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Myasthenia gravis

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MYASTHENIA GRAVIS

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HISTORY

In an intensive review of the literature, Viets[1] found that myasthenia gravis was not described with any pretense of completeness as a clinical entity until the last quarter of the 19th century. However, a reference by Thomas Willis, an astute 17th century English clinician, indicates that Willis knew of the disease and recognized the chief symptoms of asthenia of the voluntary muscles with recovery after rest. The description of the weakness in a patient in 1672, first noted by Guthrie in 1903, occurs in Willis' book, with illustrative cases, entitled "De Anima Brutorum", on the physiology and pathology of disease. Willis' description is as follows:

> "There is another kind of this disease depending on the scarcity of the spirits in which the motion falls wholly in no part or member, yet is performed but weakly only, or deprivedly by any. Those who being troubled with the scarcity of spirits, will force them as much as they may to local motions, are able at first rising in the morning to walk, move their arms this way and that, or to lift up a weight with strength; but before noon the stores of the spirits which influence the muscle being spent they are scarce able to move hand or foot. I have now a prudent and honest woman in care who for many years had been obnoxious to this kind of Bastard palsy, not only in the limbs but likewise in the tongue. This person for some time speaks freely and readily enough but after long, hasty or laborious speaking, presently she becomes mute as a fish and cannot bring forth a word. Nay, and does not recover the use of her voice until after many minutes."

Nearly 200 years were to pass before myasthenia gravis was again referred to in the medical writings. In 1877 Samuel Wilks, an English physician, gave a brief account of a girl with symptoms

suggestive of myasthenia. Although the history of his patient's illness is not entirely characteristic, difficulty in swallowing, talking, and breathing developed rapidly, and death occurred suddenly. At postmortem examination no microscopic changes were found in the medulla, strikingly in contrast to what was already common knowledge of the pathology of bulbar paralysis of the degenerative type. Wilks thus contributed the initial description of the failure to find pathological destruction of nerve tissue in the appropriate area of the central nervous system.

In 1879 Wilhelm Heinrich Erb in Germany wrote a reasonably full account of the syndrome based on the observation of three patients, one of whom died suddenly. Even though Erb's paper is not complete, it is of value in that for the first time some of the chief symptoms of myasthenia gravis are brought out clearly. An even more complete single case history was contributed by Eisenlohr in 1887, and subsequently within a few years many other reports were at hand, including an unusually detailed one by Hermann Hoppe, an American student working in Oppenheim's clinic in Berlin in 1892.

With a score or more cases reported by 1893, some with negative examinations of the pons and medulla, Goldflam (1893), added greatly to our knowledge of the disease and his name is rightfully coupled with that of Erb in the eponym, the Erb-Goldflam symptom complex. Goldflam analyzed the symptoms of myasthenia gravis in

a manner superior to any writer before him. All of Goldflam's observations are valid today; in fact, little has been added to the clinical description of the disease since this time. His paper in many ways is the most important ever written in the history of the disease.

Jolly in 1895 was the first to use the name myasthenia gravis and he added the term pseudoparalytica because of the lack of structural changes found postmortem. This name was generally accepted at a meeting of the Berlin Society of Psychiatry and Neurology, held November 13, 1899. Jolly was also the first to analyze the reaction of muscles in myasthenia gravis to electrical stimulation as well as suggesting physostigmine as a form of treatment. However, he does not seem to have followed out this latter point and it was left to Walker 40 years later to demonstrate the therapeutic value of this drug.

Up to 1895, all the reports of cases had come from England, Germany or Austria, the majority stimulated by the pioneer work of Erb, Goldflam and Jolly. Soon case reports began to come from France, Italy, and America. The first from France came from Charcot's old clinic in Paris where Marinesco found some recent hemorrhage beside the aqueduct of Sylvian and in the begal nuclei postmortem in a case formerly observed by Charcot and Brissaud. Murri (1896) reported the first case from Italy under the name of Erb's disease. His paper was illustrated by a series of myograms

far superior to those found in Jolly's paper in 1895. In 1897 Collins presented the first paper from America on myasthenia gravis. Collins reviewed the literature and presented a patient, age 27, whose first symptoms developed during pregnancy. In 1899 Sinklor reported two cases at the 25th annual meeting of the American Neurological Association being the first to demonstrate the facial appearance of a patient by photographs.

The year 1900 witnessed a great outpouring of literature on the subject. The disease became widely recognized in the minds of the British and American medical profession, chiefly owing to the paper by Campbell and Bramwell in Brain, a standard neurological journal. In this paper Campbell and Bramwell revised the entire literature up to 1900, abstracted each case, and compiled a table giving the major symptoms and signs.

By 1900 much of the symptomatology of myasthenia gravis was recognized.[2] From 1900 to 1934 the disease was considered uncommon and usually fatal. The pathologic changes were noted in the nervous system and only the thymic abnormality and "lymphorrhages" in the skeletal muscles were noted. The present day concept for myasthenia gravis came largely through the discovery of the junctional transmission of nervous effects by chemical agents by Otto Loewi (1921), Henry H. Dale (1933) and others, the striking response of physostigmine and later neostigmine in overcoming the muscular deficiency in patients by Mary B. Walker (1934) and the suggested relationship

between the thymus and myasthenia gravis by Blaloch, Keynes, Andrew Wilson and others (1941 to date). After the turn of the century the interest in myasthenia gravis had nearly died out. The above and other contemporary investigations have revived an interest in the disease and led to the establishment of a Myasthenia Gravis Foundation. The first meeting was in December 8 and 9, 1954. At this meeting the Foundation held its first Symposium for the purpose of exchanging ideas in the problems presented by twenty years of research.

NATURAL HISTORY

Even though myasthenia gravis has been recognized as a clinical entity for over half a century, reliable data on incidence and geographic distribution are meager. Estimates of the frequency of myasthenia gravis now available are based largely on the experience of interested clinicians or special clinics. The difficulty in estimating prevalence for the general population stems from the problem of defining myasthenia gravis and from the tendency of some clinicians to extrapolate population estimates from proportionate hospital admissions or case history series instead of appropriate population survey procedures.

There are no accurate figures indicating the exact number of patients with myasthenia gravis in any population group. From surveys it is estimated that the prevalence of myasthenia gravis is about 3 per 100,000 population. It is evident that the disease

is comparatively rare, even though the above figure is only approximate.[3]

Myasthenia gravis may begin at any age, although onset is most common in the third decade in women and somewhat later in men. The overall incidence is higher in women (almost two times) than in men. However, the coincidence with thymoma is greater in males.[4] Except for transient neonatal myasthenia, convincing examples of parent-child myasthenia have not been reported. Multiple incidence of the disease has been reported among siblings, however. Data on occurrence in twinships are not sufficient to be meaningful.[3]

ETIOLOGY

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.[5]

Since there is no known abnormality of central or peripheral neural function in myasthenia gravis, and since the evidence for a defect in muscle contractibility does not appear to be conclusive,[6] the manifestations of this disease are believed to be due primarily to impairment of neuromuscular transmission. The evidence at present suggests that the defect in neuromuscular transmission is due to some alteration in the acetylcholine mechanisms. This could result from (1) elevation of the excitatory threshold

of the motor end-plate to the acetylcholine released by each nerve impulse, (2) an excessive concentration of cholinesterase at the neuromuscular junction, or (3) failure of each nerve impulse to release a normal quatum of acetylcholine.

There is no evidence for excessive cholinesterase activity in the muscle of myasthenic patients. Recent studies are consistent with the first possibility and indicates that the defect in neuromuscular transmission in myasthenia is due to a competitive (acetylcholine-inhibitory) block -- the competitive block is produced by acetylcholine released in a normal manner during neuromuscular transmission, or by choline or a closely related compound following hydrolysis of the naturally released acetylcholine. It is likely that the endogenous transmitter or its products of hydrolysis play an important part in bringing about the defect, since injected acetylcholine or choline reproduces, or enhances, in myasthenic patients the defect in neuromuscular transmission characteristic of the disease.[7]

It is not clear whether the myasthenic block is the result of an abnormal response of the end-plate to substances normally released from the motor nerve endings or to the formation of an abnormal product of acetylcholine which has competitive blocking action. The former seems more likely, since the myasthenic patient reacts abnormally not only to acetylcholine and choline, but also to many other quaternary ammonium compounds, including decamethonium

and succinylcholine.[8]

Some evidence has been presented that myasthenia gravis may be due to impairment of the release of acetylcholine from the motor nerve endings. Despite normal sensitivity of the end-plate to iontophoretically applied acetylcholine, miniature end-plate potentials recorded from myasthenic muscle have been found to be diminished in amplitude. Furthermore, the post-tetanic exhaustion of myasthenic muscle resembles that of normal muscle treated with hemicholinium, which inhibits the synthesis of acetylcholine, more closely than that of normal muscle treated with d-tubocurarine.

The presence of compounds capable of producing a curare-like nondepolarization block or a depolarization block in the serum or tissues of myasthenia subjects was suggested by several investigators. At the present, the reports of demonstration of a substance in the blood of myasthenic patients capable of producing neuromuscular block in experimental animals and of a substance in serum capable of inhibiting the synthesis of acetylcholine have not been confirmed.[9]

It has been suggested that myasthenia gravis may be due to an auto-immune response in which an antibody to end-plate receptor protein is produced by the reticuloendothelial system, including the thymus. The antibody would then combine with end-plate protein and produce an alteration in the response of the end-plate to endogenous acetylcholine. This theory has been lent support by

the recent observation that the serum of myasthenic patients contains, in the globulin fraction, a substance which combines with normal or myasthenic muscle in the presence of complement.[9]

Simpson also suggested that myasthenia gravis, similar to diffuse lupus erythematosus and dermatomyositis, is an autoimmune 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.[10,42]

Myasthenia gravis is encountered infrequently 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. Ausland and Alter reviewed the reported aggregate of familial myasthenia and twin cases. The impression gained from those data also is that there is as yet insufficient evidence to suggest that genetic factors are of significance in the etiology of myasthenia gravis.[3]

Many observers have concluded that myasthenia gravis is basically an endocrine disturbance of some type in view of the frequency with which thymic abnormalities are present and the relationship to pregnancy, menstruation and thyroid disease. However, no consistent dysfunction of an endocrine nature has been

demonstrated, and treatment with various hormones, including cortisone and pituitary corticotropin, have resulted in no consistent benefit.[4,11]

PATHOLOGY

The pathology is featured by the absence of changes in the nervous system and the absence of characteristic changes in the muscular system.[11]

Isolated focal areas of muscle fiber necrosis and scattered collections of lymphocytes (lymphorrhages) are the most frequently observed pathologic changes in muscles in this disease. Russell described three types of muscle changes.[12] Type I showed advanced focal muscular necrosis, with loss of sarcolemmic structure, disruption of myofibrils, polymorphnuclear and round cell reaction, changes typical of an acute myositis, Attempts at muscle regeneration was in evidence, with numerous multinucleated giant muscle cells. This process may be limited to one fiber or so widespread as to cause naked eye changes in the muscle. Type I has been found to be most consistently associated with thymomas. Type II is the lymphorrhage, which is considered to be secondary to solitary muscle fiber atrophy with basophilia of the cytoplasm and loss of cross striation. Type III consists of a simple focal muscle change with eosinophilia and swelling but without loss of striation or inflammatory reaction. Type III is considered to be the least specific change of the three types of muscle change.

Similar changes were never found to occur in true smooth muscle. Similar changes, however, are found to occur commonly in the myocardium.[10,13]

Recent studies have described abnormalities of nerve terminals and end-plates. Coers and Desmedt have shown, by special training techniques, two changes in the terminal arborization of motor nerves. In one, the dystrophic type, there is increased branching and the terminal knobs are distributed over a wider area of the muscle fiber than usual. Since the related muscle fiber is usually abnormal, this type is probably reactive. The same type of end-plate has been found in other neuromuscular disorders. In the other type, the dysplastic, there are few terminal knobs and these are arranged serially along a scanty number of terminal branches ending on a long end-plate region. Coers and Desmedt, in their limited experience, have not found this type in any other disease.[5] Like the muscle fiber changes already described, these changes bear no direct relationship to the severity of the loss of function.[10]

In more than half of the patients there is hyperplasia of the thymus with germinal center formation; in 15 to 20 per cent, a thymoma; in about 10 per cent, a persistently enlarged thymus that is normal microscopically; and in the remainder, either a normal thymus or no detectable thymic tissue.[4,13]

The thymus gland, whether large or small, shows increased content of lymphocytes or thymocytes in cortex and medulla and

there is evidence of active formation of lymphocytes in the presence of germinal centers. This finding is very characteristic. The epithelial cells of the thymus are not proliferated unless there is a tumor but in thymomas they may be arranged in cords or tubes, giving the appearance of a secretory tissue. Even then the surrounding non-tumor gland shows the typical germinal centers.[13,14]

Thymic hyperplasia and lymphorrhages may also occur in patients with adrenal insufficiency, hyperthyroidism or acromegaly. Since muscular weakness is frequently present in these conditions, attention has been directed toward the influence of the thymus and of extracts of this gland on neuromuscular functions in experimental animals. No conclusive results have been obtained as of yet.[4,13]

CLINICAL MANIFESTATIONS

Myasthenia gravis is characterized by both a pathologically rapid fatigue of the voluntary muscle with use and a remarkably prolonged time to recover its power again. There is no other neuromuscular syndrome that involves these abnormalities together.[15]

The initial manifestations are most commonly referable to the extraocular muscles. Unilateral or bilateral ptosis is one of the most frequent signs of myasthenia gravis. Occasionally the ptosis shifts from one eye to another. In most patients ptosis is often accompanied by diplopia, blurring of vision, or nystagmus. Bright light frequently makes ocular signs and symptoms worse. Pupillary abnormalities are almost never present.[5]

The extraocular muscles are affected sometime in the course of the disease in almost every patient, and may have several episodes of transient weakness before the disease becomes persistent. The weakness in the ocular muscles may occur in almost all combinations of functional disturbance. The elevators of the lids and upward deviation of the eyes are usually most affected. Occasionally there is complete limitation of extraocular movement. The orbicularis oculi are usually also affected when ptosis is present. The result is weakness in closure of the lids which may persist even after remission of other symptoms of the disease. This is a very helpful sign in distinguishing between ocular palsy of neurogenic origin, which is usually not accompanied by orbicularis oculi weakness, and that due to myasthenia gravis or primary muscle disease.[4]

In 20 per cent of the patients with myasthenia gravis the disease remains localized to the extraocular muscles. In 80 per cent, the disease progresses to involve numerous muscles and usually becomes generalized within two years after onset. Those patients who have had ocular symptoms for more than two years without evidence of extension beyond the orbicularis oculi usually continued to have the localized form of the disease.[16]

As the disease progresses, other muscle groups are involved. Weakness of the facial muscles results in the characteristic myasthenic facies.[10] Weakness of the jaw muscles may cause

difficulty in chewing, even to the point that consumption of any solid food is impossible. Chewing difficulties are more frequently accompanied by dysphagia. Weakness in the muscles of speech results in the characteristic nasal twang of myasthenics. Often when the patient is starting to speak the voice is relatively clear; but as the patient continues to speak, the volume of the voice decreases and its clarity diminishes so that the words become indistinguishable.[17]

The muscles of respiration may be the first involved in myasthenia gravis or the last.[10] Initially weakness of cough may be the only manifestation. Later, attacks of dyspnea may appear after exertion and, finally, may occur even at rest. The greatest difficulty when the chest muscles are involved is inability to clear the respiratory tract of mucous and fluid.

The most frequently involved skeletal muscles are those of the neck, shoulder girdle, and hip. The proximal limb muscles are more severely affected than the distal. Extensor muscles are more involved than flexors in the upper limbs, but flexors are more involved than extensors in the lower limbs which are usually less severely affected than the upper.[5] It is much more common for the disorder to involve a group of muscles, a single muscle, or even part of a compound muscle. Commonly the complaint is related to the muscles fatigued by a particular movement required by the patient's work; however, systemic examination may reveal unsuspected weakness or fatiguability of other muscles. A relatively infrequent

sign of myasthenia gravis is a triple longitudinal furrowing of the tongue, called the "myasthenic tongue", described by Wilson.[10]

Early atrophic changes of muscle groups involved in the myasthenic process occurs 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.[5]

Sensory changes both in involved or uninvolved muscle groups are frequently present in myasthenia gravis. Pain is quite common in weak muscles, usually an ache which is presumably due to the extra effort required to maintain posture.[10] Lower back pain is most common in myasthenic patients. Another type of common pain is due to the arthritis that often accompanies myasthenia gravis. Other sensory changes encountered are headaches, ocular pain, paresthesias of the face, lips, tongue or extremities. Deafness, often variable, sometimes occurs from eustachian block in pharyngealparesis or an unusual deafness for low frequencies which may be caused by paralysis of the tensor tympani.

The onset is often insidious and progress slow or rapid, but in some it has a very sudden beginning. Once the disease has appeared, the course may follow many patterns. In the majority of patients there is gradual extension of the involved areas leading to a relatively steady state of weakness, which remains unchanged for many years with the exception of moderate

fluctuations in severity. Within the first three years after onset, the basic level of weakness is usually reached. Most often this basic level of weakness is reached within the first year. In patients who develop severe myasthenia, the average interval between onset of the disease and the first severe episode is eight months. This interval tends to be shorter in male patients, in whom the disease is more likely to progress rapidly than in females. In others there is rapid progress, both in the extent and severity of the involvement, leading to death within a few months. In still others, ocular manifestations may be the only evidence of myasthenia for many years.[7]

Symptoms of the disease tend to fluctuate in severity from day to day or at longer intervals in almost all patients, and approximately one-fourth have a remission lasting at least six months, with complete or nearly complete disappearance of signs and symptoms. During these, weakness of the extraocular muscle is usually the last to disappear and the first to occur with exacerbation.

Most patients have only one remission, while 10 per cent have two to four. Half of the remissions begin during the first year of illness, but others occur after as many as 17 years, with the average interval between onset of disease and remission being four years. The duration of remission varies up to 18 years, with an average of 4.6 years.[7]

Upper respiratory infection, grippe-like illnesses, emotional

tension, and the postpartum period are the factors most commonly associated with an exacerbation of the disease.[10]

DIAGNOSIS

The diagnosis of myasthenia gravis in the practice of neurology and internal medicine requires a high suspicion of the presence of the disease and a clear understanding of what the clinical presenting symptoms usually are.[18]

It is relatively easy to diagnose a moderately severe or severe case of myasthenia gravis. The diagnostic problems are posed by the mild cases, either of recent onset or of longer duration. A presumptive diagnosis can generally be made on the basis of history and physical examination alone. The diagnosis then can be confirmed by the use of mechanical aids and various pharmacologic tests.

The history of a gradual onset of muscle weakness that is transient and variable; the history of slow improvement of the fatigue state with adequate periods of rest and exacerbation of the fatigue state with ordinary voluntary use; the demonstration of muscle weakness in eye, masticatory, swallowing, or systemic muscles, unassociated with atrophy, fasciculations, or reflex changes; and the elicitation of easy fatigue in the muscles on examination are all striking evidences of the disease.[11] Fixed and permanent palsies do not have this characteristic of myasthenia.[18] In the same light, the characteristic finding in myasthenia of an

increase of the symptoms as the day wears on is the opposite of the so-called neurotic fatigue states.

Involvement of the bulbar muscles concerned with swallowing and talking is easy to identify. Speech, after a few seconds, becomes nasal in quality, a characteristic of myasthenia gravis. In this condition clear enunciation at the level of a whisper or examples of hoarseness are not found. The dysphagia usually involves the nasal regurgitation of liquids and is accompanied nearly always by extreme exhaustion of the power of chewing, so that food sometimes has to be removed by the fingers from the mouth because it cannot be broken into small enough particles to attempt to swallow.[18]

The pattern of development of myasthenia in a particular muscle group may be elicited by various simple tests designed to place the muscles at a continuing high level of activity. A most reliable clinical test consists of asking the patient to look up at the extended finger of the examiner for a period of one minute. In myasthenia gravis the lids slowly droop so that at the end of 30 seconds there is at least 50 per cent ptosis. At the end of one minute one or the other eyeball is usually covered.[15,18] Measurement can also be made of the length of time that the head and each extended leg can be elevated when the patient is in a supine position and the length of time the arms can be held above the horizontal position when the patient is sitting.[4] Grip strength

is recorded by means of a dynamometer or ergometer to measure and evaluate exhaustion of the voluntary muscles in the hand.[18]

The diagnosis is usually confirmed by the injection of an anticholinesterase preparation -- either intramuscular neostigmine (Prostigmin) or intravenous edrophonium (Tensilon). The response of the muscular weakness in this disease to the drugs is so prompt and dramatic and so slight or equivocal in other conditions that great reliability is assumed in the use of such substances.[4,5,18]

With the exception of a few patients with polymyositis, disseminated lupus erythematosus, or carcinomatous neuropathy or myopathy,[19] and with the exception of the extraocular muscles of a few patients with disseminated sclerosis or arteriosclerotic cerebral vascular disease,[7] unequivocal increase in strength does not occur in patients who are not considered to have myasthenia gravis following neostigmine or edrophonium. These responses usually are sufficiently unusual to detract little from the diagnostic value of the test.

Neostigmine[20,21] has been the most widely used anticholinesterase compound for the diagnostic test. This drug is administered in a dose of one mg. per 100 pounds body weight. Atropine sulfate (0.5 mg. per 100 pounds body weight) should be injected intramuscularly before or with the neostigmine to prevent the muscarinic effects of the latter drug on smooth and cardiac muscle and secretory glands.[9] Also, the prior injection of atropine to the anti-

cholinesterase preparation serves as a placebo control for the anticholinesterase preparation.[18] An improvement in performance indicates that emotional factors are contributing to the patient's complaint, since atropine does not alleviate weakness due to other causes.

Improvement in strength of involved muscles begins within 10 minutes after intramuscular injection, is maximal in 30 minutes, and lasts 3 to 4 hours. When the response is equivocal, the test should be repeated on another day with a dose of 1.4 mg. neostigmine and 0.7 mg. atropine per 100 pounds. Nonmyasthenic subjects experience either no change in strength or mild weakness and usually develop muscle fasciculation. Myasthenic (generalized) patients usually develop no fasciculation except in the least involved muscles. In patients with localized ocular or oculobulbar myasthenia, fasciculation frequently occurs but is usually less pronounced than in nonmyasthenic subjects.[9]

A more dramatic response within a few minutes can be produced by administering neostigmine intravenously in a dose of 0.5 mg. following 0.5 mg. atropine.[22]

A shorter-acting anticholinesterase compound, edrophonium (Tensilon),[33] has also been administered intravenously as a diagnostic test. Edrophonium has both anticholinesterase and direct depolarizing action on muscle.[8] This drug is injected in an initial dose of 2 mg., followed in 30 seconds by an additional

8 mg. if the first injection does not produce an increase in strength. Atropine need not be administered since the incidence and severity of muscarinic side effects is much less than after neostigmine. Also, its effect develops rapidly and wears off quickly so that the test can be repeated within 10 minutes. However, the brief duration of its effect (1 to 3 minutes) necessitates speed in carrying out a detailed evaluation of muscle strength.

In the majority of patients the diagnosis of myasthenia gravis can be established or excluded with the help of the response to intramuscular neostigmine or intravenous edrophonium. In very mild cases, and in the occasional patients with more severe myasthenia who responds poorly to anticholinesterase medication, 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[8,24] or gallamine. The rationale of the test is based on the fact that curare neutralizes the action of acetylcholine at the myoneural junctions and produces an artificial form of myasthenia gravis.

D-tubocurarine in a dosage of 0.5 to 1.0 mg. is administered intravenously over a period of 30 seconds. Muscle performance is assessed 5 minutes later and if no marked change is observed another 0.5 to 1.0 mg. is administered. Muscle function is again tested after 3 minutes. Following this, additional 0.5 to 1.0 mg.

doses are administered 3 minutes apart up to a maximum total of 4 mg. If a marked reduction of grip strength does not occur following the administration of 4 mg. of d-tubocurarine, it is unlikely that the patient has myasthenia gravis. After the diagnosis of myasthenia gravis is established, the residual effects of d-tubocurarine should be antagonized by intravenous neostigmine in 0.5 mg. increments. The first dose should be injected with 0.4 to 0.6 mg. of atropine.[5]

Roentgenograms of the chest at times reveals an enlargement in the mediastinum that is indicative of thymus involvement. In all cases of myasthenia gravis, routine chest films, if negative, should be followed by planography in order to determine whether thymic enlargment is present.[11]

Myasthenia gravis must be differentiated from various structural diseases of the nervous system which leads to muscular weakness in similar groups of muscles. The consistent level of the weakness, the development of atrophy and the failure of response to neostigmine are usually sufficiently clear so that no difficulty is encountered in differentiating cases of motor neuron disease, polyneuritis, muscular dystrophy and others. Amyotrophic lateral sclerosis and its bulbar syndrome are easily distinguished by the presence of muscle atrophy and fasciculations, and by evidence of systemic disease elsewhere. Multiple sclerosis is not readily confused, but may offer difficulties in rare instances. The history

of remission of symptoms and the demonstration of optic atrophy, absence of abdominal reflexes, and multiple system involvement will suffice to differentiate it. Myxedematous myopathy may also be confused with myasthenia gravis as can be myasthenia syndrome with carcinoma.[25]

TREATMENT

The purpose of drug therapy in myasthenia gravis is to restore the patient's strength to the optimum and to maintain it there with minimal deleterous side effects from the medication. This goal can be approximated in many patients with this disorder, and most of these can continue in a useful occupation. Although muscle strength usually increases during drug therapy, most patients continue to demonstrate some muscle weakness. Even when strength does not return to normal, this therapy usually is adequate for the functioning of skeletal muscles. In the ocular muscles, however, patients often find that such an incomplete return of function is inadequate and complain that partial improvement of strength is no better -- and may be worse -- than no improvement.[26]

The myasthenia patient should have special attention at the very beginning to his general medical condition such as his state of nutrition, any chronic infections in either the pulmonary or renal systems, and of course, his emotional state. It is far more difficult to handle myasthenia gravis in the presence of other diseases than it is alone.[18]

The treatment of myasthenia gravis presents unique problems. This is brought about by the great variability of the disease. The amount of drug may vary from day to day and from month to month. Also, the patient's response to the drug may vary. Thus, it is the physician's duty to instruct the patient with great care and thoroughness initially. It must also be emphasized that optimal therapy is going to depend on the intelligence of the patient and his ability to alter his program of medication as needed, within limits.[26]

The management of myasthenia gravis relies mainly on anti-cholinesterase compounds, which are administered for the amelioration of weakness. The most useful of these are the quaternary ammonium compounds, neostigmine, pyridostigmin (Mestinon),[27] and ambenonium (Mytelase).[28] Bis-neostigmine (BC-40) and bis-pyridostigmin (BC-51) are longer-acting quaternary ammonium anticholinesterase compounds which require less frequent administration but are less suitable for general use because of the danger of cumulation and overdose.

Several organophosphorus anticholinesterase compounds have also had clinical trials in the management of myasthenia gravis. These have included diisopropyl fluorophosphate (DFP), tetraethylpyrophosphate (TEPP),[16] octamethylpyrophosphortetramide (OMPA),[16] O, O-diethyl-S-2-trimethylammoniumethyl phosphorothiolate iodine (Phospholine), and isopropyl methylphosphorofluoridate

(Sarin). While these compounds are more prolonged in their action than the quaternary ammonium compounds and produce a more even and sustained increase in strength, particularly in limb and girdle muscles, following the administration of only one or two doses a day, the danger of cumulation and overdose of drug has precluded their general clinical use except under carefully controlled circumstances.[9]

The maximal strength obtained after optimal doses of any of these quaternary ammonium or organophosphorous anticholinesterase compounds is approximately the same.[7] The compounds differ mainly in their duration of action (organophosphorus compounds greater than bis-neostigmine and bis-pyridostigmine greater than pyridostigmin and ambenonium greater than neostigmine), and in the severity of their parasympathomimetic side-effects (organophosphorus compounds greater than pyridostigmin and ambenonium).[9]

The administration of graded doses of any of these compounds results in an increase in strength in muscles affected by the disease, but in patients with severe myasthenia the maximal strength attained is frequently far below normal. Before regulation of the patient is attempted, the maximal strength should be determined by the response to the intramuscular injection of 1.5 mg. neostigmine with 0.5 mg. atropine, per 100 pounds body weight. The optimal oral dose of each of the anticholinesterase compounds may then be determined by gradually increasing the dose until the

same degree of maximal improvement is attained. Further increase in dose seldom results in a further increase in maximal strength, and excessive dosage, particularly of the longer-acting compounds, is likely to produce generalized weakness -- the so-called "cholingeric crisis."

The longer the duration of action of the anticholinesterase compound, the more prolonged and even is the increase in strength which is produced, and the longer may be the interval between doses, but the likelihood of cumulative effect of repeated doses and of administration of overdose is also greater. Pyridostigmin and ambenonium are intermediate in their duration of action and danger of overdose, and generally produce more satisfactory revaluation than the other compounds when oral administration is on 120 mg. to 300 mg. of pyridostigmine or 10 to 30 mg. of ambenonium administered orally at 3 to 4 hour intervals when the patient is awake. The initial dose can generally be near the lower limit of these ranges. The dose is then increased every one to two days until no further increase in strength occurs. Further increase in dose should be avoided unless there appears to be a decrease in the patient's response to the drug, and it should then be undertaken with the same precautions.

Pyridostigmine and ambenonium produce the same peak strength as neostigmine, but their longer duration of action results in more even strength, better endurance, and greater residual effect

during the night and on awakening. This generally permits the patient to omit medication during sleeping. Also, there are less intestinal symptoms than with neostigmine, although higher doses are more likely to cause headache. Pyridostigmine is less likely to produce weakness following an overdose than ambenonium and is therefore usually the drug of choice.[9]

It is considered wise to begin patients on neostigmine, which is more likely to have muscarinic side effects on the intestinal tract if the dosage is even slightly in excess of the patient's requirements. The identification of this overdosage early in the treatment period is excellent instruction to the patient.[18]

Regulation of dose of anticholinesterase medication can be very difficult in view of the great variability of this disease. Regulation is initiated by the administration of a dose below that necessary to produce maximal strength, usually 120 mg. of pyridostigmine, 10 mg. of ambenonium, or 15 mg. of neostigmine orally every four hours when awake, or one mg. of neostigmine intramuscularly every three hours. The dose is then gradually increased until no further increase in strength occurs. The interval between doses may be decreased by one hour if this proves necessary to maintain strength. Since the duration of action of pyridostigmine and ambenonium is longer than that of neostigmine, adjustments in dose of these drugs should be made at intervals of one to two days, as increases in dose at shorter intervals may

result in cumulation of drug and overdose. Whenever augmentation in dose of any anticholinesterase drug results in no further increase in strength, the dose should be reduced to the previous level, in order to administer the least amount of drug necessary to produce a maximal level of strength.

Unfortunately, what adjustment to make in dose may be difficult to decide since the manifestations of drug overdose are often similar to the symptoms of myasthenia gravis. The problem is further complicated by the fact that the various muscle groups may have differing drug requirements so the level of drug at which overdose occurs may vary with different muscles. The muscles of the neck and of chewing and swallowing often show manifestations of overdose first; the muscles of the shoulder girdle and upper extremeties may be affected next. The pelvic girdle and extra-ocular muscles are usually most resistant to the effects of excessive drug and may be unaltered or even improved in strength when the other muscles have become weaker due to overdose. The muscles of the legs are also often at good strength at this time, though they may fasciculate, and in this manner warn of excessive drug administration.

The differentiation between overdose and underdose may be facilitated by careful attention to the time of onset of weakness. Weakness one hour after drug administration is suggestive of overdose and three or more hours after drug administration suggestive

of underdose. The compound edrophonium[5,9] may also be used to differentiate between overdose and underdose. When 2 mg. of edrophonium is injected intravenously, a transient increase in strength beginning within one-half to one minute and lasting a few minutes is an indication that the patient is in need of more anticholinesterase. A transient decrease in strength, sometimes accompanied by fasciculation and muscarinic symptoms such as lacrimation, salivation, sweating, abdominal cramps, or nausea, is an indication that the patient is already overdosed. If no changes occur, it can generally be assumed that the patient is at or near his optimal dosage level, although patients who are overdosed may experience no further changes.

The muscarinic effects of anticholinesterase compounds, such as excessive salivation and sweating, nausea, vomiting, abdominal cramps, diarrhea, bradycardia, and rarely hypotention, are prevented or suppressed by the administration of atropine sulfate orally or intramuscularly as needed. Generally, myasthenic patients have a much higher threshold for the development of these effects of anticholinesterase compounds than non myasthenic subjects. Early in the regulation of myasthenic symptoms, atropine is best administered only to ameliorate these side effects. In this manner an overdose of anticholinesterase compound may be more easily detected. After satisfactory regulation has been attained, atropine is administered if needed to prevent side effects, usually in a dose

of 0.6 mg. orally or intramuscularly every 4 to 8 hours. Propantheline (Pro-Banthine) administered in a dose of 15 mg. orally or intramuscularly every 6 hours may be used for the same purpose.

In some patients, the oral administration of ephedrine sulfate (25 mg. 3 times a day) or potassium chloride (2 mg. 4 times a day) have been shown to be useful as an adjuvant to anticholinesterase medication. The use of guanidine has been virtually abandoned. Cortisone and adrenocorticotropin have been recommended by some but were found to produce either no change or a decrease in strength.[29] Satoyoshi et al.[30] have shown that triamterene, and aldosterone antagonist, also ameliorates muscle weakness in myasthenia gravis, reducing the requirement for anticholinesterase drugs. Similar, but apparently less striking results with spironolactone were reported by Gottlieb and Laurent.[31] Reports of a beneficial effect following the administration of postpartum serum, urecholine, and glutamic acid have not been substantiated. Undergoing clinical trial is a group of alkaloid of plant origin including galantahamine and lycoramine, which have been found to have anticholinesterase activity.[9]

Certain drugs must be avoided in myasthenic patients, for they may produce a critical exacerbation of weakness. The competitive muscle-relaxing agents, such as curare and flaxedil, are the most important of these. Quinine, quinidine, and parenteral neomycin

should also be avoided, as they may increase neuromuscular block. Morphine should be used with caution since it may depress respiration and since its effect may be potentiated by anticholinesterase compounds. Demerol is generally well tolerated, but it is best to begin with half the usual dose. Mild sedatives may be used, but difficulty may be encountered with those patients who are having difficulty swallowing or breathing if too heavily sedated.[7]

Local anesthetics are well tolerated if large doses are avoided and injection is made with epinephrine to delay absorption. Ether is usually well tolerated, although smaller amounts are needed to induce and maintain general anesthesia in myasthenic patients than in normal patients. Cyclopropane is also well tolerated.[3]

Despite the evaluation of data from several large series in which thymectomy was performed, there is a wide divergence of opinions regarding the indications and results of the surgical removal of the thymus in myasthenia gravis.[9,10,32-34]

The removal of thymomas from a myasthenic patient only rarely alters the course of the disease favorably.[10] Nevertheless it is felt that a thymoma should be removed because it may extend locally and produce symptoms. Irradiation prior to excision has been recommended.

The most controversial aspect of the management of myasthenia gravis is that of thymectomy in the absence of thymomas. Recent reviewers show varying degrees of enthusiasm for elective

thymectomy in myasthenia gravis.[9] 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, especially if surgery is performed soon after the onset of the disease.[10] It has been reported by Viets and Schwab that significant objective improvement occurred after thymectomy more than twice as frequently in suitably selected patients than in nonoperated controls.[35]

The improvement produced by thymectomy seemed to be more persistent than that observed after spontaneous remissions. Many patients experienced an increase in responsiveness to, and a decrease in requirement for, anticholinesterase medication within a few days after operation. However, in some cases, beneficial effects from thymectomy did not occur until as late as three years postoperatively. In the immediate postoperative period increased anticholinesterase requirements were also observed occasionally.[5,9]

Before the effects of thymectomy on the course of myasthenia gravis may be fully evaluated, more carefully controlled studies are needed. It is extremely difficult in a disease that is so variable to know whether favorable results are due to the therapeutic procedure or to an unrelated change in the course of the disease, to increased encouragement of the patient, or to exacerbation of the myasthenia, which is sometimes followed by improvement.

At the present time, thymectomy should be limited to females

under 40 and over 5 years of age, whose disease progresses rapidly right from the start and to those patients who are becoming progressively worse despite careful medical management and in whom the chance for spontaneous remission appears to be small.[36]

Reports of a beneficial effect following carotid sinus denervation and parathyroidectomy have not been substantiated.[9]

The value of irradiation has not been demonstrated, but it is apparently not harmful in adults and may be tried in patients who are not doing well on medical management.[7]

Management of Exacerbation of Myasthenia Gravis:

Exacerbation of the disease is characterized not only by increased weakness but also by increased requirement for, and diminished response to, anticholinesterase medication.[9] Upper respiratory infection, other infectious illness, emotional tension, and the postpartum period are the factors most commonly associated with exacerbation. In addition, most women feel weakest for several days before each menstrual period. However, exacerbation of the disease sometimes occurs without evident cause. The term "Myasthenia Crisis" has been coined when the exacerbation is severe, with difficulty in swallowing and breathing.[10]

Exacerbation of myasthenia gravis is managed by increasing the dose of anticholinesterase medication and employing mechanical measures when needed to maintain respiration and remove secretions. The patient should be managed with intramuscular neostigmine,

supplemented by atropine when dysphagia or respiratory weakness is severe and oral medication should be discontinued. The longer-acting drugs, pyridostigmine and ambenonium, may also be administered parenterally in the place of neostigmine, however their longer action makes adjustment of dose and avoidance of overdose more difficult.

If upper airway obstruction, resulting from severe dysphagia and weakness of the pharyngeal and tongue muscles, is marked enough to cause cyanosis, an endotracheal catheter should be inserted. The endotracheal tube should not be left in place more than 48 hours, as this produces edema of the larynx, which may result in airway obstruction when the tube is removed. It is usually best to perform a tracheotomy under local procaine anesthesia since most myasthenic patients continue to have severe dysphagia after withdrawal of the tube. Since respiratory weakness usually develops concomitantly with pharyngeal weakness, most patients who are intubated or tracheotomized require artificial respiration.

Regardless of the means of artificial respiration employed, endotracheal intubation or tracheotomy and periodic suction should be performed as soon as needed to reduce upper airway obstruction and pooling of secretions in the pharynx and to prevent aspiration and pneumonitis. Oxygen may be administered, with nebulized moisture to prevent drying of mucous membranes and with a detergent

to assist in the removal of secretions. It is probably helpful to administer penicillin and streptomycin parenterally to patients in respirators as a prophylactic adjunct since the dysphagia and impairment of cough and respiration that precede institution of artificial respiration predispose to atelectasis and pneumonia.[7]

While the patient is in the respirator, the dose of neostigmine should be reduced to 0.5 to 1 mg. or less intramuscularly every 2 to 3 hours, as this is frequently followed by some improvement in response to the drug. Reduction in the amount of anticholinesterase medication appears to be particularly helpful in patients who had been receiving large doses and who had manifested decreasing responsiveness to this medication. Presumably, this is a result of the development of an acetylcholine-insensitive state of the motor end-plates following prolonged exposure to high concentrations of endogenous acetylcholine.[37] Reduction in the local concentration of transmitter may be responsible for improvement in responsiveness to acetylcholine and anticholinesterase agents that often occurs. Some authors have actually advocated stopping anticholinesterase drugs entirely for approximately 72 hours.[38]

In some patients the administration of potassium chloride improves the response to acetylcholine and anticholinesterase drugs, even in the absence of evidence of depletion of this ion. Reduction in body temperature has a similar effect in some patients.[37]

Fluid and electrolyte balance are maintained by intravenous administration of proper fluids. If the patient is unable to swallow by the third day, a stomach tube should be inserted and feeding begun to maintain an adequate nutritional state.[9]

Crisis:

The chief emergency that arises in the management of moderately severe myasthenia is the differential diagnosis of the cholinergic crisis from that caused by an acute exacerbation of the disease (myasthenic crisis).[18]

In management of the disease, graded doses of an anticholinesterase compound are administered until a maximal level of strength is attained in the affected muscles. Unfortunately, in patients with severe myasthenia the maximal strength attained may be far below normal. Increasing doses may result in no further increase in strength, and excessive drug may produce generalized weakness cholinergic crisis. This is attributable to the accumulation of an excessive concentration of acetylcholine at the motor end-plates and prolonged depolarization of this region, followed by refractoriness of the end-plates to the action of acetylcholine.[37]

The weakness that occurs in myasthenic patients following excessive doses of anticholinesterase compounds is in many ways similar to that produced by smaller doses of these compounds in normal subjects. However, whereas generalized muscular fasciculation and muscarinic symptoms (Nausea, vomiting, abdominal cramps,

diarrhea, sweating) invariably develop in normal subjects, fasciculation is frequently absent or minimal in patients with severe myasthenia, and muscarinic symptoms may be either pronounced, mild, or absent. Furthermore, the prior administration of atropine may suppress the muscarinic symptoms.[9]

If overdose is suspected, the simplest way of confirming this is to withhold medication for several hours and carefully observe whether the strength increases or decreases. Often it is helpful to observe the effect on the weakness of administration of the short-acting anticholinesterase and cholinergic compound edrophonium.[39] One mg. of edrophonium is injected intravenously, which may be repeated in 2 to 5 minutes if there is no effect. If the patient becomes weaker, the presence of drug overdose is confirmed and reduction in medication indicated. If the patient becomes stronger, the weakness can be attributed to insufficient anticholinesterase medication, and cautious increase in medication may be attempted. If there is no change in strength in a patient who is very weak, it is likely that the weakness is due to an acetylcholine-insensitive state, to drug overdose, or both, and reduction in medication is warranted.

The presence of drug overdose may also be confirmed by observing the effect of administration of an oxime such as pyridine - 2 - aldoxime methiodide (P-2-AM) or diacetyl monoxime (DAM) which is capable of reversing cholinesterase inhibition and

neuromuscular block produced by anticholinesterase compounds.[40] In patients who respond well to anticholinesterase medication, the intravenous injection of 500 mg. of P-2-AM or DAM may restore strength to a more optimal level if the patient was overdosed, or produce a decrease in strength if the patient was either underdosed or on an optimal dose of medication. In patients who respond poorly to anticholinesterase medication, presumably owing to the development of an acetylcholine-insensitive state, the administration of oxime may have no effect.

If the myasthenic patient is weak due to overdose of anticholinesterase medication, strength will be improved by the intravenous administration of oxime, such as P-2-AM or DAM. This is so only if the motor end-plates are capable of responding to this medication. These oximes reverse the neuromuscular action of anticholinesterase compounds. The effect of this reversal depends upon the prior action of the anticholinesterase compound. Whereas in normal subjects neuromuscular function and strength are returned toward normal, in myasthenic patients the effect depends on the status of the patient at the time of oxime administration. If sufficient anticholinesterase compound had been administered to depress function, this is restored to a more optimal level. But, if function was optimal at the time of oxime administration, it is restored toward the basal level present prior to the administration of anticholinesterase compound.[9]

While the oximes are effective in the management of anticholinesterase intoxication in myasthenic patients, administration must be made with caution. Following the amelioration of weakness due to this intoxication by the administration of 1,000 mg. of P-2-AM or DAM, repetition of this dose produces weakness in some patients with myasthenia gravis.[41] It is therefore recommended that myasthenic patients suffering from anticholinesterase intoxication be titrated with successive 500 mg. doses of P-2-AM or DAM, at 5 to 10 minutes intervals, until strength is restored to the maximal level attained following the administration of optimal doses of anticholinesterase compound. Systemic weakness produced by the recommended doses of oximes in myasthenic patients is due to reversal of the action of previously administered anticholinesterase compound rather than to the direct effect of oximes.

If the muscarinic manifestations of anticholinesterase intoxication are present, atropine should be administered in a dose of 1 to 2 mg. intravenously or intramuscularly and repeated if necessary, since these manifestations are not affected by the oximes.[9]

Upper airway obstruction due to weakness of the pharyngeal and tongue muscles and respiratory weakness are managed by endotracheal intubation and artificial respiration, just as in the management of myasthenic crisis. While prompt administration of an oxime may diminish the necessity for and duration of these measures, there should be no delay in initiating them, since the oximes will only

partially reverse respiratory arrest in the patient with cholinergic crisis.[7,9,18,41]

SUMMARY

Myasthenia Gravis was unknown until 1835, untreated until 1935. Diagnosis a generation ago took months. Once, 80 percent of myasthenia gravis cases were fatal; today the lives of 85 percent of myasthenia gravis victims are saved. In spite of this there is still no cure. In the same light, the etiology of this relatively rare disease is unknown.

Myasthenia gravis is essentially a disease of rapid pathological exhaustion of voluntary muscles with use and a slow, pathologically long period of recovery with rest. It may occur from birth to the eighth decade in life, but is more common in young females fifteen to thirty years old. Although less frequent in males, it is more common from forty to sixty years of age.

Various hypotheses have been proposed for the explanation of the myasthenic state. The hypotheses that are most favored at the present time are: (1) Deficiency in acetylcholine synthesis or release; (2) desensitization of the end-plate to acetylcholine; or (3) auto-immune mechanisms. It may also be 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.

Morphologic changes both in the muscle fiber and at the

neuromuscular junction have been reported. No gross changes have been described in the skeletal musculature with the exception of occasional early or late atrophy in the involved muscle. The most frequent findings are the presence of lymphorrhages on microscopic examination. Significant histological changes in the myasthenic end-plate and also in the distal nerve fibers have also been reported. These changes are: (1) The dystrophic end-plate; and (2) The dysplastic end-plate. In addition to the findings at the neuromuscular junction and in the skeletal musculature, significant changes were observed in the myocardium and the thymus.

The main symptom of myasthenia gravis is weakness involving the bulbar and/or limb musculature. The weakness becomes more evident on prolonged or repeated use of the muscle. Common symptoms are ptosis, diplopia, dysphonia, difficulty in mastication, dysphasia, respiratory weakness and loss of limb strength. Myasthenia is characterized by spontaneous remissions and exacerbations.

In most instances the diagnosis of myasthenia gravis can be made on the basis of history and physical examination alone. The diagnosis then can be confirmed by the use of mechanical aids. These include the use of the dynamometer or ergograph and various pharmacologic tests. The various pharmacologic tests in use are the Neostigmine Test and the Edrophonium Test, both anticholinesterase, and the Curare Test, a nondepolarizing muscle relaxant. Myasthenic patients should have annual roentgenologic examination of the chest,

including a lateral projection to rule out a mediastinal tumor which is almost certain to be a thymoma.

The management of myasthenia gravis relies mainly on anti-cholinesterase compounds, which are administered for the amelioration of weakness. Even though these compounds result in an increase in strength, in many cases the maximal strength attained is frequently far below normal.

The most useful of the anticholinesterases are the quaternary ammonium compounds, Neostigmine, Mestinon and Mytelase. Each patient has to be individually regulated on one or a combination of these drugs so that his symptoms are under the best possible control and he is kept close to normal. If an overdose of these medicines is taken, undesirable side effects are produced.

BC-40 and BC-51 are longer-acting quaternary ammonium anti-cholinesterase compounds which require less frequent administration. However, there is a greater danger of cumulation and overdose. Several organophosphorous anticholinesterase compounds have also had clinical trials in the management of myasthenia gravis. These have included TEPP, DFP, HETP and OMPA.

Crisis is the dread of the myasthenic, for it is crisis that kills. There are two kinds. Myasthenic crisis is the normal crisis of the disease. The second type is the cholinergic crisis, which is the result of an overdose of the very drug that helps the myasthenic. Restoration of adequate respiratory exchange is

the first and most important task in the management of myasthenic crisis. Drug therapy in myasthenic crisis is directed towards the control of muscarinic side effects, the improvement of muscle strength, and the prevention of infections of the respiratory tract.

Before the effects of thymectomy on the course of myasthenia gravis may be fully evaluated, more carefully controlled studies are needed. At the present time, thymectomy should be limited to females under 40 years of age, whose disease progresses rapidly right from the onset.

X-ray therapy has also been tried but without conclusive results.

In conclusion, the victory against myasthenia gravis is going to be the discovery of its etiology and its cure. This goal is going to be achieved by the activities of the Myasthenia Gravis Foundation, which include the money raised, the voluntary chapters organized, the clinics supported, the research and educational grants contributed and the information amassed and disseminated.

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