Chapter 12

CLINICAL DISORDERS OF OCULAR MOVEMENT

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I. INTRODUCTION

A. Definition of Approach

The study of "experiments of nature" (i.e., ocular motor pathology) can provide valuable insights into *normal* ocular motor physiology which may be impossible to learn from the study of normals. After nature has stressed the ocular motor system in various specific ways, its responses demonstrate inherent abilities, adaptabilities, and limitations not obvious from the study of normal subjects. The extension of clinical studies in patients by a modeling approach has further added to our knowledge of the abnormal and normal ocular motor system.

The model, to the bioengineer, is like the experimental animal to the physiologist; both are substrates upon which hypotheses can be tested quantitatively. The distinct difference between the physiologist's animal and the bioengineer's model is the fine control one has over the exact type, placement, and extent of the lesions administered to the latter. All of the constraints required for a good model of normal ocular motor function (close conformity to known anatomy and neurophysiology), apply to models of ocular motor pathology. In addition, models of disturbed eye movements must respond to appropriate "lesions" in a manner which duplicates the clinical manifestations in patients. If the model (hypothesis) is a good one, it will respond normally before it is "lesioned" and exhibit the appropriate specific abnormalities after the "lesion" is placed.

B. Value of Approach

With the modelling approach to ocular motor pathology, one is forced to think logically about function and interactions of subsystems in a framework defined by specific quantitative assumptions. As much can be learned from a negative test of the hypothesis (model) as from a positive test; the redefinition of its parts caused by the model's failure to respond properly to a stimulus may yield more insight into ocular motor function than a proper response.

In this chapter, we will discuss models of eye movement disturbances starting at the plant (the extraocular muscles) and working rostrally through the cranial nerves to the central nervous system.

II. PLANT DISORDERS

A. Ocular Myasthenia

Myasthenia gravis (MG) is a motor disorder believed to be secondary to blockade of the acetylcholine receptor at the neuromuscular junction.[1] The extraocular muscles seem preferentially involved, as almost all cases ultimately manifest, in eye muscle weakness. The study of ocular myasthenia is complicated by the fact that the neuromuscular deficit in the ocular motor plant is nonstationary resulting in saccade-to-saccade variability. Plastic changes in the central saccadic gain can only correct for some average deficit, however. The resultant eye movements, although predominantly hypometric, are at times orthometric or even hypermetric. An adequate model of such stochastic variation requires nonstationary coefficients in the plant parameters. An attempt to match the temporal randomness of the neuromuscular junction efficiency would result in an extremely complex model. We therefore chose to model the system by simulating the different states of plant efficiency with specific parameter adjustments and then study the system response to each state separately. This simpler model common in myasthenic patients. Figure 1a is a block diagram of the model, which was simulated on a Systron Donner SD-80 analog computer.[2] Both retinal feedback and

simulated on a Systron Donner SD-80 analog computer.[2] Both retinal feedback and internal monitoring (efference copy) were included in the model; proprioception (dashed line) was not. Provisions for selectively causing plant deficits were included as was the ability to simulate the increased central gain (i.e., saccadic plasticity) which occurs in MG and serves to partially compensate for the peripheral deficits. With this model, we could study saccadic metrics in MG, but not the variations in saccadic trajectories.[3]

The primary changes in MG occur in the eye plant. We simulated the plant by two cascaded "leaky" integrators (first-order lag elements) as shown in Figure 1b. Without deficit, the transfer function of the normal plant was:

$$\frac{\theta_E}{\theta_M} = \frac{K}{(T_1 s+1)(T_2 s+1)}, \; T_1 = .150, \; T_2 = .007 \text{ and } K = 7 \qquad (1)$$

Thus, for our particular simulation, the steady-state transfer function was:

$$\left.\frac{\theta_E}{\theta_M}\right|_{t \to \infty} \to K = 7 \qquad (2)$$

Note: The value of $K = 7$ has no physiological significance and was chosen because of voltage constraints of the analog computer.

Two specific types of plant disorders were simulated (also indicated in Figure 1b). One is a deficit in the tonic fibers of the extraocular muscles, with relative sparing of the phasic fibers. This was simulated by placing a resistor (R_L) around the first integrator (A1) which greatly increased its "leakiness". Although this reduced its transient response somewhat, the main effect was an inability to maintain a tonic level. When simulating a tonic deficit ($R_L = 10^6$, $R_s = \infty$) the transfer function was:

$$\frac{\theta_E}{\theta_M} = \frac{.4K}{(T_L s+1)(T_2 s+1)}, \; T_L = .06 = .4T_1, \; T_2 = .007 \text{ and } K = 7 \qquad (3)$$

which yielded the steady-state solution:

$$\left.\frac{\theta_E}{\theta_M}\right|_{t \to \infty} \to .4K = 2.8 \qquad (4)$$

Thus, the eye would not hold the proper tonic level and would decay to 40% of the level required by the saccadic motor command (pulse-step). The net result of this plant deficit in the model is a series of hypometric saccades, with overshooting trajectories spaced in time by the reaction time of the visual feedback loop (200 ms in our model), which eventually bring the eye to the target. This was a commonly observed response of MG patients.

A second plant disorder in MG is a paresis of the extraocular muscle. This was simulated by placing a saturation circuit (R_s, θ_s, and a diode) around the output integrator (A2). Small saccades (less than θ_s) would be accurate but those larger than θ_s would not. Both the point of onset (θ_s) and degree of hardness of the saturation (R_s) are adjustable. When simulating a paresis ($R_L = \infty$ and $10^6 \leqslant R_s \leqslant 10^3$), the transfer

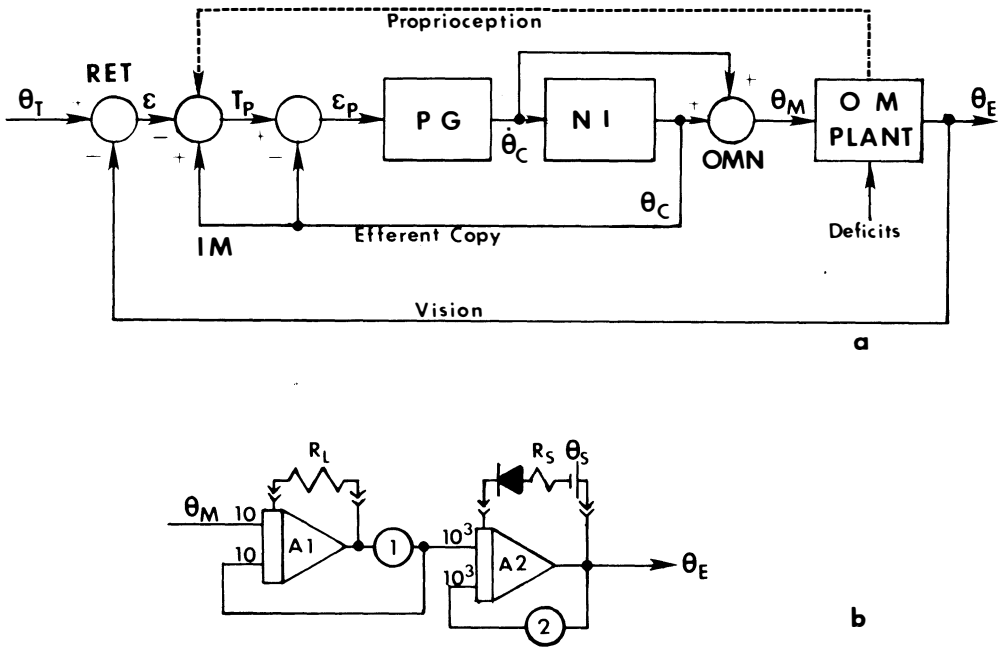

FIGURE 1. (a) Block diagram of model used to simulate eye movements of patients with myasthenia gravis; (b) analog simulation of ocular motor plant with deficits. θ_T is target angle; ε is retinal (RET) error; T_p is perceived target angle generated by the internal monitor (IM); ε_p is perceived error; PG is pulse generator; NI is neural integrator; θ_C is velocity command; θ_C is position command; θ_M is motor command from the ocular motor nuclei (OMN) and θ_E is eye angle in this and subsequent figures.

function was:

$$\left.\frac{\theta_E}{\theta_M}\right|_{\theta_M > \theta_S} = \frac{(.571—.00143)K}{(T_1 s+1)(T_S s+1)}, \quad T_1 = .150, .004 \leq T_S \leq 10^{-5} \text{ or}$$
$$.571T_2 \leq T_S \leq .00143T_2, \quad K = 7 \tag{5}$$

which yielded the steady-state solution:

$$\left.\frac{\theta_E}{\theta_M}\right|_{t \to \infty} \to (.571—.00143)\, K = .4—.01 \tag{6}$$

For $\theta_M < \theta_S$, the transfer function

$$\left.\frac{\theta_E}{\theta_M}\right|_{\theta_M < \theta_S} = \left.\frac{\theta_E}{\theta_M}\right|_{\text{normal}}, \text{ which is given in Equation 1.} \tag{7}$$

The net results of a hard saturation ($R_S = 10^3$) was a large series of very hypometric (gain = .00143K) saccades spaced at 200 ms which never reached the target. The softer saturation ($R_S = 10^6$) yielded a smaller series of less hypometric (gain = .571K) saccades which also never reached the target.

In addition to simulating the primary plant disorders caused by MG, we also used the model to simulate the secondary, central compensatory mechanisms responsible for an increased innervation level. In the MG patient, this is observed by the administration of the drug edrophonium chloride which transiently improves the deficit at the neuromuscular junction. What results are hypermetric saccades (ocular dysmetria) and, if the central gain increase is sufficient, macro saccadic oscillations. These eye movements resemble those seen with cerebellar dysfunction.[4,5] A gain between one and two produced static hypermetria and a gain which transiently rose above two caused a burst of macro saccadic oscillations.

Thus, this model stimulated both the primary neuromuscular deficit and the dysfunction secondary to central plastic changes and their dual effects on saccadic metrics in myasthenia gravis.

Our studies of myasthenia revealed frequent multiple, closely spaced saccades and dynamic overshoots. These trajectories could not be the result of efference copy by an internal monitor of eye position commands, since such commands would be larger than normal; nor could visual feedback be responsible, since this loop requires a minimum of 85 ms. Only the rapid proprioceptive loop (shown dashed in Figure 1) seemed a feasible alternative. Proprioceptive feedback was also the most reasonable explanation for our observation of saccadic intrusions during maintained gaze fatigue and increased saccadic gain after maintained gaze.[6] This presumption of the role of the proprioceptive loop is supported by the fact that in normal subjects, both closely spaced saccades and dynamic overshoots increased in occurrence with fatigue.[7] Although proprioception is known to be present, this is the first time that a function for this loop has been convincingly presented; the hypothesis resulted from the study of the ocular motor system's responses to plant pathology.

B. Strabismus

Although the primary defect resulting in malalignment of the optical axes (strabismus) is innervational, this disorder is conventionally regarded as due to muscle imbalance primarily because its treatment often involves surgery of the extraocular muscles. Models which simulate the normal plant, such as those described in an earlier chapter by Robinson, can also be used to simulate strabismus if the innervation is adjusted appropriately. Robinson addressed this topic specifically by mathematically modeling the six extraocular muscles and orbital tissues for all eye positions.[8] His modeling utilized data obtained from, and in collaboration with, the Smith-Kettlewell group who have been at the forefront of plant modeling.[9,10] Although the complexity of the mathematics requires the use of a digital computer, the program can be used to estimate the correction which would result from any particular muscle surgery. The need for a more accurate approach to strabismus surgery is evident from the number of repeat operations necessary (in the U.S., 40%). What is needed now are interdisciplinary studies using the model and, when necessary, modifying it to conform to actual surgical results. If the model proves capable of predicting the efficacy of a specific surgical procedure, it may become extremely useful to strabismus surgeons.

III. NERVE PALSIES

A. Saccadic Plasticity

A discrete cranial nerve lesion which, unlike myasthenia gravis, is time invariable, allows one to study the extent and dynamics of central adaptation (plasticity). As with MG, the ocular motor system adjusts its gain to overcome deficits which impair performance. Figure 2a outlines, in block diagram, how an automatic gain control system (AGC) might alter saccadic gain utilizing retinal error (ε), efference copy, and propri-

oceptive information as performance measures. We studied the dynamics of saccadic gain changes in a patient with an abducens nerve lesion.[11] By alternately patching, for several days, the good and paretic eyes, we were able to force the gain of the saccadic system to change in both directions. When the changes were plotted over time, we were able to approximate the transfer function as a first-order exponential with a time constant of approximately one day (Figure 2b). Any model of the adaptive gain circuitry of the *normal* saccadic system should follow the same exponential time course obtained from this study of a patient with a unilateral and uniocular paresis.

IV. CENTRAL DISORDERS

A. Pulse Generator

1. Slow Saccades

Some patients with spinocerebellar degenerations make abnormally slow saccades. There was some question as to whether the slow refixational movements were saccades or a form of substituted slow eye movement, but Zee et al.[12] found that they were, indeed, slow saccades. The long time course of these slow saccades reveal details about the mechanism involved in creating the pulse of innervation which could not be obtained from studying normally fast saccades. The two major conclusions were (1) Saccades were not preprogramed (i.e., ballistic), but could be modified in flight; and (2) Saccades were driven to an orbital position, rather than a given distance from the point of origin.

Zee et al.'s study of patients with slow saccades prompted the model of the normal pulse generator shown in Figure 3. The model used a bootstrap circuit in which the eye position command was fed back and determined pulse width. Pulse height (i.e., saccadic velocity, $\dot{\theta}_C$) was determined by a saturation nonlinearity to the forward path. By proper scaling of the velocity-amplitude nonlinearity, they were able to duplicate the responses of different patients to short and long pulses, as well as double steps of target position. Although their model used the same neural integrator as part of the pulse generator and also to generate the efferent position command and (θ_C), we have indicated in Figure 3 that perhaps these functions are separately performed (θ_C'). The reasons for this change will be discussed in the following section on gaze-paretic nystagmus.

Although patients with spinocerebellar generations may have brainstem lesions, those with slow saccades who have been studied pathologically have not been found to have lesions of the paramedian pontine reticular formation (PPRF) where the pulse generator is located. Furthermore, the other clinical conditions associated with slow saccades (congenital ocular motor apraxia, Huntington's chorea, Wilson's disease, Gaucher's disease, and progressive supernuclear palsy) do not typically have pontine lesions. In most of these cases, therefore, the slow saccades seemed to result from disturbed inputs to the pulse generator rather than a defective generator per se. It is possible that the gains of the bootstrap loop or of the $\dot{\theta}$ vs. θ element in the forward path are under extra-pontine control (i.e., cerebellar, basal ganglia, etc.) and that deficits in these structures or in their interconnections with the pulse generator are responsible for the saccadic slowing.

B. Integrator

1. Gaze-Paretic Nystagmus

Gaze-evoked nystagmus is characterized by slow centripetal drifts from eccentric eye positions interrupted by centrifugal saccades back to the target. The slow phases of the nystagmus may be linear (as in vestibular and pursuit-defect nystagmus) or have a

decreasing-velocity exponential shape. The latter is referred to as "gaze-paretic" nystagmus which has been modeled by creating a defect in the neural integrator (Figure 4).[13]

In gaze-paretic nystagmus, the fast phases are *normal* saccades indicating that the pulse generator functions normally despite the deficiency of the position-holding integrator. The magnitude of the centripetal drift (and hence, the nystagmus) varies directly with gaze angle from primary position. As alluded to in the previous Section, and as shown in Figure 4, the bootstrap circuit in the pulse generator utilizes a neural integrator that is distinct from the integrator responsible for generating eye position commands. In this way, deterioration of the latter produces gaze-paretic nystagmus without affecting refixation saccades and fast phases. The internal monitor (utilizing efferent copy of the position command) is responsible for making corrective eye movements in the absence of vision and is the driving stimulus for the fast phases of the gaze-paretic nystagmus. Neuronal pools (simulated by two integrators in parallel) were made deficient by either a "leak" or saturation circuit. Thus, variable deficits could be simulated by proportionally using both an unaffected integrator and one with either deficit. This simulated the percentage of affected neurons in the pool of neurons performing neural integration. The model duplicated normal saccades when no deficit was present and gaze-paretic nystagmus when either a leak or saturation occurred in a percentage of the integrator pool. Comparison of the transition areas between the nystagmus-free range of gaze angles and those with nystagmus produced by each method (leak or saturation) revealed subtle differences. The model, therefore, not only duplicated known clinical phenomena, but also suggested further studies on patients to elucidate the actual deficit present in such cases. In addition, since some portion of the total neural integrator pool was functioning normally, the internal monitor not only stimulated the pulse generator, but also directed the fast-phase pulses only to those integrator neurons whose output was deficient. Neural integration must be accomplished by many neurons whose outputs supply the large numbers of motoneurons with eye position commands. When a subset of these neurons is made to function inadequately by disease or trauma, only the neurons in that subset should receive additional neural pulses from the pulse generator. The healthy neurons in the integrator pool must not, lest they produce a position command greater than the correct output which they generated as a result of the initial saccadic velocity pulse. This model, therefore, also provided some insight into the complex control of redundant neuronal circuitry which would not have been apparent from modeling normal saccadic function.

C. Pause Cell

Zee and Robinson[14] attributed several saccadic abnormalities to pause cell dysfunction. Before considering these disorders, we will review the role of the pause, burst, and tonic neurons in the generation of saccadic control signals. Figure 5 (which is equivalent to the model shown in Figure 3), is a modification of a hypothetical neural network put forth by Zee and Robinson.[14] Using the perceived target position (T_p) as the desired eye position, a perceived error (ε_p) is generated by subtracting an estimate of eye position from T_p. This estimate is given by the position command (θ'_C) which is the integral of the velocity command ($\dot{\theta}_C$). The burst neurons are driven by ε_p when the pause cell (P) is inhibited by the trigger signal shown. Once the pulse is initiated, the pause cell is latched off via interneuron B_i until ε_p is driven to zero by θ'_C. The bias shown then excites P to fire at a constant rate between saccades which inhibits B. Finally, when the contralateral burst neurons fire, B_c inhibits B_i allowing P to inhibit the ipsilateral burst neurons (B). The Zee and Robinson model is compatible with the known properties of saccade-related neurons identified in monkey brainstems. Since

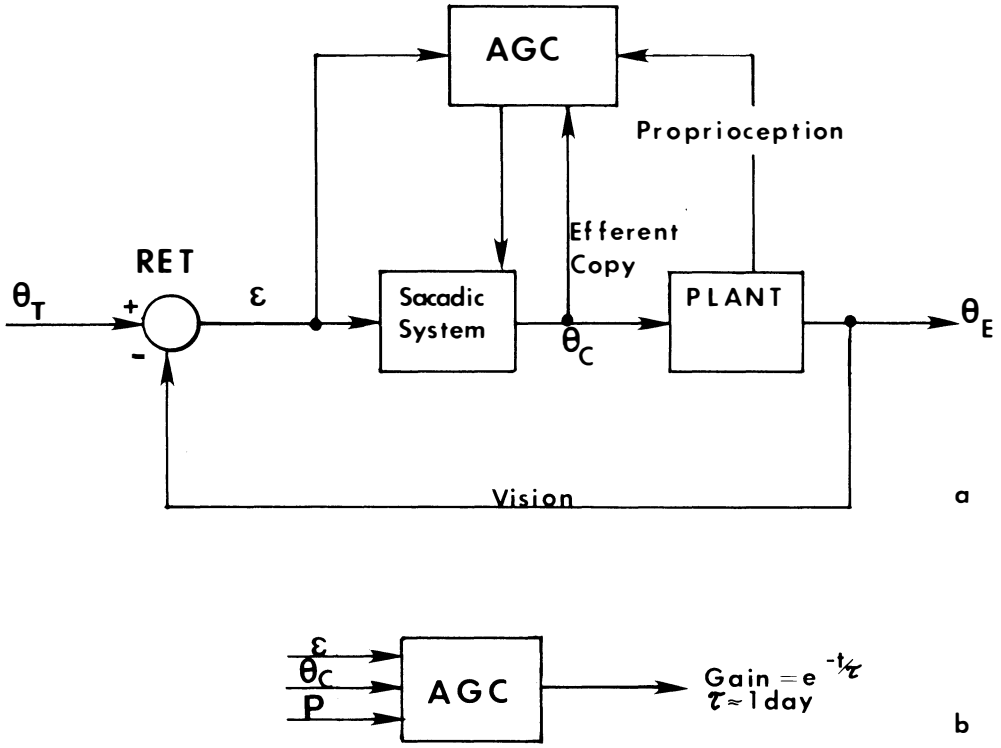

FIGURE 2. (a) Block diagram of saccadic system with automatic gain control (AGC); (b) Transfer function of AGC with a time-constant of 1 day.

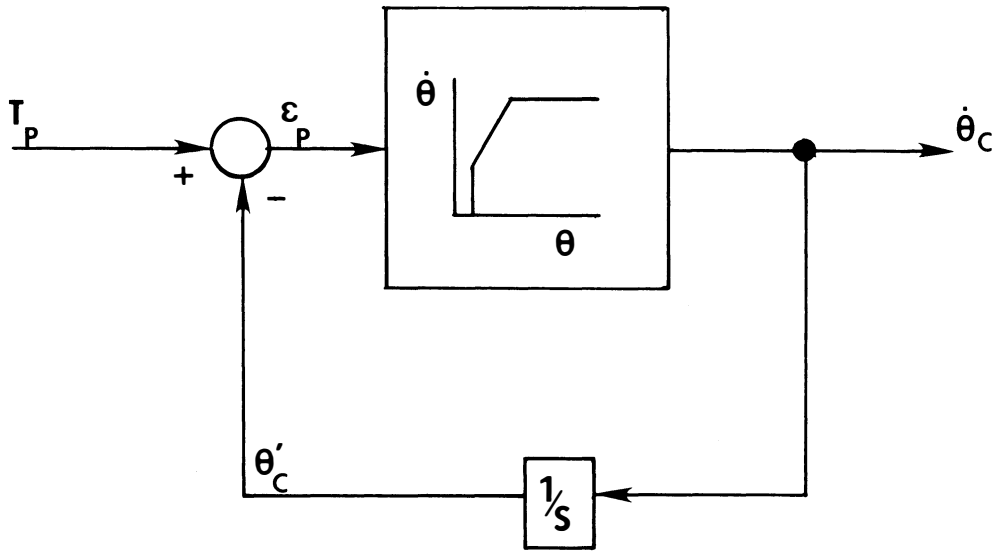

FIGURE 3. Model of pulse generator. (Adapted from Zee, D. S., Optican, L. M., Cook, J. K., Robinson, D. L., and King-Engel, W., *Arch. Neurol.*, 33, 243, 1976.).

it allows for continuous control of the pulse, a change in T_P (or a proprioceptive input as described in the myasthenia gravis section) could result in a saccade interrupted or

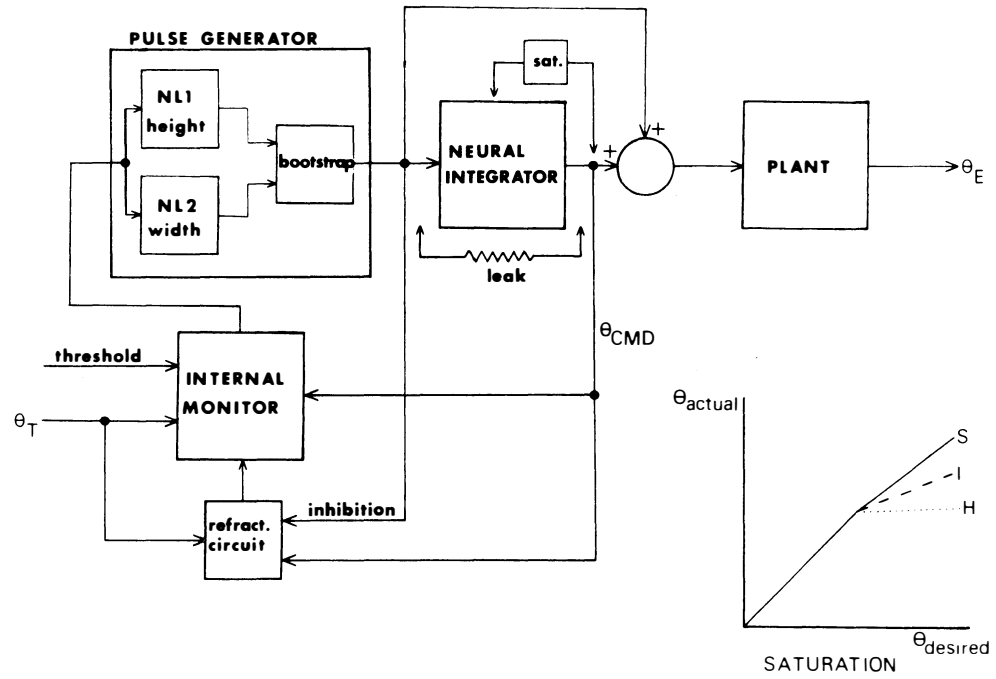

FIGURE 4. Block diagram of the model used to simulate gaze-evoked nystagmus. The input target (θ_T) is compared by the internal monitor to the eye position command (θ_{CMD}) and the necessary saccade initiated in the pulse generator. The monitor contains an error threshold below which no correction is called for. It also is prevented by a refractory circuit from calling for a correction during a saccade. The pulse generator contains nonlinearities that reproduce the physiological variations in pulse height and duration. The output of the pulse generator is integrated in the neural integrator. The pulse and step are summed, with the resulting innervation used to drive the plant to produce the desired eye position (θ_E). Both a leaky integrator and saturating integrator (SAT) are indicated as ways to produce gaze-evoked nystagmus. The inset shows typical saturation characteristics used (soft, S; intermediate, I; Hard, H). (From Abel, L. A., Dell'Osso, L. F., and Daroff, R. B., *IEEE Trans. Biomed. Eng.*, 25, 71, 1978. With permission.)

otherwise modified in flight. One additional change included in the model of Figure 5 is the positive intercept of the $\dot{\theta}$ vs. θ curve which determines B. This was proposed in the Zee and Robinson model based on the neurophysiological evidence of Keller[15] and Van Gisbergen and Robinson.[16] They found that burst neurons fire minimally (e.g., 100 spikes/sec) for ipsilateral and contralateral microsaccades, for vertical saccades, and toward the end of large contralateral saccades. The modeling implications were the positive intercept of the B curves on each side of the brainstem and that the ipsilateral and contralateral burst neurons must be connected to the ocular motoneurons in a push-pull fashion. Such a model corresponds to the correlation between saccadic velocity and difference between B_i and B_c burst rate.[15] Analysis of this model led Zee and Robinson to postulate mechanisms for flutter, "flutter dysmetria," opsoclonus, and voluntary "nystagmus."

1. Flutter

Ocular flutter is a disorder in which fixation is interrupted by bursts of high-frequency saccadic oscillations. These alternate in direction without intersaccadic intervals which creates a pendular-looking appearance. Zee and Robinson demonstrated how their model could simulate ocular flutter when a short delay is introduced into the θ'_C feedback loop. The high gain of B makes the pulse generator inherently unstable

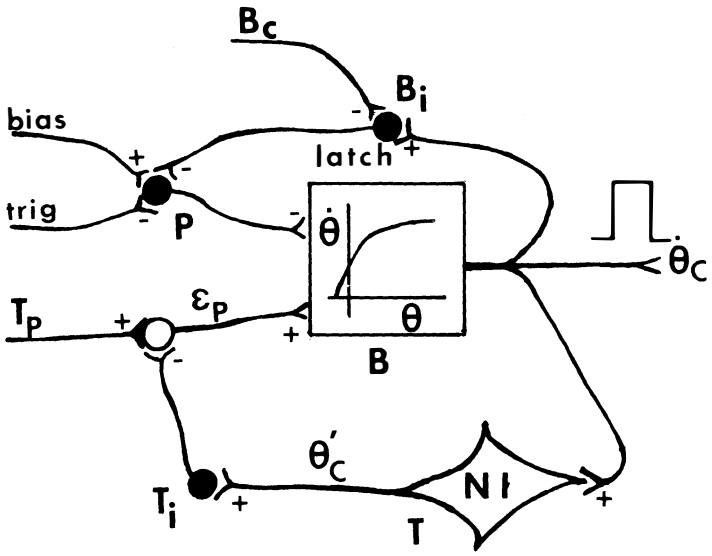

FIGURE 5. Neural model of pulse generator. (Modified from Zee, D. S. and Robinson, D. A., *Ann. Neurol.*, 5, 405, 1979.)

so that it will oscillate with such a delay. Intermittent bursts of oscillation were produced by reducing the level of tonic inhibition of the burst cells which is normally provided by the pause cells. This could be due to (a) a prolonged trigger signal; (b) an inadequate bias; or (c) unresponsive pause cells.

2. Flutter Dysmetria

Flutter dysmetria is a term which we are introducing to describe ocular flutter occurring after a refixation saccade prior to the eyes coming to rest at a new target position. The Zee and Robinson model simulates this condition by adjustment of the gain of the B curve and varying the pause cell bias to produce a variation in the number of dysmetric flutter oscillations.

3. Opsoclonus

Opsoclonus describes seemingly random, chaotic, multidirectional, conjugate saccadic oscillations. This can be regarded as secondary to simultaneous instabilities in both horizontal and vertical pulse generators and were so simulated by Zee and Robinson in their model.

4. Voluntary "Nystagmus"

Voluntary "nystagmus" is the name given to the voluntary ocular oscillation in the horizontal plane that some normal subjects are able to accomplish. As with flutter, this oscillation looks pendular, but Shultz et al.[17] demonstrated that the eye movements were back-to-back saccades and, therefore, not truly a nystagmus oscillation. The Zee and Robinson model easily simulated this oscillation when the pause cells were turned off allowing the burst cells to oscillate. This corresponds to the report of subjects who, when asked to explain how they make their eyes oscillate, generally reply that they "let it happen," suggesting that the oscillation was a natural phenomenon that only needed to be released.

Thus, the Zee and Robinson model for saccadic pulse generation led to insightful hypotheses concerning the mechanisms of three pathological and one artificially created saccadic oscillations.

D. Medial Longitudinal Fasciculus

1. Internuclear Ophthalmoplegia

Lesions of the medial longitudinal fasciculus (MLF) result in impairment of adduction in the eye ipsilateral to the lesion and abduction nystagmus in the contralateral eye. This is called internuclear ophthalmoplegia (INO). The adduction deficit can range from complete inability to move the eye past the midline (loss of both pulse and step of innervation) to a slight decrease in saccadic velocities (loss of some of the pulse). Commonly, adducting saccades appear to have a truncated fast portion followed by a slow exponential drift to the target; this corresponds to a partial loss of the pulse. This initial loss of pulse, resulting in slowed adduction saccades, is due to the inability of demyelinated fibers to transmit the high-frequencies of the pulse as well as they transmit the low-frequencies of the step. Since excitation of the agonist is responsible for most of the pulse of muscle force and only part of the step, the pulse will always be affected to a greater extent.[18] Simple superposition of the slow adduction saccadic motion and the linear slow phases induced by an optokinetic stimulus was used by Dell'Osso et al.[19] to explain the asymmetry of OKN response in INO. In the same paper, the illustration of simultaneous saccades of the abducting and adducting eyes shows both the truncated adduction saccades with following glissade and the nystagmus of the abducting eye. Careful inspection of that figure reveals small hypometric saccades superimposed on the glissade of the adducting eye; these correspond to the fast phases of the abduction nystagmus. Note that both disappear when the adducting eye reaches the target. Thus, abduction "nystagmus" may merely be pulse responses (i.e., stepless saccades) of the abducting eye corresponding to the hypometric saccades of the adducting eye which are attempting to bring it to the target. If the target is within the patient's range of adduction, the nystagmus will diminish and cease as the target is reached by the adducting eye; if not, abduction nystagmus will continue. Recordings in our laboratory with high bandwidth (DC-100 Hz) position and velocity channels have always shown the corresponding hypometric adducting saccades. Further studies of this nystagmus are required to determine if our hypothesis is valid in explaining the abduction nystagmus in patients with INO. Other hypotheses have been proposed. Pola and Robinson[18] constructed a model which included both excitatory and inhibitory fibers in the MLF. The excitatory fibers went to the ipsilateral medial rectus subnucleus and the inhibitory fibers were destined for the contralateral medial rectus, crossing at the nuclear level. Thus, an MLF lesion not only causes impaired excitation of the ipsilateral medial rectus, but disinhibition of the opposite medial rectus. This disinhibited medial rectus has a tonic innervational level incompatible with the eccentric gaze deviation and, therefore, causes a centripetal drift which is the basis for their explanation of the abduction nystagmus.

E. Vestibular

1. Alexander's Law

Inner ear disease of a variety of causes induces an imbalance between the two sides which is responsible for pathological vestibular nystagmus. The diseased end organ almost always has a decreased rate of tonic firing. The slow phase of the nystagmus, which has a linear slope, drifts toward the abnormal side and the fast phase beats in the opposite direction (i.e., toward the normal ear). Warm or cold caloric stimulation induces convection flows of the endolymph of the semicircular canal on the side of irrigation. The direction of flow depends upon the temperature of the water. Warm water results in an increase in tonic firing frequency, whereas cold water induces a decreased frequency and, therein, mimics the effect of a diseased semicircular canal. In either instance, however, an imbalance between the two sides is created, the eyes

drift to one side, and nystagmus is induced. The amplitude of vestibular nystagmus grows as gaze is increased in the direction of the fast phase and diminishes with gaze in the opposite direction. This phenomenon was described by Alexander in 1912 and is known as "Alexander's Law."

In an attempt to better understand the interaction between gaze and the vestibulo-ocular system, we modeled Alexander's Law utilizing relevant brainstem anatomy and physiology.[20] The model shown in Figure 6 represents the brainstem mechanisms that determine the gaze-dependent slope variation of the slow phase of vestibular nystagmus. Therefore, it was not necessary to explicitly model the generation of the fast phases; they were assumed to occur with a constant frequency. A model has been proposed for fast phase generation during head rotation[21] and will be presented subsequently in this chapter.

Figure 6 is a block diagram of our model. Neural signals from the semicircular canals (SCC) pass to the vestibular nuclei (VN) before being integrated by the neural integrators (NI). The NI outputs then lead to stimulation of the extraocular eye muscles (EOM) via the ocular motor nuclei (OMN). The position of the eyes is represented by θ_E. The net effect is an idealized vestibulo-ocular reflex (VOR).

In order to include a gaze-dependent variation, however, we added a slow phase modulator (SϕM) which modulates vestibular nuclei activity with desired gaze (θ_D) and a constant tone signal (T). In this manner, we were able to simulate the variation of slow phase velocity with canal imbalance and desired gaze. The fast phase stimulator (FϕS) and pulse generator (PG) are connected by dashed lines to illustrate that they were not *explicitly* modelled, although their role in the fast phase of the vestibular nystagmus was represented. The waveforms shown indicate neural firing frequencies and the resulting nystagmus of the eyes.

A signal flow diagram of the model is shown in Figure 7. The terminology *Neural Summer* is utilized to emphasize the true correspondence with actual neurons which fire with positive frequency only when the net input stimulation is excitatory.

Several characteristics were required of this brainstem model: (a) equal and opposite neural tone from each side should exist when the eyes are in primary position; (b) when a vestibular imbalance is present, a gaze angle signal should modulate the value of the drift velocity produced by the imbalance; (c) the gaze angle signal must not induce a drift velocity when no vestibular imbalance exists; and (d) the modulated imbalance must result in a constant-velocity, linear drift of the eyes.

These considerations resulted in specific model characteristics. The constant tone output requirements from each of the eye position integrators and the necessity for the integrator outputs to track each other in a push-pull fashion about that steady-state tonic level, gave rise to the push-pull connection of first-order lag elements shown in Figure 7. This solution was taken from an earlier, more complete, model of brainstem circuitry developed by Dell'Osso in 1974 (unpublished). It has the unique characteristics that yield a constant output for equal innervation to each of the integrators and an integrated output for a differential input. Satisfaction of requirements b and c resulted in a gated modulation which was present only when a vestibular imbalance exceeded a threshold. To maintain linear slow phases, desired gaze signals, rather than feedback of the output of the integrators (actual gaze commands), had to be used, as the latter would have resulted in nonlinear slow phases. As an initial simplifying assumption, the frequency of the nystagmus was held constant (at 3.33 Hz). The computer was adjusted to automatically zero its output approximately every 0.30 sec, thereby simulating the action of the fast phases of nystagmus. During this time, the slow drift increased at a rate determined by the model output.

The model suggested a possible neural configuration (Figure 8) which would produce nystagmus from vestibular imbalance which varied with gaze. The vestibular nu-

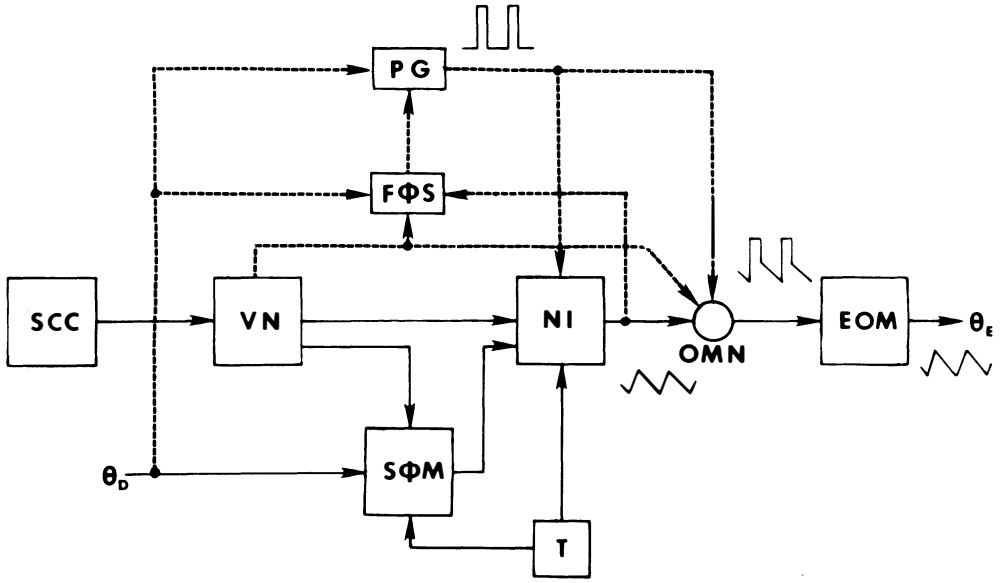

FIGURE 6. Functional block diagram of model to simulate vestibular nystagmus. Solid lines represent slow phase generation; dashed lines represent fast phase aspects. (From Doslak M. J., Dell'Osso, L. F., and Daroff, R. B., *Biol. Cybern.*, 34, 181, 1979. With permission.)

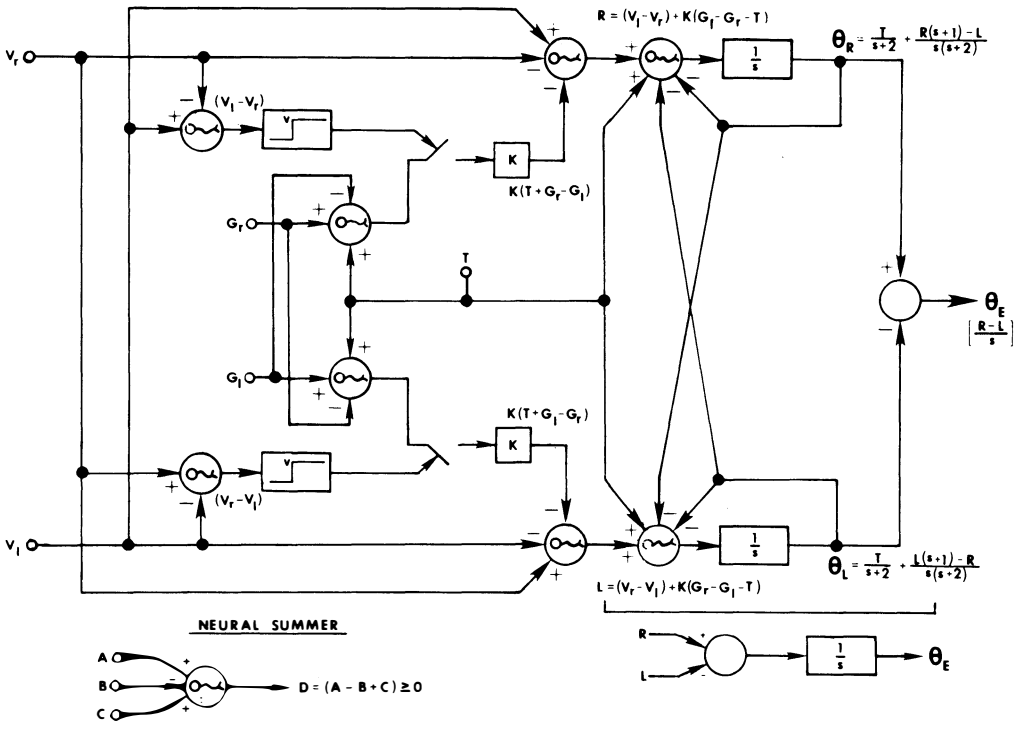

FIGURE 7. Signal flow diagram of the model shown in Figure 6 containing the necessary quantitative interaction among signals. Mathematical relationships utilize Laplace notation where applicable. (From Doslak, M. J., Dell'Osso, L. F., and Daroff, R. B., *Biol. Cybern.*, 34, 181, 1979. With permission.)

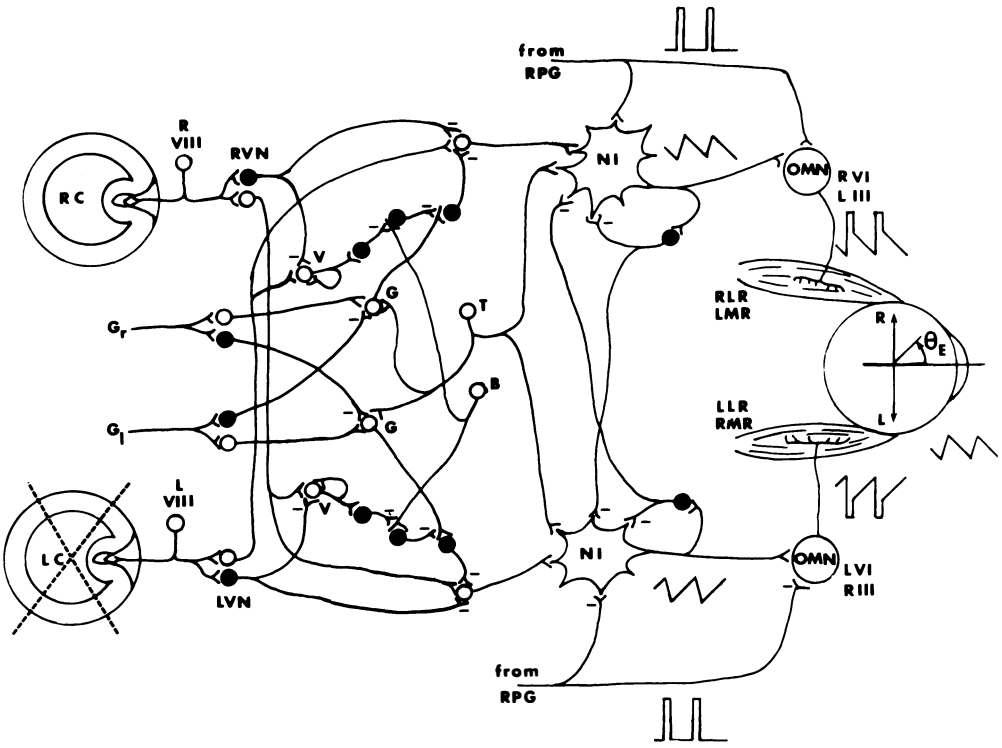

FIGURE 8. A possible neural "wiring diagram" suggested by the model in previous two figures. The upper half of the diagram corresponds to the right side of the brainstem and the lower half to the left side. Open circles represent excitatory neurons; filled circles represent inhibitory neurons. Dysfunction of the left semicircular canal is signified by a large X through LC. (From Doslak, M. J., Dell'Osso, L. F., and Daroff, R. B., *Biol. Cybern.*, 34, 181, 1979. With permission.)

clei (RVN, LVN) transfer excitatory signals contralaterally and inhibitory signals ipsilaterally to the neural integrators (NI). Prior to synapsing with the integrators, these signals are modulated by desired gaze (G_r, G_l) and tone (T) signals. When no imbalance between vestibular nerve activity from each side is present, the summed gaze and tone signals (G) are prevented from passing by means of the presynaptic inhibition supplied by a postulated bias (B). When an imbalance of vestibular activity occurs, this inhibitory bias is turned off by additional presynaptic inhibition. Such inhibition of inhibitory signals is not unusual in other areas of neurophysiology.[22] Also shown are the ocular motor nuclei (OMN) and the eye muscles. With dysfunction of the left canal (LC), the right canal (RC) leads to increased stimulation of the left lateral rectus (LLR) and right medial rectus (RMR) causing the eyes (represented here as one eye) to drift to the left. Intervening saccadic pulses from the right pulse generator (RPG) move the eyes back to their predrift position. The waveforms shown represent changes in the neural firing frequencies and eye position (θ_E).

2. Fast Phase Generation

The model for fast phase generation during head rotation proposed by Chun and Robinson[21] utilized their pulse generator (Figure 5) which was driven by two internal signals that specified the eye positions at the beginning and end of each fast phase. Both signals were generated internally and varied with the head velocity signal from

the vestibular system. One specifying signal created a "center of interest" to which fast phases drove the eyes, and a second signal was an error signal which sensed the deviation of the eyes from the "center of interest." When this difference exceeded a threshold (also determined by head velocity), a fast phase was initiated by triggering the pulse generator. The nonlinearities and dynamics incorporated into these circuits, as well as their interconnections to the pulse generator are sufficiently complex to prevent further discussion of this excellent model in this chapter.

The generation of fast phases of pathological vestibular nystagmus and the variation of their timing and amplitude with gaze angle has not been studied and, therefore, cannot be modeled adequately at this time. Studies of patients with vestibular nystagmus and normals with caloric-induced nystagmus are necessary to answer the following questions prompted by our model of Alexander's Law: (1) Is the relationship between the amplitude of the nystagmus actually linear?; (2) For a given gaze angle, is the change in nystagmus amplitude a linear function of canal deficit?; and (3) How does nystagmus frequency vary with gaze? Until answers to these questions are found, further modelling of the phenomena associated with slow and fast phase variations in vestibular nystagmus must, of necessity, be highly speculative.

F. Cerebellar

Ocular flutter, flutter dysmetria, and opsoclonus are oscillations, discussed earlier, which occur in patients with cerebellar disease. Other cerebellar eye signs are (1) macro square wave jerks (MSWJ); (2) overshoot dysmetria; and (3) macro saccadic oscillations (MSO).

1. Macro Square Wave Jerks (MSWJ)

MSWJ are spontaneous saccades which cause the eyes to move from the object of fixation to some point in space lateral to that object. After a short latency (50 to 150 msec), a corrective saccade returns the eyes to the target. Such saccades may occur singly or in bursts during fixation or following a voluntary refixation. Our study of a patient with cerebellar signs due to multiple sclerosis led us to postulate the model shown in Figure 9.[23] An ipsilateral disturbance (presumably from the cerebellum) to the pulse generator initiated the MSWJ and the corrective return saccade was mediated by an internal monitor which compared the efferent position signals from the neural integrator with the desired eye position. MSWJ are not simply square wave jerks of larger amplitude, as the name suggests, but represent a mechanistically different instability.[24]

2. Ocular Dysmetria

Ocular dysmetria is a conjugate overshooting of a refixation saccade followed by a corrective saccade after a normal intersaccadic latency of 125 to 200 msec. The correction may also be hypermetric leading to an oscillation of saccades of diminishing amplitude before the eyes come to rest on the new target. Overshoot dysmetria differs from flutter dysmetria which has no intersaccadic latency.

Selhorst et al.[4] studied overshoot dysmetria and identified the responsible control system abnormality as a gain increase in the feed-forward path to a value greater than 1.0, but less than 2.0. They simulated the disorder using the Young-Stark[25] sample-data model of the saccadic system and postulated that a lesion of the cerebellar vermis was responsible for the disturbed gain modulation in the saccadic system.

3. Macro Saccadic Oscillations (MSO)

MSO consist of a burst of to-and-fro saccades, with normal intersaccadic latencies,

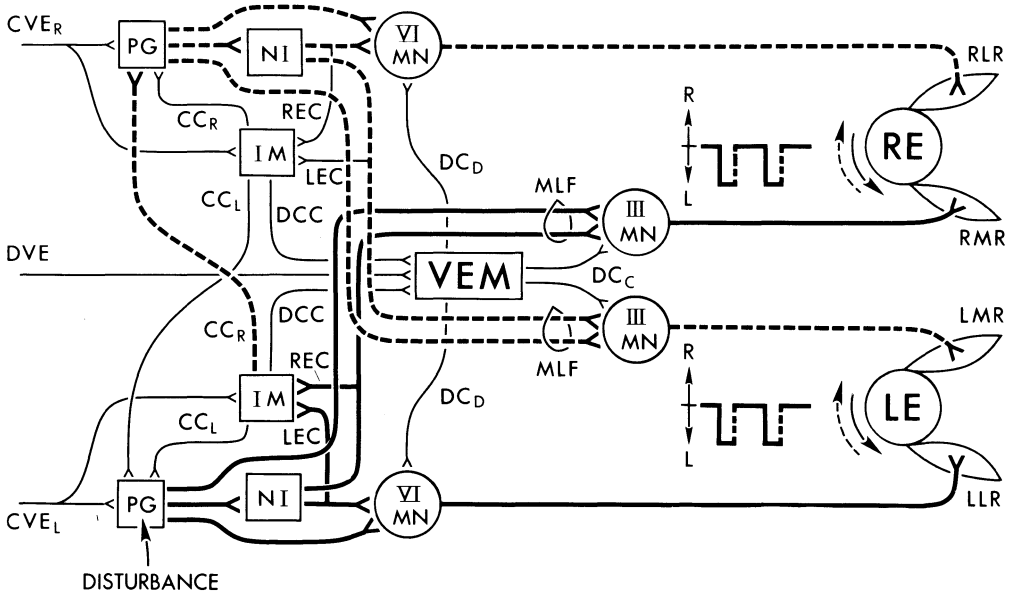

FIGURE 9. Binocular model of brainstem output portions of the horizontal fast eye movement and vergence eye movement (VEM) subsystems illustrating the functional operation of an internal monitor (IM) in the generation of corrective eye movements. Conjugate visual errors to the right and left (CVE_R and CVE_L, respectively) drive the pulse generators (PG) on their respective side to produce saccades.

The output of the pulse generator is integrated in the neural integrator (NI) and the resulting step of innervation is summed with the original pulse from the pulse generator at the motoneuron (MN). (Motoneuronal summing is provided for simplicity only; summing may actually occur at a prenuclear level.) Signals then go to the respective extraocular muscles (RLR, RMR, LMR, LLR) to drive the right (RE) and the left (LE) eyes. Disconjugate visual errors (DVE) drive the vergence eye movement subsystem to produce disconjugate commands of convergence (DC_C) and divergence (DC_D).

The IM monitors the commands to both eyes (REC and LEC), compares them with the desired output (CVE), and directs the required conjugate correction to the right (CC_R) or left (CC_L) pulse generator, as well as any required disconjugate corrective command (DCC) to the vergence eye movement subsystem. The disturbance input for this patient and the pathways for the consequent abnormal leftward saccade are in heavy solid lines, with the pathways for the corrective rightward saccade in dashed lines. The resulting macrosquare wave jerks are shown next to each eye. (From Dell'Osso, L. F., Troost, B. T., and Daroff, R. B., *Neurology*, 25, 978, 1975. With permission.)

which gradually increase and then decrease in amplitude.[5] Unlike MSWJ, MSO straddles fixation.[24] Again, using the Young-Stark[25] sample-data model, Selhorst et al.[5] produced constant amplitude saccadic oscillations when the gain was 2.0 and increasing amplitude oscillations at greater gains. By varying the gain between 2.25 and 1.75, they created oscillations which increased and then decreased in amplitude. This closely simulated the MSO recorded in their patients.

Thus, Selhorst et al.[4,5] demonstrated that both overshoot dysmetria and macro saccadic oscillations result from high loop gains in the saccadic system with the difference being the magnitude of the gain increase.

G. Basal Ganglia

1. Progressive Supranuclear Palsy (PSP)

PSP is a basal ganglionic and midbrain disorder resembling Parkinsonism. The most prominent eye signs are paralysis of downward, followed by upward gaze (pursuit and saccades) with preservation of vestibulo-ocular movements. The progression of the vertical gaze disturbance leading to paralysis has never been studied quantitatively.

Volitional horizontal eye movements may also become paralyzed and these have been studied carefully prior to the stage of total paralysis. The horizontal eye signs include: square wave jerks (SWJ); slow, hypometric, long-duration saccades; low pursuit gain (cogwheel pursuit); and inability to enhance or suppress the vestibulo-ocular (VOR) gain.[26] The pons is pathologically spared in this disease; the horizontal eye signs must be explained by lesions elsewhere. From Figure 1, it is evident that a supranuclear disorder could interfere with the generation of the signals T_p or ε_p and result in diminished saccadic gain, or stimulate the pulse generator causing SWJ. In a similar manner, such a disorder could lower the pursuit gain and, therein, prevent variation of VOR gain. However, the mechanism by which a supranuclear disorder could modify saccadic peak velocity or duration, if the pulse generator is hard-wired in the pons, as shown in Figure 5, is not as apparent. Given the model of Figure 5, we must postulate supranuclear influences impinging directly on the network responsible for the $\dot{\theta}$ vs. θ transfer function of B. This is supported by the observation that slow saccades are present in other basal ganglionic disorders such as Huntington's chorea and Wilson's disease, as well as spinocerebellar degenerations (discussed earlier). The two mechanisms postulated for the slow saccades,[26] defective pulse (pulseless) and unsustained pulse, both require malfunction of the pulse generator (Figure 5) circuitry. At present, there are not sufficient data about supranuclear connections from basal ganglia and cerebellum to the PPRF pulse generator neurons for construction of a meaningful model.

2. Parkinson's Disease

Parkinson's disease is also associated with saccadic pursuit reflecting defective pursuit gain. Saccades are hypometric, but there is disagreement as to saccadic velocities. Shibasaki et al.[27] found them to be slow, which is at variance with the normal speeds previously reported by Melville Jones and DeJong.[28] If the former authors are correct, a model for Parkinsonian saccades would have to be similar to that of PSP and require supranuclear control of the pulse generator transfer characteristics. If the saccades are not slowed, a simpler model would be applicable with only saccadic gain under supranuclear control.

V. NYSTAGMUS

Nystagmus is a biphasic ocular oscillation which begins with a slow (nonsaccadic) movement and in which both phases are approximately equal amplitude. Thus, SWJ, MSWJ, MSO, opsoclonus, flutter, flutter dysmetria, and voluntary "nystagmus" (all of which are saccadic) are not forms of nystagmus. Traditionally, nystagmus is divided into pendular and jerk types. The former is sinusoidal and in the latter, the initial slow phase is away from the object of fixation (or intended gaze angle); it is followed by a saccadic fast phase in the direction of the target. By convention, the fast phase direction defines the nystagmus direction. The waveforms of jerk nystagmus may be further subdivided on the basis of slow phase shape (Figure 10) which may be linear, increasing-velocity exponential or decreasing-velocity exponential.[29] These differences imply different control system abnormalities.

A. Congenital

Twelve distinctive forms of congenital nystagmus (CN) have been identified[30] and fall into three categories: pendular (three waveforms), jerk (eight waveforms), and dual jerk (one waveform). These waveforms, some of which are complex, are the result of basic instabilities in the slow subsystem of ocular motor control and the secondary

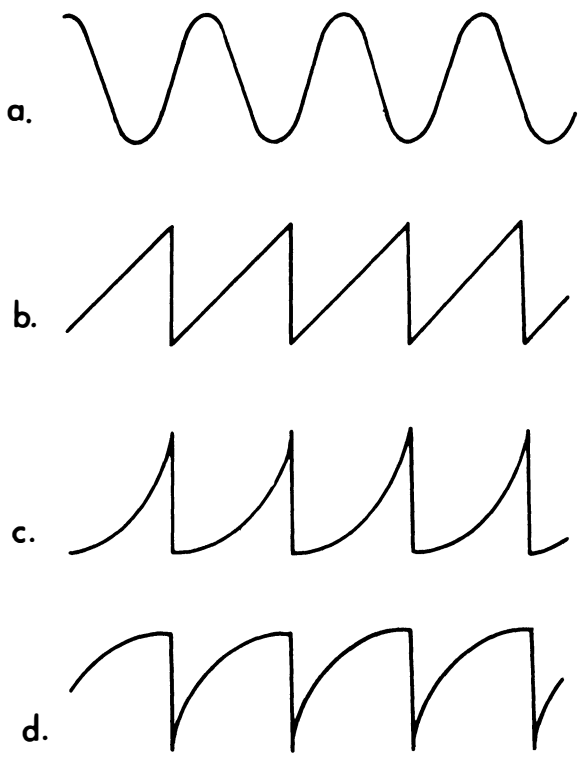

FIGURE 10. Oculographic representation of (a) pendular nystagmus and the three major types of jerk nystagmus (b, c, d). Jerk nystagmus classification is based upon the shape of slow phase: (b) linear, (c) increasing-velocity exponential, and (d) decreasing-velocity exponential. (From Daroff, R. B., *Weekly Update: Neurol. Neurosurg.*, 1, 1, 1978. With permission.)

plastic adaptations designed to maximize foveation time, thereby decreasing the visual impairment resulting from the nystagmus. Basically, all of the waveforms are variations of one of two distinct instabilities or, in the case of dual jerk, a combination of both types of instability. The waveforms of Figure 10a and 10c are the basic instabilities of CN. The pendular waveform is a high-gain instability of the slow subsystem whose roots must lie on the $j\omega$-axis as shown in Figure 11.[31] Pendular nystagmus disappears with visual inattention (low-gain) and increases proportional to greater visual attention or effort to see (high-gain). Increasing the gain appears to drive the poles up the $j\omega$-axis, since the frequency of the oscillation may increase along with the amplitude. Jerk CN behaves in a similar manner with increasing effort (gain) driving a pole further into the right half plane on the σ-axis (Figure 11). Dual jerk nystagmus supports the contention that the pendular and jerk waveforms are independent oscillations caused by different instabilities. This is a high-frequency, low-amplitude pendular oscillation superimposed on a low-frequency, high-amplitude jerk nystagmus. At times, one or the other component can be reduced or eliminated without affecting the other; one component may spontaneously diminish or increase.

Pendular CN may merely require increasing the loop gain of a normal slow subsystem with its inherent transport lags. Robinson[32] found sinusoidal oscillations of 2.9 Hz when the gain of a normal system was increased. When this was done experimen-

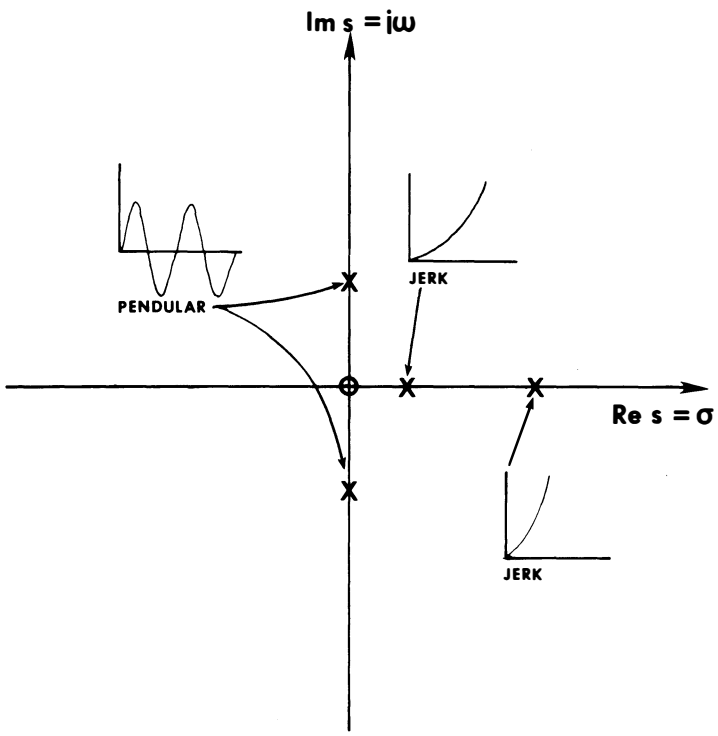

FIGURE 11. Plot of various system pole positions (X) on the complex frequency plane (s-plane) and the types of oscillations which result. See text for explanations. (From Daroff, R. B. and Dell'Osso, L. F., *Topics in Neuro-Ophthalmology,* Thompson, H. S., Daroff, R. B., Glaser, J. S., Frisen, L., and Sanders, M. D., Eds., Williams & Wilkins, Baltimore, 1979, 286. With permission.)

tally on a patient with CN, the amplitude of his existing pendular oscillations increased.[33] For the patient with pendular CN, a pair of j-axis poles with the transfer function $\frac{\omega_0}{s^2+\omega_0^2}$ (Figure 12a) might become manifest when input variables associated with effort, psychological set, and other factors surpass a threshold. It is not clear whether these inputs, which do not cause instability in the normal system, are ineffectively opposed by the system with CN or whether distinct pathology introduces the poles (not present in the normal system) that cause oscillations as gain is increased.

A possible model of jerk CN (Figure 12b) includes the addition of a positive-feedback loop around the position command (i.e., the neural integrator).

The transfer function of this model is:

$$\frac{\theta_c}{T} = \frac{\left(\frac{\tau}{1-\tau c}\right)}{\left(\frac{\tau}{1-\tau c}\right)s+1} \qquad (8)$$

When $c = 1/\tau$, the transfer function is $1/s$, an ideal integrator. If, however, c becomes greater than $1/\tau$, the pole moves into the right half plane and an increasing-velocity

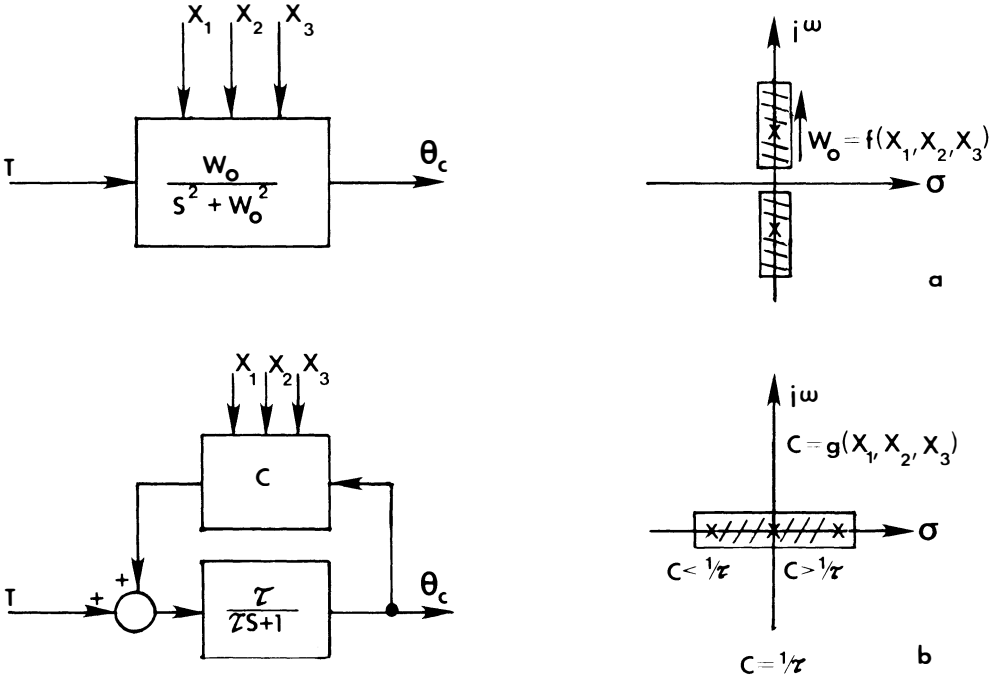

FIGURE 12. (a) Partial model for pendular congenital nystagmus and locus of pole positions; (b) Partial model for jerk congenital nystagmus and locus of pole positions. $X_1 - X_3$ are inputs from other physiological systems which affect the oscillations (see text).

exponential runaway results. If c were a function of the same factors discussed above for pendular CN, this could be the underlying mechanism for jerk forms of CN. Recently, Zee et al.[34] have proposed such a model for cerebellar-induced gain changes which caused increasing-velocity runaway slow phases in nystagmus acquired by a patient with cerebellar dysfunction. Their model was based on the known interaction of the cerebellum and the neural integrator. Since no lesions have ever been associated with CN, the exact anatomical localization of the poles discussed above is unknown.

The root locus plots of Figure 12a and b cannot be combined easily, since they represent subloops (or part of subloops) in a multiloop control system, the exact form of which is still not known. The gains of each (ω_o and c) are presumably different functions of the input variables x_1, x_2, and x_3 and, therefore, a family of root locus plots would be generated by the variations in ω_o and c; such an analysis is beyond the scope of this section.

B. Latent and Manifest Latent

Latent nystagmus (LN) and manifest latent nystagmus (MLN) have recently been studied and distinguished from CN by the slow phase waveform.[35] LN and MLN slow phases are decreasing-velocity exponentials (Figure 10d) in contrast to the increasing-velocity slow phases (Figure 10c) of the jerk form of CN. The fast phases are always directed toward the viewing eye and true binocular vision abolishes the nystagmus.

An explanation for this nystagmus was hypothesized[36] based upon the perceived angle of a target in space which, under conditions of true binocular vision, is shown in Figure 13a to be

$$\theta_{T_B} = \frac{\theta_T|_R + \theta_T|_L}{2} \qquad (9)$$

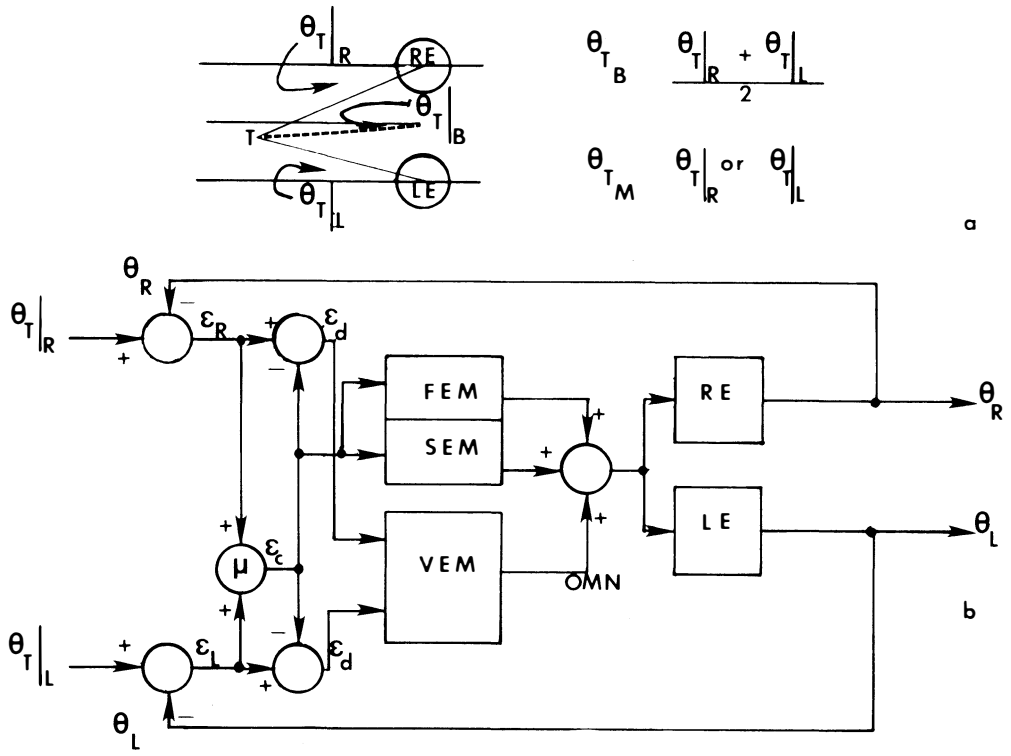

FIGURE 13. Explanation of latent and manifest latent nystagmus. (a) Definitions of target angles referenced to each eye and computation of binocular (θ_{T_B}) and monocular (θ_{T_M}) direction; (b) Model illustrating how conjugate retinal error (ε_c) and disconjugate retinal error (ε_d) might be generated from target angles referenced to the right ($\theta_T|_R$) and left ($\theta_T|_L$) eyes and their respective retinal errors (ε_R and ε_L). Their use by the version (fast eye movement [FEM] and slow eye movement [SEM]) and vergence (VEM) subsystems is indicated. The factor μ is 0.5 for binocular vision and 1.0 for monocular vision (see text for further explanation).

where, $\theta_T|_R$ and $\theta_T|_L$ are the angles of the target with respect to the right and left eyes, respectively. When only one eye is viewing, the perceived target angle is equal to its angle with respect to that eye. Thus, the brain must mathematically accomplish a switch from a summation of error signals divided by two to a unity gain acceptance of one error signal. Figure 13b is a model of how this might be done to generate conjugate error (ε_c) and disconjugate error (ε_d) signals for use by the version (comprised of fast and slow modes) and the vergence subsystems, respectively. If the mathematical switching is performed improperly when monocular vision is imposed (both LN and MLN occurred during monocular viewing conditions), a discrepancy between perceived target angle and actual target angle would be created and the eyes would move conjugately towards the improperly calculated target position (always towards the nonviewing eye). This would generate a true retinal error in the viewing eye (which was on target during binocular vision) and stimulate a conjugate saccade to refoveate the target. Repetition of this sequence could produce LN (or MLN). The decreasing-velocity slow phase may merely reflect the plant dynamics subjected to a step difference in position commands (i.e., the proper and improper target directions).

C. Pursuit-Defect

1. Downbeat, Upbeat, and Horizontal

Zee and coworkers[37] found that patients with primary position downbeating nystag-

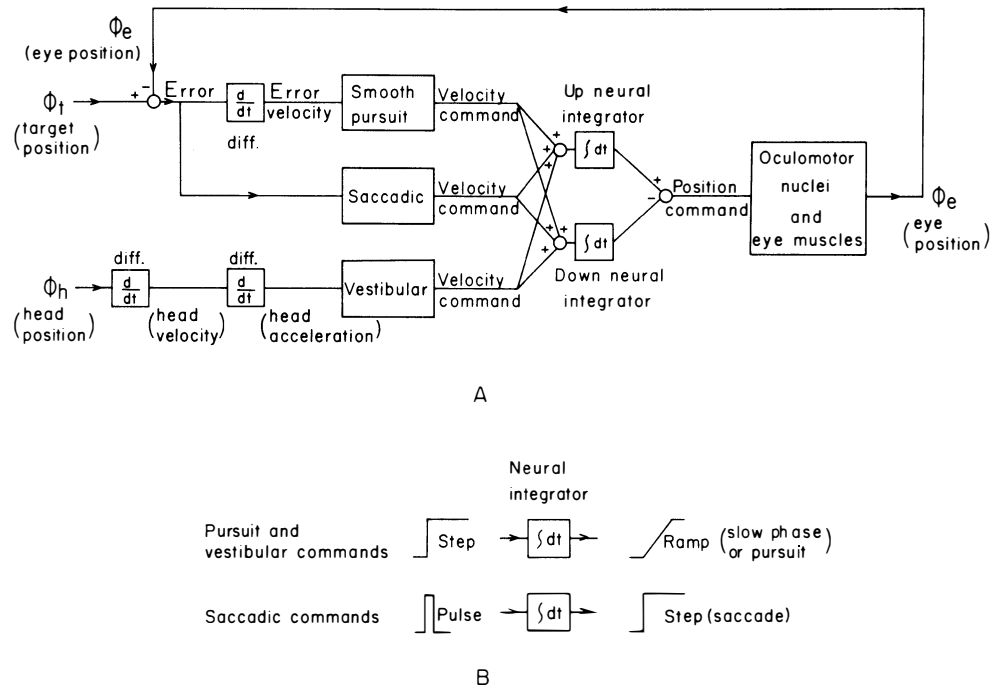

FIGURE 14. Relationship between the vestibular, pursuit, and saccadic control systems. Each system generates a velocity command that is transmitted to the neural integrators. From the integrators, a position command is then transmitted to the final common pathway. (From Zee, D. S., Friendlich, A. R., and Robinson, D. A., *Arch. Neurol.*, 30, 227, 1974. Copyright 1974, American Medical Association. With permission.)

mus had a unidirectional absence of pursuit in the downward direction. Vestibulo-ocular movements were intact, seemingly establishing the specificity of the pursuit abnormality. The nystagmus was of the jerk type with a linear slow phase (Figure 10b). They created a computer model of downbeat nystagmus by abolishing all downward pursuit commands (Figure 14). This model duplicated the linear slow phase nystagmus found in their patients. Subsequently, primary position upbeating,[31,38,39] as well as a horizontal primary position jerk nystagmus with a linear slow phase,[40,41] have been attributed to a pursuit-defect in the direction of the quick phases of the nystagmus. Modelling upbeat nystagmus would represent a mirror image of that for downbeat and the model for horizontal pursuit defect would merely require relabelling the up and down pursuit integrators of Figure 14 as right and left.

There is reason to question the basic concept of "pursuit-defect" nystagmus. We recorded a patient with spinocerebellar degeneration and periodic alternating nystagmus in whom we found alternating pursuit defects. The unlikelihood of such an alternating defect raised the question of how pursuit should be manifest in the direction of the fast phase of an on-going jerk nystagmus. The nystagmus persists and pursuit can only be expected to decrease the slow phase velocity (decrease slope) in the opposite direction. We confirmed this in a normal subject during caloric-induced nystagmus. For pursuit to be regarded as absent, no change in slope should result. This occurred in the computer model of Zee et al.,[37] but not in their patients or, convincingly, in any of the others reported. Determination of true pursuit gain would require careful study with varying velocity ramps. This must be done before causality can be established in these cases of "pursuit-defect" nystagmus.

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