neuromuscular defect, though all have found an immune thymitis. Most telling, perhaps, is that the experiments outlined in reference 31 were carried out with antigens prepared and injected by Dr. S. Whittingham who was the co-author on the original paper reporting the phenomenon. Dr. Simpson, ref 32, states flatly that "in my opinion, the circulating curare like substance is a myth."

It thus must be concluded that the etiology of myasthenia gravis remains an open question. On the basis of available evidence I favor (slightly) a pre-synaptic mechanism and am skeptical of the thymin work. I believe it likely that the end plate changes are secondary. (The role of autoimmunity in myasthenia gravis is considered in more detail in a later section.)

Clinical picture and diagnosis

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Myasthenia gravis is a syndrome characterized by increased muscle weakness upon repetitive use of involved groups which improves with rest and anticholinergic drugs. The most common initiating symptom is diplopia with ptosis, though this is present in less than half the patients at onset. In the full blown picture bulbar symptoms are very common with skeletal

muscles involved to a lesser degree. Of the latter the most frequently attacked are the neck, shoulder and hip girdle muscles. The weakness may be unilateral. An outline of symptoms is presented in the Table 4 (from ref 1).

Incidence of Symptoms

	At Onset	Current Status
Ocular		
Diplopia	43%	73%
Ptosis-Bilateral	27%	59%
Ptosis-Unilateral	40%	25%
Bulbar		
Dysarthria	27%	61%
Dysphagia	23%	63%
Chewing Weakness	16%	52%
Dyspnea	6.5%	33%
Skeletal		
Generalized Weakness	15%	45%
Facial Weakness	8.5%	38%
Neck Weakness	9%	40%
Trunk Weakness	3.5%	14.5%
All Extremities	10%	44%
One or Two Extremities	25%	45%
Atrophy	—	6.3%
Subjective Sensory Symptoms		9%

Table 4

A classification of myasthenia has proven useful in studying the progress of the disease and is given below:

Pediatric group

I. Neonatal: Only in infants born of myasthenic mothers. Self limited to 6 weeks or less.
II. Juvenile: Mother does not have myasthenia. Begins anytime from birth to puberty. Permanent, but tends to be milder than adult onset illness.

Adult

I. Ocular: Localized disease characterized by diplopia and ptosis. If no progress in 2 years after onset usually remains non-progressive.
II. A. Mild generalized: Slow onset, usually beginning with ocular disease and spreading to skeletal muscle. Respiratory muscles spared. Responds well to drugs. Low mortality.
II. B. Moderate generalized: More severe. Bulbar muscles involved, but respiratory muscles spared. Drug therapy less satisfactory. Mortality low.

III. Acute fulminating: Rapid onset, severe bulbar and skeletal muscle weakness with early respiratory involvement. Progression usually complete in 6 months. Drug response poor. Mortality high.

IV. Late severe: Severe disease developing at least 2 years after onset of group I or II symptoms.

Diagnosis of classical cases can be made by history. The primary functional testing is done with Tensilon. The patient's muscle strength is tested subjectively and objectively using the involved muscles (dynamometer, vitalometer, etc.). For muscles of mastication a piece of bubble gum can be used, counting the number of times the piece can be chewed. After a rest period of 5-10 minutes, 2 mg of Tensilon is injected through a previously established intravenous drip and muscle performance is assessed within 30-90 seconds. If no response is obtained the test can be repeated at 3 minute intervals using 5 and then 10 mg doses. Alternating placebo solutions consisting of 20 mg nicotinic acid or 200 mg calcium chloride should be used. If no response is obtained and the disease is still suspected it should be repeated during electromyography. EMG testing, as pointed out by Ozdemir and Young, should be done in at least three muscle groups if at all possible.

The most common simulators of the disease at the Myasthenia Gravis clinic of the Massachusetts General Hospital are listed below:

INCIDENCE OF SYNDROMES SIMULATING MYASTHENIA GRAVIS

	Number of Patients	Per cent
Chronic fatigue	49	37.6
Ocular - Peripheral myopathy	28	21.5
Thyrotoxic - Metabolic	10	7.7
Brain stem	10	7.7
Extrapyramidal	11	8.5
Miscellaneous	22	17.0
Total	130	100

Table 5

Muscle atrophy in myasthenia

39. Fenichel, G. M. Muscle lesions in myasthenia gravis. Ann. N. Y. Acad. Sci. 135:60, 1966.
40. Bergman, R. A., Johns, R. J., and Afifi, A. K. Ultrastructural alterations in muscle from patients with myasthenia gravis and Eaton-Lambert syndrome. Ann. N. Y. Acad. Sci. 183:88, 1971.
41. Brownell, B., Oppenheimer, D. R., and Spalding, J. M. K. Neurogenic muscle atrophy in myasthenia gravis. J. Neurol. Neurosurg. Psych. 35:311, 1972.

Multiple lesions occur, but the basic change appears to be a denervation atrophy. In some areas there is extravagant proliferation of irregular, branching and anastamosing nerve fibers. In addition myopathic lesions can be seen. A specific syndrome of fatty enlargement of the tongue coupled with muscle atrophy has been described. Brownell, et al, interpret the lesion to be primary in muscle. Drachman, on the other hand, has produced strong circumstantial evidence that the muscle

42. Drachman, D. B. Neuromuscular transmission of trophic effects. Ann. N. Y. Acad. Sci. 183:158, 1971.

atrophy may be secondary to a presynaptic lesion wherein a trophic factor ordinarily supplied the muscle is not available; i.e., the nerve ending exhibits a defect in both transmitter and trophic functions. Utilizing the chick embryo as a model (because it does not require muscular movement for respiration) he has chronically administered three different blocking agents, each of which has a different site of action:

Botulinum toxin - blocks acetylcholine release

Curare - blocks acetylcholine access to the postsynaptic receptor

Hemicholinium (HC-3) - blocks choline re-entry into the presynaptic membrane

In every case the chronic administration of the drugs produced massive atrophy of muscle with fat replacement. The nature of the trophic substance is not known, but it could, in fact, be acetylcholine itself.

43. Buller, A. J., Eccles, J. C., and Eccles, R. M. Differentiation of fast and slow muscles in the cat hind limb. J. Physiol. 150:399, 1960.
44. Buller, A. J., Eccles, J. C., and Eccles, R. M. Interactions between motoneurones and muscles in respect of the characteristic speeds of their responses.
45. Close, R. Dynamic properties of fast and slow skeletal muscles of the rat after nerve cross union. J. Physiol. 204:331, 1969.

It has become increasingly clear that the nerve carries information to muscle above and beyond its transmittal and trophic function.

Red muscles are small in size, have high activities of the enzymes of oxidative and lipid metabolism and are used primarily for maintenance of posture. They undergo continuous contraction for long periods and are supplied by nerves with low thresholds for excitation which carry large volumes of traffic. White muscles are larger, derive energy from anaerobic glycolysis, have high concentrations of myosin ATPase and contract rapidly for short intervals. Their nerves have high thresholds but conduct impulses rapidly at high frequency. It has now been shown that implanting a nerve from white to red muscle and vice-versa causes an essential change

in the muscle such that it has characteristics of the muscle from which the nerve came; i.e., the nerve itself causes differentiation of the muscle tissue into an entirely different structural and functional tissue. This mysterious observation is included to emphasize that presynaptic changes exert profound influence on the entire process of neuromuscular function. It would not be surprising, therefore, if the end plate and motor fiber changes seen in myasthenia were secondary to presynaptic disease.

Antibodies in myasthenia gravis

46. Van der Geld, H. W. R., and Strauss, A. J. L. Myasthenia gravis. Immunologic relationship between striated muscle and thymus. Lancet 1:57, 1966.
47. MacKay, I. R., Whittingham, S., Goldstein, G., Currie, T. T., and Hare, W. S. C. Myasthenia gravis: clinical, serological and histological studies in relation to thymectomy. Austr. Ann. Med. 17:1, 1968.
48. Aarli, J. A. Myasthenia gravis: results of serological investigation compared with clinical data. Acta Neurol. Scand. 47:594, 1971.
49. Bundey, S., Doniach, D., and Soothill, J. F. Immunologic studies in patients with juvenile onset myasthenia gravis and in their relatives. Clin. Exper. Immunol. 11:321, 1972.
50. Strauss, A. J. L. Myasthenia gravis, autoimmunity and the thymus. Adv. Int. Med. 14:241, 1968.

It is not uncommon for patients with myasthenia gravis to demonstrate antibodies to striated muscle and to thymic epithelial (myoid) cells. It is important to emphasize that in low dilutions (up to 1:30) essentially all sera demonstrate antibodies to skeletal muscle (normal controls, disease controls, and myasthenia gravis). In 674 disease control patients studied by Strauss, only 1 had a positive titer at a dilution of 1:60 while 99 of 336 myasthenic sera were positive in this dilution or higher (up to 1:1920). Many studies have confirmed that the incidence of muscle antibodies in myasthenia is about 30%. The antibodies tend to localize in the I band of skeletal muscle. It now seems clear that the antibodies are markers of the disease process and not causally related to it. The evidence for this statement can be summarized as follows:

(1) There is no correlation between antibody titer and clinical state; some patients with active disease never have antibodies throughout their course while others always do. In still others, antibodies come and go without relation to clinical activity.
(2) Thymoma patients have a high incidence of muscle antibodies whether or not they have myasthenia gravis.
(3) Neonatal (transient) myasthenia gravis only occurs in babies whose mothers do not have antibodies.
(4) Relatives of patients with myasthenia who do not have the disease have a high incidence of antibodies.

It should be noted that patients with myasthenia have other auto-antibodies demonstrable in high frequency. The data of Bundey, et al (ref 49) are shown.

TABLE 4. Incidence of autoantibodies, among juvenile-onset patients, their relatives, and adult-onset patients

Type of antibody	Juvenile-onset myasthenic patients	Their parents, sibs and half-sibs	Controls	Adult-onset myasthenic patients
Striated/cardiac muscle	$\frac{3}{54}$ (5·6%)‡	$\frac{20}{149}$ (13·4%)	$\frac{4}{106}$ (3·8%)	$\frac{32}{79}$ (40·0%)†
Antinuclear	$\frac{8}{54}$ (14·8%)†‡	$\frac{13}{149}$ (8·7%)	$\frac{13}{366}$ (3·5%)	$\frac{31}{79}$ (39·2%)†
Mitochondrial	$\frac{3}{54}$ (5·6%)	$\frac{6}{149}$ (4·0%)	$\frac{2}{336}$ (0·6%)	$\frac{3}{79}$ (3·8%)
Smooth muscle	$\frac{5}{54}$ (9·2%)	$\frac{18}{149}$ (12·1%)	$\frac{2}{106}$ (1·9%)	$\frac{8}{79}$ (10·1%)
Thyroid	$\frac{24}{54}$ (44·4%)†	$\frac{52}{149}$ (34·9%)†	$\frac{52}{366}$ (14·2%)	$\frac{29}{79}$ (36·7%)†
Gastric parietal cell	$\frac{6}{53}$ (11·3%)†	$\frac{14}{147}$ (9·5%)	$\frac{17}{366}$ (4·6%)	$\frac{17}{79}$ (21·5%)†

† Significantly different from controls, when adjusted for sex, and age at testing (see text); $P<0·01$.

‡ Significantly different from adult-onset patients, when adjusted for sex, and age at testing (see text); $P<0·01$.

Table 6

There is also a tendency for myasthenic patients to have other diseases concommittently. Outstanding here would be the connective tissue diseases, particularly lupus and polymyositis.

51. Johns, T. R., Crowley, W. J., Miller, J. Q., and Campa, J. F. The syndrome of myasthenia and polymyositis with comments on therapy. Ann. N. Y. Acad. Sci. 183:64, 1971.
52. Alarcon-Segovia, D., Galbraith, R. F., Maldonado, J. E., and Howard, F. M., Jr. Systemic lupus erythematosus following thymectomy for myasthenia gravis. Lancet 2:662, 1963.
53. Larsson, O. Thymoma and systemic lupus in the same patient. Lancet 2: 665, 1963.

Genetics of myasthenia

54. Herrman, C., Jr. The familial occurrence of myasthenia gravis. Ann. N. Y. Acad. Sci. 183:334, 1971.
55. Bundey, S. A genetic study of infantile and juvenile myasthenia gravis. J. Neurol. Neurosurg. Psychiat. 35:41, 1972.

Familial occurrence of myasthenia exists more commonly than can be explained by chance, but a genetic mechanism cannot be put forth at present. In one set of monozygotic twins and another set of dizygotic twins, only one twin was affected by the disease.

Treatment with anticholinergic drugs

56. Glaser, G. H. Pharmacologic considerations in the treatment of myasthenia gravis. Adv. Pharmacol. 2:113, 1963.

The use of anticholinergic drugs has been extensively discussed (refs 1 and 56 represent good reviews) and will not be covered here. The critical issue in myasthenic crisis is to decide whether or not a major component of cholinergic overdose is present. Myasthenic crisis usually presents as severe depression of respiration with paralysis of the diaphragm, laryngeal and pharyngeal muscles. Excessive secretions lead to aspiration, atalectasis, and pneumonia. Cholinergic crisis is heralded by GI cramps, excessive sweating, bronchospasm, fasciculations, increasing weakness and central nervous system signs. It must be emphasized that death in myasthenic crisis is due to respiratory failure. The invariant rule, therefore, is to hospitalize the patient, establish an airway with supported respiration, and stop the drugs. A table of the anticholinesterase medications in common use is given.

Approximate Equivalent Doses of Commonly Used Anticholinesterases

Drug	Oral Dose	Intravenous Dose	Intramuscular
Neostigmine (Prostigmin®)	15 mg	0.5 mg	1-1.5 mg
Pyridostigmine (Mestinon®)	60 mg	2.0 mg	2.0 mg
Pyridostigmine Syrup	60 mg./5 ml		
Pyridostigmine (Timespan®)	180 mg		
Pyridostigmine Chloride	50 mg		
Ambenonium (Mytelase)®	5-7.5 mg	none available	none available

Table 7

Contraindicated drugs are:

Quinine	Barbituates
Quinidine	Chlorpromazine
Procaineamide	Meprobamate
Guanethidine	Streptomycin
Kanamycin	Neomycin

Treatment with ACTH and steroids

57. Namba, T. Corticotropin therapy in patients with myasthenia gravis. Electrophysiologic, pharmacologic studies. Arch. Neurol. 26:144, 1972.
58. Namba, T., Brunner, N. G., Shapiro, M. S., and Grob, D. Corticotropin therapy in myasthenia gravis: effects, indications and limitations. Neurology 21:1008, 1971.
59. Engel, W. K., and Warmolts, J. R. Myasthenia gravis: a new hypothesis of the pathogenesis and a new form of treatment. Ann. N. Y. Acad. Sci. 183:72, 1971.
60. Jenkins, R. B. Treatment of myasthenia gravis with prednisone. Lancet 1:765, 1972.

There are no controlled, prospective studies on the use of ACTH or steroids. Proponents of the former indicate that marked to moderate improvement occurs in about half of patients given 100 units of ACTH I.V. daily for 10 days. This has to be done in the hospital since the patients get worse over the first 4-5 days. Improvement is relatively short lived and I see no real reason to recommend this approach. In regard to prednisone, Jenkins reported 3 of 9 patients were able to completely stop anticholinergic drugs on alternate day therapy of 80-100 mgs. Four others dropped their dosage to 1/3 or less of what they had taken previously. Two got worse. Engel and Warmolts (ref 59) are also enthusiastic about steroids. Prednisone therapy is probably worth a trial in severe myasthenia, particularly in preparation for surgery.

Treatment by thymectomy

61. Perlo, V. P., Poskanzer, D. C., Schwab, R. S., Viets, H. R., Osserman, K. E., and Genkins, G. Myasthenia gravis: evaluation of treatment in 1355 patients. Neurology 16:431, 1966.
62. Goldstein, G. Myasthenia gravis and the thymus. Ann. Rev. Med. 22:119, 1971.
63. Thomas, T. V. Thymus and myasthenia gravis. Ann. Thor. Surg. 13:499, 1972.
64. Kark, A. E., and Papatestas, A. E. Some anatomic features of the transcervical approach for thymectomy. Mt. Sinai J. Med. 38:580, 1971.
65. Perlo, V. P., Arnason, B., Poskanzer, D., Castleman, B., Schwab, R. S., Osserman, K. E., Papatestas, A., Alpert, L., and Kark, A. The role of thymectomy in the treatment of myasthenia gravis. Ann. N. Y. Acad. Sci. 183:308, 1971.

It now appears to be widely accepted that thymectomy is the treatment of choice for myasthenia gravis and that it should be done early in the course of the disease. The statistics are shown in the Tables below. Survival percentage in the thymectomized patients was 76% as compared to 57% in the drug treated group.

RESULTS OF TREATMENT (1,355 PATIENTS)

	Living		Dead		Lost		Total	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Drug therapy (including 41 thymomas)	619	57	261	24	199	19	1,079	100
Thymectomy without thymoma	144	76	24	13	20	11	188	100
Thymectomy with thymoma	31	35	57	65	0	0	88	100

Table 8

Morbidity in operated and non-operated patients can be deduced by comparing the status when originally seen and that at the time of last evaluation. The classification has been described earlier in the protocol. The letter A stands for complete remission (no drugs required).

COMPARISON OF INITIAL AND MOST RECENT EXAMINATIONS OF FEMALES WITH MYASTHENIA GRAVIS*

With thymectomy—Last classification

	Total	*A*	*1*	*2A*	*2B*	*3*	*4*
Initial classification							
	122	47	0	62	7	1	5
1	2	50%			50%		
2A	7	71%		29%			
2B	68	38%		54%	6%		2%
3	24	29%		63%	4%	4%	
4	21	38%		38%	5%		19%
	Worse					2%	
	Unchanged					9%	
	Improved					89%	
	Complete remission					(38%)	

Without thymectomy—Last classification

	Total	*A*	*1*	*2A*	*2B*	*3*	*4*
Initial classification							
	348	50	64	165	41	7	21
1	69	6%	83%	10%	1%		
2A	158	23%	3%	67%	4%		3%
2B	80	10%	2%	48%	36%		4%
3	16	6%		31%	19%	44%	
4	25	4%	4%	32%	8%		52%
	Worse					6%	
	Unchanged					62%	
	Improved					32%	
	Complete remission					(14%)	

Table 9

It should be noted that the operated patients were initially more seriously ill with a worse prognosis. Despite this, 38% underwent complete remission and 89% were improved. Note that only 4% of the type 3 patients (fulminant myasthenia) did not improve their status. Only 14% of the drug treated group had remissions with a 32% total improvement. Re-evaluation of the patients in 1971 (not reproduced because the tables were too small - ref 65) indicated that 41% of 225 operated patients had remissions and another 47% were improved in contrast to 17% and 4% respectively in 417 drug treated controls. Males as well as females did well.

Another important point to be noted is that remissions may occur up to 7 years after surgery; i.e., maximum benefit is not always immediate.

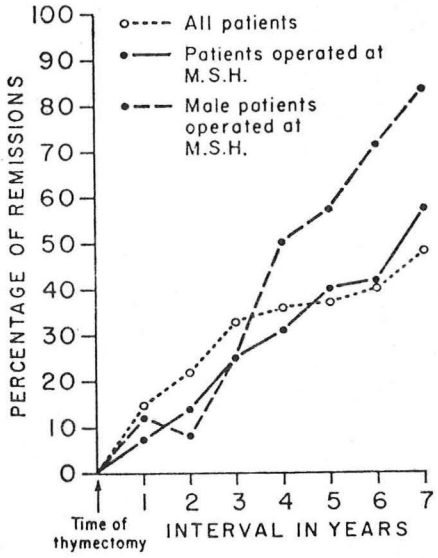

Fig 7

Overall surgical mortality is 2% utilizing a transcervical as opposed to a sternum splitting approach.

Pulumonary function in myasthenia gravis

66. Ringqvist, I., and Ringqvist, T. Respiratory mechanics in untreated myasthenia gravis with special reference to the respiratory forces. Acta Med. Scand. 190:499, 1971.
67. Ringqvist, I., and Ringqvist, T. Changes in respiratory mechanics in myasthenia gravis with therapy. Counteracting effects of anticholinesterase. Acta Med. Scand. 190:509, 1971.

In view of the critical importance of respiratory function in myasthenia, these excellent articles should be noted. Nine patients were compared with healthy controls.

Test	Value	% normal
Lung resistance (cm HOH/1/sec)	2.8	95
Lung compliance (1/cm HOH)	.16	82*
Maximal expiratory pressure (cm HOH)	109	55***
Maximal inspiratory pressure (cm HOH)	86	78***
Vital capacity (liters)	3.55	78**
Functional residual capacity (liters)	2.79	87*
Residual volume (liters(	1.61	98
Total lung capacity (liters)	5.17	84***
$FIV_{1.0}$ (liters)	3.31	85
$FEV_{1.0}$ (liters)	2.92	81
Maximal ventilation (liters)	109	76

* $p < .05$ ** $p < .01$ *** $p < .001$

In addition to muscle weakness the whole thoracic apparatus appears to become stiff, similar to the changes seen in paralyzed polio patients. The authors point out that anticholinergic drugs always make the patient feel better although respiratory function may have gotten worse via increased bronchial resistance. They suggest that ephedrine, known to be beneficial in myasthenia, be given to patients for its bronchodilator effect.