Ocular myasthenia gravis

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The symptoms, clinical classification, diagnosis and differential diagnosis, and treatment of myasthenia gravis of the extraocular muscles.

Myasthenia gravis is a disorder characterized by fatigability and abnormally rapid exhaustion, with loss of strength in muscles under voluntary control and a return of strength, at least in part, after a period of rest or administration of anticholinesterase drugs.

The term myasthenia gravis comes from the Greek μυς (muscle) plus ασθενία (weakness), and from the Latin gravis (heavy), and implies a marked or severe muscle weakness. This weakness does not necessarily have to be "gravis" to be "myasthenia." Undoubtedly, because of the mild character of the symptomatology in some cases, many remain undiagnosed and untreated.1

Pathophysiology of myasthenia gravis has been demonstrated at the neuromuscular junction, and whether this be presynaptic or postsynaptic has not been settled at the present time, although evidence leans toward the former.2 There is a lack of correlation between prominent weakness and abnormal physiologic responses of certain involved voluntary muscles and any demonstrable pathology of these muscles or evidence of any central nervous system lesion.1

Since mild myasthenia gravis often remains undetected, and occasionally fulminating cases may die undiagnosed, estimation of the true incidence of this disease is difficult. An educated guess would place the incidence in the United States at one in 20 to 30 thousand. Sex and age distribution of myasthenia has been remarkably similar in major groups of patients analyzed; incidence in female to male subjects is a 3:2 ratio. However, the greatest incidence in women is in the third decade in life whereas in men it is in the sixth or seventh decade. Onset may be at any age from birth to the ninth decade.

Symptoms

One of the commonest signs of myasthenia gravis is unilateral or bilateral ptosis. Frequently ptosis shifts from one eye to the other and when this is seen it is pathognomonic of this disease.3 Occasionally the upper lid is so retracted that the eye is kept extremely wide open and patient is unable to close the eye completely. This phenomenon is always unilateral, the other lid being ptosed. This is seen in treated cases. Although ptosis may be the only evident sign of myasthenia gravis, systemic examination may reveal unsuspected weakness or fatigability in muscles other than those obviously involved. In most patients...
ptosis is accompanied by diplopia and blurring of vision. These ocular signs and symptoms, especially ptosis, are made worse by bright light. In about 70 per cent of patients, one or another of the eye symptoms described above will mark the onset of myasthenia, and after a period of time they will be seen in at least 90 per cent of all patients. Frequently after the onset of eye symptomatology, other striated muscle weaknesses will be apparent in the form of myasthenic facies caused by weakness of facial muscles. This is responsible for the snarl which may develop when myasthenic patients are asked to smile or show their teeth. As a meal progresses, weakness of jaw muscles may cause difficulty in chewing and dysphagia, which frequently results in nasal regurgitation of fluids. Difficulty in speech in the form of dysarthria, characterized by a nasal "twang," is often heard. When starting to speak the voice is relatively clear and the speech is easy to understand; as speech continues, volume of voice and clarity of speech decrease. Respiratory distress may be seen in some cases. This may be either inspiratory or expiratory depending upon muscle groups involved. In milder cases, respiratory distress occurs only during exercise. A relatively uncommon sign of myasthenia gravis is a longitudinal furrowing of the tongue called "myasthenic tongue."

The skeletal muscles most frequently involved are those of neck, shoulder, and hip girdles. Proximal leg muscles are affected more often than distal ones; extensors of upper extremities are involved more frequently than the flexors. These symptomatologies are asymmetric in most adult patients.

Early atrophic changes of involved muscle groups do occur and do not rule out diagnosis of myasthenia gravis. Ocular pain, headache, paresthesias, and other sensory changes have been noted at one time or another in about 14 per cent of patients. The pain becomes more severe as the day progresses, but it usually responds to rest or anticholinesterase medication.

Clinical classification

Symptomatology at onset does not necessarily indicate eventual total involvement. Classification of the individual patient should be dynamic, with initial classification revised as the disease progresses. As a result of careful study of over 800 patients, a Clinical Classification has been developed which takes into account not only initial symptomatology, age at onset, and sex, but also for progress of the disease. In addition to its prognostic value, this classification is a guide for selection of therapy. According to age at onset, patients are divided into pediatric and adult groups as follows.  

Pediatric group. The pediatric myasthenia gravis group includes neonatal and juvenile patients.

Neonatal group. Neonatal myasthenia gravis occurs only in infants born of myasthenic mothers and is a self-limited condition lasting no more than six weeks. It is probably caused by transmission of an etiologic factor across the placental barrier. Progression to juvenile myasthenia has been reported in only one instance.

Juvenile group. Unlike the neonatal form, clinical myasthenia gravis is not present in the mothers of these children. The juvenile form may develop at any time from birth to puberty, and tends to be permanent. In those infants in whom the disease begins at birth, there may be an apparent confusion with the neonatal form but the mother's status and permanence of the defect soon define the actual classification. Siblings and close relatives of juvenile myasthenia patients may also have myasthenia gravis. Ophthalmoplegia with severe ptosis, bilateral, partial or complete, is common in this group and is often resistant to drug therapy. Symmetrical limb involvement is also frequently present. The nature and degree of the myasthenic defect indicate inclusion of these patients into the more descriptive divisions of the adult groups below.

Adult group. Adult myasthenia gravis patients have been divided into four groups.
Group I. Ocular myasthenia. This is a localized form frequently limited to only one eye and characterized by ptosis and diplopia. This group has an excellent prognosis and, if there is no spread of myasthenic involvement to other muscle groups within two years of onset, the disease usually remains nonprogressive. Of 833 myasthenic patients, 21 per cent are in this group.

Group IIA. Mild generalized myasthenia gravis. This form is characterized by slow onset, frequently ocular, gradually spreading to skeletal and bulbar musculature. The respiratory muscles are spared. The response to drug therapy is good and the mortality rate is very low.

Group IIB. Moderate generalized myasthenia gravis. This form has a gradual onset with frequent ocular presentation, progressing to more severe generalized involvement of the skeletal and bulbar musculature. Dysarthria, dysphagia, and poor mastication are more prevalent than in Group IIA. The respiratory muscles are not involved. The response to drug therapy is less satisfactory and the patient’s activities are restricted, but the mortality rate is low.

Group III. Acute fulminating myasthenia gravis. This form has a rapid onset of severe bulbar and skeletal muscle weakness with early involvement of respiratory musculature. Progression of the disease is usually complete within six months. The percentage of thymomas is highest in this group. The response to drugs is poor, and the incidence of myasthenic, cholinergic, and mixed crises is high; the mortality rate is also high.

Group IV. Late severe myasthenia gravis. In this form, severe myasthenia gravis develops at least two years after onset of Group I or Group II symptoms. Progression of myasthenia gravis may be either gradual or sudden. This group has the second highest percentage of thymomas. The response to drug therapy and the prognosis are poor.

Some patients in Groups II and IV may demonstrate localized muscle atrophy, not correlated with disuse and not associated with any demonstrable lesions of central and peripheral nervous systems. Electromyography of involved muscle groups reveals a characteristic myopathic pattern.

Diagnosis

Diagnosis of myasthenia gravis is simple when the patient presents classical symptoms; however, diagnosis early after onset of a mild form may be difficult, and a high degree of awareness of myasthenia gravis is necessary. Of utmost importance is diligence in eliciting the following details when obtaining the patient's history: onset of weakness and its diurnal variation; effect of rest; influence of menstrual cycle, infection, and emotional stress; response to medications; tolerance of average and unusual physical activity; possible history of remissions followed by exacerbations. Shift of ptosis from one eye to the other is almost pathognomonic of myasthenia gravis. The possibility of neurotic asthenia which may closely resemble myasthenia gravis can be excluded by critical and objective assessment of alleged weakness.

The basal state (nonmedicated) is essential for thorough physical and neurologic examination. In mild cases, physical activity may be necessary to provoke muscle weakness. Although routine laboratory tests usually have no diagnostic value in myasthenia gravis, such studies as chest radiography (with tomography if indicated), thyroid evaluation, lupus erythematosus preparations, and immunologic testing of sera may be helpful. An enlarged thymus is a common finding.

Most diagnostic doubts can be eliminated through the use of pharmacologic tests, reparative or provocative, with or without electromyography and ergography. Drugs in current use are edrophonium chloride (Tensilon), neostigmine (Prostigmin), d-tubocurarine (curare), and decamethonium. Quinine is no longer advocated as a provocative test because of attendant hazards.

To detect false-positive responses to drug tests, parallel tests should be performed.
with a placebo, preferably in a double-blind fashion.

If weakness is experienced in the pharyngeal constrictors, fluoroscopic examination during swallowing of a contrast medium before and after administration of an anticholinesterase drug often has diagnostic value.

**Edrophonium chloride test.** Osserman and Kaplan developed the edrophonium chloride test for myasthenia gravis which, in its present form, is performed as follows: the patient's muscle strength is evaluated both subjectively and objectively, measuring the width of the palpebral fissure and the range of extraocular muscle movements. For the latter, the red-glass or red-bar tests are helpful. Skeletal muscles involved in the myasthenic process are tested by using the dynamometer and the ergograph. Vital capacity is measured with a ventilation meter, and chewing and swallowing are observed. Following a 4 to 6 minute rest period, 2 mg. of edrophonium chloride is injected intravenously and muscle strength is again evaluated within 30 to 90 seconds. If an inadequate response results from this dose, increments up to 8 mg. of edrophonium chloride should be tried after a 2 minute delay. If the 2 mg. dose gives a cholinergic response, the test should be repeated 30 minutes later with a dose of 0.5 to 1.0 mg. Subjective complaints of diplopia may remain unchanged after edrophonium chloride testing although the examiner may be able to demonstrate that the original weak muscle is corrected by edrophonium, and a previously uninvolved muscle is weakened by a cholinergic response. This type of reaction to edrophonium is a positive test for myasthenia gravis. The edrophonium chloride test in a patient with oculobulbar myasthenia gravis is illustrated in Fig. 1.

If one suspects that weakness is functional or the result of other muscular or central nervous system diseases rather than myasthenia gravis, one should pair the edrophonium chloride injection in a double-blind fashion with intravenous injection of a placebo. Either 20 mg. of nicotinic acid, 200 mg. of calcium chloride, or 0.3 to 0.4 mg. of atropine will be suitable for this purpose. Advantages of the edrophonium chloride test are: it can be repeated within 10 minutes; its action is rapid and transient, enabling both physician and patient to observe repeatedly the effects of anticholinesterase medication; muscarinic side-reactions are less frequent and less severe than after neostigmine, and they disappear rapidly.

**Edrophonium chloride tonometry.** Recent reports indicate that increased tension in the eyeball of the myasthenic patient is found by tonometry when edrophonium chloride is administered. To date, at The Mount Sinai Hospital, New York, we have not evaluated this use of edrophonium.

**Neostigmine methylsulfate test.** With the introduction of neostigmine, administration of this drug became the basic procedure in diagnosis. It may be given in one of two ways: (1) intramuscular injection of 1.5 mg. of neostigmine methylsulfate alone or combined with 0.6 mg. of atropine sulfate, or (2) intravenous injection of 0.5 mg. of neostigmine methylsulfate. The commonest means of testing with this drug is the intramuscular route. The patient is given an injection and re-examined at 5 to 10 minute intervals for
45 to 50 minutes, with both subjective and objective improvement or lack of it being noted. The same observations are carried out with intravenous testing; however, the response starts within one to two minutes. False-negative results with this test may occur because of the size of the dose: the patient may be sensitive to neostigmine and with the dosage used the weakness of the disease may be replaced with the weakness of overdepolarization. This test cannot be repeated with increasing dosages at the same visit; therefore, testing with a different dosage must await a subsequent visit.

**Curare test.** Occasionally, in a patient with mild, generalized myasthenia gravis, information obtained from the edrophonium or neostigmine test may be confusing. When this occurs, additional information may be obtained by using d-tubocurarine. Because persons with myasthenia gravis are very sensitive to very small doses of d-tubocurarine, utmost caution is necessary: this test should be used only in those cases in which definite diagnoses cannot be obtained with edrophonium and neostigmine tests. When performing this test, it is imperative to have at hand drugs and equipment necessary for respiratory resuscitation and also physicians thoroughly competent in their use.

**Decamethonium test.** In myasthenia gravis there is resistance of clinically noninvolved muscles to intravenous administration of decamethonium. Because severe respiratory depression may develop during the decamethonium test, the same safeguards necessary for the curare test should be provided. In normal subjects, decamethonium produces marked reduction in height of action potential and considerable muscle weakness. Subsequent injection of anticholinesterase (e.g., edrophonium) increases generalized weakness. In myasthenic subjects, relatively large doses of decamethonium cause little or no reduction in height of action potential or strength of noninvolved muscles.

Electromyography aids in diagnosis when the evidence of abnormality of the motor unit which it reveals is or is not compatible with the clinical diagnosis under consideration. Electromyographic results must be integrated with results of other tests, clinical examination, and history in arriving at a diagnosis. However, electromyography is not a necessary routine for diagnosis. Pharmacologic tests usually are reliable and are not difficult to perform in clinic or office. The real value of electromyography is seen when other tests produce equivocal results or when objective tests are needed because of difficulty in interpreting clinical data, even though compared with a placebo test.

Breinen has developed a technique combining electromyography without stimulation and the edrophonium test. This technique requires subconjunctival insertion of fine gauge, concentric electrodes directly into extraocular muscles with the use of only topical anesthesia. This is a simple, practical procedure devoid of harmful effects; the only complication is the occasional occurrence of a subconjunctival ecchymosis, which is a cosmetic blemish of brief duration. Muscle action potentials are suitably amplified, displayed on dual-beam oscilloscopes, and recorded with moving film photography. Utilization of electromyography to evaluate drug action has revealed a striking and characteristic muscle response even though gross improvement in motility may not be evident.

In the past decade, immunologic studies have shown that an antibody may be found in the sera of 40 per cent of myasthenic patients. Weiner and Osserman have found this antibody in 32 per cent of Group I ocular myasthenia patients studied. Although this test at present cannot be used as a completely diagnostic procedure, it lends support to clinical and pharmacologic observations.

**Differential diagnosis**

Isolated ocular symptoms, either ptosis or diplopia, occur in many neurologic dis-
orders. Characteristic of strabismus seen as a congenital or heredodegenerative process is the static, nonprogressive nature of the ocular sign from birth on. But even this need not be an absolute differentiation. A patient has been seen who had congenital strabismus of the external type superimposed upon which myasthenia developed; its effects were limited to an increase in the degree of external rotation of the left eyeball and demonstrable only by the response of the eyeball to anticholinesterase medication. Congenital ptosis of the lids is perhaps most often confused with myasthenia gravis, but this, too, is a disturbance exhibited at birth and nonprogressive in nature. In these cases familial history, the static nature of the ptosis, the history of its presence since birth, as well as negative responses to anticholinesterase medication serve to differentiate the condition from myasthenia gravis.

Involvement of oculomotor, trochlear, or abducens nerves by any number of processes, including infections, trauma, and neoplasm, produces characteristic ocular palsies which do not have the fluctuating characteristics of myasthenia gravis. Myasthenic involvement of external ocular muscles may closely simulate any of the ocular palsies. It has been said that, when myasthenia gravis discretely involves one eye in a manner which produces what appears to be a typical third nerve palsy, a differential point of significance is absence of involvement of the pupil. Since peripheral involvement of the oculomotor nerve is almost invariably accompanied by an internal as well as external ophthalmoplegia, this is used as a distinguishing characteristic. There are reports in the literature of isolated cases of myasthenia gravis involving the ciliary muscle. In such rare instances, ultimate differentiation may depend upon response to anticholinesterase medication.

When diplopia and/or ptosis are accompanied by localized headache over the involved eye or by pain in the eye, one must think seriously of an intracranial aneurysm. A bruit heard over the eye is characteristic of aneurysm. If there is diminished corneal sensation in the involved eye, this diagnosis becomes a probability and myasthenia gravis is excluded. In cranial neuropathies associated with diabetes, syphilis, diphtheria, and the so-called Guillain-Barré syndrome, the total clinical picture is essential for differentiation of these conditions from myasthenia gravis. If myasthenia is still suspected, response of symptoms to anticholinesterase medication again becomes the diagnostic feature. In multiple sclerosis, ocular symptoms are most often accompanied by nystagmus, and true nystagmus is rarely seen in myasthenia gravis. Nystagmus caused by multiple sclerosis results most often from involvement of the median longitudinal bundle, with resultant horizontal and vertical nystagmus diagnostic of involvement of the brainstem. Temporal pallor of the optic disks is commonly seen in multiple sclerosis. Of course, if there is evidence of central nervous system involvement, the diagnosis is multiple sclerosis.

Unilateral ptosis as an isolated sign or symptom may be congenital, or due to involvement of the ocular sympathetic nerves or the oculomotor nerve, or it may be myasthenic in origin. Congenital ptosis, as previously described, exists from birth and does not vary. Involvement of ocular sympathetic nerves produces a Horner's syndrome, in which case ptosis is accompanied by ipsilateral miosis, enophthalmos, and diminished sweating over the same side of the head and face. Ptosis produced by third nerve palsies is accompanied by dilatation of the pupil as well as specific ocular palsies related to involvement of the third nerve. In these cases, the eye is commonly deviated externally because of unopposed pull of the external rectus muscle. Diagnosis of myasthenia gravis is confirmed by the response of the ptosis to anticholinesterase medication.

Weakness exclusively in the limbs may resemble that present in muscular dystrophy, motor neuropathies, or amyotonia con-
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Symptoms of chronic fatigue may mimic those of myasthenia gravis, but response to specific testing is different. Endocrine disorders and the "Eaton-Lambert-Rooke syndrome" also may simulate myasthenia gravis. No therapeutic test is absolutely pathognomonic. Hysteria can simulate almost any symptomatology known. False-positive or false-negative edrophonium or curare tests can result in errors in diagnosis. Proper testing with placebos in the former usually precludes this error. However, Schwab and Perlo\textsuperscript{10} reported a group of patients having a variety of neurologic syndromes who had definite false-positive reactions to edrophonium and neostigmine testing. Rare false-negative results occur when either negligible objective response is noted or overdosage with the test drug causes a cholinergic reaction. To rule out false-negative responses, any syndrome of muscle weakness, not accompanied by alteration of tendon reflexes, in which there is some improvement of strength after administration of correct amounts of neostigmine or edrophonium should be considered to be myasthenia gravis. A history of remissions in the past or evidence of thymic abnormality tends to confirm the diagnosis. A positive edrophonium or neostigmine test serves to confirm the clinical impression derived from history and physical examination. When tests are properly performed with placebos and mechanical and electrical measurements are used, the diagnosis rarely remains in doubt.

Treatment

Pharmacologic therapy depends upon a group of relatively short-acting potent anticholinesterases.

\textbf{Choice of drugs.}

\textit{Neostigmine bromide.} This drug has been used effectively for three decades. It is not habit forming; the requirement decreases if myasthenia remits. Its two disadvantages are short duration of action (approximately two hours) and side-effects (sweating, salivation, lacrimation, and epigastric distress including nausea, abdominal cramps, diarrhea, and fasciculations) which are pronounced and sometimes difficult to control even with atropine sulfate. Because atropine sulfate obscures early signs of incipient overdosage it should not be used routinely. Neostigmine bromide is available as a 15 mg. scored tablet and usually is prescribed for use every two to three hours. Dosage is variable, not only between patients but also for the same patient on the basis of stress from physical activity, menses, infection, or emotional trauma. While no specific dose can be recommended, it usually is safe to start a new patient on one tablet three times a day.

\textit{Pyridostigmine (Mestinon) bromide.} This drug is an analogue of neostigmine and more effective in relieving myasthenia symptoms in small muscles innervated by cranial nerves, particularly those involved in ptosis, diplopia, and dysarthria. Its diurnal duration of action is approximately half an hour longer than that of neostigmine. However, one of the chief advantages of pyridostigmine is its longer nocturnal action, obviating administration during the night and enabling even the patient with dysphagia to swallow the first dose in the morning. Another salient advantage of pyridostigmine over neostigmine is its smoother action, low incidence of muscarinic side-effects, and resultant marked decrease in need for routine use of atropine sulfate. Although the range of therapeutic and toxic levels of pyridostigmine is much greater than that of neostigmine, the usual side-reactions do occur with overdosage. Most patients using pyridostigmine are satisfied with the sustained feeling of well-being throughout the day. Pyridostigmine bromide is available as a \(\frac{1}{4}\)-scored 60 mg. tablet, usually replaceable tablet-for-tablet with neostigmine, and prescribed every three to four hours in most cases. Prolonged-action pyridostigmine bromide is available as a scored "Timespan" tablet containing 180 mg., which has the immediate effect of a reg-
ular 60 mg. tablet. Its slow release of pyridostigmine produces a duration of action approximately 2 to 2½ times that of a regular pyridostigmine tablet. Its primary advantage is its production of extended nocturnal relief; frequently it is prescribed for the last dose of the day, regardless of which drug may be used throughout the day.

**Ambenonium (Mytelase) chloride.** This drug is a bis molecule and is wholly different in structure from neostigmine or pyridostigmine. Its effect on involved peripheral muscles is excellent and results in more sustained increase in strength. For bulbar myasthenia ambenonium is midway between pyridostigmine and neostigmine in value. While its action is definitely longer than that of neostigmine, and perhaps slightly longer than that of pyridostigmine for diurnal use, its nocturnal effect is the same as that of regular pyridostigmine. It has fewer toxic side-effects than neostigmine, but more than pyridostigmine, and they differ in nature. More prominent are central nervous system side-effects such as headache. Other early signs of overdosage are fasciculations and muscular weakness. Gastrointestinal side-reactions are less common, but they do appear later when overdosage is imminent. For the patient on a respirator, ambenonium has the distinct advantage of causing less bronchial secretions than do other anticholinesterase drugs. Ambenonium chloride is available as scored tablets of 10 and 25 mg. Approximately 6 mg. of ambenonium chloride is equivalent to 15 mg. of neostigmine bromide or 60 mg. of pyridostigmine bromide. Ambenonium should be started cautiously with a 5 mg. dose and gradually increased to therapeutic levels.

Instillations of strong, long-lasting anticholinesterases such as echothiophate iodide (Phospholine iodide) have been advocated for treatment of ptosis and extraocular muscle weakness. When effective, these drugs usually relieve ptosis better than diplopia. These long-lasting anticholinesterases should not be administered unless red-cell esterase activity can be determined. They may be used in combination with oral neostigmine or pyridostigmine, but never with ambenonium, as there is a marked synergism with the latter, which may cause cholinergic crisis.19

**Combinations.** When a single drug will not effect adequate control, some patients may be treated more satisfactorily with combinations of anticholinesterase drugs. Pyridostigmine and ambenonium are more effective in predominately bulbar involvement, whereas neostigmine and ambenonium are better for control of peripheral muscular weakness. Combined drug therapy should be reserved for patients with relatively stable myasthenia and of proved intelligence in handling their own drug dosages.

**Adjuvant drugs.** In isolated cases, use of ephedrine sulfate and potassium salts still meets with some favor and results in occasional improvement. Ephedrine sulfate, 25 mg. three times a day, gives an increase in strength to some patients not fully controlled with anticholinesterase therapy alone. Potassium salts in liquid form, 15 mEq. three times a day, may also be helpful. Instead of potassium salts, intracellular potassium-sparing drugs such as spironolactone (Aldactone-A), 25 mg. four times a day, or triamterene (Dyrenium), 100 mg. twice a day, may be employed. Thus, ephedrine sulfate and any one of the three adjuvants affecting potassium may be used separately or together in addition to the basic treatment of anticholinesterase medications. If no improvement is evident, adjuvant drug therapy should be discontinued.

Thymectomy and radiotherapy are not indicated in the treatment of ocular myasthenia, and the use of adrenocorticotropic hormone (ACTH) has not proved to be of value in this form of the disease.19

**Edrophonium test in management**

In drug management of the myasthenic patient17, 20 there are three ways to determine optimal dosage for the selected drug: (1) use of empiric dosage by means of
clinical judgment; (2) use of the edrophonium chloride test; and (3) use of intravenous titration with pyridostigmine bromide or neostigmine methylsulfate. Extreme caution is required because of the serious hazard involved in the intravenous titration.

When the diagnosis of myasthenia gravis is established, treatment with one of the anticholinesterase drugs is started. One may empirically prescribe a tablet for use at specific intervals, usually three times a day, and observe duration of action, improvement in striated muscle strength, and occurrence of side-effects. The dosage is gradually increased until the patient obtains maximal improvement with minimal side-reactions.

For intravenous titration one gives small increments of pyridostigmine or neostigmine at 2 minute intervals until maximal improvement is obtained. This intravenous dose can then be translated into oral dosages according to a table of equivalents (Table I).

After the patient has been started on an anticholinesterase drug by either of the above methods, dosage regulation can be accomplished by performing an edrophonium test one hour after the patient has taken his treatment drug. Three possible responses are presented in Table II.

If improvement of muscle strength follows administration of edrophonium, the oral dosage may be increased by one quarter to one half of a tablet. If the patient becomes worse, the oral dosage should be decreased by one fourth to one half of a tablet. If the patient shows no change in strength, the dosage is adequate and should not be adjusted at that time. If the response is adequate but the patient is still poorly controlled, use of adjuvant drugs or possible reassessment of therapy should be considered.

In management, there are variations in amounts of edrophonium chloride used. One must differentiate between dosages recommended for diagnostic testing and dosages required for regulation and control of treatment medications. Our recommended test dosage for regulation of the required amount of anticholinesterase drug, based on thousands of tests, is 0.2 ml. (0.2 mg.) of edrophonium chloride administered intravenously one hour after intake of the oral treatment drug. With this small dose, edrophonium per se causes little interference in reaction; effects observed clearly delineate a response based on the oral drug administered one hour earlier. Other investi-
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In some myasthenia gravis patients it is important to compare the results of the edrophonium test with those of a placebo injection. The physician must be acutely aware of the fact that the myasthenic patient quickly learns to differentiate the effects of edrophonium and placebo.

The edrophonium test can be used to determine the frequency as well as the quantity requirement of anticholinesterase medication, although this use is not important in the patient who is easily controlled. Where regulation is difficult, especially in the seriously ill myasthenic patient, edrophonium testing should be performed at the end of a dose period to avoid administration of oral medication before the patient demonstrates a clear myasthenic response.

The frequency of management edrophonium tests for the patient admitted to hospital for regulation should vary from a daily basis to every two or three days. Changes in oral medication usually do not show their full effect in less than 24 to 48 hours. Because of possible differences in drug requirements during the day, it is advisable to test oral dosages administered during different periods.

In Group I (myasthenia with ptosis and/or diplopia), if edrophonium testing results in complete relief of symptomatology, anticholinesterase drugs should be started. However, two types of patients are not candidates for drug therapy: (1) those who have negligible improvement with edrophonium testing and (2) those whose ptosis responds better than does the extraocular muscle weakness, thereby giving prominence to the more disabling aspect of their problem. In these patients, resort to mechanical aids is helpful. Dark glasses may help to relieve ptosis; a plastic or wire lid crutch attached to the eyeglass frame may be worn to correct the ptosis. It may be advisable to use an eye patch or opaque corneal lens to obscure the vision of one eye and thus relieve the diplopia. Prism lenses may be prescribed to correct mild degrees of extraocular muscle weakness; however, the degree of prism needed varies with the patient's myasthenic condition, which often varies with time of day and activity. Thus, prisms are rarely successful in relieving diplopia.

Various operations have been performed to correct ptosis and diplopia. In myasthenia gravis, surgery is not justified, because the patient's condition changes with time. Unless edrophonium testing and ocular electromyography indicate that the muscle involved shows little evidence of response to neuromuscular treatment drugs, surgical procedures may prove to be a handicap.

REFERENCES

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