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Myasthenia Gravis: Analog Computer Model

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An analog computer model of the saccadic eye movement system was constructed with provisions for deficits in the extraocular muscles. The model included a fixing and patched (open looped) eye, either of which could be paretic. Simulating specific neuromuscular lesions, such as tonic fiber deficits and muscle pareses, with integrator leaks and saturation circuits, respectively, produced saccadic responses which duplicated those found in each eye of patients with ocular myasthenia gravis. Simulation of the compensatory central gain increase produced the typical eye movements of a high-gain saccadic system which matched those after edrophonium administration to the myasthenic patients. The model allowed the testing of hypotheses concerning the interrelationship between the primary neuromuscular deficit and the secondary central changes.

INTRODUCTION

In the two previous reports (9, 10), we discussed the complex saccadic eye movements and the varying effects of fatigue and edrophonium on the saccades of patients with ocular myasthenia gravis. The abnormal eye

Abbreviations: n—normal; s—slow; o—overshoot with glissadic return; u—undershoot with glissadic return; do—dynamic overshoot; m—multiple, closely spaced saccades; dd—discrete deceleration; O—orthometric; HR—hypermetric; HO—hypometric; SEM—slow eye movement; SP—saccadic pulse; DSP—double saccadic pulse; SWJ—square wave jerk; MSWJ—macro square wave jerk; MSO—macro saccadic oscillation; r—ramp drift; p—pendular drift; t—triangular drift; e—exponential runaway; C—central; P—peripheral; T—target position; pos—eye position; vel—eye velocity.

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movements resulted from both the effects of the neuromuscular disease as well as compensatory central nervous system alterations in innervation patterns in response to the muscle weakness. The determination as to whether a specific eye movement resulted from the myasthenia, the central compensation, or both was often difficult from analysis of the eye movement tracings. For this reason, we constructed a computer model to simulate the saccadic eye movements of ocular myasthenia in the expectation that it might provide insights into the interrelationships of the alternative mechanisms.

METHODS

Model. The model was implemented on a Systron-Donner SD-80 analogue computer and the simulated eye movements were recorded on the same rectilinear Beckman Type R Dynograph used for patient recording. The position records were electronically differentiated to provide velocity information; the full system bandwidth of the recording system was DC to 100 Hz.

We previously developed a model for the study of gaze-evoked nystagmus (1), but this proved too limited in capability for our present purposes. The earlier model could only generate eye movements in one horizontal direction and although it contained a corrective loop which utilized the tonic level of innervation to determine eye movement accuracy (the internal monitor), there was no feedback from simulated eye position (i.e., the visual loop). Such an omission precluded correction of errors caused by improper myasthenic extraocular muscle responses to correct and appropriate central innervation. Moreover, the previous model contained only a single eye; we needed to study the effects of switching fixation between the normal and diseased eyes. Consequently, we revised the earlier model to permit appropriate simulation of the eye movements of our myasthenic patients in addition to gaze-evoked nystagmus.

Block Diagram. The block diagram in Fig. 1 provides an overview of the organization of the model. The desired target angle (θ_T) is set and is compared with current eye position (θ_E) which is initially zero. This retinal error (ϵ) and the eye position neural firing command (E_C) are then used to generate a perceived target position (T_P). The difference between the calculated estimate of the target position (T_P) and the tonic neural activity (E_C) yield a perceived error (ϵ_P). This estimate of the difference between the actual and intended eye positions provides the input to the pulse generator portion of the saccadic mechanism. The generator circuitry produces the phasic component of saccadic innervation and its output goes to the neural integrator which provides the tonic component of innervation. The outputs

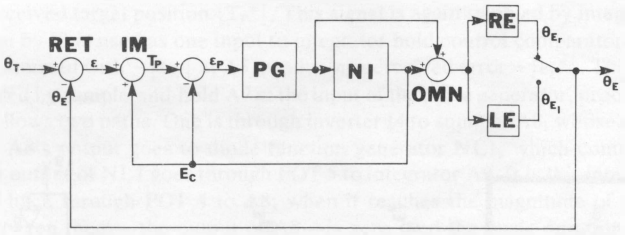

FIG. 1. Block diagram of model used to simulate the saccadic eye movements of patients with myasthenia gravis. The target angle (θ_T) is compared to the angle of the eye (θ_E) at the retina (RET) generating the error signal (ϵ). The internal monitor (IM) compares ϵ with a copy of the eye position command (E_C) producing perceived target position (T_P). The difference between T_P and E_C is perceived error (ϵ_P) which drives the pulse generator (PG) to produce the pulse of neural activity necessary for a saccade. The neural integrator (N I) produces the step of activity required to hold eye position and the sum of the pulse and step drive the ocular motor neurons (OMN) of each eye (LE and RE). The choice of which will be the viewing eye is made by the switch which chooses θ_{E_r} or θ_{E_l}.

of both the pulse generator and the integrator are then summed at the ocular motor nuclei to produce the pulse–step of agonist activity necessary for the generation of a saccadic eye movement (5, 7) and this is then conveyed to the representations of the two eyes. Although both eyes utilize the same basic linear representation, one eye has a number of different simulated myasthenic muscular defects. By selecting which eye (θ_{E_r}) or (θ_{E_l}) will be used to provide the visual feedback (θ_E), we could simulate the effects of monocular viewing and observe the differences in response depending on whether the diseased or normal eye is viewing.

Model Operation

An analog computer simulation of the model outlined above is illustrated in Fig. 2. Because of space consideration, we could not include the exact mathematical expressions in the figure; the following description does utilize these expressions for each variable. The main pathways are indicated by the heavy lines; the lighter lines are control and timing pathways, some of which were a result of modeling shortcuts or the requirements of the SD-80. The target input (θ_T) is at the upper left (potentiometers, POT 1–3; switches, S1–S4; amplifier, A1). Here at the input and also at the output (θ_E), voltage is proportional to the angle represented; elsewhere in the model the voltage corresponds to neural firing rate. Targets to the right are represented by positive and those to the left by negative voltages. The negative of the target position, θ_T, (A1 output) goes to one input of summer A2, whose other input is the position of the "uncovered" eye (θ_E). The retinal error signal, ϵ (A2 output), goes to the initial condition input of integrator A3, used here as a sample-and-hold by strobing its reset bus. This inverted sampled error ($-\epsilon^*$) goes through one of the inverter–relay stages (I2 and K1a) to allow the portions of the model which can operate only on one polarity signal to be used in the generation of bidirectional eye movements. (This is not intended as a representation of a physiological function but simply to conserve amplifiers.) The output of this stage ($-|\epsilon^*|$) goes through relay K4 to summer A4, where it is summed with the inverse of the magnitude of the eye command signal, $-|E_C|$, to

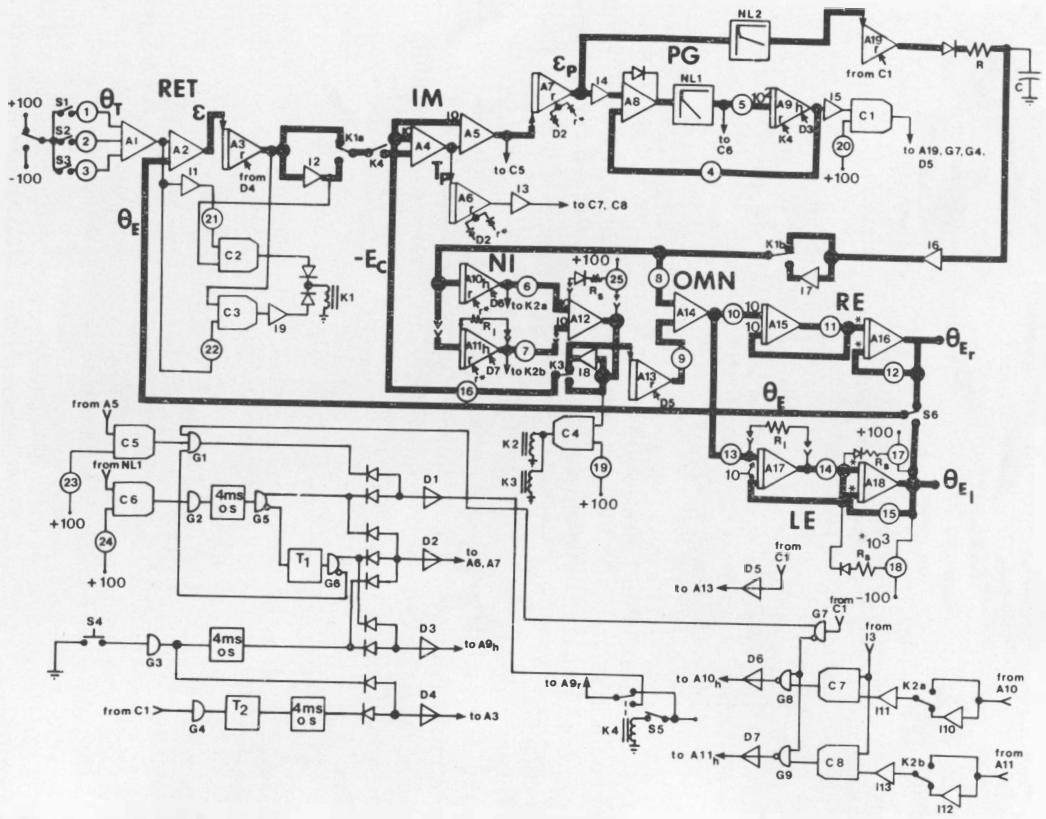

FIG. 2. The schematic of the analog computer model of the saccadic mechanism in myasthenics. For details see text.

produce a perceived target position $|T_P^*|$. This signal is again sampled by integrator A6 and after inversion by I3 is used as one input to integrator hold control comparators C7 and C8. $|T_P^*|$ also is summed with $-|E_C|$ at A5, producing perceived error $-|\epsilon_P^*|$. This error signal is again sampled by sample-and-hold A7 at the input of the pulse generator, producing $|\epsilon_P^*|^*$, which then follows two paths. One is through inverter I4 to summer A8, whose other input is from POT 4. A8's output goes to diode function generator NL1, which controls saccadic duration. The output of NL1 goes through POT 5 to integrator A9. It is this integrator whose output is fed back through POT 4 to A8; when it reaches the magnitude of $-|\epsilon_P^*|^*$, the difference between them—the output of A8—is zero, and the pusle duration determined. Thus, the circuit works in bootstrap fashion. The pulse is terminated when A9 is reset by driver D1, via relay K4. The other path taken by the output of A7 is to the other nonlinearity, NL2, which is responsible for pulse height and the nonlinear saccadic velocity–amplitude relationship. The output of NL2 is sampled by A19. This element functions as a nonholding sampler; it is an integrator patched as an ordinary amplifier, receiving its input at its initial condition terminal; therefore, it shows an output only as long as there is pulse on its reset bus. The duration of the pulse on the reset bus of A19 is determined by the duration of the pulse produced by A9 which is shaped by I5 and C1. A19 thus produces the model pulse component of innervation whose height and duration reflect the magnitude of the required saccade. This pulse is shaped by the 0.1-MΩ resistor (R) and 0.0022 μf capacitor (C) following A19. The pulse then goes through inverter I6 to another polarity-maintaining circuit, here composed of I7 and K1b. It then goes along two paths. One leads to the neural integrator, composed of A10 and A11 and the other, through POT 8, to summer A14. The neuronal pool (A10 and A11) is represented by two amplifiers permitting, if desired, a percentage of these neurons to be nonfunctional, as if by disease. Their outputs are scaled by POT 6 and POT 7 and summed by A12, producing the step of innervation. The step signal then goes in two directions. One is through the polarity-maintenance circuit of I8 and K3 to POT 16, whose output goes to A4. The other is to comparator C4, which controls relays K2 and K3. The inverted step component, taken from the output of I8, is applied to the initial condition terminal of sample-and-hold A13 and adjusted in level by POT 9; the resulting signal then goes to summer A14, where it is summed with the pulse (via POT 8) to produce the pulse–step of innervation needed to produce a saccade. A13 acts to inhibit the passage of the step to A14 during saccades and thus preserves the pulse–step envelope; without this inhibition the pusle envelope would not be a constant firing rate. Because only conjugate eye movements are modeled, the pulse–step is fed via POTS 10 and 13 to both eyes.

The eye plant representations are simple second-order linear models (time constants of 150 and 7 ms) consisting first of integrators A15 and A17 for the two eyes, respectively, whose outputs go through POTS 11 and 14. The outputs of these pots are fed back to the inputs of their respective integrators and sent to the second stage integrators A16 and A18. The integrators have feedback POTS 12 and 15. Hence, each eye is represented by a pair of cascaded leaky integrators. The position of either can be selected by S6 to be fed to A2 for comparison with the target position; that is, either eye can be selected as the viewing eye, with the other under cover.

The remaining elements of the model (shown connected by the lighter lines) perform the necessary control functions required for the proper operation of the model. These are generally based on the electronic characteristics of the analog computer elements rather than physiological parameters and will only be discussed briefly.

Comparators C7 and C8 insure that integrators A10 and All will integrate only if they are in error (i.e., their outputs do not correspond to desired eye position). Relays K2 and K3 (controlled by comparator C4) as well as relay K1 (controlled by comparators C3 and C4) are necessitated by the modeling technique of using a unidirectional pulse generator for

bidirectional initial and corrective saccades. The timing circuits T_1 (200 ms) and T_2 (50 ms), as well as the 4-ms one-shots, insure proper timing of reset, sample, the hold signals in the comparators C5 and C6 to either the last saccade (C6) or the appearance of an erroneous eye command (C5). Integrator leaks (R_l) and saturations (R_s) are shown for both central (A11 and A12) or peripheral (A17 and A18) deficits.

Myasthenic Simulation. The primary defects in ocular myasthenia are in the plant. One, initially postulated by Yee *et al.* (12) is an impairment in the tonic fibers (which hold the eyes in their intended position) and relative sparing of the phasic fibers (which get the eyes to that position). This is simulated by placing a resistor around the first integrator, A17, which has the effect of greatly increasing its "leakiness" (time constant reduced to 60 ms). Although the transient response of the integrator is somewhat reduced, a much greater effect is reflected in the inability of the eyes to maintain a tonic level. Another easily simulated myasthenic defect is paresis of the extraocular muscles. This is accomplished by placing a saturation circuit around the output integrator, A18, so that saccades within a given amplitude range are normal, whereas the gain is decreased for larger movements. The point of onset and the degree of hardness of this saturation can both be adjusted.

The secondary central compensatory mechanisms in ocular myasthenia usually involve increased innervational levels for saccades in response to paresis of an extraocular muscle. When this paresis is temporarily relieved by the administration of edrophonium, the supranormal central innervation is reflected by saccadic overshoot dysmetria. This is accomplished in our model by inserting a gain greater than one in the forward path (e.g., between K1a and K4) which simulates an increased central saccadic gain.

RESULTS

The first requirement for our model was an ability to simulate normal saccades, conjugate in the two eyes, as demonstrated in Fig. 3. The saccades had normal orthometric trajectories (O_n). In all figures, the movements of the viewing eye are described by the short-hand notation developed by Schmidt *et al.* (9). This notation, which was necessary to describe adequately both the metrics and trajectories of saccades in myasthenic patients, will facilitate comparisons between outputs of the model and eye movements of the patients; it is included for the reader's convenience.

Our clinical studies disclosed a preponderance of hypometria in 9 of the 10 patients, occasional orthometria in 4, and significant hypermetria in 1. To create hypometria, we produced a tonic deficit in the model's left eye by placing a 100-Ω resistor in parallel with the feedback capacitor of the first integrator in the plant simulation. With the left eye fixating, this produced a

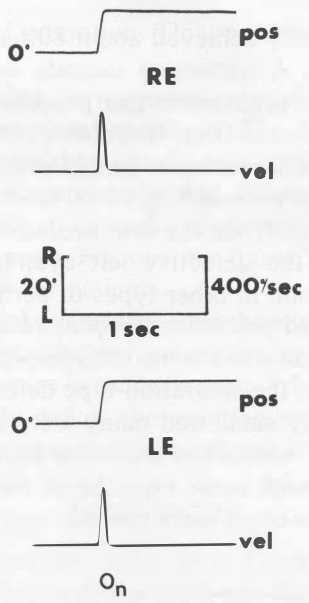

FIG. 3. Orthometric saccade with normal trajectory (O_n) produced by model. Both position (pos) and velocity (vel) of the right (RE) and left (LE) eyes are shown in this figure and Figs. 4 through 6.

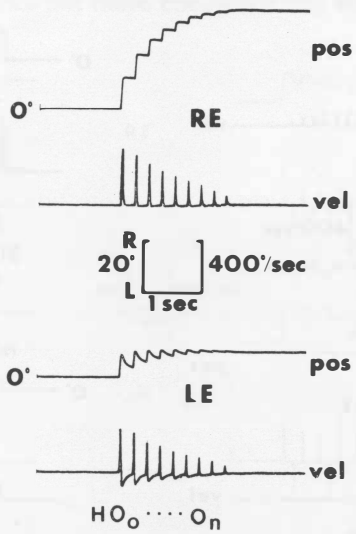

FIG. 4. Model responses of a tonic deficit in the left eye showing hypometric saccades with overshoot trajectories (HO_0) and the terminating normal orthometric saccade (O_n). Note the eye under cover (RE) overshoots the target. (See text for explanation.)

response which transiently achieved about 80% of the desired value but which rapidly decayed. A corrective saccade was then required which displayed the same characteristics. The process was repeated until the target eventually was reached (Fig. 4). This type of hypometria (HO_o---O_n) was common in myasthenic patients. In this situation the right eye under cover, which could not be contributing visual feedback, was intact so that it reached the target correctly on the first saccade. Subsequent corrective saccades, required by the defective left eye, caused the right eye to overshoot; this is common in other types of peripheral palsies (2).

The next defect studied was uniocular paresis (Fig. 5a). Again, with the affected eye fixating, there was a series of hypometric saccades. Unlike the previous case, however, the saturation-type defect caused the corrective saccades to be relatively small and many were needed to complete the movements. A "softer" saturation produced fewer and larger corrective saccades (Fig. 5b). As with some myasthenic patients, saccades smaller than the angle of paresis onset were normal, and larger movements were

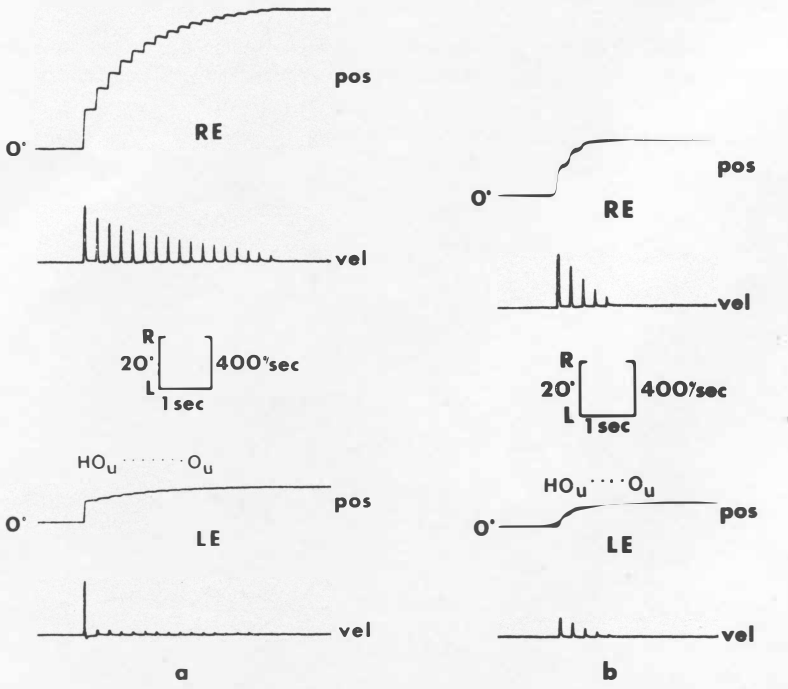

FIG. 5. Model responses of pareses in the left eye illustrating hypometric saccades with undershoot trajectories (HO_u) and the terminating undershooting orthometric saccade (O_u). Pareses are modeled by a hard (a) and soft (b) saturation.

impossible with the hard saturation. This response (HO_u--O_u) is similar to that seen in patients.

The effects of increasing the responsiveness of extraocular muscles by administering edrophonium are illustrated in Fig. 6, which shows two types of model responses. Where the saccadic gain was between one and two, a static hypermetria (HR) occurred (Fig. 6a). When the gain rose transiently above two, a burst of macro saccadic oscillations (MSO) was produced, decaying as the gain dropped (Fig. 6b). We found MSO after edrophonium administration in one of our patients.

Yee *et al.* (12) reported occasional overshooting in ocular myasthenia. We attempted to simulate this on our model by producing both a tonic deficit and a central increase in saccadic gain. When the gain increase was sufficient to just offset the deficit, the resulting waveform was orthometric but had an overshoot trajectory (O_o) as shown in Fig. 7

DISCUSSION

Our model, unlike those of Collins (4) or Clark and Stark (3), does not provide a detailed simulation of the plant nor does it simulate two of the centrally generated saccadic mechanisms found in both normal and myastenic subjects (e.g., dynamic overshoots and multiple, closely spaced saccades). Rather, like Zee *et al.* (13), we attempted to produce a model, less detailed in specifics but more encompassing in scope, including both

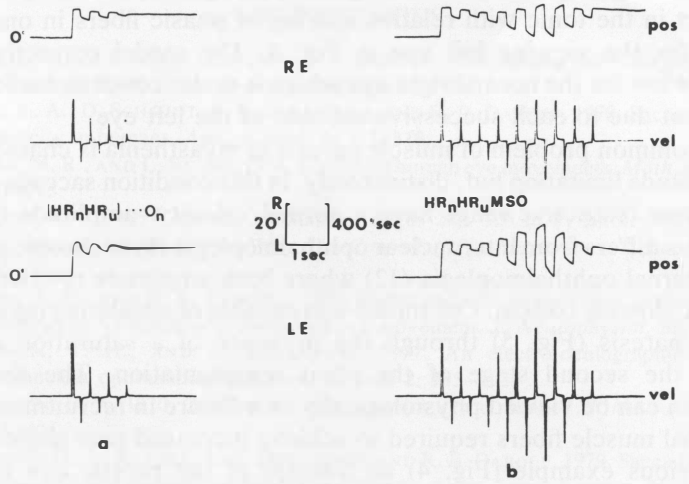

FIG. 6. Model responses to simulation of saccadic gain increases as in administration of edrophonium to a myasthenic patient. Hypermetria (HR) shown in (a) and, for even higher gain, macrosaccadic oscillations (MSO) shown in (b).

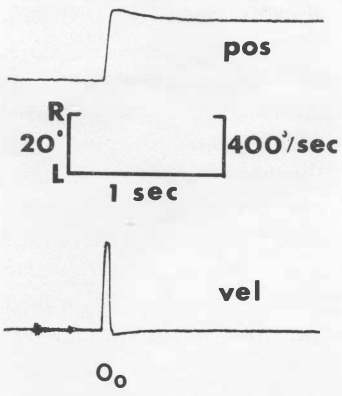

FIG. 7. Simulation of the response caused by a tonic defect and an equivalent central adaptation (i.e., increased saccadic gain) producing an orthometric response with an overshoot (O_o).

central and peripheral elements required to study the possible mechanisms underlying the variety of eye movements seen in-ocular myasthenia.

The first test of a model is its ability to simulate normalcy. This model did produce the pulse–step of innervation required to produce a saccade showing velocity–amplitude characteristics within the normal limits (8). More importantly, when proposed defects were made in the model, eye movements appropriately simulating those in myasthenia were produced. A defect in the tonic with relative sparing of phasic fibers in one eye is shown for the viewing left eye in Fig. 4. The model correctly obeys Hering's law for the normal right eye which is under cover and is forced to overshoot due to each successive saccade of the left eye.

The common problem of muscle paresis in myasthenia is characterized by amplitude limitation but, distinctively, in this condition saccades within the narrow restrictive range have a normal velocity–amplitude relationship. This differs from internuclear ophthalmoplegia (6) or chronic progressive external ophthalmoplegia (12) where both amplitude restriction and saccadic slowing coexist. Our model was capable of simulating myasthenic muscle paresis (Fig. 5) through the presence of a saturation element around the second stage of the plant representation. The amplitude limitation can be viewed physiologically as a failure in recruitment of the additional muscle fibers required to achieve increased gaze angles. As in the previous example (Fig. 4) an attempt of the paretic eye to move beyond its amplitude restriction causes the normal, covered eye to far overshoot the target. The heightened innervation which the brain stem uses to overcome the paresis overdrives the healthy eye (Fig. 5). As with cranial

neuropathy with impaired extraocular movement (2), the central nervous system responds to ocular myasthenia by increasing innervational activity in an attempt to compensate for the impairment. When there is sudden enhancement of the peripheral responsiveness through the administration of edrophonium, the increased innervation is unmasked. The functional improvement in the extraocular muscles causes the eye to overshoot the target (Fig. 6). After an appropriate latency, a corrective saccade is attempted back to the target but also overshoots. If the increased saccadic gain lies between one and two, the subsequent sequence of corrections eventually leads to correct eye position on the target. If the increased gain exceeds two, an increasing macro saccadic oscillation results. Both conditions are illustrated in the model (Fig. 6). The oscillation resembles that seen in cerebellar disease (11); the same basic mechanism of increase in the visual feedback loop gain is responsible for the oscillation with cerebellar disease and in myasthenic muscles following edrophonium. The difference is the location of the gain increase within the loop.

This type of model analysis is analogous to experimental models and neurophysiological studies in laboratory animals used to understand disease mechanisms. It provokes close examination of the effects of proposed pathological processes and allows us to test hypotheses concerning mechanisms in a situation where *in vivo* studies are impossible. We are thus able to better understand the origins of the ocular motor disturbances in myasthenia gravis.

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