Review

Myasthenia Gravis: A Guide for Anesthesiologists

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MYASTHENIA gravis is a chronic disease characterized by progressive muscle weakness and easy fatigability. It is a relatively rare condition.[132, 198] Because of its rarity many physicians, especially those practicing in smaller communities, may never have the opportunity to diagnose and treat myasthenic patients.

Anesthesiologists may be called upon to assist in or undertake the management of myasthenic patients under various circumstances. One of these is the anesthetic management of myasthenic patients to be operated on either for the removal of the thymus gland or for any other pathological condition requiring a surgical procedure. Planned operations on known myasthenics are usually performed in hospitals where internists, surgeons, and anesthetists alike have ample experience in the management of these patients. In contrast to this, the anesthesiologist may also be confronted unexpectedly with the complex problems of the management of myasthenia gravis. This can occur if the signs of the myasthenia become manifest for the first time during anesthesia [238, 276] or if respiratory emergency develops in a known or undiagnosed myasthenic patient. Consequently, the well-trained anesthesiologist must be sufficiently familiar with the diagnosis and treatment of myasthenia gravis to be able to carry on therapy, unaided, if necessary.

The purpose of this publication is to outline the principles of not only the anesthetic but also the medical management of the myasthenic patient. It is written for anesthesiologists by anesthesiologists who have had the unique opportunity to gain considerable experience in the management of myasthenia gravis patients at the Myasthenia Gravis Clinic of Western Pennsylvania, which has been under their care for over five years. The theoretical aspects of the disease will be outlined only to the extent necessary for the understanding of practical considerations. These will be discussed in sufficient detail to prepare anesthesiologists for any problem in the management of myasthenia gravis that they may encounter in their practice.

To facilitate the reader's task the generic, chemical, and trade names, and when available, the commonly used abbreviations of the anticholinesterases discussed are presented in table 1. The generic name and salt, trade name and abbreviation of all compounds will be given when first mentioned in the text. Subsequently the generic names or abbreviations will be used.

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History

The signs and symptoms of the disease now known as myasthenia gravis were first described by the English physician, Thomas Willis in 1672.[282, 283] Erb in 1879 [61] described accurately the signs and symptoms of the disease in three patients but failed to give it a name. The term "myasthenia gravis pseudoparalytica" was coined by Jolly in 1895 in describing the syndrome in two boys, aged 15 and 14.[121] Laquer and Weigert [135] reported in 1901 the finding of a thymoma at autopsy in a patient who, for two years before death, was known to have myasthenia gravis. The first thymectomy was performed in 1911 by Sauerbruck for the treatment of hyperthyroidism on a patient who also suffered from myasthenia gravis.[221] The operation was followed by marked improvement in the patient's myasthenic condition.

Until 1930, effective drugs were not available for the treatment of myasthenia gravis. In that year, Harriet Edgeworth, herself a

TABLE 1. Anticholinesterases Used in the Treatment of Myasthenia Gravis

Generic Name	Chemical Name	Abbreviation	Trade Name
Neostigmine bromide	dimethyl carbamic ester of 3-hydroxyphenyltrimethylammonium bromide		Prostigmin bromide
Neostigmine methyl sulfate	dimethyl carbamic ester of metahydroxyphenyltrimethylammonium methylsulfate		Prostigmin methyl sulfate
Pyridostigmine bromide	dimethyl carbamic ester of 3-hydroxy-1-methylpyridinium bromide		Mestinon
Ambenonium chloride	N,N'-bis 2-(diethylaminoethyl) oxamide bis-2 chlorobenzyl chloride		Mytelase
Edrophonium chloride	3-hydroxy phenyl-ethyl-dimethyl ammonium chloride		Tensilon
bis-Neostigmine	hexamethylene-bis-(N-methyl-carabaminoyl-m-trimethylammonium phenol)	BC-40	
bis-Pyridostigmine	hexamethylene-bis-(N-methyl-carbaminoyl-1-methyl-3-oxypridium bromide)	BC-51	Hexamarium
Echothiopate iodide	2-diethoxyphosphinylthioethyl-trimethylammonium iodide		Phospholine iodide
	octamethyl pyrophosphoramide	OMPA	
	diisopropylfluorophosphate	DFP	
	tetraethyl pyrophosphate	TEPP	
	isopropyl methyl phosphorofluoridate		Sarin
	hexaethyltetraphosphate	HETP	

myasthenic, discovered that ephedrine sulfate improved muscle function in this condition.[56, 57] In 1934, Mary Walker, noticing the similarity between the signs and symptoms of myasthenic patients and the effects of curare given to laboratory animals, first successfully used eserine salicylate [274] (physostigmine) and soon thereafter, neostigmine bromide,[275] antagonists of the curare-induced neuromuscular block, for the treatment of myasthenia gravis. Remen [205] had already used neostigmine for the treatment of myasthenia gravis in 1932 but "failed to realize fully the importance of the powerful instrument he had in his hand." [269]

Since 1934, in addition to neostigmine, several other anticholinesterases have been used in the treatment of myasthenia gravis. Some of these, similar to neostigmine, are relatively short-acting quaternary ammonium compounds. Others belong to the group of relatively long-acting quaternary ammonium compounds or to the group of the organophosphorus-type, irreversible, long-acting anticholinesterases. In addition to neostigmine two other quaternary ammonium-type anticholinesterases, namely, pyridostigmine bromide (Mestinon) [170, 190] and ambenonium chloride (Mytelase) [226, 229] are now widely used in the treatment of myasthenia gravis. Because of the difficulties encountered in regulating their dosage, the long-acting quaternary ammonium compounds, hexamethylene-bis(N-methylcarbaminoyl-*m*-trimethyl ammonium-phenol) (bisneostigmine: BC 40) and hexamethylene-bis(N-methylcarbaminoyl-1-methyl-3-oxypiridium bromide) (bispyridostigmine:BC 51, Hexamarium) and the long-acting organophosphorus compounds, *e.g.*, diisopropyl fluorophosphate (DFP),[43, 109] tetraethylpyrophosphate (TEPP),[96] hexaethyltetraphosphate (HETP),[281] octamethyl pyrophosphoramide (OMPA),[6, 91, 185, 208, 223] isopropyl methylphosphorofluoridate (Sarin),[93] and 2-diethoxy phosphinylthioethyl trimethylammonium iodide (echothiophate iodide; Phospholine)[187] have not been used widely in the treatment of myasthenia gravis.

In addition to anticholinesterases the therapeutic efficacy of hormones, *e.g.*, adrenocorticotropic hormone (ACTH)[97, 123, 153, 222, 242, 264] and estrogens [178] had been investigated without conclusive results. Of the many adjuvant drugs suggested [175] only ephedrine [56, 57] and potassium chloride [84, 136] have stood the test of time.

In the last two decades surgery and radiation therapy have also been used for the treatment of myasthenia gravis. The surgical procedures recommended include thymectomy,[17] denervation of the carotid sinus,[154, 255] and parathyroidectomy.[4] Of these, only thymectomy has been tried extensively. Reports on relatively large series of cases [54, 94, 126, 237, 272] state widely differing conclusions with regard to the indications and usefulness of this procedure. Opinions also vary regarding the therapeutic efficacy of roentgen-ray irradiation of the thymus first recommended by Kennedy and Moersch.[124]

The introduction of the neostigmine test by

Viets and Schwab in 1935 [271] was a significant improvement in the diagnosis of myasthenia gravis. The edrophonium-chloride (Tensilon) test recommended by Osserman and Kaplan [184] represents a further advance not only in the diagnosis but also in the regulation of the anticholinesterase therapy of myasthenia gravis.

Despite extensive research on the etiology of myasthenia gravis, its cause remains a mystery. At present, all signs point to the neuromuscular junction as the site of the main pathophysiologic defect. Recent studies [104, 165, 166, 238, 246] indicate that immunological processes, more specifically an "auto-immune response of the muscle," [238] may be responsible for the development of the myasthenic syndrome.

The Pathophysiologic Defect in Myasthenia Gravis

There is no known abnormality present in either the central or peripheral nervous system in myasthenia gravis,[95, 150] and the decrease of the contractibility of the myasthenic muscle suggested by Botelho [22] was not substantiated by other investigators.[46] At present, most evidence points to the neuromuscular junction as the probable site of the pathophysiologic defect in myasthenia gravis.

Conceivably, the changes at the neuromuscular junction responsible for the myasthenic syndrome may be morphological, *i.e.*, discernible on microscopic or electron-microscopic examination or submicroscopic, occurring in structures too small for the resolving power of presently available optical instruments, perhaps at a molecular level. Before attempting to assess the significance of the morphologic changes reported at the neuromuscular junction and the variations in the transmission process observed by physiologic and pharmacologic methods in myasthenia gravis, the schematic structure of the normal neuromuscular junction and the present concepts of the physiology of neuromuscular transmission will be reviewed briefly.

The Neuromuscular Junction

The neuromuscular junction (fig. 1) is formed by the close association of the terminal membrane of the nerve fiber and the postjunctional membrane of a specialized part of the muscle fiber called the sole plate. The terminal and postjunctional membranes are separated from each other by a submicroscopic gap called the subneural space. The subneural space is part of the extracellular compartment and, as such, is rich in sodium and chloride ions. The sole plate, which is part of the intracellular compartment, has a high potassium and low sodium content and contains large anions. Because of the unequal distribution of electrolytes on the two sides of the postjunctional membrane in the resting state, this struc-

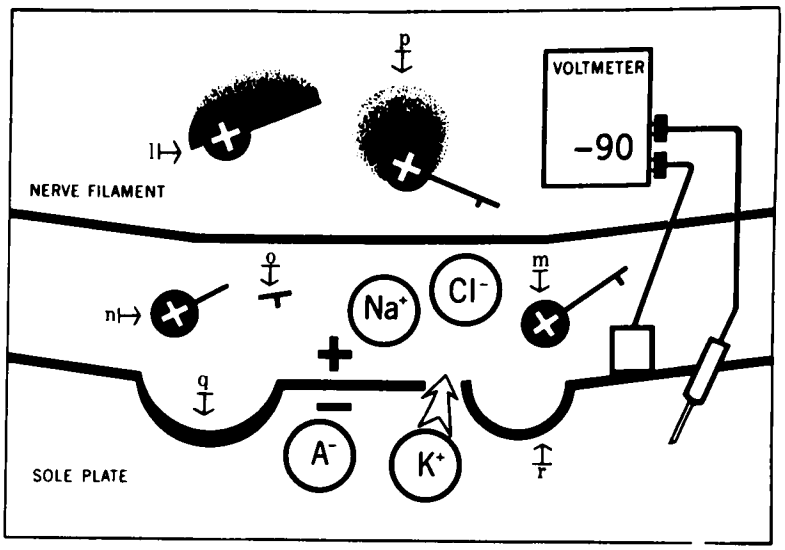

FIG. 1. The schematic representation of the neuromuscular junction with high magnification. l = choline acetylase, m = acetylcholine, n = choline, o = acetate, p = storage protein, q = acetylcholinesterase, r = cholinergic receptor, A^- = large anion, Cl^- = chloride ion, Na^+ = sodium ion, K^+ = potassium ion. Note that there is a potential difference of 90 millivolts between the outer surface and the interior of the muscle fiber.

ture is polarized. There is an electrostatic difference of 90 millivolts between the outer surface of the postjunctional membrane and the interior of the sole plate. This potential difference between the two surfaces of the postjunctional membrane is referred to as "the resting potential of the end-plate."

Neuromuscular Transmission

Neuromuscular transmission is dependent on the activity of the choline–acetylase–acetylcholine–acetycholinesterase system of the neuromuscular junction. The most widely accepted concept of neuromuscular transmission is based on the work of Nachmansohn and his associates [102, 290] and has been discussed in detail elsewhere.[63, 99] According to this hypothesis, acetylcholine synthetized by acetylcholinesterase from acetic acid and choline is kept in an inactive state bound to the "storage protein" in the vicinity of the terminal membrane of the nerve fiber. In the resting nerve small quantities of acetylcholine released cause only minor changes (miniature end-plate potential) in the electrical charge of the postjunctional membrane and are promptly broken down to acetic acid and choline by the acetylcholinesterase present at the neuromuscular junction. When the nerve impulse reaches the neuromuscular junction, some of the relatively large quantities of acetylcholine released become adsorbed to the cholinergic receptors of the postjunctional membrane (fig. 1). Presumably, the receptor protein changes its configuration after its adsorption of acetylcholine. This configuration change is associated with an increased permeability of the postjunctional membrane to sodium and potassium and causes depolarization of this structure. The change in the resting potential of the postjunctional membrane associated with the depolarization process is known as the "end-plate potential." The end-plate potential, as its name implies, is at first limited to the end-plate region of the muscle membrane. After its magnitude has increased 45 millivolts, the end-plate potential spreads to the adjacent parts of the muscle fiber where it causes depolarization. From then on, the end-plate potential loses its identity, fuses with the electrical changes caused in the muscle membrane and participates in the formation of the "action potential" which in turn, after a lag of about 2 milliseconds, initiates muscular contraction. In the meanwhile, the acetylcholine absorbed to the cholinergic receptors shifts to the acetylcholinesterase also present at the neuromuscular junction (fig. 1) and is hydrolyzed to acetic acid and choline. The permeability of the postjunctional membrane returns to its resting state and becomes repolarized. Finally, choline and acetic acid are resynthetized by cholineacetylase to acetylcholine thereby completing the cycle. Interference with either the depolarization or the repolarization phase may cause neuromuscular block.[63]

Morphologic Changes in the Muscle Fiber and at the Neuromuscular Junction in Myasthenia Gravis

Morphologic changes both in the muscle fiber and at the neuromuscular junction have been reported.

Changes in Muscle Fibers. With the exception of occasional early or late atrophy in the involved muscle no gross changes have been described in the skeletal musculature in myasthenia gravis.[150] On microscopic examination, however, the most frequent findings are the presence of 'lymphorrhages"[28] first described by Weigert [278] in 1901, and since observed by others.[141] The lymphorrhages, present in 30 to 50 per cent of myasthenic muscles, are not specific for myasthenia gravis and may also occur in exophthalmic goiter,[51] rheumatoid arthritis,[150] and other conditions. Other pathologic changes, including necrosis and progressive atrophy, were also described by Russell.[220] Although there is some correlation between the histologic changes and the degree of clinical involvement, similar changes were also encountered in muscles of nonmyasthenic subjects.[38]

Mendelow pointed out [150] that the morphologic changes present in the myasthenic muscle may represent the "point of no return," and when present, exclude the almost complete remissions occasionally seen in myasthenia gravis.

Changes at the Neuromuscular Junction. The neuromuscular junction in myasthenia gravis had been studied microscopically with conventional staining methods, the intravital methylene blue staining technique of Coërs [39]

and by electron microscopy.[298] Except for the changes in the muscle fibers already mentioned, no additional information was obtained on the structural changes using conventional histologic methods. In contrast, using the intravital methylene blue method,[39] several investigators [16, 40, 41, 42, 49, 141, 221, 294, 295] reported significant histological changes in the myasthenic end-plate and also in the distal nerve fibers.[141] Coërs and Desmedt [40] described two distinct types of end-plate abnormalities. The first variety is the 'dystrophic end-plate" characterized by abnormally profuse ramification of the terminal nerve fiber, with several expanded arborizations on a single muscle fiber. Such dystrophic end-plates are not pathognomonic of myasthenia gravis and have also been encountered in dystrophia myotonica, myositis,[40] dermatomyositis, and carcinomatous neuropathy.[16] The second variety is the "dysplastic end-plate" [40] characterized by elongation and lack of side branching of the terminal nerve fiber with a concomitant elongation of the sole plate. MacDermott,[141] using the supravital methylene blue staining method, noted, in addition to variations in the size and shape of the motor end-plates and unusual branching of the distal nerve fibers, marked changes in the axons and myelin sheaths of the terminal nerve fibers. She also encountered finely-beaded fibers. MacDermott [141] found some or all of the above abnormalities in all the eight deltoid-muscle specimens obtained from myasthenic patients, although clinical involvement or electromyographic abnormalities of this muscle could only be demonstrated in three patients. In all eight patients; however, the decamethonium [36] and the edrophonium [24] tests were positive. This indicates that morphological changes of the neuromuscular junction may precede clinical involvement in myasthenia gravis.

Electron microscopy was also utilized for the comparison of normal and myasthenic end-plates by Zachs and his associates.[298] These investigators found focal areas of decreased electron density of the sarcolemmal membrane of the secondary synaptic clefts and extensive disorganization of the end-plate structure, characterized by shrunken axon filaments, decreased number and widening of the secondary clefts, and fewer mitochondria in the sole plate area.

Other Morphologic Changes in Myasthenia Gravis

The morphologic changes found in various organs at biopsy and necropsy of myasthenic patients have been summarized.[150, 81] In addition to the findings at the neuromuscular junction and in the skeletal musculature, already discussed, the most significant changes were observed in the myocardium [151] and the thymus, with occasional findings in the pituitary, liver, hemopoetic system, and the thyroid.[81]

Heart. The predominant myocardial lesion in myasthenia gravis is spotty, focal necrosis accompanied by an inflammatory reaction.[81, 151] This change was not seen in any other pathologic condition and may be considered specific for myasthenia gravis.[81] In an analysis of 31 consecutive postmortem examinations of myasthenic patients,[81] of ten, in whom thymoma was found at autopsy, nine had marked pathologic changes in the myocardium. Of the remaining 21 patients without thymoma, moderately severe myocardial changes were found in only four. Because of their disseminated nature the myocardial lesions may be easily missed at autopsy.

Although no pathologic changes were found in the coronaries at subsequent autopsy, alterations in the ST segment and the T wave of the electrocardiographic tracing were observed in myasthenics.[81] It is possible that sudden unexpected death, not infrequently encountered in myasthenic subjects,[219] may be due to those myocardial changes.[150]

Thymus. The relationship between the thymus and myasthenia gravis was first recognized by Weigert [278] in 1901 who reported a case of thymic tumor associated with myasthenia gravis. Since, numerous publications [23, 25, 58, 160, 213, 240] commented on the close association between the presence of thymomas and hyperplastic, noninvoluted thymus glands and myasthenia gravis. In 1949, Castleman and Norris [29] reviewed 330 cases of myasthenia gravis, 97 (29 per cent) of whom had thymoma. In the remainder they found wide variations in the size of the thymus.

These variations, however, fell within the range established for normal thymuses.[104]

Histologically, the thymomas associated with myasthenia gravis are usually characterized by the presence of lymph follicles and collections of specific epithelial cells containing glycogen granules.[81] Depending on the relative preponderance of lymphoid and epithelial elements, three different types of thymomas have been described.[29] In yet another type of thymoma, the predominant histological finding is a fibroblast-like, fusiform spindle cell.[150] This type of tumor is not associated with myasthenia gravis.[81, 150]

The nonneoplastic thymus glands of myasthenic subjects also contain hyperplastic lymphoid follicles and epithelial cells with glycogen granules.[81] These structures, however, are not specific for myasthenia gravis and may also be found in thymuses of nonmyasthenic subjects, particularly in young individuals, Genkins *et al.*[81] believe that the granules are merely indicative of physiologic activity.

Thyroid. Relationship between thyroid disease and myasthenia gravis had been entertained by many investigators.[9, 21, 26, 50, 60, 130, 110, 145, 149, 155, 156, 206, 236, 258, 277] Ringertz found thyroid abnormalities in five of 17 cases of myasthenia gravis.[211] Similarly, at the postmortem examination of 31 myasthenic subjects, significant pathologic change of the thyroid was discovered in eight.[81] The findings included the histologic features of Graves's disease, hyperplasia, micro- and macrofollicular adenomata, fibrosis and atrophy. Genkins *et al.*[81] remarked that the incidence of pathologic changes of the thyroid encountered at autopsy of their 31 cases was higher than would have been expected in a similar number of non-myasthenic subjects.

Bronchogenic Carcinoma. Myasthenic weakness in a patient with bronchogenic carcinoma was first reported by Anderson *et al.*[5] Since then, numerous reports were published on the association of myasthenia and bronchogenic carcinoma.[20, 44, 133, 144, 234] On occasion, the manifestations of myasthenia gravis preceded that of the diagnosis of bronchial carcinoma.[67, 110] In most instances, the myasthenic syndrome was diagnosed during or after surgery. The pathologic lesion associated with this type of myasthenic syndrome is a small-cell bronchogenic carcinoma.[133]

Possible Mechanisms of the Neuromuscular Transmission Defect in Myasthenia Gravis

Theoretically, interference with any phase of normal neuromuscular transmission may be responsible for the muscle weakness and fatigability of myasthenia gravis. In fact, hypotheses, incriminating every phase of the transmission process, were advanced to explain the myasthenic syndrome.

Interference with Acetylcholine Synthesis or Release. This mechanism was first suggested by Torda and Wolff,[259, 260, 261, 262] who observed that serum of myasthenic patients inhibited the *in-vitro* synthesis of acetylcholine by cholineacetylase. Although this observation was not confirmed by others,[95] electrophysiologic studies [45, 46, 47, 48, 49] indicate that deficient synthesis or release of acetylcholine may be responsible for the impairment of neuromuscular transmission in myasthenia gravis. Desmedt [48] found that repeated (12 times), faradic stimulation of the nerve at the rate of 50 per second, for one second, at one-second intervals did not cause an appreciable decrease in the tetanic tension or the voltage of the action potential. When this series of tetanic stimulation was followed after one minute of rest with another one-second period of tetanic stimulation, there was a marked decrease in the response, and after a further rest of two minutes, the intensity of the neuromuscular block was even greater. These findings differ markedly from those obtained when tetanic stimulation was applied to normal muscle in which partial block was produced by depolarizing or nondepolarizing relaxants.[19, 115, 195, 299] In contrast, the pattern of the posttetanic changes of neuromuscular transmission in cat muscles following the administration of hemicholinium, an inhibitor of the synthesis of acetylcholine,[142, 143, 147] was similar to that observed on the muscles of untreated myasthenic patients.[36] Desmedt [49] concluded from his studies that the pathophysiologic defect in the neuromuscular transmission in myasthenic subjects is presynaptic and is probably due to the deficient synthesis or release of acetylcholine from the nerve fiber at the neuromuscular junc-

tion. He entertained the possibilities that either a hemicholinium-like substance is circulating in the myasthenic patient or that the cholineacetylase content of the motor nerve fibers is decreased.

The presynaptic hypothesis of the myasthenic defect of neuromuscular transmission is strongly supported by the findings of Dahlbäch and his associates.[45] These workers studied isolated intercostal muscles obtained by biopsy from normal and myasthenic subjects with intracellular electrodes. From observing the frequency of the spontaneous miniature end-plate potentials, the effect of potassium administration on this process and the amplitude of the end-plate potentials after tetanic stimulation, they also concluded that the defect of neuromuscular transmission in myasthenia gravis is presynaptic and is caused either by the deficient synthesis or release of acetylcholine.

Increased Acetylcholinesterase Activity at the Neuromuscular Junction. Following the discovery of the therapeutic efficiency of anticholinesterases,[274, 275] it was suggested that acetylcholinesterase activity at the neuromuscular junction may be increased in myasthenia gravis. There is no evidence to support this assumption.[172] Histochemical studies of the myasthenic neuromuscular junction [18] revealed no differences in the distribution of acetylcholine between normal and myasthenic subjects. Similarly, no difference was found in the muscle or blood cholinesterase activity of normal and myasthenic subjects.[287]

Circulating Neuromuscular Blocking Agents. The first suggestion of a circulating substance as the cause of impaired neuromuscular transmission in myasthenia gravis was made by Oppenheim [168] in 1901. Since then many investigators studied the effect of myasthenic sera and tissue extracts on neuromuscular transmission.[15] The presence of compounds capable of producing a curare-like nondepolarization block [280] or a depolarization block [66, 114, 167, 248, 285, 288] in the serum or tissues of myasthenic subjects was suggested by several investigators. Recently, Nastuk and his co-workers [166] compared the effects of sera obtained from 22 myasthenic and nine normal subjects on the twitch and tetanus tension of frog sciatic nerve-sartorius preparation with inconclusive results. Using sera obtained from exercised limbs after venous occlusion, Struppler [248] and Windsor [292] demonstrated the presence of a circulating neuromuscular blocking agent in myasthenic subjects. At the present, there is no conclusive evidence either in favor of or against the presence of depolarizing or nondepolarizing neuromuscular blocking agents in myasthenic sera or tissues.

Decreased Sensitivity of Myasthenic End-Plates to Acetylcholine. Decreased sensitivity of the myasthenic end-plate to acetylcholine [1, 27, 59] and other depolarizing substances, *e.g.*, decamethonium [32, 35, 232] or succinylcholine chloride,[87] has been reported. Furthermore, in contrast to normal subjects,[95, 100] the depression of the neuromuscular transmission caused by decamethonium [33] and the late depression caused by acetylcholine [95, 101] can be counteracted by anticholinesterases in myasthenic subjects.

Prolonged exposure of the end-plate of laboratory animals [75, 117, 118, 252, 253, 254] to acetylcholine and other depolarizing substances also decreased their sensitivity to acetylcholine and produced changes similar to those encountered in the myasthenic end-plate.[66] Similar changes could be induced in normal human subjects by the prolonged or repeated administration of depolarizing neuromuscular blocking agents.[73, 74, 75, 196, 202]

Since changes in neuromuscular transmission resembling those encountered in myasthenia gravis may be produced in normal subjects by the prolonged administration of depolarizing agents,[66] it is conceivable that the defect of neuromuscular transmission encountered in myasthenia gravis is caused by the prolonged exposure of the end-plate to a depolarizing agent.[66] This assumption is supported by the isolation of a depolarizing substance gamma-butyrobutaine from the thymus of a myasthenic subject.[114]

The possibility that the increased resistance of the myasthenic neuromuscular junction to depolarization is due to some submicroscopic change in the structure of the receptor protein may also be considered.[66]

Immunological Reactions. Nastuk and his associates observed a marked variation in the serum complement levels of myasthenic subjects.[163, 164, 165] This level remained relatively constant while there was no significant change

in the clinical course, dropped below normal levels when the disease was progressing, and became elevated in periods of improvement. Using an immunofluorescent technique, Strauss and his associates [210] demonstrated in the sera of myasthenic subjects, whose disease was generalized and progressive, and who had associated thymic pathologic changes, an abnormal globulin factor, not present in the sera of normal subjects. By conjugating this globulin fraction with fluorescein isothiocyanate,[147, 209] it was possible to demonstrate that it became fixed to alternate striations of skeletal muscle. The myasthenic globulin fraction also fixed guinea-pig complement to skeletal muscle. Globulin fractions obtained from normal sera did not become fixed to skeletal muscle fibers nor did they fix guinea-pig complement to it.

Nastuk *et al.*[163, 165] entertained the possibility that the complement changes in myasthenia gravis may result from its participation in some auto-immune reaction. Such reactions have also been implicated in the pathogenesis of other diseases.[138, 169, 212] Smithers [241] suggested that the changes observed in the myasthenic thymus were also suggestive of the participation of this organ in some auto-immune process.

According to Nastuk *et al.*,[165] the myasthenic subject develops an antibody against some component of his skeletal muscle. This antibody may become fixed to the muscle membrane and in turn, bind serum complement to this structure. The presence of serum complement may then cause either cytolytic destruction or subcytolitic alterations in the configuration of the muscle membrane. These changes may decrease sensitivity to acetylcholine and cause the defect of neuromuscular transmission characteristic of myasthenia gravis. Depending on the duration and severity of the above reaction, the changes may be reversible or irreversible. The structural changes observed at the neuromuscular junction and in the muscle fibers of myasthenic subjects [40, 49, 141, 220] may correspond to this irreversible phase of an auto-immune reaction.

Simpson [238] also suggested that myasthenia gravis, similar to diffuse lupus erythematosus and dermatomyositis, is an auto-immune disease and could be considered a restricted form of myositis. As a result of an infection or the dysfunction of the thymus, antibodies are formed to the end-plate protein. These antibodies may be adsorbed to the end-plate receptors, block the access of acetylcholine to these structures and thereby inhibit neuromuscular transmission.

The observations that, on one hand, the thymus plays an important role in immunological reactions,[241, 245] and on the other, that it seems to be closely associated with the pathogenesis of myasthenia gravis lend further support to the auto-immune etiology of this condition.

Consideration of the various hypotheses proposed for the explanation of the myasthenic state indicates that the etiology of myasthenia gravis is far from being clarified. Supportive, but not conclusive evidence, has been advanced by various investigators in favor of hypotheses that suggest: (1) deficiency in acetylcholine synthesis or release; [49] (2) desensitization of the end-plate to acetylcholine; [66, 95] or (3) auto-immune mechanisms [165, 238, 246] are responsible for the myasthenic syndrome. It is conceivable that the myasthenic syndrome is not a true entity with a uniform etiology and that any of the suggested mechanisms may cause a defect of neuromuscular transmission clinically manifested as myasthenia gravis. This assumption is supported by the finding that a myasthenic syndrome, associated with bronchial carcinoma, was described,[133] the characteristics of which differed considerably from those of classical myasthenia gravis. It is also possible that the auto-immune hypothesis [165, 238, 246] will prove to be the common denominator which will explain all the functional and morphological changes cited in favor of the various hypotheses of the pathogenesis of myasthenia gravis.

Incidence and Course of Disease

The incidence of myasthenia gravis has been estimated to be between 1 in 15,000 to 1 in 40,000.[53, 79, 132, 198] It occurs twice as frequently and at an earlier age in females than in males.[238] The mean age of onset is about 26 years in females and 31 years in males. Localized ocular myasthenia is more common in males.[95]

Myasthenia gravis is encountered infre-

quently in more than one member of the same family. This would indicate that genetic and environmental factors do not play an important role in its etiology. Recently, however, generalized myasthenia gravis was encountered in an elderly woman and two of her middle-aged daughters.[68] The influence of genetic and epidemiological factors were discussed in detail by Kurland and Alter.[132]

A special form of familial myasthenia is neonatal myasthenia. It may develop within a few hours to a few days after birth in some infants born of myasthenic mothers. The myasthenic state persists for a few days to a few weeks in these babies. There is only one reported case in which myasthenia recurred at the age of 2 years.[182, 183]

The onset of myasthenia gravis is usually slow and insidious. However, on occasion it may follow a fulminating course. The first symptoms often are associated with a respiratory infection or an emotional upset. Most often, the first symptoms are ptosis and weakness of the extra-ocular muscles. The disease usually progresses rapidly in the first few years. After 3 years, it often becomes stationary or continues to progress slowly. If the symptoms remain confined to the eye muscles for more than two years, it is unlikely that the disease will become generalized.[92] Death due to myasthenia gravis occurs most often during the first three years of the disease, especially in the first year. Occasionally, there is a second wave of rapid deterioration. This usually occurs after a severe infection of the respiratory tract, *e.g.*, pneumonia, or after an emotional upset.

Spontaneous remissions lasting more than one month occur in less than 50 per cent of patients. These remissions are encountered most frequently in the first three years of the disease. Beneficial effect from thymectomy can be expected most frequently if it is performed in the first five years of the disease.[238]

The signs and symptoms of myasthenia gravis usually become worse as the day progresses. In about 10 per cent of the patients, however, the weakness may be most severe in the morning and muscle strength improves later in the day.[238] About 10 per cent of all patients, especially those in whom the disease is restricted to the extraocular muscles,[238] may become unresponsive to anticholinesterase therapy.

In about 34 per cent of female patients, the signs and symptoms of myasthenia gravis become worse at the time of the menstrual period.[173] As a rule, the weakness is most pronounced premenstrually, especially if the period is delayed.

The effect of pregnancy on the course of myasthenia gravis is variable.[95] In most patients pregnancy has no effect; in about one-fourth there is improvement which becomes manifest in the first trimester; and in about one-third exacerbation occurs in the first six weeks after delivery or less often during pregnancy.

Signs and Symptoms

The main symptom of myasthenia gravis is weakness involving one or more muscle groups. The weakness becomes more evident on prolonged or repeated use of the muscle.[238] In addition to weakness a variety of signs and symptoms may be present in various combinations.

Depending on the involvement of various muscle groups, ocular, bulbar and generalized types of myasthenia gravis may be distinguished. The incidence of various signs and symptoms in large groups of myasthenic patients has been analyzed by Kennedy and Moersch,[124] Harvey,[108] and Osserman *et al.*[189]

One of the most frequent signs of myasthenia gravis is unilateral or bilateral ptosis. Occasionally the ptosis shifts from one eye to the other. This can occur with patients who do not receive anticholinesterase medication and can also be encountered during anticholinesterase therapy. Not infrequently, when a unilateral ptosis is corrected by an anticholinesterase, ptosis appears in the other eye. Ptosis may be the only evident sign of myasthenia gravis. Systemic examination including the maintenance of contraction against resistance for longer periods may reveal unsuspected weakness or fatigability in muscles other than those apparently involved in the myasthenic processes.[238] In most of patients ptosis is accompanied by diplopia, blurring of vision, or nystagmus. The ocular signs and symptoms are frequently made worse by bright light. Occasionally, pa-

tients report that sunshine causes an increase in the severity of not only ocular, but also other signs and symptoms of myasthenia gravis.[238]

Another frequent sign of myasthenia gravis is the myasthenic facies caused by weakness of the facial muscles. This is also responsible for the "vertical snarl" which develops when myasthenic patients are asked to show their teeth.

Weakness of the jaw muscles may cause difficulty in chewing, becoming more difficult as the meal progresses. In many patients, it makes the consumption of any solid food impossible. Chewing difficulties may be present alone, but more frequently they are accompanied by dysphagia. Not infrequently, the first manifestation of dysphagia is nasal regurgitation of fluids. As dysphagia progresses patients usually learn to ingest fluids, but they have greater difficulty in swallowing solid food. Occasionally, patients have to remove solid food from their mouths with their fingers because they are either unable to swallow or expectorate.

Difficulties of speech are frequently encountered in myasthenic subjects. Myasthenic dysarthria is characterized by a nasal twang. When starting to speak the voice may be relatively clear and easy to understand. As the patient continues to speak, the volume of the voice decreases and its clarity diminishes so that the words become indistinguishable.[228]

Inspiratory distress may be the first recognized sign of myasthenia gravis.[238] Whether the dyspnea is primarily inspiratory or expiratory depends on the muscle groups involved. With diaphragmatic involvement, the dyspnea is inspiratory. When the intercostal and abdominal muscles are affected, the dyspnea is primarily expiratory. In milder cases dyspnea only occurs during exercise. There is a relatively good correlation between the patient's vital capacity and his exercise tolerance. Maximal breathing capacity diminishes out of proportion to the decrease in vital capacity. In severe cases dyspnea may be present even when the patient is at complete rest. Not infrequently, such patients have to be maintained on artificially assisted or controlled ventilation for long periods. A relatively infrequent sign of myasthenia gravis is a triple longitudinal furrowing of the tongue, called the "myasthenic tongue," described by Wilson.[231]

The most frequently involved skeletal muscles are those of the neck, shoulder girdle, and hip. The proximal leg muscles are affected more frequently than the distal ones. The extensors of the upper extremities are more affected than the flexors. There can be marked difference in the strength of the two upper extremities. The degree of involvement of the lower extremities is usually more uniform.

As already mentioned, the muscle performance in myasthenic patients is affected by emotional factors. In patients with severe emotional disturbances it is frequently difficult to assess how much of their fatigue is due to myasthenia gravis and how much is caused by anxiety and depression. This type of muscle weakness was termed "psychiatric fatigue." [228] Placebos and electrophysiologic testing methods are often necessary for the differential diagnosis of this condition.

Early atrophic changes of muscle groups involved in the myasthenic process occur more frequently than formerly believed. Formerly, it was assumed that the atrophy was caused by inactivity. Atrophy, especially that of the quadriceps femoris, may occur as early as six months after the onset of myasthenia gravis.[92, 171, 216]

Sensory changes both in involved or uninvolved muscle groups are frequently present in myasthenia gravis. Patients usually have little pain in the morning, but the pain becomes more severe as the day progresses. Frequently, rest or anticholinesterase medication will give relief. The pain, in part, may be due to the extra effort required to maintain posture with the weak muscles.[238] Lower back pain is most common in myasthenic subjects. This symptom can be so marked that, on occasion, the orthopedist may be the first to see a patient with undiagnosed myasthenia gravis. Another type of common pain is due to the arthritis that often accompanies myasthenia gravis.[250] Other sensory changes encountered are headache, ocular pain, paresthesias of the face, lips, tongue or extremities.[108] According to Osserman,[189] sensory changes have been observed at one time or another in about 14 per cent of their cases.

Pharmacologic Aids in the Diagnosis of Myasthenia Gravis

The diagnosis of a moderately severe or severe case of myasthenia gravis is relatively easy. It is the mild case, either of recent onset or of longer duration, that poses diagnostic problems. In most instances the diagnosis of myasthenia gravis can be made on the basis of history and physical examination alone.[174] The diagnosis then can be confirmed by the use of mechanical aids, *e.g.*, dynamometer or ergograph and various pharmacologic tests.[89, 174, 230, 263] On rare occasions, electromyography is necessary for the final differential diagnosis.[34, 99, 100, 101, 102, 103, 120, 133, 280] Because of his familiarity with the agents used and the possibility of severe respiratory complications associated with their administration, the anesthesiologist is frequently called upon to assist in the pharmacologic testing of myasthenic patients.[218] Consequently, the technique of the various drug tests used in the diagnosis of myasthenia gravis will be discussed.

Anticholinesterases (*e.g.*, neostigmine[271] or edrophonium,[185, 186]), capable of producing an increase in the strength of the myasthenic muscle and nondepolarizing muscle relaxants, *e.g.*, *d*-tubocurarine chloride[10, 11] or gallamine triethiodide,[52] which in small doses will markedly decrease the strength of both the involved and noninvolved muscles of myasthenic subjects have been used to confirm the diagnosis of myasthenia gravis. The depolarizing relaxant decamethonium to which noninvolved myasthenic muscles may be resistant[35] was also recommended[36, 98] as a diagnostic aid.

Neostigmine Test

The use of intramuscular neostigmine for the confirmation of the diagnosis of myasthenia gravis was first recommended by Viets and Schwab in 1935.[271] Neostigmine may also be used intravenously or orally for this purpose.[174] On intramuscular administration, 1 mg. of neostigmine methylsulfate per 100 pounds of body weight is administered together with 0.5 mg. atropine sulfate per 100 pounds of body weight.[95] The simultaneous administration of atropine will prevent the muscarinic side effects of neostigmine, which on occasion may cause severe gastrointestinal symptoms, hypotension, bradycardia, block of conduction, and on rare occasions, even death.[152] Improvement of the strength of the involved muscles begins within five to ten minutes, is maximal in 30 minutes, and lasts one to three hours. Strength of the involved muscles should be tested before and at intervals after the administration of neostigmine. The disadvantage of the method is that if the dose used was too small or too large the test cannot be repeated on the same day. When neostigmine is to be administered intravenously as a diagnostic agent, the patient should be in the supine recumbent position, and an intravenous infusion of 5 per cent dextrose or normal saline should be started; 0.4 to 0.6 mg. atropine should be first administered intravenously. The initial dose of neostigmine should be 0.25 to 0.5 mg., and muscle strength should be tested five minutes later. If there is insufficient improvement, another 0.25 mg. should be injected, and muscle strength tested three minutes later. Fractional doses of neostigmine may then be administered at three-minute intervals until the last dose gives no further improvement or causes deterioration. The advantage of this method is that one is unlikely to administer too large a dose of neostigmine to the myasthenic subject tested and that, from the effect of the test dose that gives optimal results, accurate information can be obtained on anticholinesterase requirements of the patient.

The oral administration of 15 mg. neostigmine is least likely to give useful diagnostic information and is not widely employed.

Edrophonium Test

The edrophonium test for myasthenia gravis was developed by Osserman and Kaplan,[184] who originally recommended the intravenous administration of 10 mg. of edrophonium. Since this dose produced cholinergic symptoms, with less than optimal improvement of muscle power in many myasthenics, they[186] have since recommended the intravenous administration of graded doses of edrophonium, given five minutes apart, starting with a 1 mg. dose gradually increased to 10 mg.

The authors perform the edrophonium test as follows: the patient's muscle strength is assessed by both subjective and objective meth-

FIG. 2. The effect of edrophonium on myasthenic ptosis. *1.* Before edrophonium; 2. twenty seconds after the intravenous administration of 4 mg. edrophonium; 3. three minutes later.

ods, *e.g.*, dynamometer and ergograph, with special attention paid to those muscles involved in the myasthenic process. The vital capacity is measured with a ventilation meter, and chewing and swallowing are observed. After a rest period of four to six minutes, depending on the patient's physical condition, age and weight, 1 to 4 mg. of edrophonium is injected, and within 30 to 90 seconds muscle performance is again assessed. The edrophonium test on a patient with oculo-bulbar myasthenia gravis is illustrated in figure 2. (If it is suspected that the weakness is not myasthenic but is functional or is caused by other muscular or cerebral nervous system diseases, the administration of edrophonium should be preceded by the intravenous injection of a placebo. Either physiologic saline or 0.3 to 0.4 mg. atropine may be used for this purpose.[228]) The edrophonium test has several advantages. It can be repeated within 10 minutes; its effect develops rapidly and wears off quickly so that both the examining physician and the patient have the opportunity to observe repeatedly the effects of anticholinesterase medication. The incidence and severity of muscarinic side reactions is much less than after neostigmine, and, if they do develop, they wear off rapidly.

The edrophonium test may also be used for the determination of the efficacy of the patient's anticholinesterase medication. If the patient is undermedicated, the administration of edrophonium will improve muscle performance (fig. 3). If a patient is adequately medicated there is little or no change; in overmedicated patients the muscle strength decreases after edrophonium.

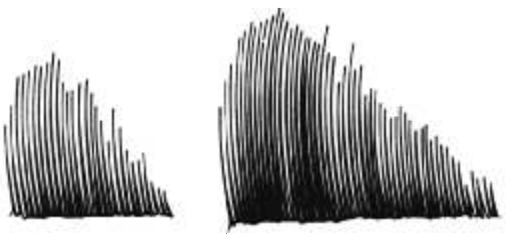

FIG. 3. Evaluation of the patient's anticholinesterase medication with edrophonium. Ergograms: *A.* Ninety minutes after 90 mg. pyridostigmine; *B.* Thirty seconds after 4 mg. edrophonium administered five minutes after *A.*

CURARE TEST

In an occasional patient, with mild generalized myasthenia gravis, the information obtained from the edrophonium or neostigmine test may be equivocal. In these patients further information may be obtained by the use of *d*-tubocurarine [10, 11] or gallamine.[52] The use of curare for this purpose was first recommended by Bennett and Cash [10, 11] and recently re-evaluated by Rowland *et al.*[218] Be-

cause of the well-known sensitivity of myasthenic subjects to even very small doses of *d*-tubocurarine, extreme caution is necessary when this test is employed. Its use should be limited to those cases where definite diagnosis cannot be obtained with the edrophonium and neostigmine test. It is essential that all drugs and equipment necessary for respiratory resuscitation, as well as individuals trained in these methods, be at hand when this test is performed.

The test is carried out as follows: with the patient recumbent, an intravenous infusion is started. Objective and subjective signs of muscular weakness are assessed just as before an edrophonium test. Following this 0.5 to 1.0 ml. of *d*-tubocurarine solution containing 1 mg./ml. is injected intravenously over a 30 second period, and muscle performance is reassessed five minutes later. If a marked change does not occur in the various parameters, another 0.5 to 1.0 mg. is administered and muscle function is again tested three minutes later. Following this, additional 0.5 to 1.0-mg. doses are administered three minutes apart up to a maximal total of 4 mg. If a marked reduction of grip strength or vital capacity does not occur following the administration of 4 mg. of *d*-tubocurarine, it is unlikely that the patient has myasthenia gravis. If less than 4 mg. of *d*-tubocurarine causes a significant decrease of either the grip strength

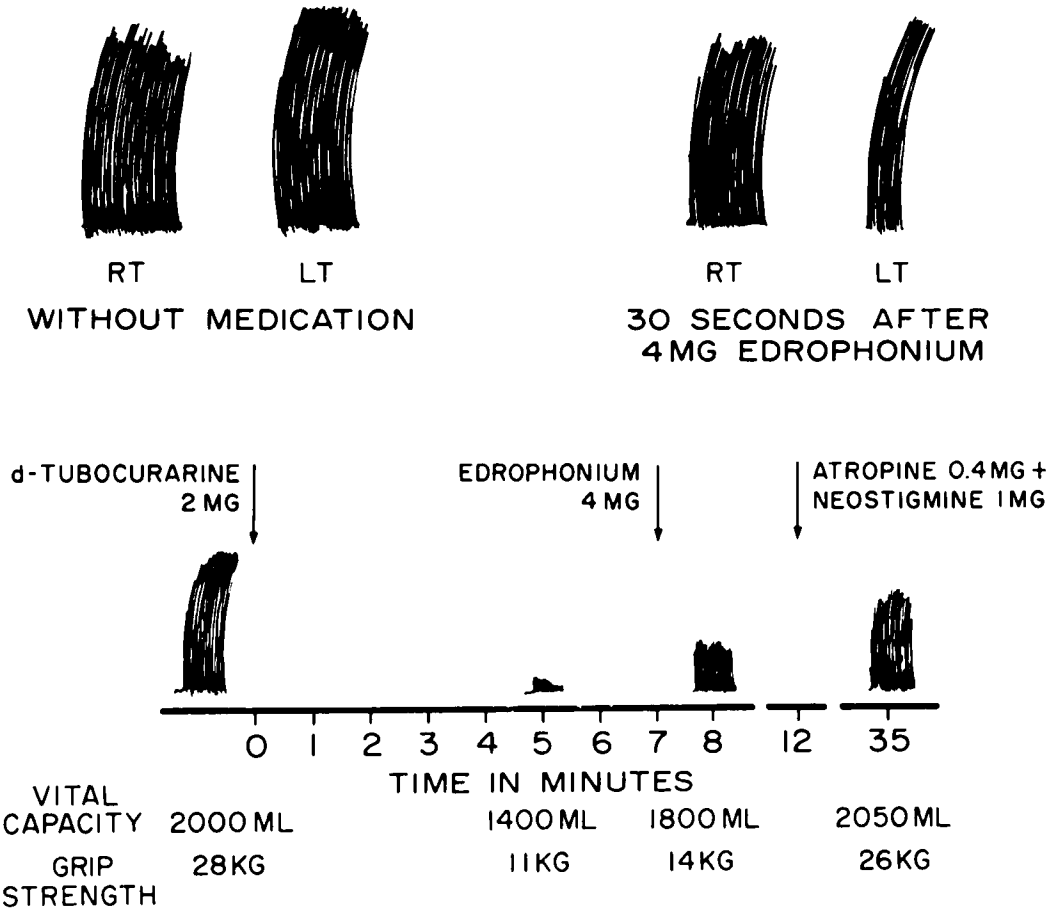

FIG. 4. *d*-Tubocurarine test. Note that edrophonium produced no improvement in the ergogram. The administration of 2 mg. *d*-tubocurarine caused a marked decrease in grip strength and moderate decrease in vital capacity. These changes were partially antagonized by edrophonium and neostigmine.

or vital capacity, the diagnosis of myasthenia gravis is confirmed. After the diagnosis is established, the residual effects of *d*-tubocurarine should be antagonized by intravenous neostigmine administered in 0.5-mg. increments. The first dose should be injected with 0.4 to 0.6 mg. of atropine. The patient may be allowed to leave the clinic after a 30-minute observation period. The diagnosis of myasthenia gravis was established with the curare test in several patients in whom no definite diagnosis could be obtained with the use of the edrophonium test. An illustrative case is presented in figure 4.

Surgical Treatment of Myasthenia Gravis

Anticholinesterases [274] and various adjuvant drugs [56] as well as radiotherapy [124] and surgery [17] have been used in the treatment of myasthenia gravis. Of the various therapeutic measures, at present, drug therapy is by far the most important. Because of the role of the anesthesiologist, however, only the surgical therapy of myasthenia gravis will be discussed.

Surgical Procedures Employed

Surgical procedures recommended for the treatment of myasthenia gravis include thymectomy,[17] denervation of the carotid sinus,[256, 257] and parathyroidectomy.[4] Of these, only thymectomy was performed on relatively large groups of patients.[54, 95, 127, 214, 215, 227]

Thymectomy. Thymectomy for the treatment of myasthenia gravis has been performed on patients with and without thymomas. Data from several large series [54, 55, 125, 214, 215, 227, 238] were recently analyzed.[272] In addition, several authors [15, 95, 113] evaluated their own postoperative results and those of others. Despite this, there is a wide divergence of opinions regarding the indications and results of the surgical removal of the thymus in myasthenia gravis.

(1) *Thymectomy in the Presence of Thymoma:* Because of the relatively poor results of radiation therapy in patients with thymomas, on both the course of myasthenia gravis and survival,[180] it is now generally agreed that thymomas should be removed surgically. In about 25 per cent of the cases, thymomas break through their capsule and may infiltrate the pericardium, large vessels, or the lung.[23, 29, 150] Although distant metastases of thymomas via the lymphatic or vascular system have not been reported, they should be considered malignant.[150]

The removal of thymomas from a myasthenic patient only rarely alters the course of the disease favorably.[157, 237, 238] It was reported that irradiation of the thymus prior to surgery [127] decreased postoperative mortality and improved the effect of surgery on the course of myasthenia gravis. It is of interest that development of myasthenia has been reported after the removal of thymomas in previously asymptomatic subjects.[146, 179, 217]

(2) *Thymectomy in the Absence of Thymomas:* This is perhaps the most controversial aspect of the management of myasthenia gravis. Recent reviewers [95, 179, 237, 272] show varying degrees of enthusiasm for elective thymectomy in myasthenia gravis. The benefits of thymectomy seem to be greater in females than in males, and better results are to be expected in patients under 40 years of age,[272] especially if surgery is performed soon after the onset of the disease.[237, 238] Viets and Schwab [272] reported that significant objective improvement occurred after thymectomy more than twice as frequently in suitably selected patients than in nonoperated controls. The improvement produced by thymectomy seemed to be more persistent than that observed after spontaneous remissions.[272] The beneficial effects of thymectomy may be immediate or may occur as late as three years postoperatively.[238] Thymectomy is often followed by an immediate or delayed decrease in the anticholinesterase requirements of the patient.[180] On the other hand, increased anticholinesterase requirements were also observed in the immediate postoperative period.[180]

More carefully controlled studies are needed before the effects of thymectomy on the course of myasthenia gravis may be fully evaluated. At the present time, thymectomy should be limited to females under 40 years of age, whose disease progresses rapidly right from the onset. In other patients, thymectomy should only be recommended under exceptional circumstances.

Management of the Myasthenic Surgical Patient

Because of the impaired activity of the respiratory system, frequently poor nutritional status, susceptibility to infections, labile emotional status, and altered reaction to many agents used during anesthesia and before and after operation, the anesthetic and surgical management of myasthenic patients presents serious problems. The fate of the myasthenic patient undergoing major surgical procedures depends upon the close cooperation of his physicians and nursing personnel. Every member of the team should have up-to-date information on the presently accepted concepts of the physiopathology and natural history of the disease and be familiar with the pharmacologic effects of drugs used in its management. Previous experience in the care of myasthenic surgical patients is a prerequisite for optimal results. Without this, anticipation and prevention of complications is almost impossible, and their treatment is difficult. The care of these patients should be centralized in relatively few institutions. Such arrangement would eliminate unnecessary multiplication of effort and create the opportunity for a team to gain experience in the surgical care of myasthenic patients.

In the last decade, the care of the myasthenic surgical patient was discussed in several publications.[30, 80, 82, 105, 131, 134, 148, 161, 180, 181, 244] Most of these dealt with the anesthetic and surgical management of patients on whom thymectomy was performed. In the ensuing pages the preparation, anesthetization, and postoperative care of the myasthenic patient undergoing a surgical procedure will be discussed.

Timing of Surgery. Thymectomy and other elective surgical procedures should ideally be performed when the patient is in remission.[30, 131, 148, 161, 180] Failing this, the patient should be hospitalized preoperatively for as long as necessary to get him in the best physical and emotional condition. In women of childbearing age, operation should not be performed before, during, or immediately after the menstrual period.[13, 80, 148] The presence of infection is a contraindication to operation.[148]

Preoperative Preparation. (1) *Physical Examination and Laboratory Tests:* Careful physical examination and laboratory evaluation should be performed on each patient. The physical examination should include determination of vital and maximal breathing capacity and the patient's ability to chew and swallow. The roentgenographic examination of the chest should include tomography.[80] In view of the possibility of degenerative changes of the myocardium,[148, 151] special attention should be paid to the status of the circulation. This should include electrocardiographic examinations.[131, 148] Because of the frequent association of thyroid disease and myasthenia gravis,[9, 21, 50, 60, 62, 130, 145, 149, 156, 211, 258, 277] if hypo- or hyperthyroidism is suspected, the basal metabolic rate should also be determined.

In addition to routine urine analysis and hematologic studies, including evaluation of the bleeding time and clotting mechanisms, blood sugar and urea nitrogen determinations, other laboratory studies should be performed as indicated. In patients with bulbar involvement whose nutritional status is questionable, serum sodium, potassium, and chloride, total protein, albumin-globulin ratio should be measured. In more severe cases, circulating blood volume should also be determined. In the presence of associated thyroid disease, protein-bound iodine and radioactive iodine uptake give useful information. In patients with impaired respiratory function, alveolar P_{CO_2}, arterial oxygen saturation, blood P_{CO_2}, P_{O_2} and *p*H should also be determined.

(2) *Correction of Patient's Physical Status:* Corrective measures should be carried out as indicated by the physical examination and laboratory findings. This includes adjustment of the patient's anticholinesterase medication to be discussed separately. Nutritional deficiencies, dehydration, electrolyte imbalance should be corrected. If the patient is unable to swallow, this can be best accomplished by feeding through a nasogastric tube. Any infection present should be treated by appropriate antibiotics. Thyroid dysfunction should be corrected by the administration of thyroid hormones, *e.g.*, triiodothyronine, or antithyroid drugs, *e.g.*, propylthiouracil. When the patient's cardiac reserve is markedly decreased,

TABLE 2. Equivalent Doses of Commonly Used Anticholinesterases

Drug	Oral Dose (mg.)	Intramuscular or Intravenous Dose (mg.)
Neostigmine (Prostigmin)	15	0.5
Pyridostigmine (Mestinon)	60	2.0
Ambenonium (Mytelase)	6	none available

prophylactic digitalization may be considered.[191] The tracheobronchial tree should be cleared of secretions, if necessary, by bronchoscopy. When the postoperative use of tracheostomy is indicated (see later), this should be performed preoperatively in patients with diminished or absent cough reflex. Patients should be taught to breathe and cough as well as possible within the limits of their disability.

(3) *Preoperative Radiation Therapy:* Irradiation of thymomas with 4,000 r. several weeks before their surgical removal was recommended by Keynes.[126] This procedure decreased operative mortality and also increased the beneficial effects of removal of thymomas on the course of myasthenia gravis.

(4) *Psychologic Preparation:* Emotional instability is often present in myasthenics to an even greater degree than that encountered in other chronic diseases.[80, 131] Because of the influence of emotional factors, *e.g.*, anxiety and fear, on the severity of myasthenic signs and symptoms,[134] special attention must be paid to the psychologic preparation of these patients.

All attending physicians and the nursing personnel should establish a pleasant rapport with the patient. No time should be spared in acquainting the patient with the planned surgical procedure and the steps necessary to prepare for it. He should be frankly appraised of the discomforts he might have to face in the preoperative and postoperative periods. He should be told that the team taking care of him has had ample experience in the management of similar cases. Visits with patients still in the hospital or with those on whom similar surgical procedures were successfully performed is a great morale builder.

The patient should be acquainted with respirators and other special equipment which might have to be used in the preoperative and postoperative periods. If tube feeding or tracheostomy is to be used, the reasons for this should be explained and their temporary nature emphasized. If anticholinesterase medication is to be reduced or withdrawn in the preoperative and postoperative periods,[80] the need for and the consequences of this measure should also be discussed with the patient.

The patient should be reassured that competent members of the house staff, experienced in the management of myasthenia gravis, will be available on round-the-clock basis. All interns and residents who might be called upon to assist in an emergency must be well-acquainted with the patient. Encountering unknown persons, when in difficulties, is upsetting to myasthenics. For the same reason, changes in the nursing personnel should be kept at a minimum.

Continuous, but not overwhelming attention of the immediate family is also essential. The family visits should be timed not to interfere with the patient's schedule. The visitors, as well as the medical and nursing staff, should maintain a cheerful, hopeful attitude.

(5) *Adjustment of Anticholinesterase Therapy:* In the preoperative period, the patient's anticholinesterase therapy should be reduced to the minimum compatible with comfort.[80] If the patient can eat and breathe adequately without anticholinesterases, it might be advisable to omit all anticholinesterase medication. With severe bulbar involvement, it might be necessary to feed the patient through a nasogastric tube to make possible the decrease of the dose of anticholinesterases. Decreasing or omitting the anticholinesterase medication will influence favorably the acetylcholine-insensitive state [95] and decrease the resistance of the patient to anticholinesterases. This makes for an easier adjustment of and response to such medication in the postoperative period.

After major surgical procedures, anticholinesterases have to be administered parenterally. It is, therefore, advisable to test the patient's parenteral anticholinesterase requirements and to maintain him on parenteral therapy for a few days preoperatively. Whenever possible, pyridostigmine bromide (2 mg./ml.);[80] if not available, neostigmine methylsulfate (0.5 mg./ml.) should be used. If the patient was maintained on neostigmine or

ambenonium, the comparable oral dose of pyridostigmine is calculated by multiplying the dose of neostigmine by 4 or that of ambenonium by 10 (table 2). The approximate parenteral dose of anticholinesterases is one thirtieth of the oral dose. Because of the wide variation in the rate and degree of absorption of these agents from the gastrointestinal tract, it is advisable to start with the intramuscular administration of one third to one half of the calculated parenteral dose (one ninetieth to one sixtieth of the oral dose).

Parenteral anticholinesterases may be also administered intravenously.[208] With this method, the parenteral equivalent (one-thirtieth) of the total daily oral dose is dissolved in 2,400 ml. of 5 per cent dextrose in water (or other suitable intravenous fluid) and is administered in continuous intravenous infusion at the rate of 1.5 ml. (about 20 to 30 drops per minute). Theoretically, because of its great flexibility, intravenous infusion should be the method of choice for the parenteral administration of anticholinesterases. In reality, however, the method needs constant attention if over- or undermedication, due to the patient's changing needs or accidental changes of the drip rate is to be avoided. In most instances, satisfactory control may be achieved with the intramuscular administration of anticholinesterases; and the intravenous route should be reserved for the management of emergency situations.

The adjustment of anticholinesterase therapy in patients maintained on long-acting anticholinesterases may present considerable difficulties. Consequently, if time permits, these agents should be discontinued well in advance of the time of contemplated surgery, and the patients gradually transferred to short-acting anticholinesterases. BC drugs [112, 192, 193] should be discontinued at least one week, organophosphorus-type compounds [207] several months before elective operations. Should this be impossible, the administration of the long-acting anticholinesterases should be discontinued as soon as it is known that the patient will undergo surgery. If the patient requires anticholinesterases in the immediate postoperative period, they should be tested very cautiously with the intravenous titration method [175] (fig. 5), starting with minimal doses of pyridostigmine. Pyridostigmine supplementation should be maintained until the patient has recovered

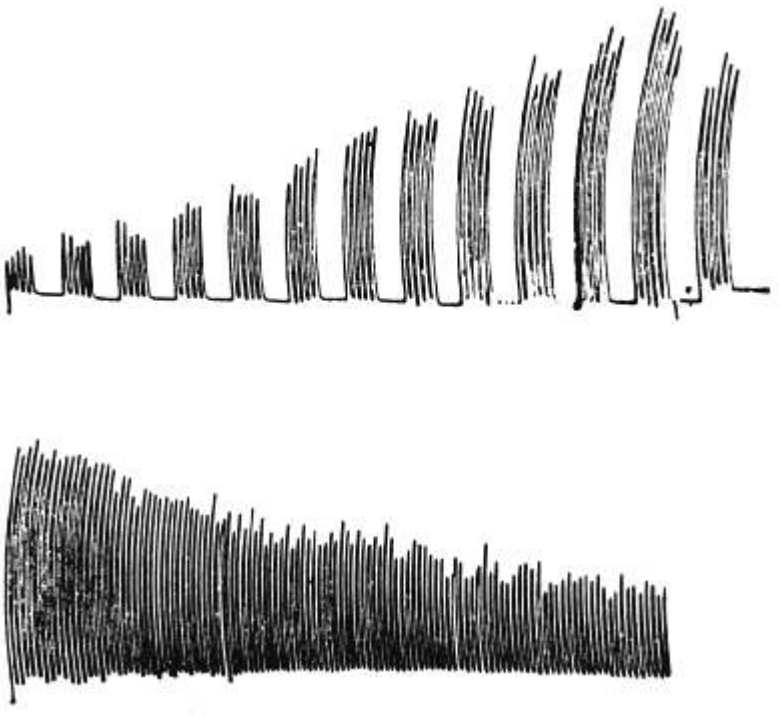

FIG. 5. Intravenous titration with pyridostigmine. Upper tracing: Ergogram before and after 0.5-mg. increments of pyridostigmine. Note that grip strength is greatest after 5.5 mg., decreases after 6.0 mg. Lower tracing: Ergogram five minutes after end of titration. (From Osserman, K. E.: Myasthenia Gravis, New York, Grune & Stratton, 1958, p. 160.)

from surgery, and the required level of the long-acting anticholinesterase is again reached.

(6) *Preparation for Emergency Surgery:* As many as possible of the measures outlined for the preoperative preparation for elective operations should be carried out before emergency operations.[180, 191] The adequacy of anticholinesterase therapy can be checked with the edrophonium test [188] or the intravenous titration method.[175] There should be no hesitancy in performing tracheostomy when indicated. It is also important to start the correction of fluid and electrolyte disturbances, the support of circulation, *e.g.*, preoperative digitalization,[191] and the prophylaxis or treatment of infections as soon as possible.

Choice of Anesthesia. There have been no controlled studies on the advantages and disadvantages of different anesthetic agents in myasthenia gravis. Most publications recommend cyclopropane as the agent of choice [30, 80, 131, 134, 148, 161, 180] and state that ether is contraindicated.[13, 148] Few anesthesiologists, including the authors, have had enough personal experience with myasthenic patients to form a valid opinion regarding the choice of anesthetic agents in myasthenia gravis. Some of the following suggestions are in contradistinction with those of most others. They are, we hope, based on sound pharmacologic principles, and they have been applied successfully on a limited number of patients.

Whenever applicable, local or regional methods should be employed. Because of the effect of high concentrations of local anesthetic agents on neuromuscular transmission,[107] techniques utilizing relatively small quantities of these agents (subarachnoid block) are preferable to those (caudal or lumbar peridural block) where large quantities of local anesthetic agents are necessary. Myasthenics tolerate local and regional methods well, and they are very cooperative if it is explained to them that this choice is in their best interest. An added reason to limit the quantity of ester-type local anesthetic agents is that these compounds are hydrolyzed to pharmacologically inactive breakdown products by the nonspecific cholinesterase of the plasma and liver.[69, 70, 72, 122, 128] This enzyme is markedly, or even completely, inhibited in myasthenics maintained on anticholinesterase therapy.[77, 187] Consequently, the toxicity of hydrolyzable local anesthetic agents will increase significantly in myasthenics.

When general anesthesia is indicated, light thiopental, nitrous oxide-oxygen, halothane-nitrous oxide-oxygen,[119, 297] ether-oxygen, or cyclopropane-oxygen may be used. Because of its parasympathomimetic effect, cyclopropane may cause bronchiolar spasm.[3, 296] In the presence of myocardial lesions described in myasthenia gravis,[81, 150] the danger of arrhythmias may also be increased with cyclopropane. Finally, the administration of cyclopropane contraindicates the use of electrocoagulation, which is a fast and efficient method of hemostasis.

In our experience, after induction with small doses (100 to 200 mg.) of thiopental, nitrous oxide-oxygen, supplemented with small doses of alphaprodine,[235] provides good surgical anesthesia with rapid postoperative recovery. If the patient's slow respiratory rate indicates depression of the respiratory center by the narcotic, this can be effectively antagonized by small doses (1.0 to 1.5 mg.) of levallorphan tartrate (Lorfan).[71]

Because of its curare-like effect at the neuromuscular junction and its irritating effect on the tracheobronchial tree, the use of ether was considered contraindicated in myasthenia gravis.[80, 131, 148] Clinical experience indicates, however, that when used in low, analgesic concentrations, for the supplementation of nitrous oxide-oxygen anesthesia, it can be used safely in myasthenic patients.[148]

The use of neuromuscular blocking agents before endotracheal intubation is seldom necessary in myasthenic subjects.[161] Endotracheal intubation may be easily performed after adequate topical anesthetization of the pharynx and larynx in light planes of general anesthesia without the use of neuromuscular blocking agents. The use of muscle relaxants in myasthenics may be indicated when muscular relaxation is required for the performance of intraperitoneal surgery in patients whose abdominal muscles are not involved in the disease. Despite the almost uniform recommendation against their use [80, 131, 148] small doses of nondepolarizing relaxants can be used for this purpose.[64] It has been shown that while clinically noninvolved muscles of myasthenics

are usually resistant to decamethonium,[34, 35, 232] involved muscles, especially muscles innervated by bulbar nerves,[14] may show increased sensitivity to it. Relatively small doses of decamethonium caused profound and prolonged block in these muscles.[14]

In view of demonstrated resistance of the myasthenic end-plate to acetylcholine [1, 27, 59, 101] and other depolarizing substances,[35, 103] it does not seem logical to try to overcome this resistance and induce neuromuscular block in myasthenics with depolarizing relaxants. In contrast, utilizing the increased sensitivity of both the involved and uninvolved myasthenic muscle to nondepolarizing relaxants,[11, 14, 52, 197] good muscular relaxation can be produced by small doses of *d*-tubocurarine (0.5 to 2.0 mg.) or gallamine (2.5 to 10.0 mg.). The course of the neuromuscular block after small doses of nondepolarizing relaxants is similar to that observed after larger doses in normal subjects. Any residual effect can be readily antagonized by edrophonium [218] or neostigmine.[14] Consequently, we believe the consistent and reliable action of small doses of nondepolarizing relaxants is preferable to the variable effect of depolarizing agents for the production of surgical relaxation in myasthenic subjects.

When relaxation is only necessary to facilitate endotracheal intubation, a single 0.4 to 0.6 mg./kg. dose of succinylcholine may be used. It may be expected that in myasthenic patients on anticholinesterase therapy, because of the inhibition of the hydrolysis of succinylcholine,[83, 265] the duration of its action will be prolonged.[69, 253]

Succinylcholine, however, should not be used for the prolonged maintenance of muscular relaxation in myasthenic subjects. This agent has a considerable inhibitory effect on both true and pseudocholinesterase [76, 293] and when used in large doses is capable of liberating histamine.[194] Succinylcholine also has a direct blocking effect on cardiac synapses.[203] Because of these factors, it may cause bradycardia, heart block,[31, 137] or bronchiolar constriction in normal subjects. Because of the already increased vagal tone caused by anticholinesterase administration, these complications are more likely to occur in myasthenics.

Premedication. The choice of premedication depends upon the anesthetic agents and methods used, on the pathological condition to be corrected by operation, and on the patient's emotional status. For more predictable effect, all drugs used for premedication should be administered intramuscularly.

When the patient is in pain preoperatively, narcotic analgesics, *e.g.*, meperidine hydrochloride (50 to 70 mg.), may be used. Larger doses of narcotics, especially those of morphine which is potentiated by neostigmine [239] and probably by other anticholinesterases, should be avoided.[14, 148] Should central respiratory depression develop after narcotics, this can be antagonized by narcotic antagonists.[71] When the patient is not in pain preoperatively, the dose of narcotics may be decreased or omitted.

In anxious patients or when the operation is to be performed under regional anesthesia, sedation, with the judicious combination of short-acting barbiturates, 50 to 100 mg. pentobarbital (Nembutal) or secobarbital (Seconal), and tranquilizers (25 to 50 mg. promethazine) is advisable.

Opinions regarding the use of atropine and scopolamine in premedication are controversial. Osserman's group [80, 131] considers that these agents may mask the cholinergic effects of an overdose of anticholinesterases and cause thickening of tracheobronchial secretions, and therefore, should not be used. Clinical experience indicates, however, that because of the parasympathomimetic effects of the agents used, when anesthesia is induced by thiopental and maintained with nitrous oxide-oxygen, cyclopropane or halothane, the possible disadvantages of atropine and scopolamine are outweighed by their advantages. With regional anesthesia, atropine or scopolamine may be omitted from the premedication.

Anesthetic Management. When regional anesthesia is employed, the quantity of agents used and the extent of the regional block should be limited to the minimum necessary. Similarly, the depth of general anesthesia should be kept at the lightest level compatible with adequate amnesia and analgesia. Supplementation of general anesthesia with local infiltration of the skin overlying the operative area or with regional nerve blocks will facilitate the surgical procedures in very light planes of general anesthesia. Regional nerve blocks, *e.g.*, paravertebral block with rela-

tively long-lasting agents, are especially advantageous in thoracic and upper-abdominal surgery. With their use postoperative pain may be reduced or absent several days postoperatively, allowing better spontaneous respiration.

With the exception of minor surgical procedures performed on myasthenics who have adequate spontaneous respiratory activity, all patients who are operated on under general anesthesia should have their tracheas intubated. As already mentioned, endotracheal intubation may be readily performed, after topical anesthesia, without the use of muscle relaxants. Endotracheal intubation is essential both for adequate ventilation and the removal of accumulated tracheobronchial secretions. Attempting to provide adequate respiratory exchange with assisted or controlled respiration without a cuffed endotracheal tube may lead to distension of the stomach. When aspirating the trachea and the main bronchi through the endotracheal tube, a soft, number 18 whistle tip suction catheter should be used. To prevent infections, the suction catheter should be sterilized. It should be handled gently to avoid trauma to the sensitive mucosa of the tracheobronchial tree.

If there is reason to believe that the patient's spontaneous respiratory activity or cough mechanism will be inadequate, prophylactic tracheostomy should be performed before removing the endotracheal tube. Elective tracheostomy should be routinely performed on every myasthenic after thymectomy [131, 180] and other intrathoracic operations and after major abdominal surgery in patients who have had respiratory difficulty preoperatively. Since the majority of postoperative deaths in myasthenics are due to respiratory complication,[13, 79, 105, 148 161, 233] indications for tracheostomy should be liberal in the postoperative myasthenic patient.

When the use of muscle relaxants is indicated, in the rare case, to facilitate endotracheal intubation or to obtain relaxation for abdominal surgery, small doses of nondepolarizing relaxants should be used.[64] The initial dose, depending on the severity of myasthenia, should be 0.5 to 1.0 mg. *d*-tubocurarine or 2.5 to 5.0 mg. gallamine. If the desired effect is not obtained within four to five minutes, half the initial dose can be injected repeatedly at two-minute intervals until the desired effect is obtained. In prolonged surgical procedures, the relaxation may be maintained by the administration of one third to one fourth of the dose required for the establishment of muscular relaxation. If the patient is expected to breathe spontaneously postoperatively, any residual neuromuscular effect should be antagonized at the end of surgery by the intravenous administration of neostigmine preceded by or administered together with 0.4 to 0.6 mg. atropine. The initial dose of neostigmine should be 0.5 mg. followed after four to five minutes by increments of 0.25 mg. at two-minute intervals until optimal effect is obtained. Patients who are to be kept on mechanically assisted or controlled respirators postoperatively need no neostigmine to antagonize the residual neuromuscular block.

Postoperative Care. All myasthenic patients should be admitted to the recovery room postoperatively. After minor surgery, if their spontaneous respiration and other vital signs are satisfactory, they may return to the ward as soon as the effect of the regional block has worn off completely or they have regained consciousness after general anesthesia. If respiratory complications develop postoperatively, they should be treated in the intensive therapy unit, similarly to the method to be outlined.

Following thymectomy or other types of major surgery, the most frequent causes of postoperative morbidity and mortality can be related to respiratory [161, 272] or circulatory complications,[150] or to overmedication with anticholinesterases.[161]

(1) *Maintenance of Adequate Respiration:* Adequate oxygenation and removal of carbon dioxide, the prevention and treatment of atelectasis, pneumonitis and pneumonia, and the treatment of pneumothorax and pulmonary collapse are the most important considerations of respiratory management in the postoperative period.

At the termination of surgery, the patient's spontaneous respiration should be checked by a ventilation meter. If pulmonary exchange is inadequate, respiration will have to be supported until the underlying cause is determined and eliminated. This may require as-

sisted or controlled respiration of minutes to weeks duration. The expansion of the lungs should be checked radiologically.[80] If this reveals atelectasis or pulmonary collapse, these should be treated immediately by bronchoscopy or removal of the accumulated air or fluid by aspirating the drainage tube inserted into the pleural cavity. This is especially important in patients in whom thymectomy was performed.[179, 181]

Subsequent management of respiratory problems will depend upon the type of surgery performed, the involvement of the respiratory muscles in the myasthenic state and the quantity and quality of tracheobronchial secretions.

Following thymectomy or other intrathoracic procedures, tracheostomy should be performed before removing the endotracheal tube.[80, 131] Assisted or controlled respiration should be carried out with a 40 per cent oxygen–60 per cent air mixture saturated with water vapor. Accumulated secretions should be removed as required by suctioning through the tracheostomy tube. In the presence of thick, viscous secretions or bronchiolar constriction, detergents (Alevaire or Tergemist)[95] or bronchodilators [131] may be added to the water used for the humidification of the gas mixture. As the patient's condition improves and his spontaneous respiratory activity becomes adequate, the use of the mechanical ventilator can be gradually discontinued. This procedure will be described later in the section on the management of myasthenic emergencies.

Adequate drainage of the pleural cavities and the mediastinum are essential for the proper ventilatory management of these patients. Even when the pleura remained intact during surgery, it should be opened on one side to prevent accumulation of fluid in the mediastinal space.[131] Drainage of the mediastinal cavity should then be performed through a tube traversing the pleural cavity and leaving the chest through an intercostal opening. The distal end of the tube is attached to water seal drain or water seal suction.[131]

Prophylactic tracheostomy is frequently necessary in myasthenics after major extrathoracic surgery. If the respiratory exchange in the postoperative period is adequate, the endotracheal tube may be removed and the patient be allowed to breathe spontaneously. These patients must be observed continuously in the recovery room and for several days thereafter in the intensive care unit. If the accumulation of troublesome secretions requiring repeated bronchoscopy or progressive deterioration of the activity of the respiratory muscles causes inadequate ventilation or threatens pneumonia or pneumonitis, there should be no hesitation to perform tracheostomy and institute the required measures discussed above.

(2) *Support of Circulation:* Morphological changes in the myocardium have been described in myasthenic subjects,[81, 150] and it was suggested that cardiac mechanisms may be responsible for some of the sudden deaths encountered in myasthenic patients.[150] Therefore, careful attention must be paid to the state of circulation in the postoperative period. Circulating blood volume and hemoglobin content should be determined and kept close to the patient's preoperative normal. Both dehydration and hyperhydration must be avoided. In addition to blood and other fluids, essential electrolytes must be administered as indicated by the determination of the patient's serum sodium, potassium and chloride levels. Large quantities of blood, fluids and electrolytes may be lost through chest drainage.

(3) *Postoperative Pain Relief:* After intrathoracic and upper abdominal survery, pain frequently interferes with adequate respiratory exchange. To eliminate this, patients must be kept as pain-free and comfortable as possible.[80, 105, 134] Any of the commonly used narcotics may be employed for this purpose.

It should be remembered that morphine [239] and probably other narcotics as well are potentiated by anticholinesterases. Patients receiving these agents should, at first, be given a smaller dose of a narcotic, increasing the dose gradually as required. Patients maintained on mechanical ventilators may receive the usual doses of narcotics. Light nitrous oxide-oxygen anesthesia has also been recommended [105] for the production of analgesia and restful sleep during the first eight postoperative hours for these patients.

If pain is accompanied by anxiety and restlessness, smaller doses of narcotics may be administered together with 12.5 to 25.0 mg. chlorpromazine (Thorazine). Most other

tranquilizers [108] and barbiturates [159] antagonize the analgesic effect of narcotics.

(4) *Postoperative Use of Anticholinesterases:* The effects of major surgery on the patient's anticholinesterase requirements are variable.[105] Both increased [30, 148] and decreased [80, 88, 131] need for anticholinesterases has been reported. Following thymectomy, most patients have a short-lasting (18 to 48 hours) remission.[80, 131, 266] The administration of the preoperative anticholinesterase doses may cause cholinergic crisis [80, 131, 180] in these patients. The muscarinic effect of these compounds may also cause accumulation of troublesome tracheobronchial secretions.

The aim of postoperative anticholinesterase therapy should be the maintenance of adequate respiratory exchange. The attainment of optimal muscle strength in the bedridden patient is unimportant.[131] As long as the patient is capable of adequate spontaneous respiration without drugs or the use of mechanical ventilators is indicated for other reasons, anticholinesterases are not administered. When the maintenance of satisfactory spontaneous respiration cannot be achieved without anticholinesterases, and the edrophonium test [186] indicates that the patient is not in an anticholinesterase refractory state, the anticholinesterase requirements should be determined with the intravenous titration method with pyridostigmine.[175] The minimal requirements necessary for the maintenance of respiration should then be administered intramuscularly.

As the patient resumes oral feeding, the parenteral administration of anticholinesterases may be discontinued. When the patient becomes ambulatory, the oral medication is adjusted to obtain optimal strength.

Withholding anticholinesterases for as long as possible postoperatively will not only help in preventing cholinergic crisis, but in many patients, will improve the response to subsequent administration of these agents.

(5) *Other Considerations:* Support of the patient's morale during the postoperative period cannot be overemphasized. Although the use of intermittent-positive-pressure or positive-negative-pressure respirators instead of the tank-type respirator makes nursing care easier and patients more comfortable, the postoperative period is still associated with considerable difficulties. How the patient will face up to these depends a great deal on the preoperative and postoperative psychologic care. It is important that the patient be able to communicate with his surroundings. If he has a tracheostomy, but able to use his hands, a writing pad and pencil should be within easy reach. If he is unable to write, his wishes and requirements should be anticipated. Postoperative myasthenic patients dread to be left alone even for brief periods. Similarly, they are distrustful of any individual with whom they are not acquainted.

Obstetric Management of Myasthenic Patients

The modal age of the onset of myasthenia gravis in females is about 20 years.[238] Consequently, pregnancies occur not infrequently in myasthenics in whom the disease developed after marriage or who married after the onset of the disease. Since pregnancy influences the course of myasthenia gravis, and the drugs used for its treatment may influence gestation, the obstetrical management of myasthenic patients merits special consideration.

The Influence of Pregnancy and the Course of Myasthenia Gravis

The influence of pregnancy on the course of myasthenia gravis is variable.[78, 106, 238, 273, 284] No change, spontaneous remissions, or exacerbations may occur with about the same frequency.[129, 181] Exacerbations usually occur in the first trimester [78, 129, 238] or in the postpartum period.[78, 129, 238] Myasthenia may become manifest late in the first trimester or in the postpartum period.[181] Spontaneous abortions are encountered more frequently in myasthenics than in the general population.[181] Spontaneous abortion is usually followed by improvement of the myasthenic condition, but artificial abortion has no beneficial effect.[181] Consequently, the termination of pregnancy in myasthenia gravis is not indicated.[181] As a rule, delivery poses no unusual obstetric problems, and the indications for elective or emergency cesarean section should be determined on the basis of obstetric considerations.[181]

Effect of Anticholinesterases on Gestation

Despite its sensitivity to acetylcholine, the uterus is relatively little effected by neostigmine and other anticholinesterases. This is probably due to the fact that there is no continuous release of acetylcholine in the uterus,[85] and the administration of an anticholinesterase will not significantly increase the acetylcholine level in this organ. Neostigmine may initiate menstruation when its delay is not caused by pregnancy. This was utilized both as a therapeutic measure for the initiation of delayed menstruation and a test to exclude early pregnancy.[243] The effect of anticholinesterases on the pregnant uterus increases near term, and at this time their intravenous use may cause premature labor.

Since in myasthenia gravis, there is an increased tendency for spontaneous abortion,[181] and edrophonium in addition to its anticholinesterase effect may also have a direct effect at cholinergic receptor sites,[86, 210] the edrophonium test should be used with great caution (small doses) and only when absolutely necessary during pregnancy.

Management of the Gestation Period

As a rule, management of myasthenics during the gestation period poses no unusual problems. Interference with respiratory exchange caused by the pressure of the enlarged uterus on the diaphragm may cause problems in the third trimester. The respiratory embarrassment is usually the greatest in the seventh and eighth months and becomes less when the head descends into the pelvis.

Management of Labor

Narcotic analgesics in combination with barbiturates and scopolamine may be used for pain relief during labor. Repeated small doses of short-acting narcotics, *e.g.*, meperidine (50 mg.) or alphaprodine (20 mg.), are preferable to longer-acting drugs, such as, morphine. Since the analgesic effect of these compounds similarly to that of morphine [239] may be potentiated by anticholinesterases, the initial dose of narcotics should be small. If larger doses of narcotics are necessary, these may be administered together with 0.5 to 1.0 mg. of levallorphan.[8]

Pregnant myasthenics as a rule are very cooperative and insist on amnesia less frequently than other patients. Consequently, scopolamine, barbiturates and tranquilizers are needed infrequently.

During labor the intramuscular equivalent of the patient's oral dose (table 2) should be used. Depending on when the last dose of anticholinesterases was administered, a full or fractional dose should be injected 15 to 30 minutes before the expected time of delivery to assure optimal muscle strength and to protect the baby from neonatal myasthenia.[181]

Anesthetic Management

In our experience the anesthesia of choice for normal vaginal delivery in myasthenics is low subarachnoid block. When subarachnoid block is contraindicated, nitrous oxide-oxygen supplemented with local infiltration of the site of episiotomy may be used.

Except in cases of neonatal myasthenia (to be discussed), the care of the newborn is the same as usual.

For elective cesarean section, the anesthesia of choice is again subarachnoid block, the level of which should not progress beyond the eighth or seventh dorsal dermatome. To avoid the need for deep ether or halothane anesthesia, elective cesarean section is prefrable to version.

Postpartum Care

As a rule, the postpartum management of myasthenics poses no unusual obstetric problems. In 28 deliveries, uterine inertia, that was corrected by the intravenous infusion of a diluted pitocin solution, only occurred once.[181]

The patient's course should be closely watched not only in the immediate postpartum periods but also for several months thereafter. Exacerbations may occur within a few days to several months after delivery.

Neonatal and Congenital Myasthenia

Occasionally infants born to myasthenic mothers may manifest signs and symptoms of myasthenia gravis. The muscular involvement is usually symmetrical and it effects predominantly the muscles innervated by bulbar nerves.[249] Extraocular muscles are rarely involved. The infants are usually limp, motionless, and their face is expressionless. Crying

is feeble or voiceless, they are unable to suck and may have breathing and swallowing difficulties.[182] If undiagnosed, these infants usually die from respiratory failure, atelectasis, or aspiration pneumonia.

The incidence of neonatal myasthenia is variable. The first case of neonatal myasthenia was reported in 1942.[247] In 1956, Teng and Osserman [249] reviewed 209 cases reported in the literature. In a series of 36 deliveries of myasthenic mothers, only three cases of neonatal myasthenia were observed.[270] In another group of seven deliveries, one infant was affected.[78] In Osserman's series [181] out of 28 live infants born to myasthenics, six had neonatal myasthenia. In three of these, probably because of protective effects of anticholinesterases administered to the mothers immediately before delivery, the condition only became manifest a few days after birth.[182] In our material, four myasthenic mothers had five pregnancies. One mother delivered stillborn infants on two occasions. Of the three live infants, one had neonatal myasthenia. The mother of this baby experienced a severe exacerbation postpartum and died ten months after delivery. Her course was complicated by anorexia and other manifestations of postpartum pituitary insufficiency.

The diagnosis of neonatal myasthenia is not difficult. If doubtful, it may be confirmed with the intramuscular injection of 0.5 to 1.0 mg. edrophonium.[249] Treatment should be aimed at the production of adequate spontaneous respiration and deglutition without attempting to improve the tone of the muscle of the extremities. It is better to undertreat than to overtreat. If the dose that produces adequate respiratory response is not enough to ensure deglutition, instead of increasing the dose, it is preferable to institute feeding through a nasogastric tube. Because of uncertainities of absorption, the intramuscular route of anticholinesterase administration is preferable to the oral one. The usual intramuscular dose of neostigmine is 0.05 to 0.1 mg. and that of pyridostigmine 0.1 to 0.4 mg. Whenever available, pyridostigmine is preferable to neostigmine. Smaller doses should be tried first, gradually increasing the dose as required. Depending on the frequency of feedings and the duration of action of pyridostigmine, a dose should be administered 10 to 15 minutes before each or every other feeding. A usually satisfactory schedule is to feed every four hours and precede each feeding with a dose of anticholinesterase.

Neonatal myasthenia may last from a few days to a few weeks. When improving strength between two anticholinesterase doses indicates improvement, discontinuation or decreasing the dose should be attempted. It is especially important in this transition period to prevent aspiration of food and treat promptly should it occur.

Neonatal myasthenia can be differentiated from congenital myasthenia which may occur in infants born to nonmyasthenic mothers.[90, 139] Osserman [249] encountered six congenital cases in his large clinical material. Recently, a case was described [90] which exhibited features of both neonatal, inasmuch as it was transient, and congenital myasthenia, inasmuch as it occurred in an infant born to a nonmyasthenic mother. The signs and symptoms in congenital myasthenia are similar to those encountered in adults except that the involvement has a tendency to be symmetrical.[249] The symptoms persist after birth and the course of the disease is similar to that in adults. The prognosis, however, in juvenile myasthenics is better than in the adults.

Management of Myasthenic Emergencies

The underlying mechanism of myasthenic emergencies may vary, but whatever their cause, when untreated, their end result is usually respiratory failure. The first and most important factor in their management is the prompt institution of adequate respiratory exchange. This will keep the patient alive until the nature of the emergency can be diagnosed and treated. In this phase, the services of the anesthesiologist become indispensable. It is not enough that he himself be available for this purpose but it is equally important that he should assume the responsibility in instructing his colleagues and all members of the house staff in simple, efficient methods of respiratory and circulatory resuscitation.

Depending on their pathophysiologic basis, three types of myasthenic emergencies may be distriguished. The first one commonly known as 'myasthenic crisis" is characterized by the

sudden increase in the severity of the myasthenic symptoms resulting in paralysis of the respiratory, laryngeal or pharyngeal muscles, or the obstruction of the tracheobronchial tree by secretions which the patient cannot expectorate. Myasthenic crisis may develop in diagnosed cases under treatment with anticholinesterases, or it may be precipitated in undiagnosed cases [111] by drugs, such as, quinidine, nondepolarizing relaxants,[251, 276] ether, infections or emotional upsets. In patients under treatment with anticholinesterases the myasthenic crisis usually develops gradually. The strength of the involved muscle groups becomes progressively less, and hitherto unaffected muscle groups, *e.g.*, respiratory muscles, may become involved, and respiratory failure develops.

The second type of myasthenic emergency, termed "cholinergic cris," [289] is caused by the nicotinic blocking action of excessive anticholinesterase medication on neuromuscular transmission. Overdosage occurs most frequently in patients unsatisfied with the improvement brought about by their prescribed dose of anticholinesterase and arbitrarily keep increasing its dose. The cumulative effect of long-lasting quaternary ammonium-type anticholinesterases,[95, 175] or organophosphorous-type anticholinesterases, *e.g.*, TEPP,[96] HETP and OMPA,[175, 223] may also cause cholinergic crisis. Finally, cholinergic crisis may develop when the dose of a short-acting anticholinesterase, especially that of ambenonium [111] is increased in an attempt to control increasing muscular weakness in a deteriorating patient. In any of these situations, the danger of undetected development of cholinergic crisis is increased when the muscarinic side effects of overmedication are masked by the simultaneous use of atropine.[225]

The third type of emergency is a less clear cut entity which is caused by the insensitivity of the neuromuscular junction to acetylcholine.[95] It has been reported that prolonged exposure of the end-plate to acetylcholine [252] and other depolarizing agents [253, 254] changes its sensitivity to the depolarizing effects of acetylcholine. Decreased sensitivity to depolarizing influences after the prolonged administration of depolarizing relaxants has also been observed in man.[66, 74, 253, 254] Similar insensitivity to acetylcholine may develop in deteriorating patients treated with increasing doses of anticholinesterases for prolonged periods. This acetylcholine-insensitive state may simulate myasthenic crisis or be associated with cholinergic crisis. It can only be diagnosed from the effects of therapeutic trials with edrophonium, other anticholinesterases or oximes.[95]

Myasthenic emergencies are more likely to occur in patients with advanced bulbar involvement where malnutrition, dehydration and electrolyte imbalance, especially hypokalemia, may aggravate the myasthenic defect.[111]

Maintenance of Respiration

Restoration of adequate respiratory exchange is the first and most important task in the management of myasthenic emergencies. Only when the patient is being adequately ventilated can attention be focused on differential diagnosis and specific drug therapy.

During respiratory resuscitation, special attention should be paid to the patency of the airway. Endotracheal intubation with a cuffed tube should be performed immediately. As soon as this has been performed, the tracheobronchial tree should be cleared of accumulated secretions by a suction catheter. If secretions cannot be satisfactorily removed with this method, as soon as conditions permit, the bronchoscope should be used.

Following intubation, controlled respiration should be maintained. If the spontaneous tidal volume is satisfactory (more than 300 ml.), indicating that the respiratory depression was due to respiratory obstruction caused by the weakness of the muscles of the pharynx, larynx, jaw or tongue, or to accumulated tracheobronchial secretions or aspirated food, the patient should be allowed to continue to breathe spontaneously through the endotracheal tube. If the tidal volume is inadequate, and the weakness of the respiratory muscles cannot be eliminated within a relatively short period with appropriate drug therapy, the endotracheal tube should be attached to a respirator. Respirators capable of either assisting or controlling respiration are preferable. The sensitivity of the assisting device should be so regulated that the patient's spontaneous

respiration can trigger it. Most patients who are capable of moving as little as 50 ml. of air tolerate assisted respiration at their own rate and rhythm better than controlled respiration.

Unless there is reason to believe that the myasthenic emergency can be rapidly terminated by drug therapy, and the patient will be able to resume spontaneous respiratory activity within a few hours, tracheostomy should be performed. The endotracheal tube should not be allowed to stay in place for longer than 24 hours otherwise laryngeal edema or pressure necrosis of the mucous membrane of the larynx may occur. This will not only necessitate tracheostomy at a time when the patient is otherwise recovering, but may also cause permanent damage to the larynx. Conscious patients are more comfortable with a tracheostomy tube than with an endotracheal tube, and tracheobronchial secretions can be removed more easily through the former.

With the improvement of the patient's condition, the respirator may be disconnected for progressively longer periods. Occasionally patients who have been kept on a respirator for a long time are psychologically reluctant to part with it.[131] Recovery from myasthenic emergencies and even remission has occurred after continuous respirator care of several months duration.[94]

Drug Therapy

Drug therapy in myasthenic emergencies is directed towards the control of muscarinic side effects, the improvement of muscle strength, and the prevention of infections of the respiratory tract. It is advisable to maintain a slow intravenous infusion of 5 per cent dextrose in water and to administer all drugs, with the exception of antibiotics, intravenously through the rubber sleeve of the intravenous tubing.

Depending on the severity of muscarinic side effects, the first intravenous dose of atropine can vary from 0.4 to 1.0 mg. Subsequent 0.3 to 0.4-mg. doses may be administered as required three to five minutes apart until the desired effect is obtained. Subsequently, the muscarinic effects may be controlled by the intravenous or intramuscular administration of 0.4 to 0.6-mg. doses. It is advisable to clear the tracheobronchial tree of accumulated secretions before administering large doses of atropine. Atropine may cause inspissation of secretions, making their removal by suctioning difficult. The mucous plugs formed may lead to atelectasis requiring bronchoscopy. Occasionally, very large doses of atropine are necessary for the control of muscarinic side effects.[95, 186]

When the endophonium test [177] indicates myasthenic crisis caused by undermedication, the cautious intravenous administration of neostigmine or pyridostigmine can be tried. Even in the absence of muscarinic side effects, the administration of these agents should be preceded by the intravenous injection of 0.4 to 0.6 mg. atropine. Neostigmine (0.15 mg./ml.) or pyridostigmine (0.6 mg./ml.) should be administered in small increments three to five minutes apart as described in the section dealing with the intravenous titration method.[176] The first dose of neostigmine should be 0.3 mg. and that of pyridostigmine 1.2 mg. Fractional doses should be half of the initial dose. After determining the optimal intravenous dose, the anticholinesterase requirements may be satisfied by the intramuscular administration of somewhat larger doses. With pyridostigmine, the intramuscular dose should be 150 per cent, with neostigmine, 200 per cent of the optimal intravenous dose.

If the edrophonium [177] or the PAM [95] test indicates cholinergic crisis, recovery may be hastened by the intravenous administration of PAM. Following the injection of the initial 500-mg. dose of PAM, fractional doses of 200 to 300 mg. may be administered three to five minutes apart until no further improvement is noticeable. Pushing the administration of PAM beyond this point may convert a cholinergic into a myasthenic crisis.[95, 111]

When the edrophonium [177] and PAM [95] tests indicate that the myasthenic emergency is due to overmedication with anticholinesterases (cholinergic crisis) or to the acetylcholine insensitive state,[95] all anticholinesterase medication should be withdrawn, if necessary, for several days, until marked improvement after a dose of edrophonium indicates that the effects of anticholinesterases overdosage have terminated or that the sensitivity of the end-plate to acetylcholine has been re-established. With the improved

methods now available for the maintenance of respiratory exchange (tracheostomy, intermittent-positive pressure or positive-negative pressure respirators attached directly to cuffed tracheostomy tube, etc.), the management of these patients presents no major difficulties.

Increasing resistance to the depolarizing effects of acetylcholine might be provoked by the continuous exposure to anticholinesterases. These agents may maintain an abnormally high acetylcholine concentration at the end-plate and, in addition, may have a direct depolarizing action of their own.[210, 279] This mechanism may partly or wholly be responsible also for the development of myasthenic crisis. The gradually increasing resistance to acetylcholine necessitates the use of higher and higher doses of anticholinesterases. This, in turn, further decreases sensitivity to acetylcholine. The vicious circle created may lead to crisis. This difficulty may be overcome by the complete withdrawal of anticholinesterases while the patient is maintained on artificial respiration. This approach to the treatment of myasthenic crisis was first recommended by Randt.[204] Churchill-Davidson and Richardson [37] went a step further and used complete "rest" of the end-plate by protecting it from the effects of endogenous acetylcholine by the prolonged administration of *d*-tubocurarine. They obtained excellent results, with remission in one patient. Others, however, were not as successful.[267] Grob [95] favors, instead of complete withdrawal, marked reduction of anticholinesterase medication while the patient is on respirator care. Because of the decreased sensitivity of the myasthenic end-plate to acetylcholine [98] and the increasing resistance of the end-plate to depolarization after the prolonged administration of depolarizing compounds,[66, 74] the problem of restoring the sensitivity of myasthenic patient to anticholinesterases by withholding these drugs for prolonged periods warrants further investigation. This form of therapy might also be successful in patients without respiratory involvement, who develop increasing resistance to anticholinesterases, but who can be maintained in bed on spontaneous respiration.

Recovery of the impaired neuromuscular function may be facilitated with the intravenous administration of potassium.[94, 95] This is especially important in patients maintained on intravenous therapy who should receive 40 to 60 mEq. (3.0 to 4.5 Gm.) of potassium chloride daily. When nasogastric feeding is instituted with a well-balanced diet, the intravenous potassium chloride can be discontinued.

Because of inability to cough up accumulated secretions, myasthenics in crisis are susceptible to pneumonia, pneumonitis, and other infections of the respiratory tract. Antibiotics, *e.g.*, penicillin, should be administered prophylactically to these patients. The prophylactic administration of penicillin to patients in impending crisis has also been recommended.[177] When ordering antibiotics, it has to be remembered that some, *e.g.*, neomycin [12, 116, 199, 200, 201] and streptomycin,[24] have a mild, but definite, nondepolarizing neuromuscular effect which may accentuate the neuromuscular block in myasthenics sensitive to these agents.[111]

Conclusions

Myasthenia gravis is a relatively rare disease of unknown etiology and often baffling course, markedly influenced by psychosomatic factors. Anesthesiologists may be called upon to undertake, or to assist in, the management of severe respiratory and circulatory emergencies that may occur in these patients or to administer anesthesia for thymectomy or other surgical procedures to be performed on myasthenic subjects. In either case, the anesthesiologist can be equal to the task only if he has prepared himself well ahead for these responsibilities, which he might have to assume without warning.

This guide was compiled to summarize, from the viewpoint of the anesthesiologist, our personal experiences and the information available in the voluminous literature on myasthenia gravis. Anesthesiologists, because of their experience in the care of patients in whom muscular paralysis has been artificially induced, have a unique opportunity to make valuable contributions to the management of myasthenics. It is our hope that the information presented will be of help to our colleagues when confronted with the care of myasthenic patients.

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