

# Control of eye movements

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ONE FEATURE of the oculomotor system that makes it easier to analyze than most other movement control systems is that it can be broken down functionally into a few subsystems; the purposes of these do not seem difficult to understand. This feature is most important because understanding a system's function is essential in designing significant experiments and correctly interpreting their results. Consequently, the first thing required in the study of eye movements is an appreciation of the purposes that eye movements serve. A phylogenetic approach is taken here; an attempt is made to understand the problem that needed to be solved and how the evolution of a particular system appeared to solve it. Although there is general agreement on the purposes of most eye movements,

there is less agreement about others and, obviously, one can only guess at the evolutionary pressures in various species that shaped their oculomotor subsystems. Consequently, certain ideas in this section express only the opinion of the author rather than a general consensus, and this is made clear where pertinent. It is so important to have a theoretical framework for understanding eye movements, however, that any reasonable working hypothesis is better than none at all. Because this section is theoretical, most literature citations are deferred to detailed descriptions in subsequent sections of this chapter.

#### PURPOSES OF EYE MOVEMENTS

It is possible to divide species roughly into two broad oculomotor categories depending on whether or not they have a fovea. This term is used here to denote any specialized region of the retina with such a high photoreceptor density that it is used preferentially for seeing. Afoveate animals are not very concerned with the position per se of images on the retina, and most of their subsystems, such as the vestibuloocular reflex and optokinetic system, simply try to prevent the images of the visual surround from slipping about on the retina. Animals with foveas have retained these image-holding reflexes, but have added others—the pursuit, vergence, and saccadic systems—designed to bring selected images to the fovea and then hold them there. Oculomotor systems may also be separated into those that relocate images on the retina and those designed to hold images relatively still on the retina for better viewing. It is well known that when images are stabilized too securely on the retina, perception of them fades (80), but none of the systems that try to prevent image slip are so successful that fading is likely in any normal situation.

#### Vestibuloocular Reflex

The greatest potential source of image slip is due to self-rotation. If one just glances over one's shoulder, the head easily achieves angular velocities of  $200^{\circ}$ – $300^{\circ}/s$ . If the eyes did not compensate by rotating at the same speed in the opposite direction, the resulting image slip would essentially preclude any type of useful vision during the head movement. This ocular reflex, which originates in the semicircular canals, probably evolved early in vertebrate evolution, since it serves the important function of allowing animals to see and move at the same time. It was so successful that it has changed very little since its origin, and the same basic design is found in widely divergent species of birds, mammals, and fish (197).

The most common use of this reflex is during the coordinated eye and head (or body) movements (Fig. 1A) that animals make when looking about (see the chapter by Bizzi in this *Handbook*). The value of

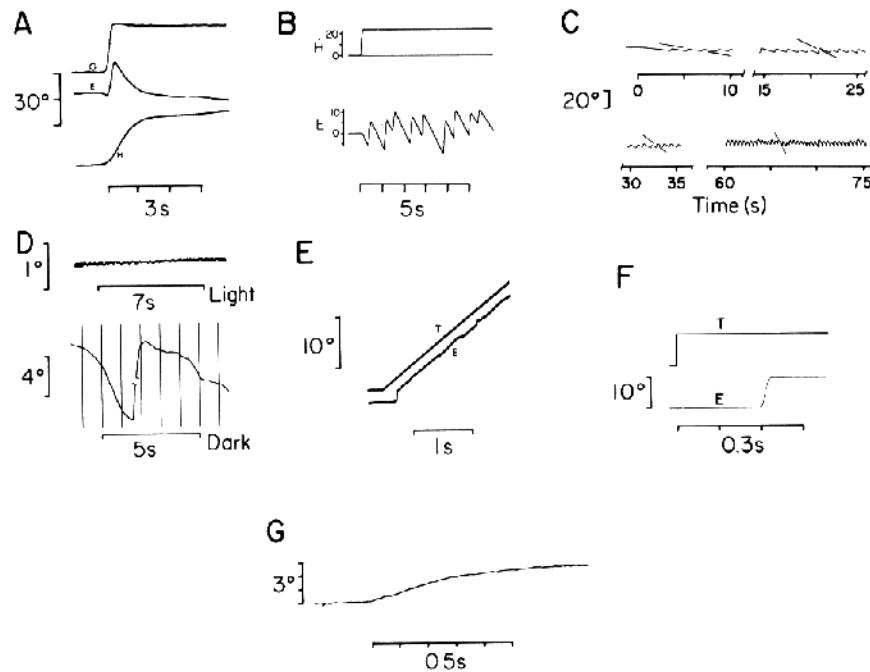
stabilizing gaze in space can be appreciated by reading the account of a physician who lost all labyrinthine function because of streptomycin poisoning (149). Initially, he could not read in bed without steadyng himself against the headboard, and even after compensation was largely complete, he still could not read signs or recognize people on the street without stopping and standing still.

The otolith organs of the vestibular complex respond to linear acceleration rather than angular motion and thus sense the tilt of the head with respect to the pull of gravity. Their signals deviate the eyes tonically to compensate for head tilt. This keeps the position and orientation of, for example, the image of the horizon constant on the retina. This reflex is quite apparent in lateral-eyed, afoveate animals (e.g., the rabbit) but is rather weak and fails to compensate for head tilt in foveate primates, probably because the saccadic system makes any other form of vertical position control obsolete and their visual systems apparently do not need the assistance of the fixed orientation provided by torsional eye movements to recognize visual objects. Therefore, one must be careful to distinguish torsional eye movements during a rapid head movement from those during a static tilt. The former are vigorous, nearly compensatory, and due to the canal-ocular reflex; the latter are due to otolith signals and, in human beings, are small and inadequate.

#### Afoveate Saccadic System

When an animal is rotated in the dark, the compensatory movements, called slow phases, are interrupted by rapid eye movements, called quick phases, creating a pattern called nystagmus (Fig. 1B). Naturally, quick phases must occur if only to reset the eye and keep it from reaching the mechanical limits. Nevertheless, as Figure 1B shows, quick phases, including the first, carry the eye well into the direction of turning and occur long before the slow phase can carry the eye close to the mechanical limits.

To explore this anticipatory nature of quick phases, consider a simpler situation: when a rabbit looks about, it makes head and eye movements similar to those shown in Figure 1A (64). Because the rabbit has no fovea, the purpose of the rapid eye movement is not, as in primates, to foveate a target. Yet the movement, like a foveate saccade, occurs at the start of the head movement and long before the eye is in danger of reaching the mechanical stops. The rapid eye movement occurs first probably for the same reason the primate saccade occurs first: visual and cognitive processing require a delay of about 0.2 s before an animal can react to any new visual stimulus. When a decision is made to reorient the head and eyes in space, it would seem useful to turn the eyes first so the visual system can be inspecting the new scene while the head and body, which move more slowly, catch up. It is



**FIG. 1.** Examples of eye movements produced by various oculomotor subsystems. Time is indicated in seconds. *A*: the most common use of the vestibuloocular reflex is to stabilize eye position in space during a rapid eye-head reorientation. The eye moves first in a saccade followed by a slower head movement (H) during which the eye rotates backward in the head (E) to compensate for head rotation and keep eye position in space, or gaze (G), fixed on new target. Data from monkey. *B*: nystagmus eye movements (E) in the cat produced by prolonged rotation in dark at a head velocity ( $\dot{H}$ ) of  $20^\circ/\text{s}$ . Slow phases have velocity of about  $18^\circ/\text{s}$  in compensatory direction. Note that quick phases keep eye shifted in direction of turning. *C*: optokinetic nystagmus in the rabbit. At zero time the drum begins rotating at  $30^\circ/\text{s}$ . Lines parallel to slow phases illustrate how slow-phase eye velocity builds up slowly. *D*: eye drift in cat during fixation in light is shown (*top trace*). Mean drift velocity (estimated over 0.2-s time intervals) is about  $0.25^\circ/\text{s}$ . Note lack of microsaccades. Eye drift increases in the dark (*bottom trace*). Sample record shows one velocity as high as  $4^\circ/\text{s}$  but  $1^\circ/\text{s}$  is typical. Broken rapid movement is a large saccade. *E*: eye position (E) of trained monkey making smooth pursuit movement in response to target (T) moving in a ramp at  $10^\circ/\text{s}$ . Movement starts with a catch-up saccade. *F*: eye position (E) of trained monkey making a saccade in response to a step of target position (T) of  $10^\circ$ . *G*: human convergence movement of  $2^\circ$  following a step in target position from far to near in midsagittal plane. [*A* from Miles and Fuller (201); *B* from Robinson (235); *C* from Collewijn (63); *D* from Winterson and Robinson (295); *E, F* from Fuchs (99); *G* from Rashbass and Westheimer (222).]

reasonable, in afoveate animals, to call this movement a saccade rather than to invent a new term, and to refer to it as an afoveate saccade in discussions where a distinction is desired.

In this sense afoveate animals also have a saccadic system. The goldfish is another well-studied example (86). Unlike foveate saccades, however, it appears that afoveate saccades must be linked to a head movement. Their purpose seems to be to reorient the eyes quickly to the visual space into which the animal is turning. It would be desirable if such movements were fast, because retinal image slip, which in this case is the sum of eye and head velocity, is so large as to prevent any useful vision during the saccade. It may be that much of the size and power of extraocular muscles is needed just to achieve this high speed (see Figs. 1*F*, 9), so that the amount of time spent moving the eye is minimized and the amount of time spent seeing is maximized.

Quick phases (Fig. 1*B*) would seem to be simply a succession of the same eye movement shown in Figure 1*A* necessitated by the continued movement of the head. Quick phases, like saccades, also anticipate the head movement and move the eyes into the direction of turning. The patterns in Figures 1*A*, *B* do not depend markedly on whether the subject is in the light or dark, since both types of movements appear to serve the same visual strategy (look where you're going) whether vision is actual or potential. The main difference, then, between saccades and quick phases appears to be not their function but their mode of stimulation. The latter are customarily associated with passive head movements and probably are stimulated by vestibular signals. The former, in most afoveate animals, are probably triggered by a central eye and head program and are therefore associated with active head movements.

### *Optokinetic System*

The vestibuloocular reflex can stabilize gaze in space during brief head movements, but the mechanics of the vestibular apparatus do not allow the reflex to maintain a response during continuous rotation. In this situation the semicircular canal signal returns to its resting level with a time constant of approximately 4–6 s for most laboratory animals. If the nervous system depended only on this signal during sustained rotation, the eyes would soon cease moving, images would slip across the retina, and clear vision, even the perception of self-rotation, would be lost. Vision itself provides the obvious solution. Retinal image slip constitutes an error signal that can be used to maintain a proper eye velocity and also to apprise the animal of its turning speed. On the other hand, because of delays in visuomotor processing of about 0.10–0.13 s, vision cannot be used to compensate for rapid head movements.

Thus, the optokinetic system and the vestibuloocular reflex complement each other: the latter deals with transient or high-frequency head movements (above about 0.03 Hz); the former with sustained, low-frequency movements. Another important consequence of this complementarity is that when a long rotation stops, the optokinetic system cancels what would otherwise be postrotatory nystagmus. The optokinetic system seems to have evolved to deal exclusively with self-rotation, and its symbiotic relationship with the vestibular system is revealed most clearly by the combining of both signals directly in the vestibular nuclei (282). It is unlikely that the optokinetic system evolved to track movement in the visual environment. In afoveate animals, for example, the system is excited only when almost all of the visual scene moves en bloc, and then it responds very slowly (Fig. 1C). The visual environment almost never rotates around a stationary animal, so there would be little evolutionary pressure for a system to evolve to deal with such a situation; however, such relative motion always occurs during self-rotation. Moreover, a subject inside a revolving optokinetic drum believes that he, and not the drum is moving (38). This illusion, called circularvection, illustrates our belief that whenever there is relative movement between us and the seen world, it must mean that we are moving, because the latter is taken by definition to represent the fixed environment.

### *Visual Stabilization*

All data processing systems are noisy, and neural systems are hardly an exception. The systems already described involve 6 canals, 12 muscles, the visual system, and the central elements that generate slow and fast eye movements. Noise in the form of unwanted eye drifts is inevitable. For example, an imbalance of only 2% between the resting activities of a push-pull pair of canals in the monkey can create a continuous

slow-phase eye velocity of  $2.3^\circ/\text{s}$  (section VESTIBULOOCULAR REFLEX, p. 1284). Oculomotor noise can be demonstrated simply by turning out the lights. Eye drift fluctuations increase from about  $0.2^\circ$  to  $0.8^\circ/\text{s}$  in various animals when the lights go out (e.g., Fig. 1D). Thus, vision attenuates eye drift, and this suggests a negative feedback scheme in which eye drift is detected by the retinal image slip it creates, which generates an oculomotor signal to cancel that drift. There are theoretical and experimental reasons (discussed in subsection *Stabilization System*, p. 1304) suggesting that stabilization is not mediated by the optokinetic system and thus might constitute a separate system in afoveate animals. In foveate animals it is possible that the pursuit system evolved from the stabilization system (see section PURSUIT SYSTEM, p. 1304). It must be stressed, however, that both these hypotheses are quite speculative at present.

### *Pursuit System*

Smooth pursuit refers to the eye movements of frontal-eyed, foveate animals when they follow an object of interest by keeping its image on the fovea (Fig. 1E). The development of pursuit is clearly associated with the evolution of the fovea. When some animals began to specialize as predators, their survival depended on how well they could pursue and catch prey. Therefore, the region of visual space directly ahead of them must have taken on special importance, since this is where the prey is located during the chase and capture. The better an animal could see and selectively concentrate attention straight ahead, the more successful it became as a predator. This fact probably contributed to the visual specializations found in most predators: large visual overlap in front (frontal eyes), high visual acuity straight ahead (fovea), and stereopsis. Once a fovea developed it was desirable to place the images of interesting objects on it and to keep them there by appropriate tracking movements. It is commonly assumed that this tracking is accomplished by using retinal image motion as an error signal in a negative feedback loop designed to move the eye so as to decrease retinal image slip on the fovea (which, of course, causes a large image slip everywhere else on the retina).

The result would be similar if the stabilization system had evolved to recognize image slip only on or near the fovea and ignore that on the peripheral retina. One feature of pursuit, which makes one suspect it may be related to stabilization, is that pursuit appears to be largely automatic and involuntary. Human beings cannot make pursuit movements when nothing visible moves. When the entire scene moves (as when looking in a rotating mirror), it is almost impossible to hold our eyes still. Thus, we cannot elect to pursue or not to pursue; we can only decide what to pursue. This suggests that fixation of a stationary target is simply

pursuing something at zero velocity. However, this hypothesis has not yet been tested experimentally.

With the development of foveate vision, a problem arises caused by the vestibuloocular reflex. Its function is to stabilize gaze in space, but this is undesirable if the fovea is to be used in tracking. When attending to or pursuing a moving object, most animals track it with head movements. If the vestibuloocular reflex forced the eyes to be stable in space in this situation, the object's image would move off the fovea, and this reflex would defeat the whole purpose of head tracking. Consequently, the original stimulus in the evolution of pursuit may have been the need to more or less cancel the effect of the vestibuloocular reflex rather than to track targets when the head was still. If canceling were achieved, the head (and body) then could be used to point the eyes, which would be especially desirable during the maneuvering needed to catch evading prey.

It is generally assumed that cancellation of the vestibuloocular reflex is done by superimposing a pursuit command upon the vestibular eye commands, and much evidence supports this view. However, a few facts, discussed in section PURSUIT SYSTEM, p. 1304, suggest that cancellation and pursuit are not identical, but these differences do not appear to warrant classifying pursuit and cancellation as the products of separate systems.

#### *Saccadic System*

The neural circuits for generating rapid eye movements that evolved in afoveate animals were triggered only by either an active or passive head movement. When the fovea evolved, the rationale for saccades expanded. Once a region of the retina had better vision, it was clearly sensible to point it at objects of interest. As the acuity of the fovea improved, visual searching behavior would increase the desirability of frequent, small saccades, and it would be less cumbersome if, unlike the case for afoveate animals, the saccades could be made without a simultaneous head movement. The rabbit, for example, without a fovea, rarely makes a saccade without moving its head. The monkey, on the other hand, makes saccades quite independently of whether its head moves. The ancient coupling of head and eye movements, however, in afoveate animals, which appears to persist in foveate animals, might account for the behavior of some oculomotor apraxic children. They can make only small saccades if asked to hold their heads still, but can make large saccades if allowed to move their heads at the same time (305). At any rate, there is little doubt that the function of most saccades is to place the image of an object of interest near or on the fovea where visual acuity is best. The situation is not so clear for microsaccades, whose purpose remains obscure (see section SACCADIC SYSTEM, p. 1297).

#### *Vergence System*

As frontal-eyed vision developed, the enlarged overlap of the visual fields of the two eyes presented a situation in which more information, such as depth perception, could apparently be gained by centrally fusing the images seen by each eye. To assist in this process it was desirable to keep the eyes in relative alignment so that the image of an object seen by each eye excited regions of the visual system that remained in a relatively constant relation to each other. This task required vertical, torsional, and horizontal fusion systems, because the visual scene in the region of binocular vision must be kept in registration between the two eyes in all three degrees of freedom. The vertical and torsional fusion systems seem to be fairly automatic, since voluntary control of them would serve no useful function. Because the eyes are displaced from each other horizontally, objects at different depths create different horizontal retinal disparities, which is the major clue for depth perception. In this dimension a special vergence system under voluntary control is needed so that the images of objects of interest at various distances can be placed on the fovea of each eye. The vergence and fusional systems respond to discrepancies in the relative positions of retinal images. These are the only other oculomotor systems (besides the saccadic system) that serve to correct retinal image position errors rather than minimizing retinal image velocity errors. The reason that vergence movements are among the slowest of all eye movements (Fig. 1G) has not been established.

#### OCULOMOTOR PLANT

In control systems terminology, that which is being controlled is called the physical plant (or plant). In this case it refers to the eyeball, the extraocular muscles, the passive orbital suspensory tissues, and the motoneurons. The input to the plant is the instantaneous discharge rate,  $R_m(t)$ , of the motoneurons together with the number recruited into activity. The output is instantaneous eye position,  $E(t)$ , which usually denotes eye rotation in the plane of a particular muscle pair under consideration (see ref. 237 for a review of the oculomotor plant).

#### *Motoneuron Behavior*

A number of studies have been made of the behavior of oculomotor motoneurons in the alert, behaving monkey (102, 130, 161, 229, 248, 261). When the animal fixates, motoneurons fire at a relatively constant rate (see Fig. 2A). Standard deviations of interspike intervals are typically 6.4% of the mean (161). As  $R_m$  either increases or decreases, the eye fixates further in the pulling direction of a motoneuron's muscle (the on-

direction), or in the opposite direction (off-direction) respectively. A plot of  $R_m$  vs.  $E$  is called a rate-position curve (e.g., Fig. 2B). Despite several interposed nonlinearities, (e.g., Fig. 3), the overall relationship conveniently forms a straight line. The mean value of the slope,  $k$ , of such a line for a large population of motoneurons from the studies mentioned is 4.0 (spikes/s)/deg. The range is 1.1–14.5 (spikes/s)/deg.

At some angle,  $E_T$ , called the threshold, the discharge rate goes to zero. The population mean value of  $E_T$  is  $-25^\circ$  (in the off-direction). The range is from  $+25^\circ$  to  $-62^\circ$ . Because the horizontal oculomotor range of the monkey is about  $\pm 45^\circ$  [ $\pm 50^\circ$  for humans and approximately  $\pm 15^\circ$ – $20^\circ$  for cat (272), rabbit (58), and goldfish (83)], many motoneurons (about 18%) never cease firing for any eye angle while the animal is awake. The discharge rate of the average motoneuron in the primary position (straight ahead) is close to 100 spikes/s. More than 70% of all motoneurons are

active (above threshold) in the primary position (163, 229) near which the eye spends most of its time.

When the eye moves, the discharge rate also varies with the velocity with which the eye passes through a given position, as illustrated in Figure 2C. A plot of  $R_m$  vs. eye velocity ( $dE/dt$  or  $\dot{E}$ ) is shown in Figure 2D. This is called a rate-velocity curve and it is also straight with a slope  $r$ . The mean value of  $r$  averaged over the studies mentioned is 0.95 (spikes/s)/(deg/s). The range is 0.25–5.0 (spikes/s)/(deg/s). The relation between discharge rate and eye velocity can be seen most clearly during saccades when  $\dot{E}$  is very large: during on-saccades the high discharge rate creates a pronounced burst of spikes (see Fig. 2E). During an off-saccade, a burst of inhibition silences the cell.

The behavior of motoneurons may be described succinctly by the relationship

$$R_m = k(E - E_T) + r\dot{E} \quad (1)$$

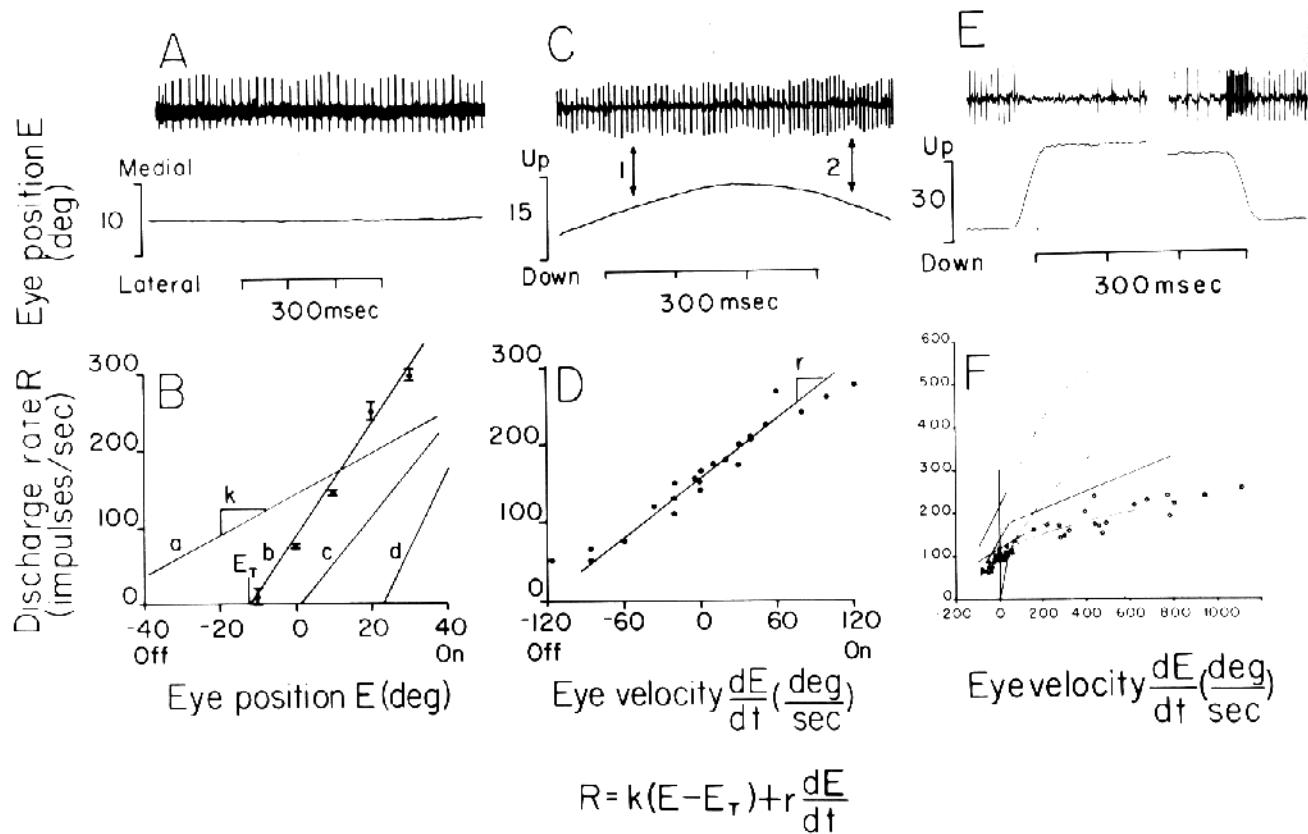


FIG. 2. Behavior of eye muscle motoneurons in the monkey. *A*: during fixation (*bottom trace*), the rate of the discharges (*top trace*) is steady. *B*: rate varies linearly with fixation at different eye positions in the on- or off-direction. Slope of rate-position line is  $k$ . Intercept is the threshold  $E_T$ . Four different cells (*a-d*) illustrate high and low threshold units. Data points for 1 cell (*b*) illustrate variability. *C*: motoneuron discharges during pursuit. Discharge rate is much lower when eye passes through any given position travelling in off-direction (*first arrow*) than when it returns travelling in on-direction (*second arrow*). *D*: rate-velocity curve. Rate varies as eye passes through given position (*closed circles*) in proportion to eye velocity ( $dE/dt$ ) with proportionality factor  $r$ . *E*: rate-velocity relationship seen most easily during saccades. Cells burst at high rates for on-saccades (*right*) and pause for off-saccades (*left*). *F*: rate-velocity curves for several cells in both pursuit ( $<100^\circ/\text{s}$ ) and saccadic ( $>100^\circ/\text{s}$ ) velocity ranges show that eye velocity increases more rapidly than discharge rate. [A-D from Robinson and Keller (239); E, F from Robinson (229).]

Using typical values of  $k$ ,  $r$ , and  $E_T$ , the discharge rate of the average motoneuron is

$$R_m = 100 + 4E + 0.95\dot{E} \quad (2)$$

For example, if the eye fixated ( $\dot{E} = 0$ )  $30^\circ$  in the on-direction ( $E = +30$ ),  $R_m$  would be 220 spikes/s. If the eye passed through zero at  $100^\circ/\text{s}$  in the off-direction, the rate would be 5 spikes/s. In general, the term  $4E$  (Eq. 2) represents the force necessary to overcome elastic elements in the plant and to thereby maintain eccentric gaze. The term  $0.95\dot{E}$  represents the force necessary to overcome the drag created by viscous elements in the orbit and move the eye at the desired velocity.

Equation 1 was originally derived from data obtained during fixation (102, 229, 248) and pursuit movements (229) and also roughly describes the burst in  $R_m$  during saccades (Fig. 2E). It was subsequently shown that Equation 1 also applied to vergence movements (161) and movements of the vestibuloocular reflex (261). An important consequence of these facts is that all motoneurons participate in the same way (according to Eq. 1) in generating all the different types of eye movements. In other words, there is not one set of "phasic" motor units just to make saccades and another "tonic" set just to make vergence movements. Motor units are used to generate force regardless of the type of movement called for, from the slowest to the fastest. The fact that both agonist and antagonist motoneurons can be described by Equation 1 means that reciprocal innervation occurs without exception. Agonist excitation is always accompanied by a corresponding decrease in  $R_m$  for antagonist motoneurons. The discharge rate ( $R_m$ ) does not appear to increase simultaneously in pairs of antagonist extraocular muscles, a situation quite different from that found in spinal motor control. The motoneurons also appear to follow a rank order of recruitment (see the chapter by Henneman and Mendell in this *Handbook*), because  $E_T$  is constant for each motoneuron.

In the quantitative analysis of eye movement control, it is often necessary to try to predict how the eye will move when  $R_m(t)$  or the parameters of the plant are altered experimentally or by peripheral or central pathology. For such purposes, especially when the plant is only one part of a complex model of oculomotor organization, it is convenient to use the concept of the transfer function, which describes mathematically how a device (i.e., the plant) transforms its input signal ( $R_m$ ) to produce the output signal ( $E$ ) in Laplace transform notation. For this purpose it is simplest to define  $\Delta R_m$  as the change in discharge rate from its primary-position value. Equation 1 then can be transformed into

$$\frac{E(s)}{\Delta R_m(s)} = \frac{1/k}{(sT_e + 1)} \quad (3)$$

where  $s$  is the Laplace complex frequency. An impor-

tant parameter of the transfer function (Eq. 3) is the time constant  $T_e$ , which is the ratio  $r/k$ . From Equation 2 the mean value of  $T_e$  for the motoneuron pool is about 0.24 s (229, 261). This means that the plant is intrinsically slower than one might guess, judging by the rapidity of saccades. If, for example,  $\Delta R_m$  is a step (a sudden change from one rate to another),  $E(t)$  approaches its new position exponentially with a time constant of  $T_e$ . This is how vergence movements occur (154). The exponential movement is essentially complete in three time constants or 0.72 s, which is quite slow. The rapidity of saccades comes from the high-frequency burst, which creates a large force for a short period of time, thereby overcoming an intrinsic sluggishness by brute force (227).

Equation 1 only roughly describes motoneuron behavior during saccades. Equation 2 would imply that during a  $700^\circ/\text{s}$  on-saccade,  $R_m$  should reach 765 spikes/s, but the typical motoneuron bursts at only 400 spikes/s. Figure 2F illustrates the consistent observation that eye velocity increases more rapidly than burst discharge rate. The source of this apparent non-linearity remains unknown.

Equation 1 also ignores a phenomenon noticeable during rapid transients in  $R_m(t)$  that occur, for example, during saccades. Close examination (114, 154) reveals that  $R_m$  is also weakly related to eye acceleration  $\ddot{E}$  ( $d^2E/dt^2$ ) and a better approximation is

$$R_m = k(E - E_T) + r\dot{E} + m\ddot{E} \quad (4)$$

A typical value of  $m$  (154) is 0.0154 (spikes/s)/(deg/s<sup>2</sup>). The last term in Equation 4 is only important when eye acceleration exceeds values on the order of  $1,000^\circ/\text{s}^2$ . This term may be partially due to the moment of inertia of the eyeball but, because that is quite small, the term probably comes instead from cascaded viscoelasticities that create the same effect (227). There is also a pure delay between  $R_m$  and  $E$ , which is most clearly seen during saccades. The burst in  $R_m$  occurs about 7 ms before the first detectable eye movement and stops about 8–9 ms before the end of the saccade (102). Little of this time should be lost in nerve conduction, synaptic delay, or in pulling the slack out of the muscle, because most fibers are already bearing tension. Therefore, it is evidently lost in the process of excitation-contraction coupling. Adding in these high-frequency factors, the plant transfer function becomes

$$\frac{E(s)}{\Delta R_m(s)} = \frac{(1/k)e^{-s\tau}}{(sT_{e1} + 1)(sT_{e2} + 1)} \quad (5)$$

where one time constant,  $T_{e1}$ , is 0.18 s, approximately  $r/k$ ; the other,  $T_{e2}$ , is 0.016 s (154), approximately  $m/r$ ; and  $\tau$  is an 8-ms delay.

In spite of the refinements just described, Equation 1 or 3 still provides a good estimate of the relationship between eye movements and the discharge rate of ocular motoneurons, which, for all but very special

purposes, allows one to predict the eye movement that would be created by any central signal reaching the motoneurons. It also provides a description of the eye movements created by abnormalities of the plant or its central control signals in a variety of clinical disorders (237, 308). An unresolved problem is hysteresis. The studies referred to above fail to find hysteresis in the relationship between  $R_m$  and  $E$  in the monkey, but one study (87) does report it. Large amounts of mechanical and innervational hysteresis have been reported in human eye muscles (70). This phenomenon certainly needs further investigation.

#### *Movement and Muscle Fiber Types*

Equation 1 implies that all motoneurons behave qualitatively in the same way. If that were the case, what is the function of the various types of muscle fibers found in extraocular muscle? Classically, these fiber types have been divided into two broad categories: phasic, to be associated somehow with motion, velocity, or transiency; and tonic, which implies steady, fixed, or enduring. Although these terms are qualitatively useful it is difficult to use them to distinguish types of motoneurons on the basis of behavior, because, as Equation 1 indicates, all motoneurons participate in movements that are both fast and slow as well as transient and sustained (237). A relationship has been established, however, between the morphology of fiber types and their fatigability (see the chapter by Burke in this *Handbook*). The latter can be related to motoneuron behavior by the threshold,  $E_T$  (Eq. 1). During natural behavior, the eyes are, on the average, looking straight ahead. Eccentric glances are either brief or followed by a head movement that recenters the eyes. Consequently, the eyes spend most of the waking day near the primary position. A motor unit with a threshold below zero (the primary position) must, therefore, be firing nearly all day; one with a threshold above zero discharges only in brief, infrequent intervals. Therefore, low-threshold motor units must be resistant to fatigue; high-threshold units need not.

In skeletal muscles the characteristics of fatigue-resistant muscle fibers are that they are small, are rich in mitochondria, have a well-developed capillary supply, are the earliest to be recruited, and are mechanically slow as determined by the rise and fall of isometric twitch or tetanic tension. Easily fatigued fibers are large, are poor in mitochondria, are recruited last when large forces are briefly required, and are fast. There is also a third type which is intermediate in its characteristics. These basic fiber types are also found in eye muscles. For some unknown reason, they are more or less segregated there. The small fibers lie mainly in a thin layer on the surface of the muscle away from the globe called the orbital layer. The large, fast fibers lie mainly in the central and global layers (6). Simultaneous, multiple, electromyographic re-

cordings in human beings (70) utilized this division to confirm that in eye muscles, as well as in skeletal muscles, the small fibers (in the orbital layer) are recruited before the large fibers (in the core and global layer).

Extraocular muscles have two additional fiber types, which have an unusual pattern of innervation. Instead of ending in the usual single cluster of motor end plates, the axons of these fibers travel along its length giving off a series of small end plates. They are called multi-innervated fibers; the more conventional are referred to as singly innervated fibers. It has been shown that one type of multi-innervated fiber conducts action potentials and produces the usual all-or-nothing twitch, whereas the other depolarizes and contracts in a slow and graded manner (11, 174). The main mechanical difference found thus far between singly innervated and multi-innervated fibers is that the latter fire at a stimulus frequency well below that at which they develop maximum tension (174). Nevertheless, the functional properties of these fibers that make them especially useful in eye muscles are unknown.

#### *Stretch Afferents*

Muscle spindles and Golgi tendon organs are found in the extraocular muscles of a wide variety of animals such as the human being, monkey, goat, and pig (292). In the cat, spindles do not occur and free nerve endings appear to play the role of stretch receptors. Probably all vertebrates have some type of proprioceptive apparatus that can provide nonvisual information about the mechanical state of the eye. The signals from eye muscle spindles seem comparable to those from skeletal muscles (see the chapter by Matthews in this *Handbook*): the discharge rate varies with muscle length and its rate of change (72). There is evidence for a  $\gamma$ -innervation to extraocular muscles (291), but no recordings have yet been made from stretch afferents in alert animals, so it is not certain just how  $\alpha$ - and  $\gamma$ -activity modulate the afferent signal during natural eye movements.

The stretch afferents in many species travel centrally on the ophthalmic division of the trigeminal nerve (72), and their cell bodies lie in the Gasserian ganglion (188). The situation is more complex in the cat; some fibers appear to take this route (20) but others return along the branches of the motor nerve. Cell bodies of stretch afferent fibers are found in the mesencephalic nucleus of the trigeminal nerve (7, 97), but whether this is the location of the majority of such cells is not known. Stretch afferent signals eventually find their way to the oral part of the descending trigeminal nucleus (189), superior colliculus (3), cerebellum (21, 101), reticular formation (110), and visual cortex (41). So little is known about the signals carried by these pathways, however, that there is very little support for any of the several hypotheses that have

been advanced to explain the function of stretch afferents in eye muscles (10).

For a long time the existence of a direct afferent pathway to the motoneurons to form a stretch reflex (as in the spinal cord) was debated. The bulk of evidence was negative (e.g., ref. 20), but the ubiquitousness of this reflex in skeletal motor systems made it difficult to believe that eye muscles would be an exception. Most theories of the stretch reflex function propose that it assists in maintaining a desired movement pattern, in spite of external perturbing forces or unexpected variations in the load (see the chapters by Houk and Rymer and by Rack in this *Handbook*). Eye muscles do not have to deal with such disturbances, and this situation provided some theoretical support for the lack of a stretch reflex in the oculomotor system.

When it became possible to record from the motoneurons of eye muscles in alert monkeys, it also became possible to reinvestigate the hypothesis of a stretch reflex in a more natural, experimental situation. Monkeys were trained to fixate a target with one eye while the other eye, covered by an opaque contact lens, was moved about by the experimenter. Ipsilateral abducens motoneurons failed completely to change their discharge rate when the lateral rectus was rapidly lengthened or shortened (160). If there were a fixed, mono- or oligosynaptic stretch reflex, this could not happen. Thus, the bulk of evidence to date indicates that there is no stretch reflex in extraocular muscles.

### Muscle Mechanics

Muscles transform the neural command  $R_m$  into a force that determines eye velocity and position. The main components in this process are the length-tension, force-velocity characteristics of muscle (see the chapter by Partridge and Benton in this *Handbook*) and the viscoelasticity of the passive orbital tissues.

**STATICS.** The elastic elements of the human eye have been measured during strabismus surgery under topical anesthesia so that muscle force ( $F$ ), length ( $L$ ), and innervation or intensity of neural activity ( $I$ ) could all be measured or controlled (70, 234, 240). In the same experiments, the eye, with the horizontal recti detached, was rotated to find the force-displacement curve of the combined passive orbital tissues. The results are shown in Figure 3. The  $F$  depends on  $L$  and  $I$ . If  $I$  is held constant, the curve  $F(L,I)$  is the length-tension relationship for that level of innervation. Several such curves for the medial rectus are shown in the top half of Figure 3 for innervations appropriate to attempted gaze angles of  $0^\circ$ ,  $\pm 15^\circ$ ,  $\pm 30^\circ$ , and  $\pm 45^\circ$ . The curves for the lateral rectus are plotted upside down and backwards, because the force of the two muscles act in opposite directions, and because one muscle lengthens as much as the other shortens.

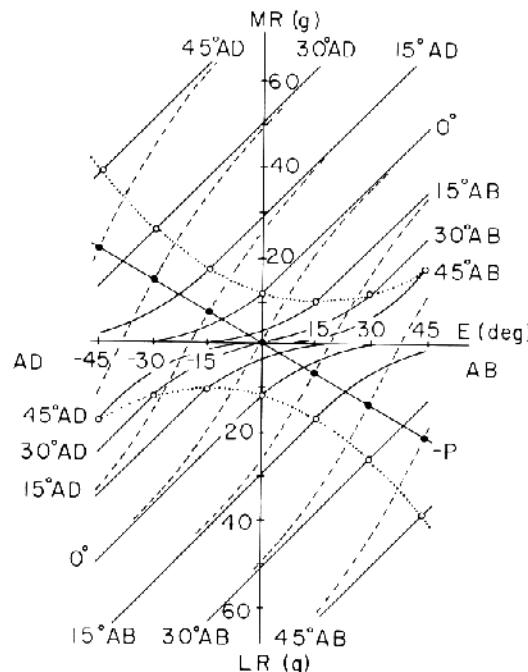


FIG. 3. Mechanics of eye positioning. *Top*, family of solid curves show medial rectus (MR) force as a function of muscle length that is shown as equivalent eye rotation (E). Innervation is changed when patient looks straight ahead ( $0^\circ$ ) or to the left and right  $15^\circ$ ,  $30^\circ$ , and  $45^\circ$  with the other eye. The amount of force exerted is measured in grams. *Bottom*, curves show similar lateral rectus (LR) length-tension-innervation curves. Force-displacement relationship of passive orbital tissues is shown ( $-P$  curve). Dashed lines indicate sum of 2 muscle forces in attempted  $0^\circ$ ,  $15^\circ$ ,  $30^\circ$ , and  $45^\circ$  gaze in abduction (AB) and adduction (AD). The eye is at rest when dashed curves cross  $-P$  curve (filled circles), because sum of all forces is zero at that point. Dotted lines and open circles show operating locus of individual muscle's force as length and innervation change normally over the field of gaze. These curves allow one to know division of forces in orbit for any angle of gaze. [Some of the data in this figure from Collins (70).]

In the primary position, each horizontal rectus exerts about 12 g. The two muscles together act like a push-pull pair of springs; their net force-displacement curve is shown in Figure 3. To adduct the eye  $30^\circ$ , for example, the medial rectus is excited and the lateral rectus inhibited to the curves marked  $30^\circ$  AD (adduction). The curve of net muscle force crosses the passive tissue curve at  $-30^\circ$ . At this point, the sum of all forces on the eye is zero, so the eye is at rest. The medial rectus exerts approximately 26 g, the lateral rectus approximately 12 g, and the passive tissues account for the 14-g difference. The dotted lines in Figure 3 show the normal muscle forces for each eye position and thus indicate the division of forces for any angle of gaze.

This sort of analysis can be extended (234) by representing each muscle's torque on the globe as a three-dimensional vector,  $F_i m_i$ , where  $m_i$  is a unit vector pointing along the axis about which the globe would turn when the force  $F_i$  of the  $i$ th muscle is applied. The passive force is also replaced by a torque vector

P. The eye is at rest when the sum of all the torques is zero

$$\mathbf{P} + \sum_{i=1}^6 F_i(L_i, I_i) \mathbf{m}_i = 0 \quad (6)$$

For a given eye position, it is possible to find  $\mathbf{P}$ ,  $L_i$ , and  $\mathbf{m}_i$  just by geometry. Equation 6 may then be solved for  $I_i$  (using reciprocal innervation to reduce the number of unknowns to three). The solution gives the six innervations required to hold the eye in any given position. The question may then be reversed. If the  $I_i$ 's are known, abnormalities can be introduced into Equation 6, e.g., simulating palsies, fibrotic muscles, and orbital floor fractures, and one may then solve for the deviated eye position that satisfies the equation. The effects of surgical manipulations, such as recessing or resecting muscles, may then be added in Equation 6 to try to predict the extent to which strabismus surgery can reduce these deviations. This sort of investigation may allow some of the findings of basic research to be of practical use in solving clinical problems.

**DYNAMICS.** The dynamics of eye movements are largely determined by viscous elements. The largest of these is the force-velocity relationship of extraocular muscles. Unfortunately there has been only one study (51), in the rat, of this relationship in an extraocular muscle. In view of the complex, fiber-type population in eye muscles and the abnormal conditions (e.g., temperature) usually associated with isolated skeletal muscle experiments, an extrapolation from the latter to the former is most uncertain. Even in skeletal muscle, a very complete description does not exist of the force-velocity relationship of active muscles during lengthening; this is a very common situation in the normal use of muscles. Active muscle slips when lengthened and the resisting force becomes almost independent of velocity, but it does depend on innervation (150). Additional information has come from force recordings during human saccades when a strain gauge was inserted temporarily during strabismus surgery (70) between a muscle's tendon and its insertion. This procedure showed that force actually rises in the lengthening antagonist muscle, even though its motoneurons are totally inhibited momentarily. This increase is due to the viscosity of passive muscle tissues and to a slow muscle deactivation time about which very little is known.

A similar lack of data exists on the viscosity of the passive orbital tissues. Attempts have been made to study this viscosity by first removing the horizontal recti and then observing the time constants of the return movement of the eye after a quick release. Results apparently differ between experiments on the cat and human (69, 70). The series-elastic element of muscle also contributes to its dynamics (293). Part of this element is probably in the tendon, but part is certainly in the sarcomere. How the latter's elastance

depends on the number of fibers stimulated, the time after a sudden change in stimulation, the rate of stimulation, and muscle length are also largely unknown.

Despite all these uncertainties, several attempts have been made to model the mechanical elements of the oculomotor plant in some detail using a good many approximations and simplifying assumptions (50, 70, 227). The models are more or less successful in simulating a variety of natural and forced eye movements and have the value of organizing diverse data into a conceptual framework. But these models cannot be used to resolve the many internal indeterminacies that come about because of the lack of good experimental data.

#### VESTIBULOOCULAR REFLEX

The vestibular apparatus consists of semicircular canals and otolith organs, which primarily respond to angular and linear head acceleration, respectively. In foveate primates the ocular responses to otolith stimulation are small, especially when compared to those due to canal stimulation (see subsection *Otolith Reflex*, p. 1288). Consequently, the term vestibuloocular reflex is used here to denote the canal-ocular reflex excited by head rotation.

#### Properties of Reflex

**HIGH FREQUENCIES.** To test the reflex at high frequencies, animals and human subjects are rotated sinusoidally in the range of 1–15 Hz, and the sinusoidal eye velocity that results is compared in amplitude and phase relative to the head velocity. If eye movements were perfectly compensatory, it would be conventional to define the gain (eye velocity divided by head velocity) as 1.0 and the phase as zero. The graph that plots gain and phase as a function of frequency (e.g., Fig. 4A) is called a Bode diagram. Experiments on human beings (31, 260) and monkeys (156) report that up to about 6–8 Hz the changes in gain and phase compared with changes in frequency are small. At higher frequencies, a phase lag appears (31, 260). Negligible phase shift up to 5 Hz has also been reported in the cat (171). Power-spectrum analysis of human head tremor suggests that 7 Hz is a rough upper limit for natural head rotations (260), and most of the experimental data suggest that the reflex works well up to that frequency. The reflex behavior is idealized in Figure 4A, which shows no dependence of gain and phase on frequency in the region of 1–7 Hz.

**LOW FREQUENCIES.** When a subject is rotated in the dark at a constant speed, slow-phase eye velocity is initially compensatory, but then slowly returns to zero. If rotation is then stopped, slow-phase eye velocity repeats its exponential response, but in the opposite direction. This is called postrotatory nystagmus and is illustrated schematically in Figure 4B. Momentarily neglecting adaptation, slow-phase eye velocity would

return to zero with a single exponential with a time constant denoted by  $T_{vor}$ , which is related to, but not identical with, the cupula time constant discussed later in this section.  $T_{vor}$  is about 12 s for the cat (235), around 16 s for the monkey (40), and 21 s for human beings (187). If one takes adaptation ( $T_a$ ) into account, eye velocity decreases more rapidly and has a long reversed tail. This is illustrated in Figure 4B using a value for  $T_a$  of 80 s (187). If one does not take the effect of  $T_a$  into account, one can seriously underestimate  $T_{vor}$  from nystagmus records (187).

These values for  $T_a$  and  $T_{vor}$  imply that for sinusoidal stimuli the gain should begin to decrease with frequency and a phase advance should appear below the region of  $1/(2\pi T_{vor})$  Hz or 0.01 Hz for the monkey. Below  $1/(2\pi T_a)$ , or about 0.002 Hz, the gain should fall even faster and the phase lead increase further as frequency decreases. These predictions are borne out experimentally (40) and are schematized by the heavy curves in Figure 4A for the monkey. Figure 4A also qualitatively describes the Bode diagram for other species (e.g., refs. 8, 171, 235), but the break frequencies depend on the values of  $T_a$  and  $T_{vor}$  for each particular animal.

**GAIN.** In the frequency range of 0.01–7 Hz, the phase shift is small and gain is the important parameter. Early experiments in human beings were complicated by the fact that when placed in the dark for very long, subjects became inattentive or drowsy, and the gain dropped markedly (71). More recently, when subjects are asked to do mental arithmetic to stay alert, their gain, around 0.3 Hz, is about 0.65 (24, 31). This might suggest that 0.65 is the “natural” gain, with vision raising it to 1.0 in the light through a pursuit mechanism. But, if a subject is simply asked to look at an imaginary spot on the wall in total darkness, the gain rises to 0.95 (24). Apparently, it is not enough that the subject be alert, he must also be attending to the environment and trying to use the reflex. In that situation, the natural gain of human beings is close to 1.0. There is evidence, however, that the ability of subjects to raise their gain in this way may not be as effective with small stimulus amplitudes (260). This problem does not arise in some animals. In the dark the gain in the cat (235) and the monkey (156) is 0.9 as long as they are simply alert. However, anything that could affect alertness, such as drugs, pain, or immobilization, might be expected to cause the gain to drop. For example, the rabbit has a gain near 1.0 when it is unrestrained (64), but in increasingly restrictive experimental situations gains are lower (8), even as low as 0.24 (146).

In summary, the gain of the reflex,  $g$ , in as normal a situation as possible, is around 0.9 (Fig. 4A). The reflex works well at the highest frequencies contained in natural head movements; its low-frequency behavior is dominated by two time constants,  $T_{vor}$  and  $T_a$ . Just as for the oculomotor plant, it is most useful in

predicting the quantitative outcome of experiments to be able to describe the vestibuloocular reflex as a transfer function between slow-phase eye velocity ( $\dot{E}_s$ ) and head velocity ( $\dot{H}$ )—or what is the same thing, between cumulative slow-phase amplitude (e.g., see ref. 192 for an example of this method) and head position—in Laplace notation

$$\frac{\dot{E}_s(s)}{\dot{H}(s)} = -g \frac{sT_{vor}}{(sT_{vor} + 1)} \frac{sT_a}{(sT_a + 1)} \quad (7)$$

The Bode diagram of this description is shown by the heavy lines in Figure 4A. The reflex may be subdivided into three parts: the canals, the central pathways, and the plant (Fig. 4C).

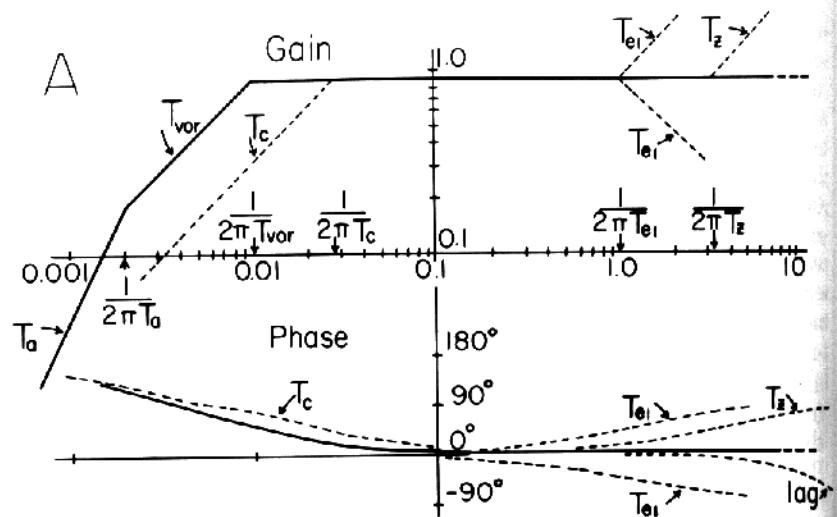
### Semicircular Canals

Because the physiology of the canals is described elsewhere in these volumes (117), this section deals only with the signal that this end organ provides to the oculomotor system. The mean resting discharge rate of primary vestibular afferents in the squirrel monkey is 90 spikes/s (116). When the animal is oscillated sinusoidally, the discharge rate ( $R_{v1}$ ) is modulated sinusoidally. The gain and phase of the modulation  $\Delta R_{v1}$  may also be expressed, relative to head position, by a transfer function (94)

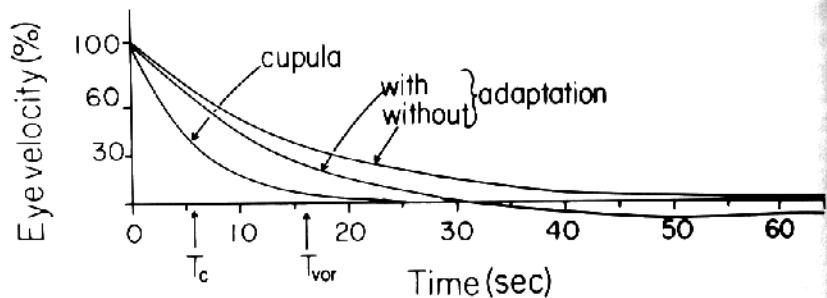
$$\frac{\Delta R_{v1}(s)}{H(s)} = sS_v \frac{sT_c}{(sT_c + 1)} \frac{sT_a}{(sT_a + 1)} (sT_z + 1) \quad (8)$$

The operator  $s$ , the first term on the right, simply indicates that over a wide range of physiological frequencies (about 0.03–3 Hz) the canal output is proportional to head velocity ( $sH$ ). The typical velocity-sensitivity factor ( $S_v$ ) of a fiber may be found by dividing the average acceleration sensitivity of 2.24 (spikes/s)/(deg/s<sup>2</sup>) by the average cupula time constant  $T_c$  of 5.7 s (94). Thus,  $S_v$  is 0.39 (spikes/s)/(deg/s) for the squirrel monkey. These numbers allow one to calculate that if the resting activity of one canal changed by only 2%, a persistent nystagmus would occur with a slow-phase velocity of 2.3°/s. Thus, eye stability requires constant and accurate balancing between the activity of each canal in a push-pull pair.

The second term  $sT_c/(sT_c + 1)$  describes the fact that when the canal cupula is suddenly deflected by an impulse of acceleration, it slowly returns to its neutral position because of its elasticity. The time constant ( $T_c$ ) of the returning movement is determined by the ratio of the viscous drag coefficient of the endolymph to the elasticity of the cupula in the torsion-pendulum model of the canal (268, 301). Individual fibers located in different parts of the crista show different time constants, suggesting that the cupula may not move en bloc but may have a distribution of internal strains (209). Nevertheless, a single, average time constant accounts for most experimental vestibuloocular results. There is a second, smaller time constant in the torsion-pendulum model, but it is



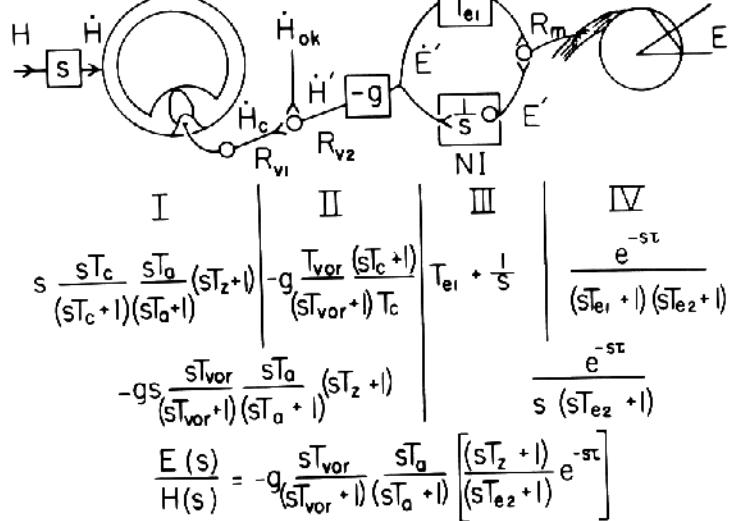
A Frequency (Hz)



B

Frequency (Hz)

C Canals | Central | Plant



estimated to be so small (about 3 ms) that its effect may be neglected, since it would only be seen above 53 Hz (94).

The third term in Equation 8,  $sT_a/(sT_a + 1)$ , describes adaptation that affects the results of sinusoidal or step stimulation as shown in Fig. 4A, B.  $T_a$  is 80 s for the squirrel monkey (94) and similar large values are reported in other studies (301). These values are so large that adaptation is unlikely to play any role in regulating normal head-eye movements but may reflect a homeostatic mechanism to maintain long-term balance between each canal in a pair. The fourth term ( $sT_z + 1$ ) was an unexpected finding.  $T_z$  is about 0.049 s, which means that above  $1/(2\pi T_z)$  or 3.3 Hz a phase lead occurs so that  $\Delta R_{v1}$  becomes more proportional to head acceleration than head velocity. Nevertheless, over the frequency range 0.028 Hz, [ $1/(2\pi T_c)$ ], to 3.3 Hz (about 2 log units), which covers the range of most normal head movements, the signal arriving in the vestibular nucleus,  $R_{v1}$ , is proportional to head velocity ( $H$ ) and in this range can be expressed more simply by

$$R_{v1} = 90 + 0.4H \quad (9)$$

### Central Pathways

The first step in processing the canal signal is the connection of pairs of canals lying in the same plane so that their signals drive cells in the vestibular nuclei in a push-pull manner. For the horizontal canals, for example, type I cells in the nuclei are excited during ipsilateral head turning both by excitation from the

ipsilateral canal afferents and by disinhibition from the opposite canal relayed through a commissural projection and type II inhibitory cells (253). These connections reinforce the  $R_{v1}$  signal but do not alter it qualitatively, and the discharge rate modulation of most second-order vestibular neurons is also proportional to head velocity (e.g., refs. 100, 158).

**TRANSFORMING CUPULA TIME CONSTANT.** For a long time it was assumed, more or less tacitly, that the behavior of slow-phase eye velocity reflected the motion of the cupula. It has already been mentioned, however, that  $T_{vor}$ , the eye velocity time constant, is 12 s for the cat and about 16 s for the monkey, yet  $T_c$ , the cupula time constant, is 4 s for the cat (196) and 5.7 s for the monkey (94). Thus, the whole reflex acts as though the canal time constant were three times larger than it actually is. During postrotatory nystagmus, for example, eye velocity decreases three times more slowly than the time course of the cupula (Fig. 4B). The effect for sinusoidal stimuli is to extend the low-frequency range over which the reflex works properly from about 0.03 Hz to 0.01 Hz, using data from monkeys (Fig. 4A). This transformation takes place in the vestibular nucleus where cells, many of which must be second-order vestibular neurons, respond to rotation in the dark with the time constant  $T_{vor}$ , not  $T_c$  (41). The transfer function that describes the transformation between the discharge rate of first- and second-order neurons ( $R_{v1}/R_{v2}$ ) is given as transformation II, Figure 4C. When transfer functions I and II are multiplied, the terms containing  $T_c$  cancel out and the result shows an "effective" cupula time con-

FIG. 4. Vestibuloocular reflex. See text for more complete explanation. A: Bode diagram of vestibuloocular reflex showing behavior of gain and phase with frequency. Heavy lines indicate overall behavior; dotted lines show contributions of various components. Effect of neural transformation II shown in Fig. 4C is to extend low-frequency range over which reflex works properly from about 0.03 Hz (dashed curves marked  $T_c$ ) to 0.01 Hz (using data from monkeys) as shown by solid curves. B: postrotatory nystagmus. When prolonged head rotation at constant velocity  $\dot{H}$  suddenly stops, cupula is displaced and returns with exponential time course with time constant  $T_c$  (curve marked *cupula*). Slow-phase eye velocity  $E$  decreases, however, with time constant  $T_{vor}$ , which is about 3 times larger than  $T_c$  (curve marked *without adaptation*). Adaptation alters this ideal curve by causing it to fall faster and by adding prolonged reversed tail. C: signal processing in reflex showing, in Laplace transform notation, transfer functions of sensory (canals), central, and motor (plant) parts of reflex in 4 stages (I-IV). Stage I describes the canals according to Equation 8. First step in central processing (stage II) is to convert main reflex time constant  $T_c$  to  $T_{vor}$ . When transfer functions I and II are multiplied, terms containing  $T_c$  cancel out and the result reflects effective cupula time constant of  $T_{vor}$  shown on the left in *second row of equations*. Next central step (III) is integrating velocity command (1/s) and compensating for plant lag by velocity feedforward path,  $T_{e1}$  (*right equation, second line*). Stage IV describes the plant as in Equation 5. Final transfer function (*bottom line*) is similar to that measured experimentally assuming that high-frequency terms in brackets more or less cancel out.  $H$ , head position;  $\dot{H}_c$ , head velocity as coded by the canals;  $\dot{H}_{ok}$ , a central signal that effects transformation II;  $R_{v1}$ , discharge rate of primary vestibular neurons;  $R_{v2}$ , discharge rate of second-order vestibular neurons;  $H'$ , central head velocity signal;  $E'$ , vestibular eye velocity command;  $E$ , eye position; NI, neural integrator;  $R_m$ , discharge rate of motoneurons;  $-g$ , overall reflex gain.

stant of  $T_{vor}$ . Because this transformation disappears with anesthesia (40), it is undoubtedly created by the addition of another signal to second-order neurons coming from more central structures. This signal is denoted  $\dot{H}_{ok}$  in Figure 4C because  $R_{v2}$  is driven by optokinetic stimuli (131, 282) and also reflects the slow-phase, eye velocity signal during optokinetic aternystagmus (281). These facts strongly suggest that the added signal is related to the optokinetic system (see section OPTOKINETIC SYSTEM, p. 1293).

**NEURAL INTEGRATOR.** The signal in the vestibular nucleus is proportional to head velocity ( $\dot{H}$ ) which is, with a sign change, an eye velocity command  $\dot{E}'$  (Fig. 4C). Equation 2 indicates that to perform the eye movement  $E(t)$  the motoneurons must receive both an eye position command  $4E'(t)$  and an eye-velocity command  $0.95 E'(t)$ . The signal  $0.95 E'(t)$  is obviously available directly from the vestibular nucleus. The eye position signal  $4E'(t)$  must somehow be created. There must exist some neural network (233, 261) to convert (mathematically integrate)  $\dot{E}'(t)$  to produce  $E'(t)$ . The location and mode of operation of this neural integrator are unknown, but the cerebellum and reticular formation seem to be involved.

The poor high-frequency response of the plant due to  $T_{el}$  in Equation 5 would cause a gain decrease and phase lag above  $1/(2\pi T_{el})$  or about 1.0 Hz (Fig. 4A, lower dashed curves marked  $T_{el}$ ). To prevent this, the velocity feedforward path provides a phase lead and gain increase, which cancels the major lag of the plant. In this way, eye position continues to equal the time integral of the eye velocity command from the vestibular nucleus above 1.0 Hz. To do this correctly, the ratio of the gain of the direct path relative to the integrator path must be  $T_{el}$  (approximately equal to  $r/k$ ; see Fig. 4C). Analytically, the transfer function of the two paths together (Fig. 4C, transformation III) is  $T_{el} + (1/s)$  or  $(sT_{el} + 1)/s$ . The lead term  $(sT_{el} + 1)$  cancels the similar lag term in the plant transfer function in transformation IV, thereby overcoming the poor high-frequency response of the plant.

**SUMMARY.** Figure 4C summarizes the signal processing believed to occur along the entire reflex. All scale factors ( $S_v$ , Eq. 8;  $1/k$ , Eq. 5) have been replaced by one, equivalent, net gain ( $g$ ), which is about 0.9. The canals provide the first estimate of head velocity ( $\dot{H}_c$ ) coded in the signal ( $R_{v1}$ ) according to Equation 8 and dominated by the canal time constant  $T_c$ . The first central step is to improve the low-frequency response according to transformation II, which effectively replaces  $T_c$  by  $T_{vor}$ . This transformation is effected by the addition of a central signal that is a part of the optokinetic system. The signal ( $R_{v2}$ ) is an improved estimate of head velocity ( $\dot{H}'$ ). When multiplied by  $-g$  it becomes a vestibular eye velocity command ( $\dot{E}'$ ). The direct central path, in parallel with the integrator, cancels the main lag element,  $T_{el}$ , in the plant (transformations III and IV). The final result is that up to

about 3 Hz the dynamic behavior of the entire reflex (Eq. 7; Fig. 4A) can be accounted for in terms of physiologically determined sensory, central, and motor components (Eqs. 5, 8; transformations II, III in Fig. 4C).

Above 3 Hz complications arise. There is a phase lead above 3.3 Hz associated with  $T_z$  (Fig. 4A) and a phase lag associated with  $T_{el}$  (Eq. 5). Because  $T_{el}$  is about 16 ms, this lag occurs above 10 Hz and is not shown in Figure 4C. There is a pure delay in the plant of 8 ms. The shortest path in the reflex is a 3-neuron arc (see subsection VERTICAL REFLEX SIGNALS, p. 1289) and 2 ms is a generous estimate of its delay; the overall delay should be around 10 ms. This delay causes a phase lag at high frequencies (Fig. 4A, lag). At 8 Hz, for example, the lag is  $29^\circ$ . These lead and lag terms (Fig. 4C) fight each other in the range of 3–8 Hz. There may be other, as yet unknown, sources of high-frequency lead and lag. At the moment, all one can say is that their effects appear to more or less cancel out, so that net phase remains small up to 8 Hz.

Conceptually, the signal processing of the central pathways in Figure 4 is straightforward; however, the central part is schematic only. It illustrates what must be done, overall, but as is shown in the following section, the signals actually carried by many of the central neurons accomplish the same job but in a different way.

#### Otolith Reflex

When most afoveate animals are tilted out of the vertical in any direction (roll or pitch), their eyes assume a position that partially compensates for the steady tilt and attempts to restore the eyes to the orientation, with respect to the visual environment, found in the normal upright position (e.g., refs. 9, 139). An excellent description of the signals provided by the otolith organs is available in an article by Fernandez et al. (95). In human beings, voluntary control of vertical eye movements supersedes any steady, otolith pitch signals, and torsional deviations, compensatory for roll deviations, are small. In one study, a roll angle of  $45^\circ$  produced a steady ocular counterroll of only  $5^\circ$  (203), although larger but still inadequate deviations have been reported.

#### Neurophysiology of Reflex

**SPATIAL ORGANIZATION.** There are three canals on each side of the head arranged approximately at right angles to each other and parallel to the planes of the canals on the opposite side (89). Each canal behaves as though its fluid ring lies in a single plane, so it responds maximally to rotation around an axis perpendicular to that plane. Rotation of the head about any arbitrary axis excites each canal by an amount proportional to the projection of the head velocity vector onto the canal's axis of maximum sensitivity. Centrally, the canals lying in nearly parallel planes are

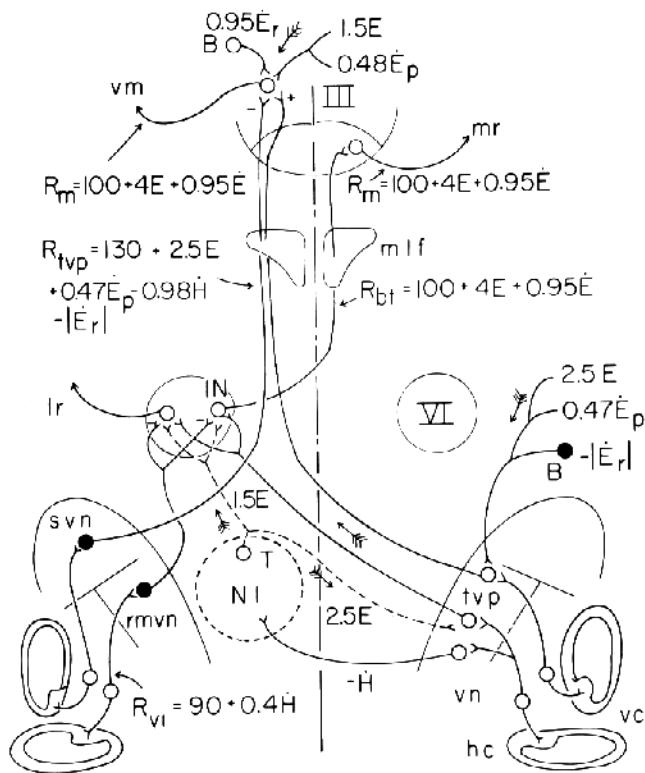


FIG. 5. Schematic of major pathways and signals mediating vestibuloocular reflex. A head velocity signal ( $\dot{H}$ ) is relayed from horizontal (hc) and vertical canals (vc) by the discharge rate ( $R_{vi}$ ) of primary vestibular afferents to tonic-vestibular-pause cells (TVP) in the vestibular nucleus (VN). Excitatory cells are indicated by open circles; inhibitory cells by filled circles. Excitatory vertical reflex is relayed via discharge rate  $R_{tvp}$  of TVP fibers in the contralateral medial longitudinal fasciculus (MLF) to motoneurons of vertical muscles (vm) in the oculomotor nucleus (III). Eye position ( $E$ ) and eye velocity commands ( $E_p$ ,  $\dot{E}_p$ ) are added both at level of VN and motoneurons. It is hypothesized that the horizontal reflex is also mediated by TVP fibers projecting to lateral rectus (lr) motoneurons in abducens nucleus (VI) and relayed to medial rectus (mr) motoneurons via internuclear neurons (IN) in VI. Dashed line, eye position signals of 1.5E and 2.5E may come from tonic cells (T) in neural integrator (NI). Equations for signals  $R_{vi}$ ,  $R_{tvp}$ ,  $R_{bt}$ , and  $R_m$  are explained in text. Inhibitory cells for vertical reflex lie in superior vestibular nucleus (SVN) and ascend in ipsilateral MLF. Other excitatory and inhibitory fibers appear to lie in rostral medial VN (RMVN). B, burst cells;  $R_{bt}$ , burst-tonic signal;  $-|\dot{E}_r|$ , pause created by inhibitory burst cells;  $R_m$ , motoneuron signal.

connected to form three push-pull pairs: 1) the right and left horizontal canals, 2) the left anterior and right posterior canals, and 3) the left posterior and right anterior canals. Thus, every head rotation creates three central, canal-pair signals, each represented by both excitation and inhibition, which uniquely specify the axis and speed of the head rotation in the coordinate system of the canals.

Similarly, each eye is driven by three pairs of muscles that work in planes again arranged (very roughly) at right angles. Each muscle has a unit action vector,  $m_i$  (Eq. 6); these may be paired to form three push-pull unit vectors directed along the axes about which

each muscle pair rolls the eye. If the eye is to counterroll around the axis of the head velocity vector, the intensity of the push-pull neural signals from the motor nuclei must be correctly specified in the coordinate system of the muscles. Consequently, it is possible to regard the brain stem connections between canal pairs and the muscle pairs of each eye as a  $3 \times 3$  matrix, which transforms the head rotation vector from the canal to the muscle coordinates. When one calculates the elements of such a matrix, one learns that every canal pair must be connected to every muscle pair. The principal projections are those that connect each canal pair to the muscle pair lying closest to its plane: the horizontal canals project to the horizontal recti; the left anterior and right posterior canals project to the left vertical recti and right obliques; and the right anterior and left posterior canals project to the right vertical recti and left obliques (181, 273). Many of the other canal-muscle projections, however, are not small. When one takes into account that all these connections involve both excitatory and inhibitory pathways and that second-order canal neurons are not segregated topographically by canals in the vestibular nucleus (2, 278), it is no wonder that lesions in the vestibular nucleus cause axon degeneration in almost all of the oculomotor nuclei (45, 278). Nevertheless, certain general principals of these projections have emerged. For the vertical muscles (recti and obliques), inhibitory neurons appear to lie in the superior vestibular nucleus (SVN) and to ascend in the ipsilateral medial longitudinal fasciculus (MLF); excitatory neurons lie in the rostral medial vestibular nucleus (RMVN) and ascend in the contralateral MLF [Fig. 5; (18)].

Although many details remain to be resolved, the spatial transformations between canals and muscles are conceptually straightforward; however, less is known about the temporal signal processing in this reflex. The signal entering the vestibular nuclei is described by Equation 9; the signal leaving the motor nuclei is described by Equation 2. How is one signal converted to the other and where are the cells that do this?

**VERTICAL REFLEX SIGNALS.** More is known about the interneurons of the vertical reflex because all its motoneurons lie some distance away from the vestibular nuclei (VN) in the oculomotor and trochlear nuclei, which makes it easier to study the pathways between them. The MLF is a major connecting link, and it has been demonstrated by lesions (45, 106, 278) and tracers (123) that a large number of cells in the VN project into the MLF and contact vertical motoneurons. Many of them are second-order vestibular neurons (18) and, thus, constitute the middle leg of a 3-neuron arc connecting the canals to the eye muscles (181, 275). Bilateral lesions of the MLF in monkey abolish the vertical reflex (91), which suggestss that the MLF carries all or most of the signals that mediate the reflex.

These findings indicate that the main signal, which the VN sends to the vertical motoneurons, should be observable on the fibers of the MLF. This signal has been studied by King et al. (164) and by Pola and Robinson (215). In the monkey, 45% of all MLF fibers were associated with vertical gaze. Only one signal type was found on these fibers, indicating that this is also the signal carried by the middle leg of the 3-neuron arc. The discharge rate of the average fiber was related to eye and head movement by

$$R_{TVP} = 130 + 2.5E + 0.47\dot{E}_p - 0.98\dot{H} - |\dot{E}_r| \quad (10)$$

The mean resting discharge rate in the primary position was 130 spikes/s. The rate was modulated by eye position (2.5E) which, by custom, is called tonic activity; the on-direction was either up or down. It was also modulated by head velocity ( $-0.98\dot{H}$ ); the minus sign indicating that the eyes go in the direction opposite to the head. This component was found to be purely vestibular, because it did not change when the monkey canceled its vestibuloocular reflex (164). The term  $-|\dot{E}_r|$  is a way of indicating that the fiber paused during all rapid eye movements when the large saccadic or quick-phase eye velocity signal,  $\dot{E}_r$ , drove the cells into inhibition. Because of these three predominant features, the cells of these fibers have been called tonic-vestibular-pause (TVP) cells. These cells also participate in smooth pursuit movements (Eq. 10, the term  $0.47\dot{E}_p$ ).

This complicated signal is not what one would expect from the simple arrangement in Figure 4C. It is the components proportional to eye movements that are surprising, because they indicate convergence on the VN cells of fibers from more central areas carrying oculomotor signals. Many studies on anesthetized animals found that VN cells appear simply to repeat the canal signal, and this finding led, unintentionally, to the belief that the signal sent by the VN to the motoneurons was just a copy of  $-\dot{H}$ . When recordings were made in the alert monkey VN, however, many cells in the SVN and RMVN were found to have discharge rate components that were proportional to various combinations of head and eye movements (100, 158, 199). Other evidence supports the idea that the main signal from the VN is partly oculomotor and partly vestibular. The axon terminals of second-order VN neurons recorded in the trochlear nucleus in the cat carried an eye position signal (18). Axon terminals in the abducens nucleus, also in the cat, carried an inhibitory signal from second-order ipsilateral VN neurons that also varied with eye position (138).

To date, the evidence, which is based mainly on behavioral data from alert animals, indicates that the MLF is the principal central pathway of the reflex (Fig. 5) and that the signal it carries is that described by Equation 10. Nevertheless, there are complications, because the oculomotor nucleus also receives fibers from the prepositus (hypoglossi) nucleus (PN), which, in turn, receives a disynaptic vestibular input and

contains cells that act in a manner very similar to TVP cells during vertical and horizontal eye movements (17). Thus, there is unquestionably another, slightly longer path through the PN mediating the vestibulo-ocular reflex, although its synaptic influence on the oculomotor nucleus would appear to be less than that from the VN (17). Whether this secondary path is simply redundant or serves a unique function is unknown. Recently a third path has been described from the superior VN through the brachium conjunctivum to motoneurons of the superior recti (111); the function or signal carried by this pathway is also unknown.

**HORIZONTAL REFLEX SIGNALS.** Numerous pathways from the VN to the horizontal motoneurons have been found (218), but understanding what role they play must wait until more is known about the signal each carries. One might hope that the signal processing in the horizontal and vertical systems is similar. Inhibitory TVP-like signals have been seen on the axon terminals of second-order VN cells in the abducens nucleus (138). Similar horizontal activity has been seen in the PN (17). Studies in the VN of alert monkeys (100) have found some TVP-like cells associated with the horizontal reflex and many more have been found recently (S. Lisberger and F. A. Miles, unpublished observations). The suggestion in Figure 5 that the signal the VN sends to the abducens nucleus is also similar to that described by Equation 10 is only an hypothesis at the moment and is used only to facilitate subsequent discussion.

It seems certain that medial rectus motoneurons receive almost their entire innervation from the MLF fibers associated with horizontal gaze (40% of all MLF fibers), and, in fact, these fibers carry a burst-tonic signal (Fig. 5,  $R_m$ ) that, in monkey, is identical to that carried by the motoneurons [Eq. 2; (164, 215)]. In addition, MLF lesions effectively paralyze the ipsilateral medial rectus for all conjugate eye movements (a syndrome called internuclear ophthalmoplegia in human beings). The cell bodies of most of these MLF fibers lie in the contralateral abducens nucleus and are called internuclear neurons [Fig. 5; (77, 123, 135)]. Consequently, the main pathway for the horizontal reflex (Fig. 5) is from one VN to lateral rectus motoneurons and internuclear neurons in the contralateral abducens nucleus, possibly on TVP fibers. The internuclear neurons then relay not only the vestibulo-ocular reflex but also the completely assembled motoneuron command to the motoneurons of the opposite medial rectus. This arrangement, which causes the circuit to the medial rectus to differ from all others, may be due to the fact that medial rectus motoneurons are located in an area otherwise devoted to the organization of vertical eye movements. The internuclear neurons appear to act like surrogate motoneurons, which substitute for medial rectus motoneurons in the caudal pons where horizontal eye movements are organized.

Again, there are complications, because there are other cells that carry the horizontal burst-tonic signal (Eq. 2) in the RMVN and pontine reticular formation (100, 157, 158, 182), which might project to motoneurons. Because lesions of the VN do not abolish horizontal eye movements (280), the possible contribution of these cells might be small. There is also a pathway from the VN through the PN to the motoneurons just as for the vertical reflex (17). In addition, there is an extra-MLF pathway in the ascending tract of Deiters' from the VN to medial rectus motoneurons (19). The function and importance of these alternate pathways relative to the main paths (Fig. 5) remain to be determined.

**CELL TYPES IN BRAIN STEM.** The challenge in the findings in the previous subsection is to discover how the signal  $R_{v1}$  (Eq. 9) is changed into  $R_{tvp}$  (Eq. 10) in the VN and how that is changed into  $R_m$  (Eq. 2) at the motoneurons (or internuclear neurons). The next two subsections speculate about these questions because they represent the major problems now facing oculomotor neurophysiology. When they are solved we will largely understand how oculomotor brain stem circuits create most eye movements.

Other cells in the brain stem that carry signals such as eye position ( $E$ ), pursuit velocity ( $\dot{E}_p$ ), and rapid eye movement velocity ( $\dot{E}_r$ ) obviously participate in

these signal transformations. They generally lie in what is called the paramedian pontine reticular formation (PPRF) [Fig. 6; (30, 115, 122)]. For horizontal gaze this region includes parts of the nucleus reticularis pontis oralis and caudalis and, in the rostral medulla, the nucleus reticularis gigantocellularis (122). A similar region for vertical gaze is apparently the mesencephalic tegmentum in the region of the accessory oculomotor nuclei (42, 43, 162, 163, 274). Lesions of the PPRF create severe and permanent oculomotor deficits (115). In addition to purely vestibular cells (Eq. 9) and TVP cells, there are three other cell types that appear to play a major role in conjugate eye movements, including the vestibuloocular reflex.

**Burst cells.** These cells are found throughout the PPRF and are associated with rapid eye movements (52, 114, 155, 182). There is a variety of burst cell types (182). The cells most directly associated with rapid eye movements are called medium-lead burst cells. They burst vigorously during on-saccades or quick phases and are otherwise silent; their instantaneous discharge rate is highly correlated with instantaneous eye velocity (114); they clearly carry a signal proportional to  $\dot{E}_r$ . It is generally accepted that they contact motoneurons, probably directly, and create the burst by which motoneurons generate saccades (Fig. 2E). Inhibitory burst cells inhibit motoneurons during off-saccades (136, 137). Burst cells associated with hori-

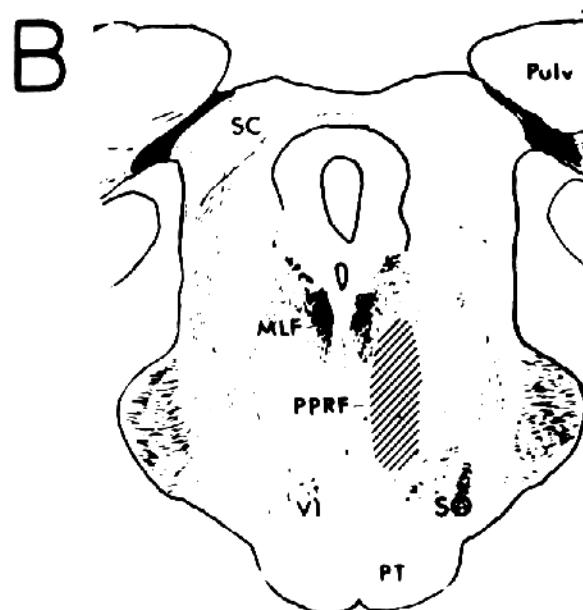
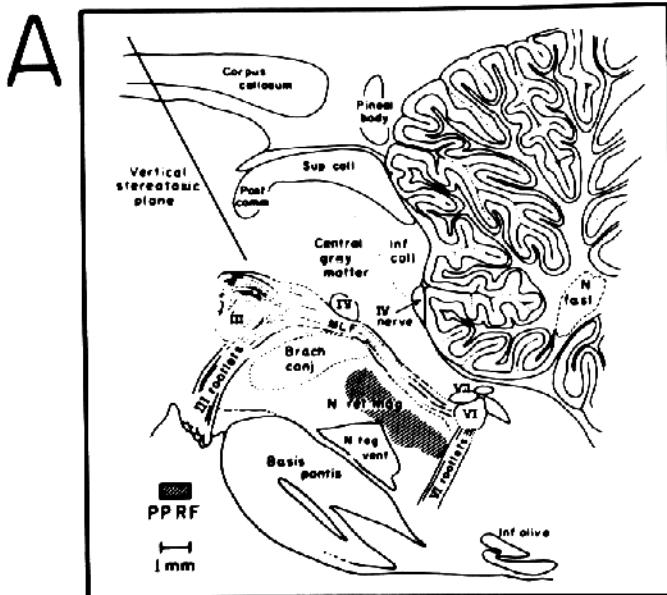


FIG. 6. A: sagittal section of the monkey brain stem showing the region (stippled) in which lesions cause severe deficits in eye movements and which is now loosely called the paramedian pontine reticular formation (PPRF). Brach conj, brachium conjunctivum; Inf coll, inferior colliculus; Inf olive, inferior olive; MLF, medial longitudinal fasciculus; N fast, fastigial nucleus; N ret mag, nucleus reticularis magnocellularis; N teg vent, nucleus tegmenti ventralis; Post comm, posterior commissure; Sup coll, superior colliculus; III, oculomotor; IV, trochlear, and VI, abducens nucleus. B: cross section of the monkey brain stem, cut in stereotaxic vertical (see slant line top left in A for orientation) in a plane just posterior to the trochlear nucleus and just anterior to the abducens nucleus. Lined region is the PPRF. PT, pyramidal tract; Pulv, pulvinar; SO, superior olive; SC, superior colliculus; VI, abducens nerve rootlets. [A from Goebels et al. (115); B from Cohen and Komatsu (54).]

zontal movements are found in the PPRF, including the rostral medulla (155, 182). Cells with vertical on-directions are also scattered through the PPRF, but these are found exclusively in the mesencephalic reticular formation at the level of and rostral to the accessory oculomotor nuclei (42, 162).

**Tonic cells.** Such cells are also found in the PPRF in the region of the abducens nucleus. Their on-direction is usually horizontal and ipsilateral, and their discharge rate is mainly related to eye position (103, 155), although this relationship is usually nonlinear. These do not burst or pause during saccades; the rate simply goes smoothly from the pre- to the postsaccadic level. The discharge rate in some cells (155) is also weakly proportional to eye velocity during pursuit ( $\dot{E}_p$ ) and vestibular movements ( $-\dot{H}$ ), although the sensitivity to the former is always greater than to the latter. The rate-velocity curves for both pursuit and vestibular stimuli are very nonlinear. Tonic cells with vertical on-directions have not yet been observed (42, 163).

**Burst-tonic cells.** These behave much like motoneurons [Eq. 2; (17, 42, 77, 100, 155, 157, 158, 163, 182)]. Furthermore, this term is occasionally used to include motoneurons. The tonic rate of these cells is related to eye position. They burst during on-saccades (or quick phases) and pause during off-saccades. When tested they have been found to carry an eye velocity signal for all conjugate smooth movements. During head rotation, discharge rate modulation stops if a monkey cancels its vestibuloocular reflex (157, 163). Close scrutiny of rate-velocity curves showed, however, that some cells, for example, in the VN (157), carry the pursuit and vestibular eye velocity signals at different gains. Burst-tonic cells are widely scattered in the pons and medulla. Cells associated with horizontal gaze are found in the RMVN (100, 157, 158), the PN (17), as internuclear neurons in the abducens nucleus (77), and rostral to that nucleus in the dorsomedial PPRF (182). Cells associated with vertical gaze are found in the PN (17) and in the mesencephalic tegmentum at the level of the oculomotor nucleus (42, 163).

**SIGNAL CONVERSIONS.** Several signals are added to TVP cells (Eq. 10) besides the canal signal (Eq. 9). As shown in Figure 5, they are  $2.5E$ ,  $0.47\dot{E}_p$ , and  $-|\dot{E}_r|$ . The pause ( $-|\dot{E}_r|$ ) is undoubtedly created by omnidirectional inhibitory burst cells (Fig. 5), although its function is not known. Because the TVP fibers form the main path for the vertical vestibuloocular reflex, the pause means literally that the reflex is momentarily disconnected during saccades and quick phases. This idea is in apparent conflict with other studies (206) that indicate that the vestibular and saccadic eye velocity commands simply add during eye and head movements in the monkey; however, this apparent problem remains unresolved.

The most important signal appearing in  $R_{tvp}$  is the

eye position signal  $E$ , which is the time integral of the eye velocity command  $-\dot{H}$ . The fact that lesions of the PPRF (76, 115) abolish all ipsilateral eye movements suggests that essential parts of the neural integrator are located there. This would mean, as suggested in Figure 5, that the signal  $-\dot{H}$  must leave the VN, enter the PPRF, become converted to the signal  $E$  by the neural integrator, and then return to the VN to appear on cells there such as TVP neurons. Anatomical pathways are certainly available for such reciprocal connections (39). The tonic cells (Fig. 5) seem to reflect most closely the activity of the integrator output because their predominant signal is  $E$ . It is possible that TVP cells receive their eye position signal from tonic cells in the contralateral PPRF (Fig. 5).

When the TVP signal reaches the motoneurons, several more signals must be added to make up the final motoneuron signal (Eq. 2). As shown in Figure 5, they are  $1.5E$ ,  $0.48\dot{E}_p$ , and  $0.95\dot{E}_r$ . The most noticeable is the burst of activity during on-saccades (or quick phases) and the pause during off-saccades; in short, the  $\dot{E}_r$  signal, which undoubtedly comes from excitatory and inhibitory burst cells located in the nearby pontine or mesencephalic tegmentum (42, 155, 162). For the vertical system, the additional signal components may come largely from the mesencephalic reticular formation (42, 43, 162) and the interstitial nucleus of Cajal (163). The latter nucleus contains vertically acting, burst-tonic cells. It also projects to vertically acting motoneurons and receives a disynaptic input from primary vestibular afferents, probably via axon collaterals of MLF fibers. For the horizontal system, the signal  $1.5E$  may come from tonic cells as suggested in Figure 5. When the monkeys cancel their vestibuloocular reflex, eye movements stop despite the persistence of the term  $-0.98\dot{H}$  (Eq. 10) from TVP cells. Consequently, some as yet unknown arrangement is needed at the motoneuron level to cancel this signal at such times.

Except for the main connections running in the MLF, Figure 5 represents a working hypothesis that rests on an interpretation of the data available to date. The secondary connections are shown to pose questions rather than to represent facts. Many other pathways have been omitted to emphasize what appear to be the major paths. The resolution of the questions posed by Figure 5 is the most exciting and active area of research in oculomotor neurophysiology today.

**CEREBELLAR CONNECTIONS.** Grossly, the vestibuloocular reflex appears to be unaffected in the cat and monkey by total cerebellectomy. Both slow and quick phases seem normal and even the transformation of  $T_c$  to  $T_{vor}$  (Fig. 4C, transformation II) is retained (235), but closer examination reveals some abnormalities. The time constant of the neural integrator (Fig. 4C) drops from over 25 s to 1.3 s in the cat (232). Consequently, cerebellar lesions create gaze nystagmus (232, 311); if the animal (or human being) looks eccentric-

cally, the eyes cannot be held deviated but slide back toward the primary position. This is primarily a problem of fixation, and it is barely discernible during vestibular stimulation because of the continuous resetting action of quick phases. There is also a deficit in the ability to use vision to modify eye velocity during the vestibuloocular reflex. These problems represent, however, disorders of the stabilization and pursuit systems (see next section). There are also small changes in the gain of the reflex ( $g$ ) in the dark (Fig. 4C). In the cat,  $g$  increases from 0.9 to 1.15 (235). All these dysmetrias are of secondary importance, because the main elements of the reflex clearly lie outside the cerebellum. The most dramatic change after loss of the cerebellum or vestibulocerebellum (primarily the flocculi and nodulus) is the complete loss of adaptive plasticity of the gain (see section PLASTICITY AND REPAIR, p. 1309). Thus, one role of the vestibulocerebellum seems to be to use vision to effect both prompt modifications of undesirable or inadequate vestibuloocular movements and long-term plastic adjustments of the reflex. To effect these actions, there are a variety of reciprocal, vestibulocerebellar connections. The primary vestibular afferents send collaterals to the vestibulocerebellum, and there are reciprocal connections between this structure and the VN and PN (4, 144). The canal signal is seen repeated in many elements of this cerebellar subdivision (112, 176, 202). Also, there is a large representation of the  $H$  signal in the fastigial nuclei (107), and a crossed inhibitory pathway that runs through these nuclei (105) has been reported between the two VN.

#### OPTOKINETIC SYSTEM

As indicated (see the section PURPOSES OF EYE MOVEMENTS, p. 1276), the optokinetic system appears to have evolved to complement the vestibular system. Both are involved in generating eye movements needed during self-rotation. The latter system deals effectively with transient (high-frequency) head rotations, but not with sustained (low-frequency) rotations; the opposite is true of the optokinetic system. The combined action of the two systems is illustrated schematically in Figure 7A for an afoveate animal.

In nature, of course, the optokinetic and vestibular systems are always stimulated together when the animal turns within the stationary visual world. Experimentally, it is more convenient to hold the animal stationary and move its visual world by rotating a drum around it. This is, of course, a rather unnatural situation, which seldom occurs in real life. Nevertheless, the results obtained in this way constitute useful data on how the system can behave. The only danger is that such experiments in the past have diverted attention away from the major function of the optokinetic system—that of complementing the vestibular system—and led many investigators to regard it in-

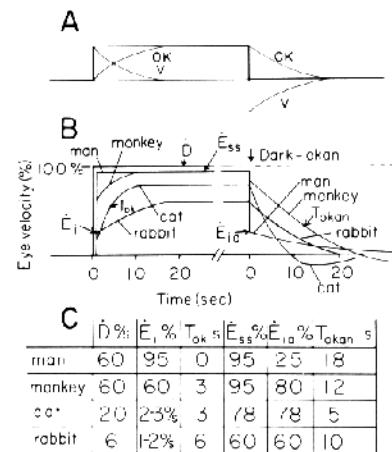


FIG. 7. Time course of optokinetic nystagmus for 4 species. A: when animal rotates in light at constant velocity (left), vestibular signal (V), as a function of time, falls back to zero, whereas optokinetic eye velocity command (OK) rises with a complementary time course. The sum provides an eye velocity command (heavy line) that compensates for head velocity for both transient and sustained parts of rotation. When rotation stops (right) optokinetic and vestibular signals cancel and the eye comes to rest. B: when an optokinetic drum starts to rotate at velocity  $\dot{D}$  about a stationary animal, eye velocity jumps to initial value  $\dot{E}_1$  and then rises slowly with time constant  $T_{ok}$  to a steady-state value  $\dot{E}_{ss}$ . When lights are turned out (vertical arrow) eye velocity falls quickly to the level  $\dot{E}_{in}$  and then falls back to zero slowly with time constant  $T_{okan}$ . C: values of characteristic constants for optokinetic nystagmus in deg/s, percent, or seconds, for 4 species at typical drum speeds. Note  $T_{okan}$  for cat is small because this animal has a pronounced optokinetic after-nystagmus that was not taken into account. [B, C species data obtained from the following sources: human being from B. Cohen and V. Henn, unpublished observations; monkey from Cohen et al. (55); cat from Haddad et al. (125); rabbit from Collewijn (63).]

stead as a visual following system. The latter view is almost certainly incorrect and provides no explanation for such phenomena as circularvection and optokinetic afternystagmus.

#### Properties of Optokinetic Nystagmus

The optokinetic system is maximally excited when the entire visual surround moves en bloc. Afoveate animals, such as the rabbit, do not track small moving objects, and a large portion of the retina must be stimulated to obtain an optokinetic response (82). For this reason, the best method of stimulating the optokinetic system is to entirely enclose the animal or human subject within an optokinetic drum. Usually the inside of the drum is covered with vertical black and white stripes to provide a high-contrast, contour-rich, visual surround. It has been shown that random check patterns stimulate direction-selective cells in the rabbit's visual system more effectively than stripes and produce a higher eye velocity for a given drum velocity (62, 82). When the drum rotates, nystagmus occurs (Fig. 1C). The slow-phase eye velocity is con-

sidered the main output variable of interest, because this system, even in this unnatural situation, still tries to reduce retinal image slip by making slow-phase eye velocity equal to drum velocity.

Figure 7B shows the time course of eye velocity  $\dot{E}$  for several species. The eyes respond after the drum starts to move with a latency of 0.1–0.13 s (60), of which about 55 ms occurs in the retina (62). At that time, eye velocity jumps to an initial value ( $\dot{E}_i$ ) and from there rises slowly to a steady-state value  $\dot{E}_{ss}$  (Fig. 7B). If drum velocity is denoted by  $\dot{D}$ , the gain (closed loop) of the optokinetic system is defined as the ratio  $\dot{E}_{ss}/\dot{D}$  and is considered to be the most significant parameter in describing the system. The slow rise is often approximated by an exponential increase and described by the time constant  $T_{ok}$ , which is the time required for eye velocity to increase by 63% of the way from  $\dot{E}_i$  to  $\dot{E}_{ss}$ . If the drum should stop in the light, eye velocity falls quickly back to zero with a time constant that is usually less than that of the rise (55).

The more usual test is to turn the lights out when a steady state has been reached to study optokinetic afternystagmus (OKAN). In some species, eye velocity drops quickly in the dark to some initial value for the afternystagmus ( $\dot{E}_{ia}$ ) and then decreases more slowly with, again, a time course often fit by an exponential and described by its time constant  $T_{okan}$ . In most animals, OKAN is followed by a longer period called optokinetic after-afternystagmus, in which eye velocity is smaller and reversed in direction (e.g., see ref. 38).

The differences in the initial rise in eye velocity for different species (Fig. 7C) probably reflects the extent to which a species has or uses a smooth pursuit system, which can change eye velocity very quickly. Human beings and monkeys have a well-developed pursuit system and the slow-phase eye velocity (Fig. 7B) jumps rapidly to large values. On the other hand, the rabbit has no pursuit system and  $\dot{E}_i$  is very small. The component of the time course for the monkey, which builds up slowly during stimulation and falls off slowly during OKAN, resembles the time course in the rabbit. The simplest hypothesis is that the behavior in the rabbit is due largely to the optokinetic system (the small, fast component could be attributed to the hypothetical stabilization system; see section PURSUIT SYSTEM, p. 1304), whereas that of the monkey is due to a combination of an optokinetic system (the slow part) and a pursuit system (the fast part). This interpretation is supported by the fact that in patients with deficient pursuit but preserved optokinetic responses, the buildup of slow-phase eye velocity is slow just as in the rabbit (300). This observation is also consistent with the idea that the optokinetic system augments the vestibular system (Fig. 7A), because during rotation at a constant velocity in the light, the optokinetic system need only develop eye velocity at the same rate at which eye velocity due to the vestibular stimulation is decreasing. The latter is characterized by

the cupula time constant  $T_c$  (Eq. 8), which is in the range of 4–7 s for the species listed in Figure 7C and is comparable to the values given there for  $T_{ok}$ . Note that such long-response times would make the optokinetic system rather ineffectual in trying to track any visual motion relative to a stationary animal.

The values of  $\dot{E}_i$  and gain all depend markedly on drum speed, because the optokinetic system saturates at different velocities in different animals. In the rabbit and cat,  $\dot{E}_i$  saturates at very low velocities and remains constant at the values listed for higher drum velocities (60, 63, 125). In the rabbit, saturation of  $\dot{E}_{ss}$  begins just above  $1^\circ/\text{s}$ : the gain typically falls to 0.5 when  $\dot{D}$  is about  $10^\circ/\text{s}$  (56). There is a pronounced increase in the velocity of saturation in primates, and one must now recognize that the fast (pursuit) and slow (optokinetic) systems saturate at different speeds. In the monkey, the latter system appears to saturate at  $90-120^\circ/\text{s}$  and total eye velocity can reach  $200^\circ/\text{s}$  (221). Because the rise and fall in  $\dot{E}$  are not truly exponential, perhaps because of the saturation effect,  $T_{ok}$  and  $T_{okan}$  also depend somewhat on  $\dot{D}$ . The reason that different species have such different ranges of optokinetic eye velocity is unknown.

The amount by which the optokinetic and pursuit systems contribute to the total, steady-state response is revealed when the lights are turned out (Fig. 7B). Pursuit cannot occur in the dark so the rapid drop in  $\dot{E}$  would seem to reflect the loss of the pursuit component, and the initial eye velocity for OKAN,  $\dot{E}_{ia}$ , reflects the contribution that the optokinetic system was making just before the lights went out. Although the pursuit system in human beings masks the slow rise of the optokinetic component at the start of stimulation, the presence of the latter is revealed during OKAN when pursuit is removed. It is not understood why humans seem to rely more on their pursuit systems and less on their optokinetic systems than monkeys. If a subject fixates a stationary point inside the drum, the pursuit system dominates and nystagmus is suppressed. But, when the lights go out, OKAN in the usual direction still occurs, indicating that the optokinetic system was activated even though eye movements were prevented (37). The time constant  $T_{okan}$  is close to the time constant  $T_{vor}$  of vestibular nystagmus (see the section VESTIBULOOCULAR REFLEX, p. 1284). This is not a coincidence, because it appears that the same central mechanism creates both responses. Thus the circuit that augments  $T_c$  to  $T_{vor}$  (Fig. 4C; transformation II) is the same as that which produces OKAN.

Clinically, eye movements are often tested by spinning a small hand-held drum placed a few feet from the patient. This evokes pursuit movements, but it does not stimulate the optokinetic system as defined in this section. Moving stripes projected on a tangent screen are better, but these would be inadequate if large portions of the room are also clearly visible. Inside a moving drum, subjects experience circularvection: they believe that they and not the drum are

rotating (38). This is a strong behavioral argument stating that the optokinetic system is not a visual following system, but that it deals with the visual consequences of self-rotation in the seen environment. The absence of circularvection is probably a good indication that a given stimulus is not activating the optokinetic system. Of course, during the period appropriate to OKAN, when one can observe the action of the optokinetic system alone without interference from pursuit, a lack of OKAN in most normal subjects would also suggest that a given stimulus method, other than a drum, was inadequate.

#### *Model of Optokinetic-Vestibular Cooperation*

Conceptually, it is useful to formulate a model or working hypothesis of the organization of the optokinetic system; this could offer an explanation for the behavior shown in Figure 7 and also could make quantitative predictions to guide future research. Such a model is shown in Figure 8. The summing junction on the left simply expresses the fact that the rate at which images slip across the retina ( $\dot{e}$ ) is the difference between the angular velocity of the visual world ( $\dot{W}$ ) and the angular velocity of the eye in space, or gaze ( $\dot{G}$ ). Normally  $\dot{W}$  is zero; the visual world does not move. Inside an optokinetic drum,  $\dot{W}$  would be drum velocity. The summing junction on the right expresses that the velocity of the eye in space ( $\dot{G}$ ) is the sum of angular head velocity in space ( $\dot{H}$ ) and eye velocity in

the head ( $\dot{E}$ ). Both the vestibuloocular reflex and the optokinetic system are concerned only with eye, head, and retinal image velocities. Thus the model need not show the position variables explicitly. For the same reason quick phases can also be ignored. The vestibuloocular reflex (Fig. 4C) can be simplified by neglecting very high- and low-frequency terms, assuming that the gains of the oculomotor plant and the overall reflex (Fig. 4C) are both 1.0, and allowing the canals to be represented simply by the cupula time constant  $T_c$ .

Direction-selective cells in the rabbit retina provide the signal  $\dot{e}$  (212). A nonlinearity,  $f(\dot{e})$ , has been suggested based on the fact that there are two groups of such cells: one sensitive to retinal slip below  $1^\circ/\text{s}$  and the other above  $1^\circ/\text{s}$  (59); however, subsequent studies make the shape of this curve uncertain (62). After some central signal processing, the optokinetic signal finally shows up in the vestibular nuclei (Fig. 8) where, of course, it constitutes an eye velocity command through the path shared with the vestibuloocular reflex (282). The signal is denoted  $\dot{H}_{ok}$  (Fig. 4C, 8). The arrangement of the model described so far is generally accepted, and the challenge is to determine what occurs in the box marked S in Figure 8, which transforms  $\dot{e}$  into  $\dot{H}_{ok}$ .

The visuomotor part of Figure 8 is a negative feedback system, because the eye always moves ( $\dot{G}$ ) to lessen retinal slip ( $\dot{e}$ ), which is the error signal. Negative feedback occurs extensively in biological control systems because it permits a system to perform its function (called the closed-loop response) despite large

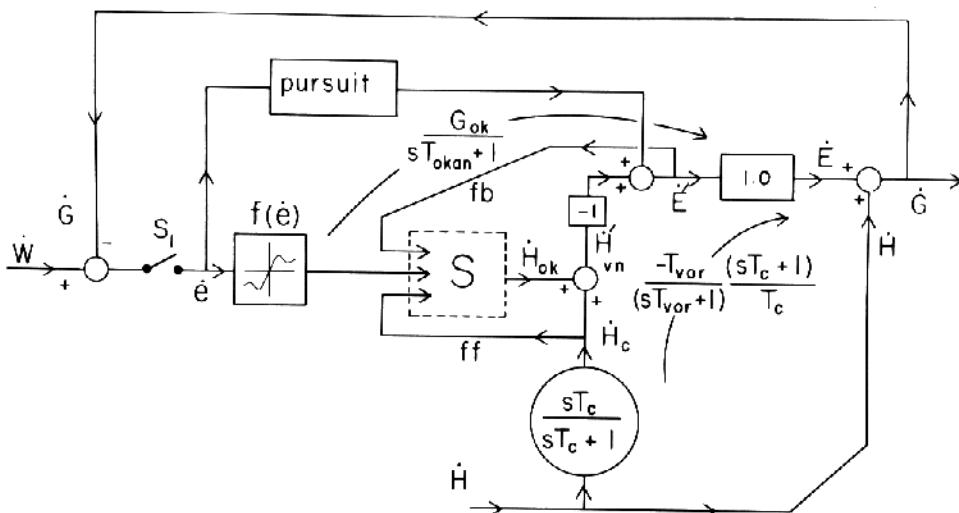


FIG. 8. Schematic representation of optokinetic system. For pure optokinetic stimulation  $W$  (head velocity  $\dot{H}$  equal to zero), a storage element  $S$  accumulates a signal due to retinal slip and produces an output  $\dot{H}_{ok}$  that appears in vestibular nucleus (VN). Transfer function between retinal slip  $\dot{e}$  and eye velocity command  $\dot{E}'$  (above) is characterized by a gain  $G_{ok}$  and a long time constant  $T_{okan}$  that accounts for OKAN. Same storage element also can account for the long time constant  $T_{vor}$  of rotatory nystagmus in dark as shown by transfer function between the canal signal  $\dot{H}_c$  and  $\dot{E}'$  (right). Element  $S$  can achieve this behavior by receiving either a direct canal input via the feedforward pathway (ff) or a feedback pathway (fb) from the eye velocity signal. See text for detailed explanation.  $\dot{E}$ , eye velocity in the head;  $f(\dot{e})$ , nonlinearity in visual pathway;  $\dot{G}$ , velocity of eye in space;  $S_I$ , switch that removes all retinal input in the dark;  $T_c$ , cupula time constant.

changes in the behavior of its parts. Thus, the very virtue of feedback hides the nature of the elements in S (Fig. 8) and to observe them one must open the feedback loop. This has been done, for example, in the rabbit by mechanically immobilizing the seeing eye and covering the moving eye (56). The actual open-loop behavior is complicated by system nonlinearities, but it can be roughly characterized by a gain ( $G_{ok}$ ) and a lag with a time constant  $T_{okan}$ . When stripes move at approximately  $0.1^\circ/\text{s}$  before the fixed eye, the slow-phase velocity of the eye under cover is about  $10^\circ/\text{s}$ . Thus,  $G_{ok}$  is about 100. Unfortunately, according to theory, the steady-state, closed-loop gain, E/W, should be  $G_{ok}/(1 + G_{ok})$ . Experimentally, this value is only 0.8–0.9, which would require that  $G_{ok}$  be only about 6. This large discrepancy remains unexplained.

Another way to open the loop is simply to turn out the lights. This removes all retinal slip input as indicated by switch  $S_1$  (Fig. 8). If the system had been activated by optokinetic stimulation before the loop was opened,  $\dot{E}$  would return to zero exponentially, which shows that the time constant of the lag element is simply  $T_{okan}$ . It must be stressed that this description is a great oversimplification and is given only to point out the major features of the simplest form of a model for the system (59).

The large time constant ( $T_{okan}$ ) of the lag has caused the latter to be likened to a storage element (Fig. 8, box S). Optokinetic stimulation ( $\dot{e}$ ) causes a signal to accumulate in this element, which then discharges slowly when stimulation ceases by turning out the lights. It is possible to attach a functional significance to this storage element if one considers the purpose of OKAN. When one is inside a rotating drum, one experiences self-rotation, because the stimulus is exciting cells in the vestibular nucleus, the same cells that are also stimulated by actual rotation. Naturally, this leads to circularvection and compensatory nystagmus, but one certainly does not think that rotation has stopped if the lights suddenly go out. The neural mechanisms that deal with the motion of the body must take into account Newton's first law of motion: when a body (the subject) is set in motion it will remain in motion until acted upon by another force. The latter event would be reported by the canals, and in its absence the logical conclusion is that one is still rotating. In fact, one does experience after-circularvection (38), and the continued compensatory nystagmus is called OKAN. Viewed in this way, OKAN is a very purposeful behavior and the storage element may be viewed as a device for keeping track of the velocity of self-rotation and attempting to maintain it in the absence of any new information. The signal  $\dot{H}_{ok}$  may be thought of, therefore, as the best estimate of head velocity according to the visual system.

This interpretation, which is not new (220), reemphasizes the symbiotic relation between the optokinetic system and the vestibuloocular reflex. A model

of one system without the other would be incomplete, since it could not, for example, simulate rotation in the light, which is the usual stimulus with which both systems appear to have been designed to deal. The augmentation of  $T_c$  to  $T_{vor}$  (Fig. 4C, transformation II) is another form of attempting to maintain an appropriate head velocity signal for as long as possible, and the fact that  $T_{vor}$  and  $T_{okan}$  have the same value makes it almost certain that the same circuit, the storage device, is responsible (221). This means that the storage element must have access to the vestibular signal, and the two ways to do this are shown in Figure 8. One model proposes that the eye velocity signal ( $\dot{E}'$ ) is fed back to the storage element (Fig. 8) to form a positive feedback loop (236). Another model proposes a feedforward path (Fig. 8) from the vestibular signal (221). Both models seem able to simulate the behavior of eye velocity under a variety of combinations of optokinetic and vestibular stimulation; however, recent evidence (47), described in the next section, favors the former hypothesis. In any event, at least there is agreement at the moment that there is one storage element (for canals in a given plane) that is shared by the optokinetic and vestibular systems, which generates both OKAN and influences per- and postrotatory nystagmus in both the light and dark. This concept naturally accounts for many of the similarities in vestibuloocular and optokinetic behavior (276). Finally, a pursuit system is added (Fig. 8) to remind one that in foveate animals this system is always brought into action by optokinetic stimuli. In afoveate animals, a similar role could be played by the stabilization system (63).

#### *Neurophysiology of Optokinetic System*

**INPUT.** In the rabbit, the optokinetic input signal  $\dot{e}$  is clearly represented by the discharges of direction-selective cells in the retina (212). In the cat, such a signal may be carried by some of the thin-axoned, slowly conducting W-cells (271). For the optokinetic system, the most important destination for these signals is the nucleus of the optic tract (NOT) in the pretectum (62, 140). Stimulation of the NOT produces vigorous nystagmus in the rabbit (61). In the retina, the direction-selective cells respond to sets of edges or spots moving in a certain direction anywhere within rather large receptive fields. In the NOT, the receptive fields are even larger as though the results of retinal cell activity had been pooled. The dichotomy seen in the rabbit retina of cells that respond best to either small or large ranges of  $\dot{e}$  appears to be lost in the NOT. Direction-selective units do not appear to exist in the monkey retina. Either they have been so far undetected or geniculostriate (or other) pathways may be required to provide the  $\dot{e}$  signal in primates. There is considerable disagreement about whether optokinetic movements are preserved after complete lesions of the

striate cortex in the human and monkey; therefore, the question of a subcortical optokinetic pathway in primates is unsettled (see ref. 36 for a discussion).

**OUTPUT.** The optokinetic signal shows up as an eye velocity command (79) in the vestibular nucleus (VN). Cells in this nucleus, which respond to the vestibular afferent signal, are driven by optokinetic stimulation in the unanesthetized monkey (131, 282). The discharge rate of the cells responds to vestibular stimulation (a step in  $\dot{H}$ ) in the dark with a prompt transient response, but no sustained response (e.g., Fig. 7A, curve V). The cells respond to optokinetic stimulation (Fig. 8, a step in  $\dot{W}$ ) with a slow rise and a sustained response like the curve OK in Figure 7A. They respond to rotation in the light with the sum of the rapid and sustained responses, which is a better copy of head velocity than either of the signals alone. Although it is possible that optokinetic signals project to motoneurons by routes other than through the VN, it seems, at the moment, an unnecessary hypothesis, because optokinetic and vestibular generation of eye movements seems to be adequately explained by the behavior of VN neurons alone. This idea is reinforced by the discovery that OKAN is abolished by bilateral labyrinthectomy in the monkey (280); an observation that is confirmed in human beings (312). This is presumed to be due to the loss of spontaneous activity of second-order vestibular neurons, so they cannot transmit the optokinetic signal. This finding at first appeared peculiar until the important role of the VN in the optokinetic system was appreciated.

If labyrinthectomy blocks OKAN, why doesn't it also block optokinetic nystagmus itself? Human beings and monkeys, of course, have excellent pursuit systems and, consequently, still have (pursuit) nystagmus during optokinetic stimulation after loss of vestibular function (280, 312). But the rabbit has no pursuit system and, in fact, labyrinthectomy does abolish optokinetic nystagmus in the rabbit (63). A remnant nystagmus, about  $2^\circ/\text{s}$ , does remain that could be due to a stabilization system (see the section PURSUIT SYSTEM, p. 1304). Thus, the suggestion is that the optokinetic system acts through the VN, and any lesion that blocks OKAN has actually blocked all optokinetic movements. In foveate animals, this loss is masked by the pursuit system but becomes manifest in the dark when the pursuit system cannot operate and OKAN should, but doesn't, appear.

**CENTRAL.** In the rat (47) and cat (219) the projection from the NOT to the VN appears to pass through the nucleus reticularis tegmenti pontis (NRTP). Lesions of this nucleus abolish, or greatly reduce, optokinetic nystagmus and the response of cells in the VN to optokinetic stimulation. Stimulation and recording experiments (47) indicate that leftward motion of the visual field seen by, say, the right eye excites cells in the left NOT, which in turn excite the cells of the left

NRTP. The latter then excite type II cells in the left VN, which, by inhibiting left type I cells, causes the eyes to follow the visual stimulus to the left. This pathway has only recently been discovered and further research is needed to enlarge our knowledge of it. There are alternate pathways: in the rabbit and cat, visual responses (the  $\dot{e}$  signal) appear in the flocculus from both climbing fiber and mossy fiber activation (see refs. 185, 256 for a review) and are relayed from there to the VN by Purkinje cells (144). The climbing fiber pathway goes through a subdivision of the inferior olive called the dorsal cap of Kooy and has been investigated by stimulation, lesions, and recording from cells in the olive (22). Cerebellectomy in the rabbit (57) and cat (232), and destruction of the inferior olive (125) in the cat, however, do not greatly affect optokinetic responses. Moreover, optokinetic stimuli still drive cells in the VN of the rat and cat after cerebellectomy (47, 159) or in the cat after olivary lesions (219). These results indicate that the major pathway for the optokinetic system in these animals lies in the brain stem, although the cerebellar paths are undoubtedly important for other types of visual-vestibular interaction. Nevertheless, such a conclusion is obscured by the fact that in the monkey, although flocculectomy interferes only slightly with optokinetic responses (310), total cerebellectomy does abolish them (288). These findings confuse the issue of the relative functions of the brain stem and cerebellar pathways and species differences clearly exist.

Recordings from cells in the NRTP (W. Precht, unpublished observations) confirm that they are excited by the cells of the ipsilateral NOT and also reveal that they are excited by type I cells from the contralateral VN. The activity of NRTP cells excites type I cells in the contralateral VN by means of the vestibular commissural system so that, if the former are also excited by the latter, a positive feedback loop (path fb in Fig. 8) is formed. If the VN-NRTP projection is regarded as an eye velocity command rather than a canal signal, the NRTP would appear to combine a corollary discharge of eye velocity in the head with the velocity of the seen world with respect to the eye ( $\dot{e}$ ). This would create an output signal proportional to the velocity of the head relative to the visual environment—a signal most suitable for relaying to the vestibular nucleus (236). The VN-NRTP projection may be the first neurophysiological demonstration of a feedback copy of an efferent signal being used in the central processing of visual afferent signals.

#### SACCADIC SYSTEM

##### *Properties of Rapid Eye Movements*

**METRICS.** The size of the smallest voluntary human saccade is approximately 3 min arc (128); that of the largest possible is about  $90^\circ$ . Over this three-log unit range there is a close relationship between saccade

size and peak velocity (16, 34, 142, 286). The data from a few studies appear in Figure 9. For example, one study (34) surveyed a human population and found large differences in this relationship between individuals. Moreover, this figure also shows the relationship for several other species. Monkeys have very fast saccades (99) with velocities that can exceed  $1,000^{\circ}/\text{s}$ ; cats and goldfish, on the other hand, make slower saccades (74, 85, 90). The bandwidth of the recording device is important or eye velocity can be underestimated (14); 0–150 Hz seems adequate. Also, there is a corresponding relationship between saccade duration and amplitude (81, 227). Saccades in the dark are slower than in the light (25, 243), and patients with an hemianopsia have slower saccades into their blind half-field than in the other direction (168). The acceleration of the eye is large [e.g.,  $40,000^{\circ}/\text{s}^2$  for a  $10^{\circ}$  saccade (50)]; peak velocity is reached roughly one-third of the way through, and deceleration is more gradual. Usually eye velocity comes smoothly, but quickly, to zero at the end of a saccade to give the visual system prompt access to the new scene. This is done by actively braking the eye at that time by a small, momentary activation of the antagonist muscles (257). If the duration of the reversal pulse is too long, the eye actually turns around and makes a small backward saccade: a phenomenon called dynamic overshoot (14). This reversal is more pronounced for small saccades, because the amplitude of the second saccade becomes an increasingly larger proportion of

the final gaze displacement. The function, if any, of dynamic overshoot is unknown. Saccades normally fall short of a target (e.g., ref. 25) even for small saccades (133) by roughly 10% of the target's jump. This appears to be a deliberate strategy of the saccadic system, but the purpose of this is unknown (132). The subsequent saccade that puts the eye on target is called a corrective saccade.

Occasionally, saccades are followed by small, drifting movements called glissades (284). Often they are monocular and could represent a fusion movement (see the section VERGENCE SYSTEM, p. 1306). Saccades are made by a pulse-step innervation (Fig. 2E; see the section OCULOMOTOR PLANT, p. 1279) and the postsaccadic drift could also be caused by a mismatch between the intensity of the pulse and step of motoneuron activity (15, 84, 231). In many pathological situations, such as internuclear ophthalmoplegia, myasthenia gravis, and muscle palsies, large, exponential, postsaccadic drifts occur that are clearly due to mismatches between the pulse and step (237, 308).

**TIMING.** Saccades occur frequently. During inspection of the visual world, they occur at about 3/s or 173,000 in a 16-h day. When a target suddenly jumps to one side, a saccade follows in about 0.2–0.23 s. The latency depends on the subject, attention, luminance, size of the target displacement, target disappearance and reappearance schedule, and the difficulty of decision (see ref. 46 for a discussion). This variability probably reflects cognitive processing. The typical latency of 215 ms seems to consist of about 55 ms lost in the retina and about 25 ms lost in the premotor circuits and muscles (230, 242), leaving around 135 ms for central processing.

If the primary saccade falls short of the target, the corrective saccade occurs with a latency of only 130 ms (25). The saccadic system seems to be able to sense, either before or just after the first saccade, that it is too small and, thus, is prepared to execute another in much less time. The central delay for the corrective saccade is only 50 ms. If the target jumps and is then moved again at the time of the first saccade by less than about  $4^{\circ}$ , the corrective saccade has its normal, short latency. But if the target reappears too far away from its expected position, the next saccade has the usual 0.2-s latency (217). Thus, if expected error is not reinforced by visual experience, precalculated data are discarded and the full cognitive processing must start again. A similar phenomenon occurs with predictive tracking (75, 264). When a target jumps periodically, an internal clock is apparently set in motion and target jumps are anticipated. Saccades, then, no longer lag the target by 0.2 s but can be coincident with the jump or even lead it. This is not very surprising and is no different from other predictive, rhythmic group behavior such as singing and dancing.

**SACCADES AND QUICK PHASES.** It is generally accepted that saccades (movements to a specific visual target)

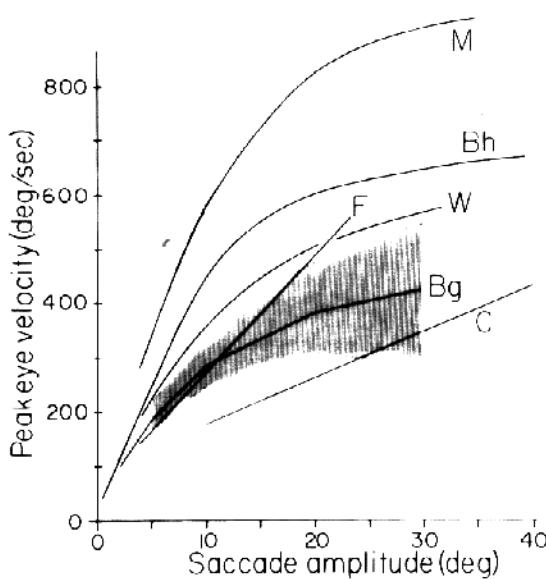


FIG. 9. Relationship between peak saccadic eye velocity and saccade amplitude. Curve Bg comes from study that surveyed population of human subjects. Shaded area indicates normal limits for mean velocities of individual subjects in that study. [Data for human saccades obtained from the following sources: curve Bh from Bahill et al. (16); curve W from Westheimer (286); curve Bg from Boghen et al. (34). Animal data obtained from following sources: curve M (monkey) from Fuchs (99); curve F (goldfish) from Easter (85); curve C (cat) from Crommelinck and Roucoux (74).]

and quick phases (rapid movements evoked by passive head rotation, usually in the dark, with no specific target involved) are made by the same premotor circuit (e.g., ref. 243). All neurons in the brain stem observed to discharge in relation to saccades (e.g., burst cells) behave similarly during quick phases when so tested. In the monkey, saccadic eye velocity in the head slows down during a head movement in the same direction by just the speed of the latter (206). If this did not happen, the head movement would carry the eye past the target. One might suppose that this action is mediated by the summation of the saccadic and vestibular eye velocity commands ( $\dot{E}_r$  and  $-\dot{H}$ ) on the motoneurons, but several facts complicate this explanation. In VESTIBULOCULAR REFLEX, p. 1284, it was pointed out that the vertical vestibulocular reflex is abolished by lesions of the medial longitudinal fasciculus (MLF), and the signal carried by the MLF is described by Equation 10. These two observations, if true, mean that the vertical reflex is carried exclusively by tonic-vestibular-pause fibers in the MLF. Because these fibers pause during saccades, the vestibular command is lost at such times; the reflex is literally disconnected during such rapid movements. Other evidence from the human (152) and cat (127) indicate that saccadic and vestibular signals are not just added together, and the way they are combined may depend on whether a rapid eye movement during a head movement is a foveate or an afoveate saccade or a quick phase. These problems do not cause doubt that saccades and quick phases are generated by the same circuits but do suggest that the circuits might be driven in different ways depending on the type of rapid eye movement required.

#### *Properties of Quick-Phase System*

When a subject is suddenly rotated in the dark, a rapid eye movement occurs within 180 ms (23), long before the slow phase has carried the eye very far. In a cat that is rotated suddenly at  $60^\circ/\text{s}$ , the first quick phase occurs within 70 ms (48). These short intervals mean that (unlike saccades) the latency for a quick phase can be less than 200 ms; the period between quick phases can also be less than 200 ms. In the cat this interval is commonly 100 ms and occasionally is as low as 50 ms (48). The initiation of a rapid eye movement by the vestibular signal does not involve the long delays associated with the visual system. There may also be less cognitive processing involved for quick phases, because the purpose of the movement seems to be to look quickly into the direction of turning in a rather automatic way (see the section PURPOSES OF EYE MOVEMENTS, p. 1276).

During continued rotation, slow phases return the eyes to near the primary position in the cat and quick phases then reset them by about  $12^\circ$  in the direction of turning, so that mean eye position is in the anticompen-satory direction (49). A similar behavior has been

observed in humans (193). Quick phases carry the eye to a point in the orbit that is less variable than the point at which the quick phases are initiated. This means that the size of the quick phase is determined primarily by the amplitude of the previous slow phase (48). It would be of value to learn more about the behavior of the human quick-phase system, since it is probably a rather basic pontine circuit and abnormalities could have diagnostic value.

#### *Properties of Saccadic System*

MICROSACCADES. For some time it was believed that microsaccades were an involuntary component of fixation and that their purpose was to keep images from fading on the retina. When subjects are asked to stop making microsaccades, however, they do so and images do not fade (270). Microsaccades as small as 3 min arc can be made voluntarily (128). Subjects performing a task requiring good visual acuity tend to make fewer, not more microsaccades (294). Although monkeys seldom make saccades less than  $0.5^\circ$ , they can be trained to make microsaccades (e.g., 5 min arc) by tasks requiring vigilance and high acuity (262). Cats seldom make microsaccades (295). Consequently, it is not clear whether nonhuman species make microsaccades naturally, just how often (outside the laboratory) humans make microsaccades, and, most important, what these are supposed to accomplish.

SAMPLED-DATALIKE BEHAVIOR. A major feature of larger, tracking saccades is an apparent refractory period of about 0.2 s between one saccade and the next. Refractoriness is demonstrated when a target jumps from point A to B and, after, for instance, only 0.1 s jumps to point C. By the time the second jump is seen by the cortex (155 ms after the first jump) only 60 ms remain before saccade A-B should occur, assuming a 215-ms latency. If 25 ms is the motor delay, only 35 ms remain before the decision must be made to execute the A-B saccade. Generally, the system cannot change its intent in 35 ms, cancel the A-B saccade, and begin calculations on the A-C saccade instead (285). One interpretation of this behavior is that when the A-B retinal error signal is received a process is started that cannot be stopped, and the system is refractory to subsequent target behavior. This pattern is characteristic of a class of control systems called sampled-data systems, and the mathematics developed to analyze such systems has been applied to saccades (304).

Nevertheless, closer inspection showed that whether an A-B saccade occurred or the eye went directly to C was probabilistic (290). The incidence of the A-C saccade decreased as the time between the target jumps increased. The system was not refractory, but it was less likely to "change its mind" the later new information was received. Because parallel processing is probably common in the nervous system, two different neural processes could be dealing simultane-

ously with the A-C vs. A-B problem (244); their results contending with each other with a success rate that depends on the interval between target jumps (231). If that interval is 135 ms, the second jump is most likely to be seen too late to stop the A-B saccade. Put another way, visual events occurring about 80 ms (the sum of the sensory and motor peripheral delays) before an impending saccade cannot affect it. Actually, the decision is not just an A-C vs. an A-B saccade, because the A-B saccade, when it occurs, is modified in amplitude by the occurrence of the B-C target jump (27). If C lies beyond B or nearer than B, the A-B saccade is increased or decreased in amplitude so the eye lands somewhere between B and C. Thus, saccades for a given initial retinal error are not all-or-nothing events. Their amplitude can be modulated by new information, which is received centrally, right up to the last instant (about 25 ms before they occur). These findings indicate that there is no obligatory, refractory period of 0.2 s, and the action of the saccadic system is only very roughly approximated by a sampled-data system.

Whereas saccades usually occur separated by intervals of about 0.2 s or more, smaller intervals of any size are not uncommon (12). Dynamic overshoot (14) and voluntary nystagmus (255) are examples of a zero intersaccadic interval, but a zero interval can also occur for two large (e.g., 30°) saccades when the target jumps twice in rapid succession (26). The results of all these exceptions to rules proposed for saccadic behavior (i.e., sampled data, refractory period, preprogrammed, and ballistic) suggests that saccades are influenced by parallel cognitive processes, in complicated ways, right up to and possibly during the time of their execution. These complications do not mean that the basic idea of sampling is not worth retaining in some modified form, although they do appear for the moment to have discouraged further attempts at modeling the behavior of the saccadic system.

**PERCEPTION OF VISUAL DIRECTION.** A major problem in understanding the saccadic system is establishing how the directions of visual objects are coded in the nervous system and how they are converted into the specifications of saccade amplitude and direction. Skilled feats such as sinking basketballs from mid-court remind us of the incredible accuracy with which the position of a target on the retina, the eye in the head, and the head on the body can be used to locate a target with respect to the so-called egocentric or body-image frame of reference (e.g., ref. 252). This ability indicates that the position of the eye in the orbit must be known with some accuracy. The hypothesis, that this knowledge comes from proprioceptive (muscle) feedback, is called the inflow theory; the alternate hypothesis, that it comes from monitoring the efferent command at some level (e.g., Fig. 4C, E'), is called the outflow theory (see the chapter by

McCloskey in this *Handbook*). The outflow theory has gained the wider acceptance. Objects in space seem to be localized primarily by adding retinal position (the distance of the image from the fovea) to the position where the eye ought to be, according to the effort to look, not where the eye actually is (258). In any event, a signal is available by which eye position in the head is known and it is used to calculate the position of seen objects in a body-image coordinate system for use in object-oriented body movements, for example, pointing, throwing, and dodging (259). It would seem reasonable that eye movements should be similarly directed—the body-image theory for saccades—but there is another, seemingly simpler possibility, considered in the next section, which utilizes retinal error alone.

**COORDINATE SYSTEMS.** It is possible that the saccadic system operates entirely within a retinal coordinate system. If a target is 10° to the right of the visual axis, a 10° rightward saccade should occur regardless of where the target is with respect to the head. This seemingly simpler scheme (called here the retinotopic theory) avoids the transformation into a body-image reference frame. This theory, which is the basis for most models of the saccadic system (231, 304), is given apparent support because stimulation of the superior colliculus in the monkey produces saccades of a given size and direction regardless of initial eye position (230, 249). The saccades, like the visual input, are organized entirely retinotopically. It should be appreciated, however, that this observation can easily be accounted for in either theory. Moreover, stimulation of the cat superior colliculus apparently reveals two regions: one in which saccades are retinotopically organized and another from which eye and head movements may be evoked. The eye movements are goal directed in the head, that is, the eyes are brought to the same position in the head regardless of initial position; the head movements are goal directed in space with the result that eye movements are goal directed in space (73).

The simplicity of the retinotopic theory is illusory if one takes into account that many saccades are made to stimuli heard or felt, which are clearly localized in a body-image reference frame and which would then have to be converted back into a retinal frame. Thus, a coordinate transformation is required by either theory. If a target jumps from A to B, and then, just at the start of the A-B saccade, it jumps back to A for 2 ms and then disappears, a subject told to follow the target completes the A-B saccade and then, after 0.2 s, looks back at point A even though, when last seen, target retinal error was zero (129). Clearly, retinal error was updated in the dark by an internal signal accounting for the A-B movement. This result appears to support the body-image theory; however, no evidence thus far can reject either theory, and neither or both may be correct.

### Neurophysiology of Saccades

**BURST CELLS DRIVE SACCADES.** The evidence cited in the section VESTIBULOOCULAR REFLEX, p. 1284, (especially refs. 52, 114, 155, 162) makes it fairly certain that medium-lead burst cells in the pontine reticular formation contact motoneurons, create the burst of high-discharge rate in them (Fig. 2E), and thereby make saccades. Burst cells start firing about 4 ms before the beginning of the motoneuron burst. The mean firing rate of burst neurons increases with mean eye velocity reaching 1,000 spikes/s for large on-saccades in the monkey (155). Changes in burst cell activity are associated only with changes in the component of saccade size in the on-direction and not with changes in the perpendicular direction (52, 114). The discharge rate of these cells is clearly related to saccadic eye velocity in the on-direction.

Some burst neurons are inhibitory and create the pause in motoneurons during off-saccades. Thus, each motoneuron is driven in a push-pull manner by excitatory and inhibitory burst neurons (see Fig. 10). Most burst cells associated with horizontal gaze have ipsilateral on-directions, which indicates that abducens motoneurons and internuclear neurons (Figs. 5, 10) are excited by ipsilateral burst cells and inhibited by contralateral cells. Cells of the latter type have been located in the rostral medulla (136, 137). The push-pull nature of the connections becomes especially important for microsaccades and saccades in the perpendicular direction, because burst cells also fire at such times. When one takes into account that the motoneurons are driven by the difference between excitatory and inhibitory burst cell activity, it is possible to construct a strict mathematical relationship between instantaneous burst rate difference and instantaneous eye velocity, thereby strengthening the general belief that medium-lead burst neurons create saccades (114).

**INTEGRATION OF PULSE.** It is necessary to generate a step change in the discharge rate of motoneurons to hold the eye in its new, postsaccadic position. This is the eye position component ( $k_E$ ) in Equation 1. If saccades originate in burst cell activity, which is clearly an eye velocity command, the burst (or pulse) must be integrated to produce the eye position signal or step (see Fig. 10). This is just the same situation faced by the vestibuloocular reflex where an eye velocity command had to be integrated (Fig. 4C, NI). Exactly the same signal processing is needed in both cases, and it is reasonable to hypothesize that the same circuit integrates both signals.

There are good reasons to suppose that there is only one integrator shared by all conjugate eye movement systems. Suppose the neural integrators in Figure 10 (for saccades and quick phases) and Figure 4 (for vestibular commands) were separate elements. That would require the existence of neurons that modulate their firing rates in proportion to eye position, but only

for certain types of eye movements and not others. During nystagmus, for example, one set of neurons (the quick-phase integrator) would accumulate all rapid changes in eye position in one direction, whereas another set (the slow-phase integrator) would accumulate all slow changes in eye position in the other. This is absurd on theoretical grounds, since each output signal would soon grow to enormous amplitudes; moreover, neurons have never been observed that do this. Different cell types carry eye velocity commands that differ in relative strengths for different types of eye movements (e.g., Eq. 10), but all cells studied so far, which carry an eye position signal, have that signal related to position in a way that is independent of the type of movement. This suggests the existence of a single neural integrator, a push-pull pair (e.g., Fig. 10) for each plane of motion, that responds to a variety of velocity commands and produces a single eye position command (233).

**MODELS OF PONTINE-PULSE GENERATION.** How is the shape of the burst determined to create saccades of just the desired amplitude from 0.1°–90°? Both burst intensity (instantaneous discharge rate) and duration

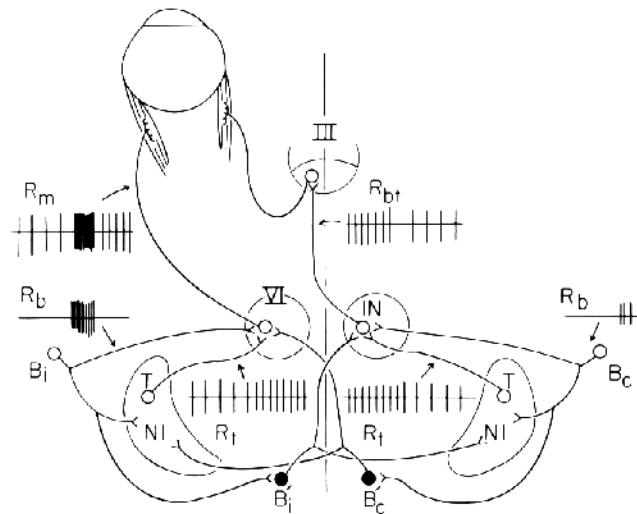


FIG. 10. Push-pull arrangement by which burst cells create saccades. Ipsilateral burst cells ( $B_i$ ) discharge at high rates ( $R_b$ ) during leftward saccades. They excite ipsilateral abducens motoneurons in abducens nucleus (VI) and relay an inhibitory burst through  $B'_i$ , located in ipsilateral rostral medulla, to burst-tonic, internuclear neurons (NI) in contralateral VI, which fire at rate  $R_{bt}$ . This inhibitory burst silences contralateral IN cells and ipsilateral medial rectus motoneurons in oculomotor nucleus (III) during the saccade. Burst rate ( $R_m$ ) in lateral rectus motoneuron is difference between rates  $R_b$  of  $B_i$  and that of contralateral inhibitory cells  $B'_c$ , relayed from contralateral burst cells  $B_c$ . Neural integrator (NI) must be formed by a pair of reciprocally acting circuits in paramedian pontine reticular formation with midline symmetry. They are represented by tonic cells (T) and must also be stepped up or down (discharge rates  $R_t$ ) by the push-pull action of burst cells to produce the final pulse-step  $R_m$  (or pause-step  $R_{bt}$ ) in agonist (or antagonist) motoneurons. Closed circles, inhibitory cells; open circles, excitatory cells.

must be accurately controlled to obtain the desired saccade size. In the retinotopic theory for saccades there is so far no specific hypothesis for a neuronal network that translates retinal error into burst intensity and duration. Possible candidates for such a circuit are, however, long-lead burst neurons seen throughout the paramedian pontine reticular formation (PPRF) (52, 155, 182), in the deep layers of the superior colliculi (249, 263, 297), and in the thalamus (251). About 0.1–0.15 s before a saccade, these cells begin to fire in a ragged, low-frequency preamble and then usually burst before, during, or after the saccade. There is a variety of such cell types (52), and the details of their behavior have not yet been well described; however, they all appear to participate in saccades in a manner independent of initial eye position, which gives the impression that they operate in the coordinate system of the retina. It would seem reasonable that some of those cells in the PPRF are presynaptic to medium-lead burst neurons, although their discharge rates are very poorly related to eye velocity, saccade amplitude, or saccade timing (114). Whether these can be woven into a reasonable hypothesis that explains their own behavior and various other properties of saccadic eye movements remains to be seen.

An alternate theory for controlling the burst size has been proposed on the basis of the body-image coordinate theory (114, 307, 309). It suggests the possibility of a local, negative feedback loop in the pons. The output of the neural integrator (Fig. 10, rate  $R_t$ ) is a copy of instantaneous eye position. If higher centers, which selected the target, made available a signal representing the location of the target with respect to the head, the difference between the target and eye signals would be the neurally encoded motor error: the angle between where the eye is and where it ought to be. If this signal drove the burst neurons, their firing rate would drive the eyes at a high velocity until the error was zero, and at this time the burst would stop. This hypothesis guarantees that all bursts automatically have the correct size for each saccade, because the burst always continues until the eye is on target.

Therefore, the hypothesis predicts that instantaneous burst rate should be a unique function of motor error. Experimentally, this was discovered to be the case for most burst neurons (114). This hypothesis offers an explanation of how saccades are generated that have the correct velocity and duration for all possible sizes (Fig. 9) and can simulate slow saccades seen in patients thought to have paramedian pontine reticular formation (PPRF) lesions (307). The model also relies on an important class of cells called pause neurons located on the midline in the pons, which fire at constant rates, but pause during all rapid eye movements (155, 223). Stimulation of these cells prevents an animal from making any rapid eye movements at

all (155, 287) and can stop saccades in midflight (92). It is probable that pause cells inhibit burst cells and disable the pulse generator when saccades are not wanted. Because of burst and pause cell interactions, the model can, in a very simple way, simulate microsaccadic oscillations in the human being and monkey (114), dynamic overshoot in humans, voluntary nystagmus, and pathological exaggerations of these phenomena called, clinically, ocular flutter (309). This model is attractive because it can explain a large variety of saccadic behavior with only a few assumptions, but obviously more knowledge must be obtained about anatomical connections and signals before any scheme for the control of the pulse generator can be confirmed.

**CEREBELLUM.** Lesions of the cerebellum interfere with the neural integrator (Fig. 10), and this disturbs gaze holding and causes the eye to slip back toward the center after an eccentric saccade (78, 232). Especially lesions of the flocculus and nodulus create this effect (310), which results in what is called, clinically, gaze paretic nystagmus. Nevertheless, even total cerebellectomy does not interfere with the ability to make the rapid movement itself, indicating that the pulse generator is not in the cerebellum. As with other motor systems, cerebellar lesions create dysmetria (225, 311). The vermis, lobes V–VII, seem to be the area most concerned with saccades. Lesions of this area alone create saccadic dysmetria (225). Stimulation of this region produces saccades in the alert monkey (242), and single cells in the vermal region burst during saccades (180). The function of the cerebellar vermis seems to be to modulate saccades in some way for some unknown purpose. Lesions of this region abolish the ability to repair saccadic dysmetria created by lesions elsewhere (see the section **PLASTICITY AND REPAIR**, p. 1309), suggesting that one modulatory purpose is to maintain long-term saccadic accuracy. Unfortunately, the anatomical pathways from the cerebellum to the PPRF, by which any sort of modulation might be mediated, are quite unknown.

**SUPERIOR COLICULUS.** Stimulation of the superior colliculus in the alert monkey evokes all-or-nothing saccades with an amplitude and direction that moves the fovea to the point in visual space that formerly projected, via the retinotectal map, to the site stimulated (230, 249). Cells in the deep layers fire in relationship to saccades and do so most vigorously for saccades of the size and direction appropriate to the cell's location in the retinotopic map (249, 263). Cells in intermediate layers have both a visual receptive field and discharge (even in the dark) for saccades that would foveate a visual stimulus in that receptive field location (204, 249). The simple interpretation is that visually evoked activity in the superficial layers descends to the deeper layers and triggers a saccade, which foveates the visual stimulus. The missing ele-

ment in this scheme is selection. A normal visual scene creates a jumble of neural activity over the tectal surface, and one might question which stimulus is allowed to trigger a saccade. Obviously, target selection occurs more centrally. A current hypothesis is that when a selection has been made a signal is sent to the colliculus (via the deep layers) to reinforce visual activity at the selected site in the intermediate layer, which then initiates the foveating saccade (204).

These saccade-related cells behave, temporally, like long-lead burst neurons in the PPRF. There is a long (e.g., 100 ms), low-frequency preamble of firing before the burst, which may reflect part of the selection process. When a trained monkey sees a target jump from point A to B (which would normally elicit a saccade for which the cell would respond), but which then jumps to point C, the monkey occasionally cancels the A-B saccade and instead makes an A-C saccade for which the cell does not respond. In this case only the preamble may occur with no burst, as though one were seeing the plan to make the A-B saccade being formulated and then being discarded (263).

Lesions of the superior colliculi do not seriously disturb the ability to make saccades. After a unilateral lesion there is a transient increase in latency for contralateral saccades (205, 298) and a slight, enduring asymmetry in saccade amplitudes (134, 298). Nevertheless, when one considers that saccades are made to vestibular stimuli and to things felt, heard, and remembered, as well as seen, the lack of a major saccadic deficit after lesions might not be surprising, because the visual system, and in particular the superficial layers of the colliculus, appear to be only one input to the saccadic generator. Most tectobulbar fibers disappear into the PPRF and their signals presumably undergo some polysynaptic processing before emerging as a motor command on medium-lead burst neurons. For example, stimulation of the colliculus reveals monosynaptic colliculoreticular projections to long-lead burst neurons in the PPRF but not to medium-lead burst cells (223). Oddly, pause cells are also monosynaptically activated in both the monkey and cat (153, 223). In the cat, a number of excitatory and inhibitory interneurons in a tectoabducens relay have been located in the brain stem reticular formation (121). Although more knowledge of these anatomical connections is needed, this would be of only potential value until we also know what signals such pathways carry.

**HIGHER CENTERS.** Oculomotor activity occurs in the thalamus and resembles that of long-lead burst neurons (251). Discharge rates appear to be a function of saccade amplitude and direction. The activity of some cells depends on initial eye position in the head, so they do not operate in a retinotopic coordinate system. Cells in the parietal lobe of the alert monkey com-

mence firing about 0.1 s before a saccade, reach a peak rate just at saccade onset, and then decrease their rate, often continuing to discharge for 0.1–0.2 s after the saccade is over (183). Discharge rate usually depends on saccade direction but is largely independent of saccade size and initial eye position. The stimulus must be novel or related to a food reward; these cells do not discharge when the monkey just looks around the laboratory. It has been suggested that the responses of some parietal lobe, saccadic neurons are visual responses that have been greatly enhanced by motivation, with receptive fields that are so large that the enhancement occurs for saccades of almost any amplitude and direction to novel stimuli (241). In any case, the monkey's interest in what is going on is a clear requisite for such activity, and these cells probably lie deep within central cognitive processing. However, such neurons do not appear to carry much information about which target was selected or where it is.

For many years it was thought that the frontal eye fields (Brodmann's area 8) contained an "upper motoneuron" for eye movements. Since 1874 it was known that stimulation of this area produced contralateral eye movements (96). In 1969 studies in the alert monkey showed such movements to be all-or-nothing saccades roughly organized into a motor map (238). Throughout the intervening century, a large number of studies had convinced everyone that this area was a cortical motor outlet for saccades. Nevertheless, single-cell recordings revealed that only a very small percentage of cells in this area had their discharge rate closely coupled to all eye movements and those that did modulated their rates after, not before, the eye movement (33). Lesion experiments supported this finding, because in the monkey lesions appear to affect saccades, and even something as subtle as search strategy (173), very little. Unilateral lesions are more disturbing than bilateral; they cause a tonic ipsilateral gaze deviation and contralateral visual neglect, but the effects in the monkey are rapidly compensated.

Nevertheless, it has recently been demonstrated that a large number of frontal eye field neurons respond to visual stimuli and that the visual response is greatly enhanced only when the monkey intends to make a saccade to that stimulus (118). The neural activity occurs just after the visual stimulus but before such a saccade. These cells do not discharge when the monkey looks around a familiar laboratory scene, so that in such an experimental situation these cells would not appear to be related to eye movements. Thus, there is, after all, a great deal of neural activity in the frontal eye fields before a saccade but only when the target is interesting, a term which at least includes targets that are novel or associated with a reward. These findings reinstate the frontal eye fields as an important premotor structure in eye movements, but only for those eye movements that are the result of complex central processing that involves such poorly

defined concepts as cognition and motivation. Also, this finding is reinforced by the discovery that when both the frontal eye fields and the superior colliculi are removed bilaterally saccades are very nearly eliminated (250). The monkeys are still able to make all types of eye movements but cannot move their eyes more than about  $5^\circ$  from the primary position. This restriction even includes the slow phase of vestibular nystagmus, but the range of this type of movement does recover after several weeks. The effect of these lesions on nonsaccadic eye movements presents a mystery. The effect of saccades suggests that the frontal eye fields and the deep layers of the superior colliculi represent the two main inputs to the saccadic pulse generators; however, either is able to effect saccades alone. It remains unclear just which aspects of the visual data gathering determine the division of labor between these two structures.

#### PURSUIT SYSTEM

The first section of this chapter suggests the need, in the evolution of vision, of a separate system to suppress eye motion that is created by internally generated neural noise and proposes the name: the stabilization system. It is presumed to use simple negative feedback (similar to that shown in Fig. 8) to reduce retinal slip. It was also tentatively suggested that the pursuit system may have evolved from the stabilization system by concentrating image stabilization just to whatever was on or near the fovea. Consequently, it might be well to begin an inspection of smooth pursuit by examining ocular stabilization.

#### *Stabilization System*

Oculomotor noise, fluctuations, and drifts in sub-human species (66, 68, 262, 295) do not appear very different from human oculomotor noise (269). Rabbit eye drift in the dark is about  $0.7^\circ/\text{s}$ ; in the light it decreases to about  $0.2^\circ/\text{s}$  (66, 68). Eye drift in the cat is  $1.0^\circ/\text{s}$  in the dark and drops to  $0.25^\circ/\text{s}$  in the light [Fig. 1D; (295)]. In the dark, the standard deviation of monkey eye drift is  $0.83^\circ/\text{s}$ ; in the light this decreases to  $0.2^\circ/\text{s}$  (262). The standard deviation of human eye drift in the light is  $0.13^\circ/\text{s}$  (269). This has not been measured in the dark but is estimated not to exceed  $1.0^\circ/\text{s}$  in normals. There is also a nonrandom source of drift that depends on eye position. The neural integrator (Figs. 4C, 10) is not perfect. It behaves like a leaky integrator with the transfer function  $T_n/(sT_n + 1)$  in which  $T_n$  is about 25 s (28). A consequence of this is that for any eccentric eye position ( $E$ ) the centripetal eye drift should be  $(E/T_n)^\circ/\text{s}$ . If  $E$  is, for example,  $30^\circ$ , the drift rate is  $1.2^\circ/\text{s}$  in the dark and such drift is also greatly decreased in the light. The fact that eye drift is attenuated in the light by a factor of about 5 means that the gain of the central pathways must be about 4.

An important but unanswered question is whether stabilization is a separate system or is simply part of the optokinetic system in afoveate animals. The hypothesis of separate systems is suggested because the problems solved by each—suppression of noise vs. assistance in self-rotation—seem basically different, and the nature of the responses demanded is different. A stabilization system need not produce eye movements much faster than  $1\text{--}2^\circ/\text{s}$  to compensate noise drifts. Little attention has been paid to the power spectrum of noise-drift velocities, but inspection of records indicates that this system must deal with spectral components at all frequencies, up to at least the region of 3.0 Hz (e.g., Fig. 1D). The optokinetic system, on the other hand, must produce much larger eye velocities (e.g., Fig. 7B, C;  $10\text{--}60^\circ/\text{s}$ ) and need not respond to frequencies in excess of  $1/(2\pi T_c)$ , or about 0.04 Hz. Thus, the optokinetic system should be slow with a large velocity range, whereas stabilization should be fast but needs to have only a small range. This idea is compatible with the fact that the optokinetic responses (Fig. 7B) contain an initial fast response that saturates at  $1\text{--}2^\circ/\text{s}$  in the rabbit and  $2\text{--}3^\circ/\text{s}$  in the cat (Fig. 7C), which could be due to a stabilization system, followed by a much slower rise in eye velocity that is obviously created by the optokinetic system.

This hypothesis certainly needs testing in some direct, neurophysiological way. At the moment, the supporting evidence is only circumstantial. In the labyrinthectomized rabbit, the slow, large component of the response to optokinetic stimulation is gone, but the small, fast component remains (63). This at least indicates that the slow and fast elements depend on separate anatomical pathways. Moreover, the flocculus seems to be important for stabilization. In the cerebellectomized and vestibulocerebellectomized cat, eye drift in the light and dark is abnormally large (126, 232), and unwanted nystagmus (e.g., caloric or due to a lesion) is suppressed very little by vision in cats (126) or monkeys (277) with flocculus lesions. Vision can also rapidly aid or oppose the vestibuloocular reflex in the rabbit (147) and cat (235), but fails to do so after flocculectomy. These data cannot, however, support the hypothesis of a separate stabilization system until the visuomotor role of the vestibulocerebellum is further clarified.

As suggested in the section PURPOSES OF EYE MOVEMENT, p. 1276, pursuit in foveate animals may have evolved from stabilization. The automatic nature of pursuit and its clear connection with the flocculus (see subsection *Neurophysiology of Pursuit*, p. 1305) are both compatible with this notion, but the idea needs to be tested. In any event, the main difference between pursuit and afoveate stabilization is that the pursuit system can stabilize images on a remarkably tiny part of the retina and can ignore large amounts of image slip everywhere else. The stimulus need not cover the fovea; a spot (e.g., 10-s arc) much smaller than the

fovea, which is about  $1^\circ$  wide, can be used for fixation, whereas moving background stripes, also in the fovea, are ignored (207). The stimulus need not even be on the fovea. Parafoveal targets on an otherwise blank field can be pursued by eccentric vision (296). Thus, the selection of which part of the retina is to be used for stabilizing images is not determined by the anatomy of the retina but by a central selection process.

#### *Properties of Pursuit*

The upper limit of normal pursuit velocity in man is not certain. There are reports that the eye begins to lag the target significantly above  $30^\circ/\text{s}$  (285), whereas others claim good tracking at  $130^\circ/\text{s}$  (175); the reasons for such differences are not known. A visual acuity task associated with the target may help to increase maximum velocity but does not appear necessary (175). A large angular range available for target motion may help to obtain large eye velocities. The latency to a sudden change in velocity is about 0.13 s (228). If 55 ms are lost in the visual system and 25 ms in the motor system, only 50 ms are left for central processing, which seems to correlate with the more automatic nature of pursuit compared to saccades.

Once the eye starts to move, it accelerates slowly (compared to saccades) and takes another 0.13 s to approach final velocity (228). The eye apparently never quite matches target velocity but, without long periods of practice, tracks at 80%–90% of it (169). This means that the steady-state forward gain of the pursuit system (eye velocity/retinal slip velocity) needs only to be between 5 and 10. Such studies have been done at low velocities over a limited movement range (169), and larger ranges and higher velocities need to be investigated in this regard. The pursuit system appears to behave as a continuous rather than as a sampled-data system (228): the eye simply changes velocity one reaction time after the target with no obligatory refractory period. Tracking unpredictable stimuli becomes more difficult in the frequency range above 1–2 Hz due to, in part, the phase lag created by the reaction time, e.g., a theoretical  $94^\circ$  lag at 2 Hz (75, 93, 264, 265). Unfortunately, in many such studies the saccadic and pursuit tracking movements are not separated, so the response of the pursuit system by itself is not determined. Like the saccadic system, the pursuit system anticipates periodic target motion, and the latency and phase lag are much less when the target moves in this fashion (75, 198).

Although the main stimulus for pursuit is the velocity of image slip on the retina, the pursuit system also apparently responds to the position of a target with respect to the fovea. For example, when catching up to a moving target, the eye often momentarily goes faster than the target (228). When an after image is placed near the fovea and a subject attempts to look at it (which is, of course, impossible), a slow, smooth movement starts in that direction (166). Also, subjects

can prevent their eyes from slowly drifting away from a target for long periods of time without microsaccades (270). In these examples, retinal error position, not velocity, would appear to be the stimulus, and this has been confirmed by more direct experiments (216). Even abstractions from retinal images can drive pursuit. If nothing can be seen by a subject except two lights opposite each other on the rim of a rolling wheel, the invisible center of the wheel can be pursued although nothing on the retina is moving in that direction at that speed (267). Pursuit movements can also be produced, although rather poorly, by attempting to track one's hand or finger in the dark (108, 266).

If a target is tracked with the head, which is the usual case in normal behavior, the vestibuloocular reflex would take the eye off the target, so it must be canceled. The simplest assumption is that this is done by an equal and opposite pursuit command so the eye can rotate with the head. This idea is supported by the fact that most problems in patients that interfere with pursuit, such as cerebellar degeneration, also interfere with cancellation of the vestibuloocular reflex (311). Also, Purkinje cells in the flocculus modulate their discharge rates similarly during pursuit and cancellation of the vestibular reflex (176, 202). On the other hand, subjects can voluntarily raise the gain of their vestibuloocular reflex to 1.0 or lower it to 0.2 in the dark by trying to look at an imaginary target on the wall or rotating with the subject (24). Because pursuit movements cannot be made in the dark, the pursuit system, as conventionally defined, cannot be responsible for this ability. This finding suggests that cancellation and pursuit are intimately related but not identical; the former, for example, might involve voluntary parametric changes in the vestibuloocular reflex.

Monkeys have a well-developed pursuit system and routinely achieve speeds of  $120^\circ/\text{s}$  and higher (e.g., ref. 261); rabbits, of course, have no pursuit. Cats appear to lie in between. When trained, they can pursue large targets up to about  $8^\circ/\text{s}$  with a fixed head but are reported to be essentially unable to pursue small spots (90). Nevertheless, when hungry, they can pursue a plate of cat food up to an apparent maximum velocity of  $20^\circ/\text{s}$  (G. M. Haddad and D. A. Robinson, unpublished observations). This animal, with a coarse area centralis, may have only learned to stabilize rather large images on the retina. When the head is free, however, the cat can easily cancel its vestibuloocular reflex at head velocities up to  $60^\circ/\text{s}$  (127). This again suggests that those properties of pursuit that depend on vision when the head is still may be different from the ability of nonvisual components of the pursuit system to manipulate the vestibular control of eye movements (cancellation).

#### *Neurophysiology of Pursuit*

Presumably, direction-selective cells in the visual

cortex detect retinal slip, but before some signal can descend as a motor command, some selection process may have to decide which retinal slip belongs to the target and which does not. This would seem like a process that might require more than 50 ms unless the strategy is to track first (whatever is approximately on the fovea) and to ask questions later. The only neurons observed at a cortical level that are concerned with pursuit are in the parietal lobe (183). These cells discharge only when a monkey tracks a moving target of interest, and the discharge rate depends on target direction but not speed. The oculomotor decussation at the mesencephalon-pontine border (29, 30) apparently pertains only to the saccadic system: unilateral cortical lesions (frontal and parietal) interfere with contralateral saccades but interfere with ipsilateral pursuit (279). Stimulation of the brain above a mid-collicular level in alert animals always produces saccades but not pursuit, probably because the evoked saccades have a lower threshold and obscure any possible pursuit component. The only site, other than the PPRF (54), where stimulation produces pursuitlike movement is the cerebellar hemispheres (242). The result is that very little is known about pathways descending to the brain stem mediating pursuit.

**FLOCCULUS.** Cells that appear to be directly related to pursuit are found in the flocculus (176, 177, 202). There, some Purkinje cells in the alert monkey modulate their discharge rates in proportion to gaze velocity in space ( $\dot{G}$ ): the sum of eye velocity in the head ( $\dot{E}$ ) and head velocity in space ( $\dot{H}$ ). The discharge rate ( $R_g$ ) of the average gaze (velocity) Purkinje cell is described by

$$R_g = 79 + 0.90(\dot{H} + \dot{E}) = 79 + 0.9\dot{G} \quad (11)$$

(176). When the animal is rotated in the dark, the vestibuloocular reflex makes  $\dot{E}$  equal to  $-0.9\dot{H}$ . Therefore the term  $(\dot{H} + \dot{E})$  is nearly zero, and there is only a small modulation of  $R_g$ . During pursuit with the head still,  $R_g$  modulates in proportion to pursuit eye velocity ( $\dot{E}$ ). When the monkey cancels its vestibuloocular reflex,  $\dot{E}$  is zero and modulation is proportional to  $\dot{H}$ . As indicated in Equation 11, all these combinations of  $\dot{E}$  and  $\dot{H}$  can be simply replaced by  $\dot{G}$ . It is interesting that these cerebellar cells reflect the activity (velocity) of a motor element (the eye) with respect to space rather than with respect to the head.

In support of these findings, it has been shown that cerebellectomy abolishes pursuit in monkeys (288) and vestibulocerebellectomy interferes with it (310). Diffuse cerebellar lesions in humans almost always produce a pursuit deficit (311). In primates, there is little doubt that the cerebellum, the flocculus in particular, is important in mediating pursuit. The monkey flocculus is also related to other types of eye movements, however, and contains a variety of mossy fibers and other types of oculomotor cells in addition to gaze Purkinje cells (177, 208).

**BRAIN STEM.** It is presumed that the gaze Purkinje

cells inhibit cells in the ipsilateral vestibular nucleus (VN), because it is well known that the flocculus projects there and that floccular stimulation inhibits vestibuloocular pathways (144, 254). But, because all cells recorded so far in the VN of the alert monkey, except for purely oculomotor (burst-tonic) neurons, do not modulate, as would be predicted by Equation 11 during pursuit or cancellation (100, 158), it is uncertain where gaze Purkinje cell axons go. For example, tonic-vestibular-pause cells do not change their rate modulation during cancellation (Eq. 10), so they cannot receive the signal in Equation 11. Just how gaze Purkinje cells participate in pursuit cannot really be understood until their connections are known; they could, for example, mediate their effect through the prepositus hypoglossi nucleus.

In the pons, the pursuit eye velocity command is one component of the signal carried by motoneurons, burst-tonic cells, some tonic cells, and tonic-vestibular-pause cells (see the section VESTIBULOOCULAR REFLEX, p. 1284). Recently, cells have been found just ventrocaudal to the abducens nucleus that carry a discharge rate largely proportional to ipsilateral-pursuit eye velocity (88). Such cells do not modulate during the vestibuloocular reflex; cancellation was not studied. These cells could carry the pursuit velocity command and could be related to gaze Purkinje cells.

#### Models of Pursuit

Primitive models of the pursuit system do exist (302, 306) but bear little relationship to neurophysiology. Open-loop behavior is difficult to study by immobilizing one eye (165), because it is not easy to distinguish the responses of the pursuit and optokinetic systems. Models incorporating gaze Purkinje cells have been suggested (176, 200) but not analyzed. In view of the evidence (see subsection *Properties of Pursuit*, p. 1305) about the different properties of pursuit during visual only or vestibular stimulation, it would be most challenging to model not only pursuit, with the head still, but also to demonstrate how pursuit and vestibular signals interact when animals engage in the natural behavior of tracking with eye and head. When head motion is involved, the optokinetic system is always brought into play, and there are interesting results from experiments in which the pursuit and optokinetic systems are pitted against each other (37). Therefore, it becomes more and more important in the development of models of eye movement control to try to explain not only how single systems work in isolation but also how they work together, as they do in most natural situations (53).

#### VERGENCE SYSTEM

##### Properties of Vergence Movements

Vergence movements are slow (Fig. 1G), and the response to an abrupt change of retinal disparity (a target jump from far to near) is roughly exponential, with a time constant of about 0.2 s (222). Recordings

from motoneurons indicate that this movement is created by a step change in discharge rate (154), so that plant dynamics (see the section OCULOMOTOR PLANT, p. 1279) largely determine the system's response and account for its slowness. Divergence is often slower than convergence (313), which must be a central characteristic, because the plant responds linearly to other commands.

A control system with unity negative feedback that behaves this way to a step input must have a net-forward-path transfer function of  $5/s$ , so the closed-loop transfer function is  $(5/s)/(1 + 5/s)$  or  $1/(0.2s + 1)$ . Thus, the entire forward path (including the plant) must behave like a pure integrator ( $1/s$ ) with a gain of 5.0, and experiments showed this to be approximately the case (222, 313). The loop was opened by recording eye position and then stabilizing the position of the target on each eye, so that eye movement could no longer affect retinal disparity. For a constant disparity, the eyes converged or diverged at a constant velocity with a proportionality constant close to  $5^\circ/s$  per deg disparity (222, 313). If target location on the retina is manipulated to increase the amount of negative feedback, rather than remove it, the vergence system oscillates at 2.5 Hz, which is close to the value predicted by theory (313). Much of the  $180^\circ$  phase lag required for oscillation comes from the delay due to the system's latency, which is about 0.16 s.

If the total forward transfer function is  $5/s$  and that of the plant is  $1/(0.2s + 1)$ , the transfer function of the central pathways (excluding the delay) must be  $5(0.2s + 1)/s$ , or  $1 + 5/s$ . This indicates that once retinal disparity is known centrally a signal proportional to both the disparity and 5 times its time integral ( $1/s$ ) is sent to the motor apparatus. Obviously, this neural integrator is not the one shared by all the versional systems, because it moves the eyes disconjugately. Tracking experiments show a system bandwidth of about 1 Hz with a decrease in phase lag when the target motion is periodic and predictable (313). Experiments with short pulses of disparity show continuous control as opposed to sampled-data behavior (313).

Usually, when a subject looks from point A to D (see Fig. 11A), the eyes initially begin to diverge more or less symmetrically to point B, because the latency for vergence is smaller than that for a saccade. The latter then moves both eyes equally to point C where the lines of sight just straddle the target at D; the divergence then continues until the eyes are aligned on D (299). It has been suggested by Alpern (5) that Hering's law, which implies that the two eyes usually move by the same amount in the same direction, be modified to include a vergence system, which also moves the two eyes by the same amount, but in opposite directions. Thus, although while tracking in three dimensions the two eyes may appear to be doing quite different things, their motions are supposed to be always the instantaneous sum of a perfectly conjugate movement and a perfectly symmetrical vergence movement.

Figure 11B illustrates a special case of this type of movement called asymmetric vergence in which the near and far targets are aligned with one eye. In this situation, the left eye must make a divergence movement to the left that is mixed with a saccade to the right in order to end up back where it started. In fact, this often happens (5, 224, 313), and this illustration was deliberately chosen to agree roughly with this interpretation of Hering's law. But, because binocular recordings (13, 210, 213, 224) often show gross violations of Hering's law in the situations in Figure 11, this "law" must be regarded as only a rough approximation. Eye dominance may play some role in such movements. This hypothesis would suggest that the dominant eye might get on target more quickly with a large saccade and only a small vergence movement, whereas the other eye might make a smaller saccade and a larger vergence movement. The recording in Figure 11C is an example: the convergent movement of the left eye is small; the saccade is large. The right eye makes a small saccade, a large vergence movement, and arrives on target late, as though the left eye got near the new target as soon as possible and stayed near it while the other eye was left to catch up as best it could. It is clear that a modified Hering's law does not apply at all to those movements (49). An extreme example of dominance is accommodative convergence in which one eye is covered. The seeing eye is totally dominant and makes no vergence movement in looking between two targets aligned on its visual axis, whereas the covered eye makes all of the vergence movement. The factors that govern such behavior are unknown, and it is by no means clear that eye dominance alone can explain the many violations of Hering's modified law that can be seen in abundance once one looks for them.

The stimulus for vergence is retinal disparity, and neurons in the visual cortex do respond maximally to stimuli falling on each retina with a certain mismatch from perfect correspondence (32). These disparity detectors would seem suitable to drive the vergence system if, as usual, some cognitive process selects which disparity detectors responding to which visual object are to be used. Vergence can be triggered, however, by grossly dissimilar patterns projected to each eye (289). For example, a cross can be presented to one eye and a circle to the other, each in disparate positions, and a vergence movement is still initiated. Obviously, disparity-detector neurons would simply not be excited by such stimuli. At a higher level of organization, it appears that there is a desire to put the images of the "things" on the left and right retina together, regardless, at first, of what those things are.

#### *Neurophysiology of Vergence*

The vergence system is the least neurophysiologically explored of all the oculomotor systems. Since the time it became possible to record from intracranial neurons in alert, behaving monkeys, investigators have

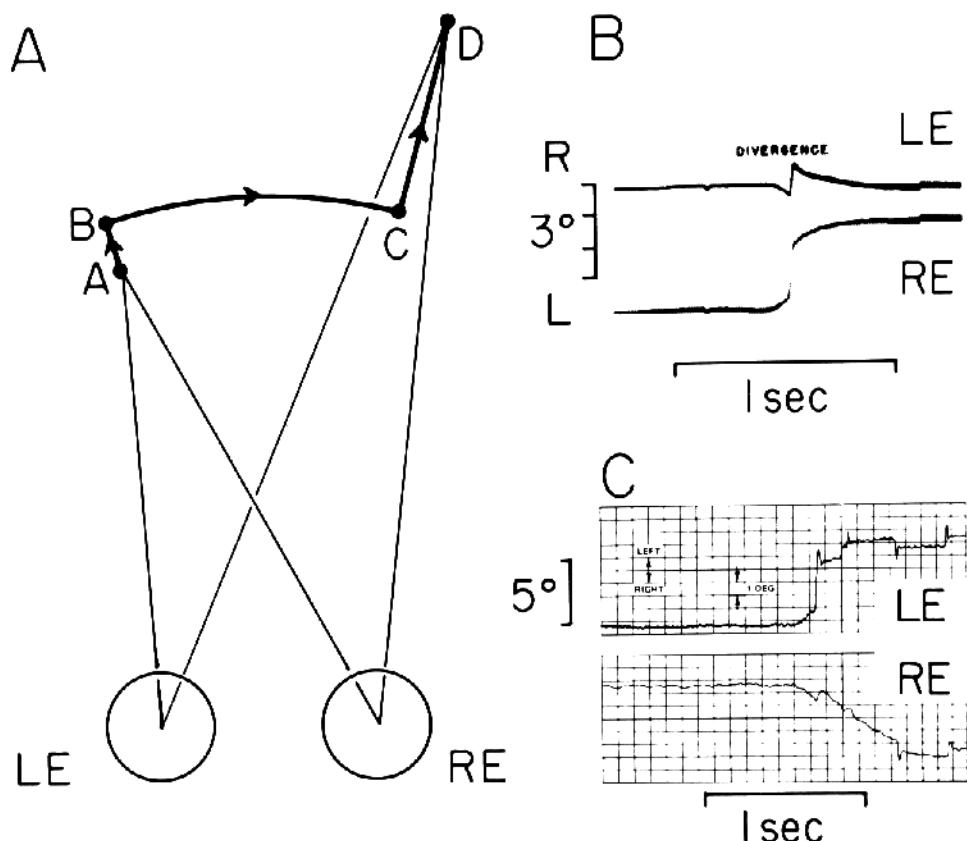


FIG. 11. Hering's law for mixed conjugate and vergence movements and violations of that law. A: schematic diagram shows how intersection of visual axes gets from A to D (arrows) with combined vergence and conjugate movement according to modified Hering's law. B: example of a special case of the situation in A. Two targets are aligned on the axis of one eye, the left eye in this case. Left eye (LE) makes a combined saccade and divergence movement with no net displacement. Hering's law is approximately obeyed although saccade in the right eye (RE) is clearly half again as big as that in the left eye. C: example in which Hering's law is grossly disobeyed. This shows a case of symmetric divergence in which near and far targets lie in a midsagittal plane. Initial saccade of the left eye is much larger than that of the right eye; opposite is true for vergence movements. [B from Riggs and Niehl (224); C from Clark and Crane (49).]

been preoccupied by the more obvious conjugate movements. Peripherally, experiments have shown that the properties of the plant are the same for vergence and version movements, since Equation 1 also holds for both types of movements (154). This means that vergence movements are made neither by a special subset of muscle fibers, such as the small, multi-innervated fibers, nor by a special group of motoneurons, such as those in the nucleus of Perlia; a nucleus that, it now appears, does not exist (283).

Because vergence is usually spared by lesions of the medial longitudinal fasciculus (MLF), it has long been thought that vergence commands did not ascend in this tract, and this has recently been confirmed by recording from the MLF in alert animals (77). Nevertheless, there are neurons in the oculomotor nucleus, which are not motoneurons and which project to the abducens nuclei (184). These could form a vergence pathway to the lateral recti that must, of course, be

reciprocally driven with respect to the medial recti. Neurons, such as tonic cells, burst-tonic cells (especially in the mesencephalon), tonic-vestibular-pause cells, other VN neurons, and gaze Purkinje cells, which all modulate vigorously for conjugate movements, have not been studied for vergence activity, but one suspects they do not participate directly in vergence. On the other hand, when the head rotates on the body, the eyes swing through an arc of radius R about the vertebral column (about 10 cm). Therefore the gain of the vestibuloocular reflex should be 1.0 when looking at infinity, but should be  $(1 + R/D)$  when the eyes are converged at a target D cm away. The gain of this reflex might be automatically adjusted by convergence or accommodation, and such an indirect effect should be observable on the neurons listed in this paragraph. Nevertheless, a direct vergence signal, presynaptic to motoneurons, remains undiscovered. Stimulation of cortical areas 19 and 22 evoked a near response (con-

vergence, accommodation, and pupil constriction) in the anesthetized monkey (148), but this has not been confirmed in alert animals.

Recently, it was reported that when kittens were made strabismic (surgically) and reared in the dark, fewer cells in the visual cortex responded to binocular stimulation than when kittens were reared in the dark without strabismus (186). The implication was that an extraretinal signal that indicated correct eye alignment, presumably muscle proprioception, was needed to allow normal development of binocular cells in the visual cortex. This hypothesis suggests that muscle proprioception should project to the visual cortex and evidently it does (41). This is an interesting hypothesis and certainly should be explored further.

#### PLASTICITY AND REPAIR

The ability of the nervous system to repair itself is essential for survival; it is the envy of modern technology. How plastic adaptation of motor systems, sometimes called motor learning, occurs at the synaptic level is unknown. The oculomotor system offers a good opportunity to study this phenomenon, because in its subsystems it is usually easy to create dysmetria, quantify it, control the stimulus, and measure the adaptive response.

#### Gain of Vestibuloocular Reflex

The overall gain of this reflex is close to 1.0 in its operating frequency range (see the section VESTIBULOOCULAR REFLEX, p. 1284) so that eye velocity compensates for head velocity. Figure 4C shows that this system operates in an open-loop manner. Negative feedback allows the operation of a control system to be relatively independent of large changes in the parameters of its individual parts, but an open-loop system has no such protection. Any change in the elements (Fig. 4C) due to the cumulative effects of trauma and disease over the entire life of the animal causes the gain to change and to create vestibuloocular dysmetria. During development the system must also be continually recalibrated as growth occurs and as the size of the eyeball and its muscles changes. Because calibration is established and maintained throughout normal life, a mechanism must exist to effect it. The process must be directed by vision, which can determine if the gain is 1.0 by whether images slip on the retina during head turning. Rabbits reared in the dark, for example, have a gain only one-third the normal value (65), probably because this calibration could not occur.

The plasticity of the vestibuloocular reflex may be demonstrated by optically dissociating head and eye movements. If 2 $\times$  telescope lenses are worn, the seen world moves twice as fast as the head, in the opposite

direction, during head turning. If this "dysmetria" is to be repaired, the gain of the reflex should approach 2.0 and it does over a course of about 5 days (109, 201). If reversing (Dove) prisms are worn, the seen world moves in the wrong direction. In this case, the gain of the reflex also reverses, and the eyes actually go in the wrong direction with a gain of about half normal (119). Even short exposures, from a few minutes to a few hours, of making a visual scene move abnormally in relation to a head movement will produce noticeable changes in the gain (120, 146, 235). Such experiments have been done on human beings (109, 119, 120), monkey (201), cat (195, 235), rabbit (146), goldfish (247), and chicken (124).

The neural substrate for this plasticity is unknown, but the cerebellum had been suggested (143), and a visual pathway subsequently was discovered (Fig. 12A) through the accessory optic tract, relaying in the nucleus of the optic tract, again in the inferior olive, and ascending to the flocculus on climbing fibers (185). This climbing fiber path is essential for plastic changes. Either floccectomy or olivary lesions abolished plastic adaptation of the reflex in the rabbit (145, 146) and cat (125, 235). Figure 12B shows the time course of the plastic decrease in gain when cats are made to wear reversing prisms chronically and also shows that after vestibulocerebellectomy the gain rose to 1.15 and could no longer be modified by wearing reversing prisms.

It has been suggested that motor learning can occur in the cerebellar cortex by the activity of climbing fibers modifying the strengths of the synapses of parallel T-fibers on Purkinje cell dendrites (143, 190). In Figure 12A, this would change the gain of the reflex

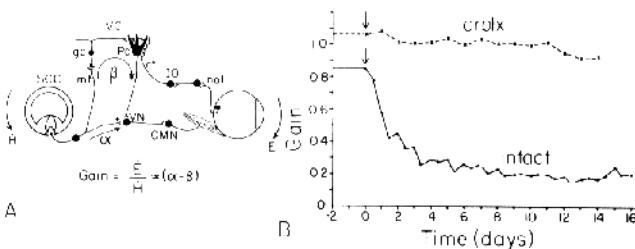


FIG. 12. Plastic adaptation of gain of vestibuloocular reflex. A: one hypothesis for adaptation is that output of semicircular canal (SCC) projects directly to vestibular nucleus (VN) with gain  $\alpha$  and indirectly on mossy fibers (mf), granule cells (gc), parallel T-fibers, and Purkinje cells (Pc) in the vestibulocerebellum (VC) with gain  $\beta$ . Retinal image slip signal projects from retina through nucleus of optic tract (not) and inferior olive (IO) to Purkinje cells (Pc) on climbing fibers (cf). If cf activity could change mf-Pc synaptic gain  $\beta$ , gain of the entire reflex could be changed to eliminate retinal slip during head movements. E, eye velocity; H, head velocity; OMN, oculomotor nucleus. B: filled circles and solid line show that gain of reflex is driven from about 0.9 (left) down to about 0.1 in 8 days after cats begin to wear reversing prisms chronically (arrow). Crosses and dashed line show that after vestibulocerebellectomy (crblx) gain can no longer be modified by wearing reversing prisms. [From Robinson (235).]

by changing the gain of the side path  $\beta$  through the cerebellum in a plastic way. Support for this sort of theory remains circumstantial (113). It is possible that the plastic changes occur elsewhere and that the modified signals are only transmitted by the climbing fiber pathway through the vestibulocerebellum. Although the location of the modifiable synapses is not yet known, at least it is clear that the vestibulocerebellum and olive are essential, in one way or another, for plastic adaptation of the gain of the vestibuloocular reflex.

#### *Recovery from VIIth Nerve Lesions*

In primates, an imbalance between the resting activities of a push-pull pair of semicircular canals of only 10% can create a nystagmus of  $11.5^\circ/\text{s}$  (see the section VESTIBULOOCULAR REFLEX, p. 1284). Such an imbalance would create vertigo and have a more serious effect on vision and balance than a 10% change in the gain of the reflex. Consequently, it is most important that lesions that create vestibular imbalance be repaired promptly. Compensation of the nystagmus that results from such lesions occurs in about 3 days in the cat (126). The decrease in slow-phase eye velocity is roughly exponential with a time constant of 10 h in the cat and 3 h in the guinea pig (245). Recovery from unilateral labyrinthectomy in human beings ranges from weeks to months depending on age. When compensation of the loss of one labyrinth is complete, removal of the other naturally creates a reversed nystagmus called Bechterew's phenomenon, which is then also compensated.

The role of the cerebellum in this type of compensation or balance control has been the subject of controversy. As early as 1891 it was shown that cerebellectomy did not release nystagmus that had been compensated (172). Other early studies were inconclusive, but more recent work on the guinea pig showed that cerebellectomy slowed compensation of spinal effects such as head twisting but did not slow the compensation of nystagmus at all (246). Such reports suggested that the cerebellum might play some minor role in recovery (191), but was not essential for oculomotor balance control. Different results were obtained from experiments on rats (178, 179). First, it was shown that compensation of VIIth nerve lesions did not occur after destruction of the inferior olive, and after a prior compensation, such a lesion released the original nystagmus. This finding indicates that the climbing fiber system is essential, in some way, for both gain and balance control and perhaps for all types of cerebellar-related motor learning. Nevertheless, after rats compensated for unilateral labyrinthectomy, removal of the entire cerebellum also released the original nystagmus contrary to older reports. Compensation still occurred after total removal of the cerebellar cortex, but again in conflict with previous results (246) total cerebellectomy prevented compen-

sation. These observations on rats led to the conclusion that the climbing fiber collateral pathway through the deep cerebellar nuclei was essential for compensation, but that the Purkinje cells were not.

There is a problem with using these results to conclude that the flocculus is not the seat of plasticity for gain control, because one must assume that gain and balance control are mediated by the same structures; this is not the case. When gain (wearing reversing prisms) and balance (vestibular nerve lesion) experiments were both done on the same vestibulocerebellectomized cat, gain control was absent, but a vestibular nerve lesion was compensated in the normal amount of time (126). Thus, gain and balance repair are mediated by different pathways, and the site of modifiable synapses in either case remains unknown.

#### *Saccadic Plasticity*

The signals that create saccades do not arise in the cerebellum. But, because cerebellar lesions cause saccadic dysmetria (see the section SACCADIC SYSTEM, p. 1297), the cerebellum might function to adjust saccades to be of the appropriate size. The dysmetria created by such lesions is never compensated, thus further implicating the cerebellum in the repair of saccadic dysmetria. To see if this is the case, first it is necessary to show that the saccadic system is capable of plastic adaptation. This was demonstrated in monkeys by tenectomizing both horizontal recti of one eye and then placing an eye patch over that eye (211). The muscles reattached but the eye was permanently weakened so that, for example, it moved only one-third as far as the normal eye (Fig. 13A). When the patch was switched to cover the normal eye, the saccades of the seeing eye were initially hypometric.

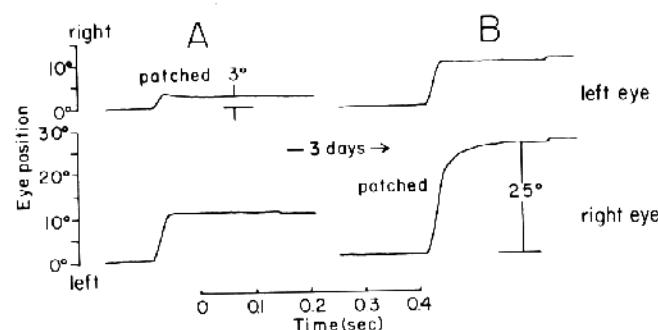


FIG. 13. Saccadic plasticity. A monkey is trained to follow a spot that jumps, in this example, by  $10^\circ$ . A: its left eye is weakened by tenectomy and patched. That eye subsequently makes hypometric saccades one-third as large as those of the normal eye and with a backward postsaccadic slip (top left). B: 3 days after switching the patch, weakened eye has regained ability to make orthometric saccades, while the good eye, under cover, makes hypermetric saccades with postsaccadic slip in opposite direction (bottom right). This demonstrates that central nervous system can repair dysmetria (created by a peripheral lesion) in this case by increasing gain (saccade size/retinal error) of central part of saccadic system. [From Optican and Robinson (211).]

Over the course of 3 days, the saccades of the weakened eye increased to the correct size, because the central nervous system increased the intensity of innervation sent to that eye. The eye under cover now went almost 3 times as far as the target. Switching the patch back to the operated eye initially caused the seeing eye to make grossly hypermetric saccades but they returned to normal in 1½ days. A similar saccadic adaptation may be seen when a patient with a palsy of an extraocular muscle is forced by a patch to use the palsied eye (1, 167).

Large lesions of the midline cerebellum including the vermis and paravermis of lobes V-VII and most of the fastigial nuclei removed the adaptive response to switching the patch (211). Although these experiments reveal nothing about the location of the modifiable synapses, they again implicate the cerebellum in the repair of yet another type of dysmetria.

#### *Plasticity of Vergence Tone*

When one eye is covered as a subject looks at a distant target, the visual axes move apart by an idiosyncratic angle called the phoria. If base-out prisms are placed on a subject, the eyes must converge by the prism angle for fusion. If one eye is covered so that fusion is broken, it will, of course, swing out by the sum of the prism angle and the phoria. After wearing such prisms for two hours, however, the eyes adapt by developing a tonic-vergence angle equal to the prism angle; therefore when one eye is covered, it deviates only by its original phoria. This is a form of plastic vergence adaptation. Patients with signs of a cerebellar disorder that affects eye as well as limb movements show no such adaptation to the prisms (G. Milders and R. D. Reinecke, unpublished observations). Here again, another oculomotor system shows plastic adaptation but fails to do so after cerebellar lesions.

The four examples of plastic adaptation mentioned in this section are in oculomotor subsystems. One suspects that there must be continual plastic repair and recalibration of hundreds of motor processes and programs throughout the body. Such activity is probably universal in motor systems but, since its action is particularly clear and analyzable in the oculomotor system, it may be possible to utilize this system to pinpoint the locus of such motor learning and especially to clarify the role played in it by the cerebellum.

#### MEASURING EYE MOVEMENTS

Eye movement recording methods may be broadly subdivided into those that either do or do not require physical contact with the eye; the former are almost always more accurate than the latter. Within each category one may further rank methods by how much they cost. Usually, the more expensive a method, the more accurate, elaborate, and difficult it is to maintain.

Because reviews of the methods of recording eye movements may be found elsewhere (46, 303), this section can be brief and only describes methods commonly used.

#### *Noncontact Methods*

One should not overlook the large amount of information to be obtained by observing animals in situations that are as natural as possible. One can discover, for example, that rabbits, on rare occasions, do make saccades (141) with the head still. One can also discover a great deal simply by inspecting the eye movements in patients, either at their bedside or in a clinical examination (e.g., ref. 308). The experienced clinician can even make good estimates, for example, of gains, time constants, dysmetrias, and velocities as long as he knows what to look for. Only those eye movements where objective quantification is interesting or diagnostic need be recorded.

**PHOTOGRAPHY.** In 1901, Dodge and Cline (81) were the first to devise a practical method of measuring eye movements by photographing the corneal reflection. This method is still used (194) with more modern cameras and has the advantage of reasonable accuracy and the ability to cover the entire movement range in all three degrees of freedom including, in particular, torsion. This method is successful as long as the camera and head can be held still relative to each other, which is a problem, for example, with pilots during high-acceleration, aerospace maneuvers. The disadvantage of this method is that it does not provide an analogue signal of eye position and requires frame-by-frame analysis. Since the invention of the television camera, which allows means of analyzing the image patterns and extracting analogue signals, the use of photography to measure eye movements has declined.

**ELECTROOCULOGRAM.** This method, which is called electronystagmography by otolaryngologists, is the cheapest, the most widespread, and the most potentially inaccurate. It utilizes the standing corneoretinal potential, which makes the cornea positive with respect to an indifferent electrode. Differential recordings are made between two skin electrodes placed close to each corner of an eye. When this eye looks, for example, to the left, the left electrode becomes more positive than the right.

The use of skin electrodes introduces base-line drift, noise, and muscle potentials (especially jaw muscles). The corneoretinal potential, itself, changes with time and the state of dark adaptation, which introduces more base-line drift and large changes in gain (170). To avoid the drift and low-frequency noise, it has been common practice to use AC-coupling in the amplifiers. Unfortunately, this does not allow one to know eye position. Although there are a few specific things one can still measure in this way, such as saccade velocity or the slow-phase velocity of nystagmus, many eye

movement abnormalities are position dependent and one can miss many significant findings if one uses AC-coupling. For this reason, it is infrequently used today.

DC-coupling can be used successfully if one keeps the subject in a constant ambient illumination for 15 min before and during the recording and calibrates about every 5 min by asking the subject (or patient) to fixate known target locations. Despite some overly critical comments by Byford (44), one can, with these precautions, usually obtain a resolution of about  $1^\circ$  and, with care, even  $0.5^\circ$ . This is more than adequate for most of the gross abnormalities one sees in clinical practice. However, high-frequency noise in the electrooculogram (EOG) limits the bandwidth over which one can electronically differentiate the signal to obtain eye velocity, and this can lead to an underestimation of peak saccadic eye velocity (34). An advantage of the EOG is that this method measures eye position with respect to the head independently of head motion; a disadvantage is that lid movements cause blink artifacts and inaccuracies in measuring vertical eye movements.

The EOG is usually used in animals by implanting the electrodes under the skin (35). Often the method is used simply to confirm that a trained animal is fixating a given spot (e.g., ref. 297). There are various ways to calibrate the EOG in untrained animals, e.g., by optokinetic stimulation (55), and such methods give adequate results for many purposes.

Despite its shortcomings, the fact that it can give good results when carefully used, combined with its low cost, simplicity, and ease of application, causes the DC-EOG technique to remain the preferred method in many applications, especially in the clinic, despite the developments of modern technology.

**CORNEAL REFLECTION.** Because the center of curvature of the corneal bulge differs from the center of rotation of the globe, eye movements displace the corneal highlight reflected from a light source. The motion of this light spot can be detected in a variety of ways from the photographic method first used by Dodge and Cline (81) to photoelectric detectors (214). This method was widely used between the two world wars by applied psychologists to study eye movements during reading, looking at an advertisement, or controlling an automobile or airplane.

The disadvantage of this method is that relative motion between the head and the recording apparatus is indistinguishable from an eye rotation. Therefore, it is necessary to immobilize the head as much as possible by a forehead-chin rest (which gives poor stabilization) or a dental impression, bite bar, which reduces drift due to head movement over 1 min to about 6 min of arc (98). For this reason, it is useful for many studies of macro-eye movements in cooperative subjects, but it is more difficult to apply in clinical situations. The method is also nonlinear and has a range of less than  $20^\circ$  depending on eye and light source alignment. The

method becomes difficult to use when large horizontal and vertical movement occur simultaneously. A unique application of this method occurs in animal studies (214) when head movements can be essentially eliminated by a skull implant. In such a case, resolutions as small as 2–5 min of arc can be achieved.

**DIFFERENTIAL LIMBUS REFLECTION.** This method uses the light reflected from the border of the iris and conjunctiva (the limbus), and photodiodes detect this light from each side of the eye. When the eye turns, the diode in that direction receives less light because more of the dark iris is exposed; the opposite diode receives more light because more of the white conjunctiva is exposed. The light source can be, for example, infrared and modulated at a high frequency to eliminate interference from room lights. The photoelectric elements are usually mounted on a spectacles frame but to get reasonable accuracy, the subject should sit fairly still and relax the muscles around the nose and temples. Best results still require a bite bar, and when this is used, resolutions of about  $0.1^\circ$  can be achieved by placing the elements very close to the limbus. In normal operation, the maximum range is about  $\pm 15^\circ$  with a resolution of  $0.5^\circ$ . Because of the eyelid, it is difficult to measure vertical eye movements with this method, and range and accuracy are poorer. The photoelectric method is commercially available and only moderately expensive.

**DOUBLE-IMAGE TRACKING DEVICES.** Because most methods of measuring eye movements are susceptible to artifacts created by head movements, a number of methods record the position of two images, which are affected differently by head and eye movements. For example, the distance between the pupil center and the corneal reflection of a spot of light does not change if the head translates but does if the eye rotates. The most common of these methods is the so-called Purkinje-image eye tracker, because it is commercially available (see ref. 49 for a more detailed description and for source references). Light reflected from the cornea is called the first Purkinje image; that from the back of the lens is the fourth Purkinje image. The separation between these images is proportional to eye rotation but not head translation. Nevertheless, the system is usually used in conjunction with a bite bar, and in this case has a resolution close to 1 min of arc over a range (horizontal and vertical) of  $\pm 12^\circ$  with a frequency response of 300 Hz. It is quite useful for the purpose for which it was originally designed: measuring miniature eye movements in psychophysical experiments without a contact lens. It is less useful for other purposes such as clinical investigations because it is expensive, requires a bite bar, has a limited range, and is massive and unwieldy if, for example, one wants to rotate it with a patient to study the vestibuloocular reflex. In subjects with small pupils, a mydriatic is needed to expose the fourth Purkinje image. Other

methods have been devised using various landmarks on the eye and other image-converting devices, especially television cameras (see refs. 46, 303 for reviews). Each was developed in a single laboratory but seldom adopted by other investigators because of size, cost, complexity, or the need for engineering skills.

#### Contact Methods

Once one has attached some object to the eye, there are dozens of ways to measure the movement of that object. For example, one can attach an accelerometer to it or a metal plate the motion of which changes the capacitance in an oscillator circuit. A black stalk has been held to the goldfish eye and its position measured by the point in the cycle at which it interrupts a scanning light beam (83). Of course, many of these methods may be just as susceptible to head movement artifacts as the noncontact methods. The techniques discussed in the following subsections were designed to overcome that problem.

**OPTICAL LEVER.** In this method a light beam is reflected from a plane mirror attached to a contact lens fitted to the eye. A laser beam is convenient, since it eliminates optics for focusing. The position of the reflected beam, measured by some photoelectric device at some distance from the eye, is only slightly or not at all changed by pure translations of the eye or head but is very sensitive to rotations of the mirror. The longer the reflected beam length becomes the larger is the sensitivity to rotation compared to translation, hence the name optical lever. This method was made popular around the middle of this century by psychologists wishing to study miniature eye movements, because it can resolve movements of the mirror on the order of seconds of arc. The problem has always been whether the eye and contact lens moved together; however, if the lens is molded to the eye or held on by a strong suction, lens slippage can evidently be kept negligible as long as the subject does not blink or make a large eye movement. This method is obviously devoted to a very special purpose and is not useful for measuring the larger eye movements that are usually of interest in most oculomotor applications. Because most miniature eye movements can now be recorded by the Purkinje-image eye tracker, use of the optical lever method will probably decline.

**MAGNETIC SEARCH COIL METHOD.** When a coil of wire (called a search coil) is placed in an alternating magnetic field (typical frequencies used are 5–30 kHz), a voltage is generated in it that has an amplitude proportional to the sine of the angle by which its plane is tilted with respect to the magnetic field. Using two fields, one vertical and one horizontal 90° out of phase, one can sort out the voltages induced by each by means of a phase detector and measure horizontal, vertical, and even torsional eye movements simultaneously with a bandwidth of at least 1 kHz (226).

There are a variety of modifications on this scheme. The magnetic field generating coils may be small and placed near the eye in the case of a restrained animal. On the other hand, the coils may be so large that eye and head movements (the latter may be measured by a coil mounted on the head) may be measured in a human subject free to move about (260). In the latter situation it should be noted that the system measures eye position in space (with respect to the coils) not in the head, but the latter signal is easily obtained by subtracting out the head position signal. The method is insensitive to translations of the head as long as the head is in a region of space where the magnetic field is uniform, because the voltage in the eye coil is changed only by rotation. The system is relatively inexpensive; the coils can be made easily in one's laboratory, and the most expensive element is a two-channel phase detector. The range is  $\pm 50^\circ$  and is linear provided one corrects for the sine function. The resolution at this range setting is about  $0.25^\circ$ , but by turning up the gains of the amplifiers, the resolution can be greatly increased (see Fig. 1D, *upper trace*). The signal-to-noise ratio is so inherently large that this method can measure the smallest eye movements and is comparable in this regard to the optical lever system. An obvious advantage is that by a simple switching of gains one can measure either the largest or the smallest possible eye movements.

The method was originally designed for use in animals that had this coil surgically implanted (104). By rotating the field coils about the animal, it is possible to objectively calibrate the gain of the coil in untrained animals, which is a great convenience. Once calibrated, the gain of the coil is stable for months and need not be constantly recalibrated. A disadvantage of the method is that the coil surgery sometimes makes animals strabismic, although newer surgical techniques may have eliminated this problem (151).

The method can be used in humans by using either a fitted contact lens with a coil embedded in it or by molding the coil into a silastic rubber annulus, which lies on the conjunctiva (without touching the cornea) and is kept from slipping by an elastic suction grip (67). This method can even be used to record miniature eye movements so long as the subject does not blink. The coil is uncomfortable to wear, however, even with a topical anesthetic; this is mainly because the wire leaving the coil is felt by the eyelids during blinks. This is not a problem for experienced subjects who simply refrain from blinking, but it is not clear whether patients, who react to the coil quite idiosyncratically, can tolerate the coil on repeated visits. The clinician may wish to supplement the EOG method with a more accurate one. It is not yet clear, however, whether the magnetic field method, which outperforms the Purkinje-image eye tracker in all regards and is cheaper and more versatile, should be preferred over a method that avoids physical contact with the eye.

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