Principles of Applied Vestibular Physiology

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Key Points

• The vestibular system primarily drives reflexes to maintain stable vision and posture.
• By modulating the non-zero baseline firing of vestibular afferent nerve fibers, semicircular canals encode rotation of the head, and otolith organs encode linear acceleration and tilt.
• Stimulation of a semicircular canal produces eye movements in the plane of that canal.
• A semicircular canal normally is excited by rotation in the plane of the canal bringing the head toward the ipsilateral side.
• Any stimulus that excites a semicircular canal’s afferents will be interpreted as excitatory rotation in the plane of that canal.
• High-acceleration head rotation in the excitatory direction of a canal elicits a greater response than does the same rotation in the inhibitory direction.
• The response to simultaneous canal stimuli is approximately the sum of the responses to each stimulus alone.
• Nystagmus due to dysfunction of semicircular canals has a fixed axis and direction with respect to the head.
• Brainstem circuitry boosts low-frequency vestibulo-ocular reflex (VOR) performance through velocity storage and neural integration. Failure of these mechanisms suggests a central pathologic process.
• The utricle senses both head tilt and translation, but loss of unilateral utricular function is interpreted by the brain as a head tilt toward the opposite side.
• Sudden changes in saccular activity evoke changes in postural tone.
• The normal vestibular system can rapidly adjust the vestibular reflexes according to the context, but adaptation to unilateral loss of vestibular function may be slow and susceptible to decompensation.

Principles

Principle 1: The Vestibular System Primarily Drives Reflexes to Maintain Stable Vision and Posture

Anatomic and Physiologic Basis

The vestibular system’s main function is to sense head movements, especially involuntary ones, and counter them with reflexive eye movements and postural adjustments that keep the visual world stable and keep us from falling. The labyrinth of the inner ear senses head rotation and linear acceleration and sends that information to secondary vestibular neurons in the brainstem vestibular nuclei. Secondary vestibular neuron signals diverge to other areas of the central nervous system to drive vestibular reflexes. Specifically, neurons encoding head movement form synapses within the ocular motor nuclei to elicit the patterns of extraocular muscle contraction and relaxation needed for the vestibulo-ocular reflex (VOR), which stabilizes gaze (eye position in space). Other secondary vestibular neurons synapse on cervical spinal motor neurons to generate the vestibulocollic reflex (VCR), or to lower spinal motor neurons to generate the vestibulospinal reflexes (VSRs). These reflexes stabilize posture and facilitate gait. Vestibular sensory input to autonomic centers, particularly information about posture with respect to gravity, is used to adjust hemodynamic reflexes to maintain cerebral perfusion. Finally, vestibular input to the cerebellum is essential for coordination and adaptation of vestibular reflexes when changes occur such as injury to a vestibular end organ or alteration in vision (e.g., a new pair of glasses).

Vestibular signals also reach cortical areas to mediate the perception of movement and orientation. Nevertheless, the common head movements of everyday life usually go unnoticed, which is why ves-
tibular sensation is not included among the vernacular “five senses”—
sight, smell, taste, touch, and hearing. Yet the loss of vestibular sensation
causes distinct and often severe symptoms. This distress has perhaps
been best captured in the first-hand account of J.C., a physician who
lost his vestibular sense to an ototoxic aminoglycoside antibiotic: “By
bracing my head between two of the metal bars at the head of the bed
I found I could minimize the effect of the pulse beat that made the
letters on the page jump and blur… In these corridors I had the pecu-
liar sensation that I was inside a flexible tube, fixed at the end nearest
me but swaying free at the far end.”

Like many other patients who have lost vestibular function,
J.C. soon recovered and resumed most of his usual activities without
the distressing sense of oscillopsia, the perception that the world is
moving whenever the head is moved. This recovery is due to a combi-
nation of central adaptation to abnormal vestibular signals and the
use of information from other sensory systems that provide information
about movement and posture. For example, somatosensory infor-
mation from proprioceptive sensors in the limbs contributes to the
sense of vertical body orientation. Proprioceptors in the neck mediate
a cervico-ocular reflex that can augment the deficient VOR. Likewise,
postural information may be supplied by gravity receptors in the
major blood vessels and abdominal viscera. Because head movements
may be also sensed by their impact on the retinal image, vision-based
oculomotor systems can partly supply a deficient VOR. For example,
smooth pursuit is a type of reflexive eye movement that helps to
stabilize images on the retina. During smooth pursuit, movement of a
target image on the retina causes a conjugate following movement of
the eyes to keep the target fixed on the fovea. The stimulus for this
reflex is the difference between the velocity of the visual target and
the velocity of the eye, which is called retinal slip velocity. This visual
error is computed by the primary visual cortex; transmitted to the
brainstem and cerebellum to generate the oculomotor command
signals. The multiple synapses involved in this reflex impose a long
latency (approximately 100 msec), and the reflex breaks down at rela-
tively modest velocities (more than approximately 50 degrees/second)\(^6\)
and frequencies (more than approximately 1 Hz).\(^7\) Optokinetic nystag-
mus, which elicits eye rotation in response to optokinetic flow of the visual
scene, operates over a range of velocities and frequencies similar to
smooth pursuit. These limitations make these visually driven reflexes
inadequate to stabilize vision during many common head movements.
For example, the head pitches up and down at a frequency of approxi-
mately 2 Hz and velocity of approximately 90 degrees/second during
walking, while during running head pitch harmonics may extend to
15 to 20 Hz. Voluntary head-on-body horizontal rotations can reach
800 degrees/second and can also have significant harmonics to 15 to
20 Hz.\(^8\)

The limitations of smooth pursuit and optokinetic nystagmus
illustrate the important concept that reflexive sensorimotor systems
have optimal operating ranges. Smooth visual pursuit functions best
for low-frequency and slow head movements. Autonomic gravity receptors
function best for static and very low-frequency conditions. These and
other reflexes overlap with the vestibular system for part of its operating
range, but nonvestibular systems largely break down during quick head
movements. Therefore, the vestibular system is essential for gaze sta-
bilization during high-frequency, high-velocity, and high-acceleration
head movements.

Clinical Importance

The reflexive nature of the vestibular system is central to understanding
vestibular neurophysiology. The brainstem interprets imbalances in
vestibular input due to pathologic processes in the same way that it
interprets imbalances due to physiologic stimuli. Therefore, the cardin-
al signs of vestibular disorders are reflexive eye movements and pos-
tural changes. These reflexive signs can largely be understood as the
brainstem’s responses to perceived rotation around a specific axis or
perceived tilting or translation of the head, even though the head is still
and upright. Knowing the effective stimulus for each vestibular end-
organ allows determination of which end organ or combination of end
organs must be stimulated to produce the observed motor output.

Working backwards in this fashion, the end organs affected by pathol-
ogy can usually be inferred.

In interpreting reflexive eye movements and postural changes in the
search for vestibular dysfunction, an important consideration is that
vestibular reflexes may be observed only in isolation under certain
conditions. For many conditions, in fact, other reflexive systems can
compensate for the loss of vestibular reflexes, thereby masking any
deficit. For example, a patient with well-compensated, longstanding
bilateral loss of vestibular function may surprisingly appear to have no
problem keeping vision fixed on the examiner as the examiner rotates
the patient’s head slowly from side to side. In such persons, smooth
pursuit, optokinetic nystagmus, and (to a lesser extent) the cervico-
ocular reflex make up for the vestibular deficit. This is an example of
a head movement that can be sensed by the vestibular system, but which
is not in the range of frequencies and accelerations sensed exclusively
by the vestibular system. However, when the examiner suddenly and
rapidly rotates the head to either side, the eyes do not stay on target.
The vestibular deficit can thus be unmasked by very dynamic head
movements.

Principle 2: By Modulating the Non-Zero Baseline Firing of
Vestibular Afferent Nerve Fibers, Semicircular Canals
Encode Rotation of the Head, and Otolith Organs Encode
Linear Acceleration and Tilt

Anatomic and Physiologic Basis

Sensory Transduction

The labyrinth of the inner ear houses a set of inertial sensors that detect
rotary and linear acceleration. Each bony labyrinth encloses a mem-
brous labyrinth consisting of three semicircular canals arrayed roughly
at right angles to each other and two roughly orthogonal otolith organs,
the utricle and saccule (Fig. 163-1). Semicircular canals primarily sense
rotational acceleration of the head. The utricle and saccule primarily
sense linear acceleration in horizontal and vertical (superoinferior)
directions, respectively.

Sensation by semicircular canals works as follows. When the head
accelerates in the plane of a semicircular canal, inertia causes the endo-
lymph in the canal to lag behind the motion of the membranous canal,
much as coffee in a mug initially remains in place as the mug is rotated
about it. Relative to the canal walls, the endolymph effectively moves
in the opposite direction as the head. Inside the ampulla, a swelling at
the end of the canal where it meets the utricle, pressure exerted by
endolymph deflects the cupula, an elastic membrane that spans a cross-
section of the ampulla\(^9\) (Fig. 163-2). Vestibular hair cells are arrayed
between the cupula on the surface of the cristae ampullaris, a saddle-
shaped neuropsytelium. Hair cells are so named for tufts of stereocilia
that project from their apical surfaces. These stereociliary bundles are
coupled to the cupula so that its deflection creates a shearing stress
between the stereocilia and the cuticular plates at the tops of the hair
cells.

Stereocilia deflection is the common mechanism by which all
hair cells transduce mechanical forces (Fig. 163-3). Stereocilia within
a bundle are linked to one another by protein strands called “tip links”
that span from the side of a taller stereocilium to the tip of its
shorter neighbor in the array. The tip links are believed to act as gating
springs for mechanically sensitive ion channels, meaning that the tip
links literally tug at molecular gates in the stereocilia.\(^10\) These gates,
which are cation channels, open or close (or, more precisely, spend
more or less time in the open state), depending on the direction in
which the stereocilia are deflected. When deflected in the open or “on”
direction, which is toward the tallest stereocilium, cations, including
potassium ions from the potassium-rich endolymph, rush in through the
gates, and the membrane potential of the hair cell becomes more
positive (see Fig. 163-3B, C). This in turn activates voltage-sensitive
calcium channels at the basolateral aspect of the hair cell, and an influx
of calcium leads to an increase in the release of excitatory neurotrans-
mitters, principally glutamate, from hair cell synapses onto the ves-
tibular primary afferents (see Fig. 163-3D). All of the hair cells on a
semicircular canal crista are oriented or “polarized” in the same direc-


A gelatinous membrane sits atop the macula, and microscopic stones made of calcium carbonate, the otoliths (or otoconia), are embedded on the surface of this otolithic membrane. The saccule (or saccule), located on the medial wall of the vestibule of the labyrinth in the spherical recess, has its macula oriented vertically. Gravity therefore tonically pulls the saccular otolithic mass inferiorly when the head is upright. The utricle (or utricle) is located above the saccule in the elliptical recess of the vestibule. Its macula is oriented in roughly the same plane as the horizontal semicircular canal, although its anterior end curves upward. When the head tilts out of the upright position, the component of the gravitational vector that is tangential to the macula creates a shearing force on stereocilia of utricular hair cells. The cellular transduction process is identical to that described above for the crista. However, the hair cells of the maculae, unlike those of the cristae, are not all polarized in the same direction (Fig. 163-6). Instead, they are oriented relative to a curving central zone known as the striola. The utricular striola forms a C shape, with the open side pointing medially. The striola divides the utricular macula into a medial two thirds (polarized to be excited by downward tilt of the ipsilateral ear) and a lateral one third polarized in the opposite direction. Hair cells of the sacculus point away from its striola, which curves and hooks superiorly in its anterior portion. Each macula is essentially a linear accelerometer, with the saccular macula encoding acceleration roughly within a parasagittal plane (along the naso-occipital and superoinferior axes), and the utricular macula encoding linear acceleration roughly in an axial plane (along the naso-occipital and interaural axes). A given linear acceleration may produce a complex pattern of excitation and inhibition across the two maculas (Fig. 163-7), a pattern that encodes the direction and magnitude of the linear acceleration. By contrast, each of the three semicircular canals senses just a one-dimensional component of rotational acceleration.

Modulation of neurotransmitter release from hair cells within each vestibular endorgan modulates the action potential frequency, or firing rate, of vestibular nerve afferent fibers (Fig. 163-8). The afferents have a baseline rate of firing, probably due to a baseline rate of release of neurotransmitter from the vestibular hair cells. Changes in vestibular nerve afferent firing are conveyed to secondary neurons in the brainstem. Baseline firing gives the system the important property of bidirectional sensitivity: Firing can increase for excitatory head movements and decrease for inhibitory head movements. Thus, loss of one
Part 7  Otology, Neuro-otology, and Skull Base Surgery

\[
\sum T = I \alpha, \quad \text{where } T \text{ is torque, } I \text{ is the moment of inertia, and } \alpha \text{ is rotational acceleration.}
\]

For the rotating semicircular canal, the equation can be written

\[
\sum T = \sum (T_{\text{elastic}} + T_{\text{viscous}}) = I \ddot{X}(t). \quad \text{Eq. 163-1}
\]

Equation 163-1 says that the sum of the elastic and viscous torques acts on the moment of inertia \(I\) of the endolymph and cupula to accelerate the endolymph through space by \(\ddot{X}(t)\). (Overdots are used to denote time derivatives, so \(X(t)\), \(\dot{X}(t)\), and \(\ddot{X}(t)\) are endolymph rotational position, velocity, and acceleration, respectively.)

The elastic torque exerted by the cupula is proportional to the deflection of the cupula from its resting position (light blue in Fig. 163-9). That deflection is given by the difference between how far the head moves in space and how far the endolymph moves in space:

\[
\Theta(t) = H(t) - X(t). \quad \text{Eq. 163-2}
\]

Therefore, the elastic torque is

\[
T_{\text{elastic}} = K \Theta(t). \quad \text{Eq. 163-3}
\]

The viscous torque is proportional to the velocity of the endolymph relative to the walls of the canal. Differentiation of Equation 163-2 gives this relative endolymph velocity:

\[
\dot{\Theta}(t) = \dot{H}(t) - \dot{X}(t). \quad \text{Eq. 163-4}
\]

Therefore,

\[
T_{\text{viscous}} = \mathcal{B} \dot{\Theta}(t). \quad \text{Eq. 163-5}
\]

Finally, to get endolymph acceleration, \(\ddot{X}(t)\), we differentiate Equation 163-2 and rewrite it as

\[
\ddot{X}(t) = \ddot{H}(t) - \ddot{\Theta}(t) \quad \text{Eq. 163-6}
\]

Now Equation 163-1 can be written as

\[
K \Theta(t) + \mathcal{B} \dot{\Theta}(t) = I \ddot{H}(t) - I \ddot{\Theta}(t). \quad \text{Eq. 163-7}
\]

Figure 163-6. Morphologic polarizations of the stereociliary bundles in the maculae of the utricle (A) and saccule (B). The “on” direction of stereociliary deflection is indicated by the arrows. In the utricle (A), hair cells are excited by stereociliary deflection toward the striola (curving central zone). In the saccule (B), hair cells are excited by stereociliary deflection away from the striola.
Figure 163-7. Estimated patterns of excitation and inhibition for the left utricle and saccule when the head is (A) tilted with the right ear 30 degrees down, (B) upright, and (C) tilted with the left ear 30 degrees down. The utricle is seen from above, and the saccule from the left side. The midpoint of the color scale represents baseline activity, whereas dark orange and white represent depolarization and hyperpolarization, respectively. (Modified from Jaeger R, Takagi A, Haslwanter T. Modeling the relation between head orientations and otolith responses in humans. Hear Res. 2002;173:29.)

Figure 163-8. A vestibular afferent nerve fires actively at rest (center). Its firing rate is modulated by sensory transduction. The afferent is inhibited when its hair cells' stereocilia are deflected in the “off” direction (away from the kinocilium, in dark blue left panel) and excited when the stereocilia are deflected in the “on” direction (toward the kinocilium, right panel).
The movement of the cupula can now be described as a function of head acceleration:

$$K\dot{\Theta}(t) + B\ddot{\Theta}(t) + \dot{\Theta}(t) = I\ddot{H}(t)$$  \hspace{1cm} \text{Eq. 163-8}$$

The full solution to Equation 163-8 is derived in the Appendix, but considerable insights can be gained without the full solution simply by inserting measured values for the physical constants in Equation 163-8 and considering the behavior under special circumstances.

For example, during a constant, low-acceleration head rotation (Fig. 163-10A), cupular deflection eventually reaches a steady-state constant value. Because cupular velocity and acceleration eventually decay to zero under these circumstances, Equation 163-8 reduces to

$$K\dot{\Theta}(t) = I\ddot{H}(t)$$  \hspace{1cm} \text{Eq. 163-9}$$

and cupular deflection (and afferent firing rate) is approximately proportional to head acceleration. The time course of cupular displacement in response to a constant acceleration approximates a single exponential growth, and the time constant with which cupular displacement reaches its maximum deflection is approximately 10 seconds, the time constant of the cupula (see Appendix). When the constant acceleration stops, the cupula returns to its zero position exponentially with the same time constant.

The same time constant governs the cupular response to very brief pulses of head acceleration. Figure 163-10B shows the predicted cupular deflection to an impulse of acceleration, which brings the head to a constant velocity plateau until an impulse of deceleration stops the rotation. Such “velocity steps” are often done as part of clinical rotary chair tests. However, the measured value of the time constant of the VOR in such testing is generally much longer than what would be anticipated by this calculated cupular response because of further processing by the brain (This is addressed later in the discussion of Principle 9.)

During sinusoidal head rotations in the range encompassing most natural head movements (approximately 0.1 to 15 Hz), viscous friction dominates the cupular response, and Equation 163-8 reduces to

$$B\dot{\Theta}(t) = I\ddot{H}(t)$$  \hspace{1cm} \text{Eq. 163-10}$$

This implies that

$$\Theta(t) = \frac{I}{B} \ddot{H}(t)$$  \hspace{1cm} \text{Eq. 163-11}$$

Figure 163-9. The torsional pendulum model of the mechanical forces acting on the cupula and endolymph of the left horizontal canal during leftward angular head acceleration as seen from above. As the head rotates through space over an angle $H$, endolymph inside the canal also rotates through space, but over a slightly smaller angle $X$. The difference between the angles through which the head and endolymph rotate in space is $\Theta$, which approximates the angular deflection of the cupula. This creates an elastic torque proportional to the deflection: $T_{\text{elastic}} = K\Theta$. A viscous or drag torque is produced by the relative flow of endolymph along the walls of the canal and is proportional to the endolymph velocity relative to the canal: $T_{\text{viscous}} = B\dot{\Theta}$ . The sum of these torques will equal the moment of inertia of the cupula and endolymph times their acceleration: $K\dot{\Theta} + B\ddot{\Theta} = I\ddot{H} - I\dot{H}$. The movement of the cupula can therefore be described as a function of head acceleration:

$$K\dot{\Theta}(t) + B\ddot{\Theta}(t) + \dot{\Theta}(t) = I\ddot{H}(t)$$  \hspace{1cm} \text{Eq. 163-8}$$

Figure 163-10. Patterns of cupular displacement in response to rotational head movements as predicted by the torsional pendulum model. A, A step of constant head acceleration (red tracing) results in a constant cupular deflection (blue) after an exponential increase in deflection with a time constant of about 10 sec. B, A step of constant velocity is produced by an impulse of acceleration in one direction followed by an impulse of deceleration in the opposite direction (acceleration impulses are shown in red). The cupula is transiently displaced, returning to its resting position with a decay time constant of about 10 sec. C, Sinusoidal acceleration of the head red yields a response in phase with head velocity.
so that cupular deflection is proportional to head velocity. This is demonstrated in Figure 163-10C. Note that the cupula’s predicted response is not in phase with the sine wave that describes head acceleration (red). Rather, the cupula’s motion appears to peak one-fourth cycle in advance of the head’s motion. This 90-degree phase advance in the cupula’s motion can be represented by a cosine wave, which is the integral of the sine wave. The endolymph and cupula thus act as a mechanical integrator of the input head acceleration. The integral of acceleration is velocity, so the important point here is that the cupula encodes head velocity over its physiologically relevant frequency range, even though the stimulus acting on the endolymph is head acceleration. Because of this, and because retinal image slip velocity is an important determinant of visual acuity, clinical and experimental tests conventionally report findings with respect to head velocity.

Response of the Otoconial Membrane

An approach similar to the analysis of cupular motion yields an equation relating the predicted movement of the otoconial membrane to head acceleration. Unfortunately, the otoconial membrane is an inhomogeneous structure whose complexities make it difficult to estimate the physical parameters in the model that would predict its responses under different conditions. The membrane consists of the dense otoconial layer on top, a stiff mesh layer in the middle, and an elastic gel layer on the bottom. At the macular surface it is presumably fixed. It is unclear how tightly otoconial displacement is coupled to the motion of the stereocilia. These uncertainties lead to models that variously predict that the otoconial membrane responds to linear acceleration or velocity, but the actual behavior remains unresolved.

Encoding by the Afferents

Morphologically, mammalian vestibular afferents can be grouped into calyceal, bouton, and dimorphic fibers (Fig. 163-11). Calyceal fibers (see Fig. 163-11A and B) form chalice-shaped calyx synapses on one or several neighboring type 1 hair cells. Each calyx engulfs the basolateral membrane of the enclosed type 1 hair cell(s). At the other end of the morphological spectrum, a bouton fiber (see Fig. 163-11H) forms 15 to 100 button-like synapses on multiple type 2 hair cells distributed over 25 to 75 µm. Dimorphic fibers (see Fig. 163-11C to G) include 1 to 4 calyceal synapses with type 1 hair cells and 1 to 50 bouton-type synapses with type 2 hair cells. The spatial distribution of afferent endings within the sensory neuroepithelium differs for these three different morphologic groups (shown to the right in Fig. 163-11). Calyceal afferents in the crista are found exclusively in the central zone (on the top of the crest) and in the macula exclusively in the striola. Bouton fibers mostly arborize in the peripheral zone of the crista and in the extrastriolar zones of the maculae. Dimorphic afferents innervate all regions of the vestibular sensory epithelia, and are the dominant fiber type.

In mammals, physiologic response characteristics segregate vestibular nerve afferent fibers into two classes based on the regularity in the spacing of spontaneous action potentials (as reviewed by Goldberg and Fernández). Regular afferents (Fig. 163-12A) fire at 50 to 100 spikes/second at rest, with very little variation in resting rate for a given
In general, they respond to vestibular stimulation with tonic responses. That is, their firing modulates about the baseline, going up and down in close approximation to the stimulus acting on the hair cells. For the otolith organs, the presumed stimulus acting on the hair cells is linear acceleration. The regular afferents in the macula fire in close approximation to linear acceleration. For the semicircular canals, the effective stimulus acting on the hair cells turns out to be rotational velocity, not acceleration, as explained earlier and in the Appendix. Regular afferents innervating the crista respond with firing rate variations that closely approximate the head velocity signal. Regular units typically have a relatively low sensitivity (change in spike rate for a change in stimulus) to head rotation, to activation of efferent pathways, and to galvanic stimulation. Regular afferents typically have medium or thin axons with bouton-only or dimorphic arborizations in the peripheral zones of cristae or otolithic maculae.

In contrast with regular vestibular afferents, irregular afferents are thick to medium-sized axons that end in calyceal or dimorphic terminals in the central (or striolar) zones of vestibular end-organs. Their interspike intervals are much more variable (see Fig. 163-12B). As a population, irregular afferents have a wider range of spontaneous rates than do regular fibers. Irregular units show phasic responses to the stimulus acting on the endorgan. That is, the response is more transient, and it approximates the rate of change of the stimulus acting on the endorgan rather than simply the stimulus itself. Thus, irregular units in the crista approximate the head’s rotational acceleration, which is the rate of change of velocity. Irregulars in the macula approximate the linear jerk, the derivative of linear acceleration. Irregular units may have very high sensitivity to vestibular stimuli, except for a unique group of low-sensitivity calyx units in the crista, whose function is still unclear. Sensitivities to activation by efferent pathways and to galvanic stimulation also are generally greater for irregular afferents.

Smith and Goldberg have described a model of vestibular nerve afferent spike-initiation dynamics that accounts for many of these observed differences between classes of afferent discharge (Fig. 163-13). After the peak of an action potential (caused by inward sodium currents), outward potassium currents briefly hyperpolarize the vestibular afferent membrane. The potassium conductance decays in a time-dependent manner, and the membrane potential rises again toward the threshold voltage for spike generation. Excitatory postsynaptic potentials (EPSPs) due to synaptic neurotransmitter release superimpose on this repolarization. The model assumes that variations in this potassium conductance between different afferents accounts for their regularity of discharge. In regularly discharging afferents, the model proposes that a
large potassium conductance decays slowly but inexorably, so that the repolarization continues in a deterministic fashion until the membrane potential again reaches firing threshold (see Fig. 163-13A). The model assumes that quanta of neurotransmitter released from hair cells cause relatively little variation in the trajectory of the repolarization. This deterministic nature of the repolarization means that the membrane reaches the threshold for another spike at almost the same time for each spike. Thus, the interspike intervals are all similar, and the unit’s discharge is regularly stochastically independent synapses.38

Because regular and irregular vestibular nerve afferent fibers have distinct anatomies in so many respects, it seems likely that they mediate different functions.37 One hypothesis holds that regular and irregular afferents may help compensate for different dynamic loads of the different vestibular reflexes. Regular afferents carry signals roughly in phase with head velocity, the expected output of the mechanics of the semicircular canals (as described; see also the Appendix). Irregular units with high gains have responses more in phase with head acceleration than velocity. The VOR for low-frequency head rotations requires a signal that approximates head velocity, and the regular afferents seem to provide an ideal input for this reflex.39

By contrast, the VSIs involve very different mechanical loads and may require inputs from the labyrinth that better reflect the head’s acceleration, a task to which the irregulars seem better suited.40 Anatomically, regular and irregular afferents overlap extensively in their distributions to the central vestibular nuclei.41-43 However, physiologic evidence suggests that there is some segregation of regular and irregular inputs between central projections to the ocular motor centers and the spinal motor centers.44,45 Another role for the irregular afferents may be to initiate the vestibular reflexes with a very short latency for rapid head movements.46 Finally, some evidence suggests that the dynamics of irregular afferents are better suited to provide the modifiable component of the VOR when gain must be changed rapidly. Examples are the higher gain needed when the eyes are verged on a near target,47,48 the change needed to adapt to magnifying or “minifying” spectacles,49,50 that vestibular efferents may act to balance firing between the two labyrinths, a role that may be particularly important after some degree of loss of unilateral function.

**Principle 3: Stimulation of a Semicircular Canal Produces Eye Movements in the Plane of that Canal**

This important principle often is referred to as Ewald’s First Law. Ewald cannulated the individual membranous canals in pigeons and observed the effects of endolymph motion on body, head, and eye movements. Although Ewald may have codified this principle on the basis of his work, it is clear that earlier workers like Flourens and Mach recognized that manipulations of an isolated semicircular canal in experimental animals produced eye or head movements in the plane of that canal.51

**Anatomic and Physiologic Basis**

The anatomic basis of this principle begins with the anatomy of the semicircular canals. The arrangement of the canals places fluid motion sensors at the ends of relatively long, slender, fluid-filled, donut-shaped tubes. Each tube lies more or less in one plane. The most effective stimulus to move the fluid in such a planar semicircular tube is angular acceleration in that plane, about an axis perpendicular to the plane and through the center of the “donut hole.”

The three semicircular canals of the labyrinth are roughly orthogonal to each other, so that one labyrinth can sense any rotation in three-dimensional space. Canals in the two labyrinths are arranged in complementary, coplanar pairs.52 The two horizontal canals are roughly in one plane, which is nearly horizontal when the head is in an upright position. The left anterior canal is roughly coplanar with the right posterior canal in the LARP (left anterior–right posterior) plane, which lies approximately 45 degrees off the mid sagittal plane with the anterior end toward the left and the posterior end toward the right. And the right anterior canal is roughly coplanar with the left posterior canal in the RALP (right anterior–left posterior) plane, again roughly 45 degrees off the sagittal plane and orthogonal to the LARP and horizontal planes (Fig. 163-14). These canal planes define the cardinal coordinate system for vestibular sensation.

The power of this principle goes beyond the notion that the canal planes simply provide a coordinate system for vestibular sensation. Canal planes also provide the coordinate system for the final motor output of the VOR (and for the vestibulo-colic neck reflex). The beauty of this canal-fixed (and thus head-fixed) coordinate system for eye movements is that it reduces the neural computation required for oculomotor output to exactly compensate for the head movement.

How is this coordinate system preserved in the central connections of the VOR? Figure 163-15 shows the connections from the left horizontal canal that mediate the VOR when that canal is excited. We have already seen how this movement excites the afferents from this canal; the inset demonstrates this increase in firing from the baseline rate. Secondary vestibular neurons in the ipsilateral vestibular (medial and superior) nuclei receive these afferent signals and connect to the ipsilateral ocular nuclei controlling the medial and lateral rectus muscles, which also lie roughly in a horizontal plane. Secondary vestibular neurons carry excitatory signals to the ipsilateral third nucleus and contralateral sixth nucleus to excite the ipsilateral medial rectus and contralateral lateral rectus, respectively. These muscles pull the eyes toward the right as the head turns toward the left, accomplishing the goal of keeping the eyes stable in space. Other secondary vestibular neurons carry inhibitory signals to the contralateral third and ipsilateral sixth nuclei to simultaneously relax the antagonist muscles, the contralateral medial rectus and the ipsilateral lateral rectus, respectively. This reciprocal activity is typical of the extraocular muscles, which work in contraction-relaxation pairs.53,54

Just as the extracocular muscles work in reciprocal pairs, so too do the coplanar semicircular canals. Like the left horizontal canal, the right horizontal canal is also stimulated by the horizontal head turn (Fig. 163-16). However, because the polarity of stereociliary bundles in the
Figure 163-14. Orientation of the semicircular canals. A, When the head is upright, the horizontal canal (or lateral canal [LC]) is tilted approximately 20 degrees upward from the horizontal plane at its anterior end. B, The vertical canals are oriented in planes roughly 45 degrees from the midsagittal plane. The right anterior canal (AC) and left posterior canal (PC) lie in the same plane, the right anterior–left posterior (RALP) plane. The left anterior and right posterior canals lie in the left anterior–right posterior (LARP) plane. (Adapted From Barber HO, Stockwell CW. Manual of Electronystagmography. St Louis: Mosby; 1976.)

Figure 163-15. Neural connections in the direct pathway for the vestibulo-ocular reflex (VOR) from excitation of the left horizontal canal (HC). As seen from above, a leftward head rotation produces relative endolymph flow in the left HC that is clockwise and toward the utricle. The cupular deflection excites the hair cells in the left HC ampulla, and the firing rate in the afferents increases (inset). Excitatory interneurons in the vestibular nuclei connect to motor neurons for the medial rectus muscle in the ipsilateral third nucleus (III) and lateral rectus muscle in the contralateral sixth nucleus (VI). Firing rates for these motor neurons increase (mini bar graphs). The respective muscles contract and pull the eyes clockwise, opposite the head, during the slow phases of nystagmus. Inhibitory interneurons in the vestibular nuclei connect to motoneurons for the left lateral rectus and right medial rectus. Their firing rates decrease, and these antagonist muscles relax to facilitate the eye movement.
The alignment of canal planes and extraocular muscle planes is not exact, and the excitation of a single canal pair does not solely produce activity in a dedicated pair of extraocular muscles. Other muscles must be activated to compensate for a head rotation even when it is purely in the plane of one semicircular canal. However, this arrangement between semicircular canals and extraocular muscles is remarkably constant across vertebrate species, even allowing for the shift between lateral-eyed species (e.g., rabbits) and frontal-eyed ones (e.g., humans). Because the vestibular labyrinth evolved before movable eyes,64 extraocular muscles may have evolved to pull in the preexisting canal planes. Robinson65 has argued that there is an evolutionary advantage to keeping the extraocular muscles aligned with the semicircular canals. Such an arrangement minimizes the brainstem processing
When the patient lies down and turns the head toward to rest in one of the semicircular canals (typically the posterior semicircular canal). BPPV, otolith crystals displaced from the utricular otoconial mass come causes contractions of the utricular and the saccular otoliths resulting in the symptoms of BPPV. In the most widely accepted current model of BPPV, otolith crystals displaced from the utricular otoconial mass come

Clinical Importance

Because of the primacy of the canals in determining how the eyes move under vestibular stimulation, it is helpful to think about vestibular eye movements in a canal-fixed frame of reference. A good example of the power of this approach is in investigation of benign paroxysmal positional vertigo (BPPV). In the most widely accepted current model of BPPV, otolith crystals displaced from the utricular otoconial mass come to rest in one of the semicircular canals (typically the posterior semicircular canal). When the patient lies down and turns the head toward the affected side, aligning the posterior canal (PC) with the pull of gravity (the left Dix-Hallpike maneuver), the otolith crystals fall toward what is now the “bottom” of the canal. As the otoliths fall, they push endolymph ahead of them, causing cupular deflection and exciting hair cells on the posterior canal crista. Nystagmus develops during the time that endolymph moves. Ewald’s First Law predicts the direction of that nystagmus: It will be in the plane of the affected posterior canal, independent of pupil position or head position.

Trying to apply this principle to PC-BPPV confuses many novice examiners. They observe instead that the nystagmus seems to change direction depending on where the patient directs the gaze. When the patient looks out to the side (toward the affected ear), the examiner sees a primarily torsional movement of the eyes. When the patient looks up toward the ceiling (away from the affected ear), the eyes appear to move vertically (Fig. 163-18). With the eyes in a neutral position (straight-ahead gaze), the nystagmus is a mixture of vertical and torsional movements. How can the principle be valid if the nystagmus changes directions?

In reality, no change occurs in the direction of the nystagmus with respect to the canal planes; it is a figment of the wrong frame of reference. In examining eye movements, we are accustomed to thinking in an eye-fixed reference frame in which the line of sight (the line extending forward from the pupil) determines what is up, down, left, right, clockwise, and counterclockwise relative to that axis. But Ewald’s First Law demands that we abandon this oculocentric view of eye movements and instead see them in a canal-centric view. In this view, the location of the pupil does not matter. The globe continues to rotate around the axis parallel to the one passing perpendicularly through the posterior canal that is being stimulated (shown in blue in Fig. 163-18). The pupil is simply a surface feature going along for the ride, wherever it happens to be directed. Ewald’s First Law states that the eyes will move in the plane of the stimulated canal no matter where gaze is directed. In fact, the apparent variation in pupil movement with gaze direction during nystagmus can be used to an examiner’s advantage in trying to discern which canal is affected in BPPV (or any other cause of single-canal dysfunction). By asking a patient to look parallel and perpendicular to the plane of the canal in question during periods of nystagmus, one should observe that when the pupil is in the plane of the affected canal, the nystagmus moves the pupil most obviously. This is because the pupil is at the equator of the rotating globe, where rotation will carry it the farthest. When the patient’s gaze is directed perpendicular to the plane of the affected canal, the pupil is at the pole of the rotating globe, and eye movement is limited to cyclotorsion about the axis of rotation, which

Figure 163-17. The left anterior–right posterior canal (LARP) plane aligns with the pulling directions of the left superior rectus (SR) and inferior rectus (IR) muscles, as well as the right superior oblique (SO) and inferior oblique (IO) muscles. As indicated by the shading, excitation of the left anterior canal (and inhibition of the right posterior canal) causes contraction of the left superior rectus and right inferior oblique muscles and relaxation of the right superior oblique and left inferior rectus muscles. As indicated by the shading, excitation of the left anterior canal (and inhibition of the right posterior canal) causes contraction of the left superior rectus and right inferior oblique muscles and relaxation of the right superior oblique and left inferior rectus muscles.

Figure 163-18. Excitation of the left posterior canal (PC) by moving canaliths in benign paroxysmal positional vertigo (PC-BPPV) causes slow phase eye movements downward in the plane of the affected PC. The eyes rotate around an axis parallel to the one going through the center of the affected PC. A, When gaze is directed perpendicular to the axis of eye rotation, the pupil appears to move up and down in an eye-fixed reference frame. B, When gaze is directed parallel to the axis of eye rotation, the pupil appears to move torsionally in an eye-fixed reference frame. In either case, the eyes rotate around the same axis when considered in a canal-fixed frame of reference.
can be subtle to detect. Finding these two gaze directions can identify and confirm the canal (or at least the coplanar canal pair) causing the nystagmus.

**Principle 4: A Semicircular Canal Normally Is Excited by Rotation in the Plane of the Canal Bringing the Head toward the Ipsilateral Side**

**Anatomic and Physiologic Basis**
A semicircular canal crista is excited by rotation in its plane in one direction and is inhibited by rotation in its plane in the opposite direction. Another look at Figure 163-9 shows that turning the head toward the left in the horizontal canal plane produces endolymph rotation to the left relative to space. But that endolymph rotation is less than the head rotation by the angle \( \Theta \). Thus, relative to the canal, there is endolymph rotation of \( \Theta \) to the right, and the cupula is deflected toward the utricle. The pattern of afferent activation results from the polarization of the stereocilia of the hair cells on the cristae. In the horizontal canal, the taller ends of the bundles point away from the utricle. Flow of endolymph (relative to the head) toward the ampulla—ampullopetal flow (from Latin petere, to seek), therefore excites the horizontal canal afferents, and flow of endolymph away from the ampulla—ampullofugal flow (from Latin fugere, "to flee")—inhibits these afferents. Thus, relative to the head, endolymph flow toward the ampulla occurs when the head is turning in the plane of the horizontal canal toward the same side.

The vertical canals, however, have the opposite pattern of hair cell polarization. The taller ends of the bundles point away from the utricle, so that flow away from the ampulla (ampullofugal) excites their afferents. For the left anterior canal, whose ampulla is at its anterior end, turning toward the head up and rolling it to the left in the plane of the left anterior canal results in relative endolymph flow that is ampullofugal. For the left posterior canal, whose ampulla is at its posterior end, turning the head up and rolling it to the left in the plane of the left posterior canal moves its endolymph away from the ampulla and excites its afferents. The mirror-image rotations would pertain to the right vertical canals.

Fortunately, keeping track of ampullopetal and ampullofugal flows is unnecessary. Instead, one need only recall that a semicircular canal is excited by rotation in the plane of the canal bringing the head toward the ipsilateral side. For example, the right horizontal canal is excited by turning the head rightward in the horizontal plane. The right anterior canal is excited by pitching the head nose down while rolling the head toward the right in a plane 45 degrees off of the mid sagittal plane. The right posterior canal is excited by pitching the head nose up while rolling the head rightward in a plane 45 degrees off the mid sagittal plane. In the case of each semicircular canal on the right, the rotation exciting that canal brings the head toward the right in the plane of the canal. In the case of the horizontal canals, the nose is turned toward the right. In the case of the vertical canals, the top of the head is rotated toward the right.

It should be obvious by now that a semicircular canal is inhibited by rotation in the plane of the canal toward the opposite side. As described previously, the arrangement of canals is such that when head rotation excites one, it inhibits its coplanar mate. Thus, the rotations explained in the last paragraph would produce inhibition of the left horizontal, posterior, and anterior canals, respectively.

**Clinical Importance**
This principle eliminates the need to memorize the orientations of stereocilia in particular ampullae and whether ampullopetal or ampullofugal flow excites a given canal. In fact, it is easier to deduce the basic anatomy and physiology from this principle than vice versa. For example, rolling the head toward the left and bringing the nose up excites the left posterior canal according to Principle 4. As noted earlier, endolymph flows relative to the membranous canal in a direction opposite to the head rotation. Thus, the left posterior canal is excited when endolymph flows upwards and toward the right in the canal—that is, ampullofugal. The stereocilia of this canal must be polarized with the tall ends away from the utricle. A considerable amount of anatomy and physiology is condensed into this simple principle.

**Principle 5: Any Stimulus That Excites a Semicircular Canal’s Afferents Will Be Interpreted as Excitatory Rotation in the Plane of That Canal**

**Anatomic and Physiologic Basis**
Perhaps because the VOR is critical to the survival of any vertebrate that needs to see and move about its environment, evolution appears to have placed a high premium on maintaining parsimonious and rapid neural connections of head rotational sensors to eye muscles. This allows for optimal performance when the system is working normally. However, by devoting dedicated lines of communication from the canals to the extraocular muscles, nature has effectively made the eyes slaves to the vestibular system. Designed, as it is, to expeditiously and reliably produce the eye movements needed to counter a sensed head movement, the system cannot help but produce those eye movements when the vestibular afferent firing rate changes from some other cause. Likewise, the systems mediating postural reflexes and perception of spatial orientation will respond to pathologic alterations in peripheral vestibular input in the same way that they do to tilting or translational movement. An important point is that the brainstem (and patient) will interpret any change in firing rate from vestibular afferents as indicating head rotation, tilt, or translation that would normally produce that same change in firing rate. Secondary vestibular neurons relay the same misinformation to other reflex control centers and higher areas of conscious sensation. This leads to autonomic and postural disturbances as well as the noxious sensation of vertigo, an illusion of self-motion.

A pathologic asymmetry in input from coplanar canals causes the eyes to turn in an attempt to compensate for the “perceived” head rotation. However, given the mechanical constraints imposed by the extraocular muscles, the eyes cannot continue to rotate in the same direction that the canals command for very long. Instead, rapid, resetting movements occur, taking the eyes back toward their neutral positions in the orbits. The result is nystagmus, a rhythmic, slowly forward–quickly backward movement of the eyes. The quick resetting movements (similar to saccades) are termed quick phases of nystagmus, and the vestibular-driven slower movements are slow phases. Unfortunately, convention dictates that nystagmus direction is described according to the direction of the quick phases, because these are more dramatic and noticeable. However, an important point is that the slow phases are the components driven by the vestibular system. By focusing on the direction of slow phases, one reduces the number of mental inversions required to identify the pathologic canal causing an observed nystagmus. This principle holds almost universally true for brief, unpredictable changes in afferent firing, but not necessarily for persistent stable changes. Fortunately, the nystagmus caused by sustained imbalances in afferent vestibular tone eventually abates as brainstem and cerebellar neural circuitry adapt to the imbalance, as discussed later on (Principle 12). Still, this principle’s explanation of responses to brief changes in labyrinthine activity provides a powerful clinical diagnostic tool in localizing disease processes to individual canals.

**Clinical Importance**

**Posterior Canal Benign Paroxysmal Positional Vertigo**
In the example of PC-BPPV introduced above, we saw how loose otoconia and endolymph flowed in an ampullofugal direction when the affected PC was oriented vertically in the Dix-Hallpike position. From Principle 4, this direction of endolymph flow would excite the PC afferents. From Principle 3, the eye movements resulting from excitation of the PC will be in the plane of that PC. Principle 5 predicts the direction of the slow phases of the nystagmus in this plane. Excitation of the PC afferents will be interpreted as an excitatory rotation of the head in the plane of the PC, and the nystagmus generated would be compensatory for the perceived rotation. For the left PC, excitatory rotation consists of rolling the head toward the left while bringing the nose up. To keep the eyes stable in space, the VOR generates slow phases that move the eyes down and roll them clockwise (with respect to the patient’s head).
The quick phases are opposite; they beat up and counterclockwise with respect to the patient’s head.

**Superior Canal Dehiscence Syndrome**

In another example of a disorder causing isolated stimulation of a single semicircular canal, a young woman complains that exposure of the left ear to loud sound “makes the world flutter up and down.” Applying a loud sound to the left ear through a headphone causes her to develop vertigo and nystagmus. When she is directed to look 45 degrees to her left, one observes that the slow phases of her nystagmus move her pupils up and down. When she looks 45 degrees to her right, the slow phases appear to be cyclotorsional movements of her pupils clockwise (from her perspective). As she attempts straight-ahead gaze, the nystagmus becomes a mixture of these vertical and torsional movements. The examiner must think in a canal-fixed coordinate system and recognize that in each case, the eyes rotate around the same axis, or in the same plane. In this case, the eyes are moving in the LARP plane and in the direction anticipated for excitation of the left anterior canal or inhibition of the right posterior canal. Because only the left ear is receiving the sound stimulus, the problem must lie in the left anterior canal.

This is an example of *superior semicircular canal dehiscence syndrome* causing a *Tullio phenomenon*. Tullio\(^\text{68}\) experimented with sound as a stimulus for the labyrinth in pigeons after he fenestrated their semicircular canals. He observed that this caused eye and head nystagmus in the plane of the fenestrated semicircular canal, another example of Ewald’s First Law. Huizinga\(^\text{69}\) proposed that the fenestra created a third “mobile window” in the labyrinth, in addition to the oval and round windows. This window opens another route for sound pressure dissipation in the labyrinth. This new route is along the affected canal, so endolymph moves through the semicircular canal under the influence of sound or other pressure changes applied to the oval or round windows (Fig. 163-19A). By Principle 5, the fenestrated superior canal exposed to loud sound encodes the resulting endolymph flow as it would a head rotation in the plane of the affected canal and toward the affected side. Superior canal dehiscence syndrome was only recently discovered.\(^\text{70}\) It was the observation of nystagmus just as described here and the line of reasoning presented by Principles 1 to 5 that led investigators to suspect that the superior canal was the source of the nystagmus, which CT scanning confirmed (see Fig. 163-19B).

**Nystagmus during Caloric Testing**

In the caloric test, warm or cool water is irrigated in the external auditory canal. Thermal transfer across the mastoid and eardrum changes the temperature, and therefore density, of the endolymph in the lateral part of the horizontal semicircular canal. That endolymph becomes lighter (by heating) or heavier (by cooling) than the endolymph in the rest of the labyrinth. When the subject is placed supine (with the head up approximately 20 degrees) so as to bring the horizontal canal into a vertical plane, endolymph in the lateral part of the canal made lighter by warming rises toward the ampulla. This is equivalent to the movement caused by turning the head ipsilaterally in the head-horizontal plane. By Principle 4, this maneuver excites that canal. By Principle 5, the compensatory eye movements, the slow phases of nystagmus, are in the horizontal canal plane and toward the contralateral side. The quick phases are directed toward the ipsilateral side. By reverse reasoning, for cool irrigation, the horizontal canal is inhibited, and the quick phases are directed toward the contralateral side. (The mnemonic COWS—cold opposite, warm same—can be used to recall the direction of the beating of the nystagmus.) A major advantage of the caloric test is that unlike rotational tests, it applies a truly unilateral stimulus. Diminished caloric responses on one side often help to localize a hypo-functional labyrinth. More details on the caloric test can be found in Chapter 164, Evaluation of the Patient with Dizziness.

Unfortunately, the caloric test has several disadvantages. Testing predominantly stimulates the horizontal semicircular canal, and little information is provided about other canals and the otolith end organs. Judging from the nystagmus it produces, a caloric stimulus is approximately equivalent to a 5- to 10 degrees/second squared (sec\(^2\)) acceleration to a sustained horizontal rotation of approximately 50 to 100 degrees/second. The nystagmus typically persists in one direction for 120 seconds or longer. A comparable head rotation would be a half-cycle of a sine wave with a period of 240 seconds, or a frequency of 1/240 second ≈ 0.004 Hz. This stimulus is well below the ideal operating range of the semicircular canal (see Appendix). Nevertheless, the caloric test remains one of the cornerstones of vestibular evaluation because it gives information about one labyrinth in isolation, which low-frequency rotational tests cannot do.

**Principle 6: High Acceleration Head Rotation in the Excitatory Direction of a Canal Elicits a Greater Response than the Same Rotation in the Inhibitory Direction**

**Anatomic and Physiologic Basis**

Ewald made a second important observation in his experiments in which he moved endolymph in individual semicircular canals.\(^\text{71}\) Movement of endolymph in the “on” direction for a canal produced greater nystagmus than an equal movement of endolymph in the “off” direction. This observation, Ewald’s Second Law, indicates an excitation-inhibition asymmetry. Excitation-inhibition asymmetries occur at multiple levels in the vestibular system. First, in the hair cells there is an asymmetry in the transduction process. Figure 163-20 shows that in vestibular hair cells there is a larger receptor potential response for stereociliary deflection in the “on” direction than in the “off” direction. A second asymmetry is introduced by the vestibular nerve afferents. Recall that the afferents fire even when the head is at rest, and that this firing is modulated by the hair cell responses to head acceleration after the endolymph and cupula integrate the signal to yield one representing head velocity (Principle 2). Vestibular afferents in mammals...
have baseline firing rates ranging from 50 to 100 spikes/second. Although these firing rates can be driven upwards to 300 to 400 spikes/second, they can be driven no lower than zero. This inhibitory cutoff is the most obvious and severe form of excitation-inhibition asymmetry in the vestibular system. Even in the range in which there is no inhibitory cutoff, responses for some vestibular afferents show excitation-inhibition asymmetry, with excitatory rotation causing a greater change in vestibular nerve afferent firing rate than does an equal and opposite inhibitory rotation. Using galvanic currents to stimulate vestibular afferents independent of their hair cells, Goldberg and coworkers showed that this asymmetry is more marked for irregular afferents.

These peripheral asymmetries may be mostly eliminated in the central vestibular connections because of the reciprocal characteristics of signals from one side compared to another. In fact, such a combination of nonlinear sensors acting reciprocally on a symmetrical pre-motor system can increase the linear range of the vestibular reflexes when both sides are functioning appropriately. However, nonlinearities in the VOR become pronounced when labyrinthine function is lost unilaterally.

**Clinical Importance**

Aw and colleagues demonstrated that rapid passive rotary head movements elicit markedly asymmetrical VOR responses in humans after unilateral labyrinthectomy. These “head thrusts” are unpredictable, high-acceleration (3000 to 4000 degrees/sec²) head rotations through amplitudes of 10 to 20 degrees. When the head is thrust in one of the semicircular canal planes so as to excite the canal on the intact side, the VOR that results is nearly compensatory for the head movement (Fig. 163-21, right panels). By contrast, the head thrust in one of the semicircular canal planes so as to excite the canal on the labyrinthectomy side generated very minimal VORs in the period up to peak head velocity. After approximately 90 msec, the visual system registered the retinal slip and triggered a visually guided eye movement to reset gaze on the target (arrow). AC, anterior canal; PC, posterior canal. (Data from Carey JP, Minor LB, Peng GC, Della Santina CC, Cremer PD, Haslwanter T. Changes in the three-dimensional angular vestibulo-ocular reflex following intratympanic gentamicin for Meniere’s disease. JARO. 2002;3:430.)
the head is completing its movement, and it may take some experience to spot the saccade while the head is still in motion. By contrast, when the head thrust is in the excitatory direction of an intact canal (and nerve), the patient’s gaze remains stable on the examiner’s nose throughout the movement.

The HTT can localize isolated hypofunction of individual semicircular canals. Figure 163-23 shows an example of the quantitative head thrust test applied to all of the canals in a patient with a large (5-mm) dehiscence of the right superior canal. The VOR gain is reduced only for the affected superior canal, probably because large dehiscences allow the brain and dura to completely compress the membranous canal, thereby blocking endolymph motion in the canal. The appearance of such a large dehiscence on computer tomographic (CT) scanning is shown in Figure 163-19B.

Principle 7: The Response to Simultaneous Canal Stimuli Is Approximately the Sum of the Responses to Each Stimulus Alone

This principle allows an intuitive approximation of the direction and magnitude of nystagmus caused by excitation (or inhibition) of any combination of semicircular canals.

Anatomic and Physiologic Basis

From Principle 3 and Principle 4, it should be clear that rotation of the head purely in one of the canal planes produces eye movements in
that canal plane. In reality, few natural head movements align solely with one canal plane, and most rotations stimulate two or even all three of the pairs of canals. How much is each canal stimulated in such a rotation? The motion of the endolymph in each canal (relative to the canal) will determine the degree to which the hair cells in that canal are stimulated. The endolymph motion in each canal is proportional to the component of the head’s rotational velocity acting in the plane of that canal. A convenient way to view this is by the use of vector notation to describe the rotations.

The rotation of an object can be represented graphically with a vector that has direction and magnitude that uniquely describe the rotation. The vector lies along the axis about which the object is rotating. The direction of the vector along this axis is given by the right-hand rule (Fig. 163-24A). If the right hand were wrapped around that axis with the ends of the fingers pointing in the direction of the object’s rotation, the thumb would point in the direction of the arrow of the vector. The length of the vector describes the magnitude of the rotation (e.g., degrees of angular displacement or degrees/second of angular velocity).

Using vector notation, the rotations that maximally excite each of the semicircular canals can be depicted as shown in Figure 163-24B to D. The axis of each of these rotations is perpendicular to the plane of the canal and is called its sensitivity axis. In the case of a head rotation that is not confined along one of these axes, the component of head velocity acting on each of the canals can be determined by graphically projecting the head velocity vector onto each of the sensitivity axes. For example, in Figure 163-24E, a head rotation to the left with the head upright mostly stimulates the left horizontal canal. The component of head rotation operating on the horizontal canal is the projection onto the horizontal canal’s sensitivity axis. However, note that the projections onto the sensitivity axes of the superior and posterior canals indicate an excitatory stimulus acting on the ipsilateral superior canal and an inhibitory stimulus acting on the ipsilateral posterior canal.

Mathematically, the magnitude of the stimulus projected onto the canal’s sensitivity axis is the magnitude of the head velocity vector times the cosine of the angle between the axis around which the head rotates and the sensitivity axis of the canal.

Because the canal planes are approximately orthogonal to each other, the sensitivity axes are also approximately orthogonal. The pattern of activity induced in the ampullary nerves therefore effectively decomposes a head rotation into mutually independent simultaneous components along the sensitivity axes. The actions of pairs of extraocular muscles are similarly combined. The extraocular muscles are arranged in pairs that approximately rotate the eyes around axes in the orbit that parallel the sensitivity axes of the canals. Simultaneous activation of extraocular muscle pairs in proportions similar to the propor-
workers used both cineoculography of eye movements and electromyographic recordings from extraocular muscles in cats while electrically stimulating ampullary nerves alone and in combinations. They observed that even highly nonphysiologic combinations of ampullary nerve stimuli caused eye movements and extraocular muscle activity that could be predicted as the vector summation of responses to each stimulus alone (Fig. 163-25). Individual stimulation of the left semicircular canals caused eye movements that were rightward (for the left horizontal canal), upward and clockwise (for the left anterior canal), or downward and clockwise (for the left posterior canal) with respect to the animal's head. In a canal frame of reference, each of these eye movements is in the plane of the stimulated canal, as predicted by Ewald’s First Law (Principle 3). Simultaneous stimulation of the left horizontal and anterior canals caused eye movements that were rightward, upward, and clockwise. In a canal frame of reference, the axis of these eye movements is a weighted vector sum of the responses of stimulated horizontal and anterior canals. Simultaneous stimulation of the left horizontal and posterior canals caused eye movements that were rightward, downward, and clockwise—that is, around an axis given by the sum of two equal vectors along the sensitivity axes of the horizontal and posterior canals. Simultaneous stimulation of the left anterior and left posterior canals caused eye movements that were clockwise, as would be expected from cancellation of the pitch (up and down) response components when vectors along the sensitivity axes of these two canals are summed. Finally, simultaneous stimulation of all three left canals caused eye movements that were rightward and clockwise, again the prediction from a sum of equal vectors along the sensitivity axes of these canals.

**Clinical Implications**

This last experiment, by Suzuki and coworkers, models what occurs when all of the canals on one side become excited from their baseline firing rates. The slow phase of the observed nystagmus has a horizontal component toward the contralateral side and a torsional component that moves the superior pole of the eye toward the contralateral side. The nystagmus beats to the ipsilateral side both horizontally and torsionally. There is no vertical component to this nystagmus. This irritative nystagmus can be seen when the labyrinth is irritated, for example, early in an attack of Menière's disease, after stapedectomy procedures, and early in the course of viral labyrinthitis.

The same static imbalance in firing rates between sides occurs with unilateral labyrinthine hypofunction. Consider the case of left unilateral labyrinthectomy, in which case all three canals on that side are ablated. Unopposed activity of the right lateral canal contributes a leftward slow phase component. Unopposed activity of the right anterior canal contributes an upward and counterclockwise slow phase component. Finally, unopposed activity of the right posterior canal contributes a downward slow component. These components combine, with the up and down components canceling each other, and with the net result being a leftward and counterclockwise slow phase (rightward- and clockwise-beating) nystagmus.

Quantitative application of this principle has yielded important information about the pathophysiology of vestibular neuritis. Fetter and Dichgans measured three-dimensional eye movements in 16 patients with spontaneous nystagmus 3 to 10 days after the onset of vestibular neuritis. Their spontaneous nystagmus axes clustered between the direction expected from hypofunction of the horizontal canal and the direction expected from hypofunction of the anterior canal on the affected side. Hypofunction of the posterior canal did not seem to contribute to the nystagmus, and head thrusts in the plane of the ipsilateral posterior canal showed preserved function. These investigators proposed that vestibular neuritis is therefore usually a disease of the organs innervated by the superior vestibular nerve—that is, the horizontal and anterior canals and the utricle. In support of this hypothesis is the observation that vestibular-evoked myogenic potentials (VEMPs) (a test of saccular function—see Principle 11) usually are preserved in these patients. Furthermore, the frequent (approximately 21%) occurrence of ipsilateral posterior canal BPPV in these patients makes sense under this hypothesis. Function remains intact in the posterior canal, which can mediate BPPV if damage to the utricle releases otoconia into that canal.
Principle 8: Nystagmus Due to Dysfunction of Semicircular Canals Has a Fixed Axis and Direction with Respect to the Head

Anatomic and Physiologic Basis

The concept of a fixed axis of nystagmus for stimulation of an isolated semicircular canal has already been demonstrated for posterior canal BPPV, under Principle 3. In that case, the eyes always rotated about the sensitivity axis of the affected posterior canal. Having the patient direct gaze orthogonal to and along the sensitivity axis of the posterior canal showed that there was really no change in the direction of nystagmus when considered in the canal-fixed reference frame (despite the dramatic change in the eye-fixed reference frame).

This principle extends that concept to any axis of rotation resulting from stimulation or inhibition of any combination of semicircular canals. Consider again the patient with acute unilateral hypofunction of all of the right semicircular canals. There is relative excitation of all the left canals. As demonstrated previously, the nystagmus will beat toward the left both horizontally and torsionally. Changing gaze direction does not change the leftward direction of the fast phases of this nystagmus. Thus, it is a direction-fixed nystagmus. In general, peripheral nystagmus has a fixed axis and direction.

Clinical Implications

This principle helps to distinguish nystagmus from a peripheral vestibular disorder from nystagmus due to a central disorder. In the case of the latter, the axis or direction of nystagmus may change depending on the direction of gaze. It is important to note that the magnitude of the nystagmus is not fixed depending on gaze. The reason for this is discussed in the next principle.
Principle 9: Brainstem Circuitry Boosts Low-Frequency VOR Performance through Velocity Storage and Neural Integration; Failure of These Mechanisms Suggests Central Pathology

The description of the VOR up to this point has depicted little role for brainstem and cerebellar signal processing, other than passing on the vestibular signals to the appropriate ocular motor nuclei. This “direct pathway” is the classical three-neuron reflex arc. However, the brainstem does more than serve as a conduit for the vestibular afferent signals. An “indirect pathway” through the brainstem circuits also must account for the poor performance of the vestibular endorgans at low frequencies and the need for further integration of the incoming head velocity signal to generate fully compensatory eye movements. The brainstem accomplishes these tasks through processes called velocity storage and velocity-to-position integration. These two processes also lead to several important clinical phenomena, such as post-rotatory nystagmus, post-head-shaking nystagmus, and Alexander’s Law. The last of these is another one of the cardinal signs that differentiates peripheral from central causes of nystagmus.

Anatomic and Physiologic Basis

Velocity Storage

For head rotations at frequencies below approximately 0.1 Hz, the vestibular nerve afferent firing rate gives a poor representation of head velocity (see Appendix). In response to a constant velocity rotation, the cupula initially deflects but then returns back to its resting position, with a time constant of approximately 13 seconds. Thus, nystagmus in response to a constant-velocity rotation would be expected to disappear after approximately 30 seconds (see Fig. 163-10B). The effect of adaptation is to make afferents respond more transiently to static and low frequency cupular displacements. Thus, some canal afferents end up carrying a transient signal in response to low frequency and constant velocity rotations. This signal more closely reflects the rate of change of head velocity—that is, acceleration—that velocity itself.

Despite these tendencies for the peripheral vestibular signals to decay prematurely, experimental observations in humans have shown that the time constant of the decay of the angular VOR for constant velocity rotation is about 20 seconds, longer than would be expected based on the performance characteristics of the canals alone. Neural circuits in the brainstem seem to persevere canal signals, stretching their low-frequency cutoff. The important physiologic consequence of this effect (historically called velocity storage, because it appears to “store” the head velocity information for some period of time) is that it allows the vestibular system to function better at low frequencies. Because of velocity storage, the lower corner frequency of the system is extended to approximately 0.08 Hz. This allows sufficient overlap between the VOR and lower-frequency gaze-stabilizing systems (smooth pursuit and optokinetic nystagmus) to avoid having a region of frequency in which neither system works well.

Robinson proposed that velocity storage could be accomplished by a feedback loop operating in a circuit including the vestibular nuclei. Lesion studies in monkeys suggest that velocity storage arises from neurons in the medial vestibular nucleus (MVN) and descending vestibular nucleus (DVN) whose axons cross the midline.

Velocity-to-Position Integration

A second problem arises in matching the signals coming out of the semicircular canals to those needed to act on the eye muscles. For all eye movements, in order to move the eye, the contraction of an extraocular muscle must not only overcome the force of viscous drag (friction), which is proportional to eye velocity. It also must overcome the elastic restoring force that arises principally from stretch of the antagonistic extraocular muscle with which it is paired. This elastic restoring force is significant, even though the antagonist muscle receives an inhibitory command. This force, analogous to that produced by a spring, is proportional to the eye’s displacement or position. Experimental evidence shows that the oculomotor neurons receive a signal that includes signal components for both the desired eye velocity $\dot{E}(t)$ and the instantaneous eye position $E(t)$:

$$\text{firing rate} = k\dot{E}(t) + \dot{\dot{E}}(t)$$  \hspace{1cm} \text{Eq. 163-12}^{26}

In making a horizontal saccade, for example, a velocity command is generated by an excitatory burst neuron in the paramedian pontine reticular formation (PPRF) (Fig. 163-26). This command is a pulse of neural activity, which is sent along a direct path to the abducens and oculomotor nuclei. Alone, it would provide only the term proportional to desired eye velocity, and the eye would slide back to its neutral position in the orbit without the ongoing pull from the muscle to overcome the elastic restoring force. The ongoing pull from the term proportional to eye position is obtained by way of an indirect path through neurons that mathematically time-integrate the pulse (a transient or phasic command) to yield a step (a tonic command). The final signal carried by the oculomotor neuron is thus a pulse-step (phasic-tonic) signal of the form of Equation 163-12.

For the VOR as well, the oculomotor neurons need to receive both an eye velocity and eye position command (Fig. 163-27). The desired eye velocity $\dot{E}(t)$ is easily obtained; it is simply equal and opposite to the head velocity $H(t)$, a quantity approximately provided by the signals from the semicircular canals. The estimate of eye position $E(t)$ is provided by the brainstem velocity-to-position integrator, which integrates the velocity signal provided by the canals to give an estimate of position. All types of conjugate eye movements—the VOR, optokinetic nystagmus, saccades, and pursuit—are initiated as velocity commands that are passed both directly to the oculomotor neurons and indirectly through this shared neural integrator. This neural integrator likely is a circuit of recurrently connected neurons in which signals reverberate and produce synaptic changes, a form of short-term memory. For horizontal eye movements, the integrating neurons lie in the nucleus prepositus hypoglossi region of the pons. For torsional and vertical eye movements, they lie in the interstitial nucleus of Cajal.\(^{12}\)

Clinical Implications

Pre- and Post-rotatory Nystagmus

Velocity storage is responsible for the prolonged nystagmus that occurs after sustained constant-velocity rotation in one direction (Fig. 163-28). Rotation to one side generates a positive change in afferent firing on the ipsilateral side and a negative change on the contralateral side. The important change is in the excitatory-inhibition asymmetry inherent in the semicircular canal signals (Principle 6), the net result is not zero change in the afferent firing rate sensed by the brainstem, but rather a net excitation on the ipsilateral side. The velocity storage mechanism perseveres this net excitation beyond the time that the cupula deflection has returned to zero (see Fig. 163-10B). The brainstem thus perceives that the head continues to rotate toward the same side, and it generates an angular VOR for that perceived rotation. The slow phases of nystagmus are directed toward the contralateral side, and the fast phases are directed toward the ipsilateral side. This nystagmus decays exponentially as the velocity storage mechanism discharges with the time constant of approximately 20 seconds.

Head-Shake Nystagmus

If the head is rotated side to side in the horizontal plane in normal subjects, the velocity storage mechanism is charged equally on both sides. There is no post-rotatory nystagmus as the stored velocities decay at the same rate on either side. However, nystagmus does occur after head shaking in subjects with unilateral vestibular hypofunction. In the clinical head-shaking test, the examiner passively rotates the subject’s head horizontally at 1 to 2 Hz for 10 to 20 cycles of rotation. Once the rotation stops, the eyes are observed under Frenzel lenses in order to prevent visual suppression of the nystagmus. As the head is shaken from the lesional side toward the intact side, net excitation is stored by the velocity storage mechanism. In fact, the net excitation...
Figure 163-26. The motor command for the saccade originates in the paramedian pontine reticular formation (PPRF) as a pulse of neural firing. This activity is transmitted along a direct path to the ocular motor nuclei as a pulse. The pulse also is integrated into a step of neural discharge and transmitted to the ocular motor nuclei along an indirect path. The final motor signal is thus a pulse-step combination, as required by the dynamics of the eye muscles.

is greater than in normal subjects because there is no inhibitory signal coming from the lesioned labyrinth. When the head is turned and rotated toward the lesioned side, there is no excitatory stimulus sent to the brainstem from that side, and only a small inhibitory stimulus from the intact labyrinth. After multiple cycles of back-and-forth rotation, a marked asymmetry develops in the velocity storage mechanism, one that signals illusory continued rotation toward the intact side. As a result, when the head stops rotating, the nystagmus is as would be expected for continued rotation toward the intact side: The slow phases go toward the lesioned side, and the fast phases toward the intact side. This pattern may even reverse after several seconds, presumably because neurons affected by velocity storage adapt to the prolonged change in firing from their baseline rates.

The head shaking test provides another very useful means of localizing labyrinthine loss, one that complements the information derived from caloric testing and head thrust testing. As noted previously, caloric testing measures the function of an isolated semicircular canal at relatively low frequency. The head thrust test uses rapid, brief rotations with frequency content in the range of 3 to 5 Hz. By providing information about the function of the labyrinth at 1 to 2 Hz, the head-shaking test may provide information not available from the other two tests.

**Alexander’s Law**

The brainstem integrator also manifests characteristic findings in vestibular pathology. In the acute period after loss of unilateral labyrinthine function, the integrator becomes dysfunctional or “leaky.” In part, this may be an adaptive strategy by the brain to minimize nystagmus. As we have already seen, integration of the vestibular signal increases the drive to the extraocular muscles that pull the eye in the direction of the slow phases. By shutting down the integrator, the brain may decrease the slow-phase velocity of nystagmus. However, because the integrator is shared by other oculomotor systems, including the saccadic system, the ability to hold the eye in an eccentric position in the orbit is impaired when the integrator is leaky. As a result, the eyes tend to drift back to the center position in the orbits (Fig. 163-29). This centripetal drift has an important effect on the observed nystagmus. When the eyes look toward the direction of the fast phase of nystagmus, the drift due to the “leakiness” of the integrator adds to the slow-phase velocity due to the vestibular imbalance, and as a result the nystagmus slow-phase velocity increases. However, when the eyes look toward the direction of the slow phase, the centripetal drift due to the leaky integrator subtracts from the slow-phase velocity due to the vestibular imbalance, and the nystagmus slow-phase decreases or may disappear. This observation has come to be known as Alexander’s Law. Although occasionally seen in central lesions, peripheral types of nystagmus generally will obey Alexander’s Law, making it an important neuro-otologic examination finding in distinguishing nystagmus of central origin from that of peripheral origin.

**Interpreting Rotary Chair Tests**

Dysfunction of the neural integrator and velocity storage can also be seen in the results of rotary chair testing. Rotary chair testing may consist of either steps of constant-velocity rotation or sinusoidal harmonic oscillations, typically from 0.01 to 0.6 Hz. Velocity steps may be delivered by suddenly starting the rotation of the chair from zero velocity to a sustained constant velocity in one direction (as in Fig. 163-8B). Alternatively, the equivalent stimulus may be obtained by braking the chair after a prolonged constant velocity rotation in the
Figure 163-27. Signals from the canals also pass through direct and indirect pathways to the ocular motor nuclei. The direct excitatory pathway for the horizontal vestibulo-ocular reflex (VOR) is depicted in detail in Figure 163-15. The indirect pathway through the velocity-to-position integrator provides the final ocular motor signal with a component proportional to eye position. HC, horizontal canal.

Figure 163-28. Per- and post-rotatory nystagmus in a monkey in response to a step of head velocity to 50 degrees/second. While the chair continues to rotate at 50 degrees/second constant velocity, the initial nystagmus decays more slowly than would be predicted based on the cupula’s time constant. After the chair rotation stops, the nystagmus appears again but in the opposite direction. This after-nystagmus also decays more slowly than would be anticipated. The prolongation of the nystagmus after rotation is a manifestation of velocity storage. (Modified from Cannon SC, Robinson DA. Loss of the neural integrator of the oculomotor system from brain stem lesions in monkey. J Neurophysiol. 1987;57:1383.)
The utricle senses linear accelerations that are tangential to some portion of its curved surface. Most of the utricle is approximately in the plane of the horizontal canal, although its anterior end curves upward from this plane. The baseline firing of utricular afferent fibers is therefore best modulated by linear accelerations in the horizontal plane—that is, fore-and-aft or side-to-side. Hair cells in the utricle are polarized such that stereociliary deflections toward the striola excite the hair cells, and deflections away from the striola inhibit them. Because the orientations of the stereociliary bundles vary over the surface of the utricle, the organ’s overall pattern of responses to a given linear acceleration can be quite complex (see Fig. 163-7). Linear accelerations in different directions probably activate unique ensembles of activity in the afferents of the utricle, with some areas being excited and others inhibited. These ensemble responses may encode the direction of head acceleration.17

Excitation or inhibition of all regions of the utricle does not occur under normal conditions of vestibular stimulation. Thus, predicting what the brain will perceive during pathologic conditions resulting in stimulation of the whole utricle is less straightforward than was the case for the semicircular canals, whose hair cells are all polarized in the same direction. However, studies in cats  and monkeys  have demonstrated a 3:1 predominance of afferents arising from the medial aspect of the utricle, which is sensitive to accelerations produced by ipsilateral tilts. Thus, the brain interprets a tonic increase in firing from the utricle on one side as a net acceleration of the otoconial mass toward the ipsilateral side. Conversely, the brain interprets a decrease or loss in firing from the utricle on one side as a net acceleration of the otoconial mass toward the contralateral or intact side.

However, the brain must still decide how to interpret this signal representing a net acceleration of the otoconial mass to one side. Such acceleration could be produced by an ipsilateral tilt or by a contralateral translational movement of the head. There is little physical difference between the shear forces acting on the hair cells of the otolith organs in these two circumstances, but the expected reflexive response of the vestibular system would be quite different depending on the interpretation. If tilt is perceived, then the appropriate compensatory reflexes would be counter rolling deviations of the eyes and head. If translation is perceived, the appropriate reflexes would be horizontal eye movements.

Just how the brain distinguishes utricular signals due to tilt from those due to translation remains one of the ongoing controversies in vestibular physiology. The equivalence of tilt and translation provides the brain a seemingly irresolvable ambiguity in the utricular afferent signals. Nevertheless, the brain is somehow able to correctly resolve the source of the ambiguous stimulus under normal conditions, so that an interaural translation produces horizontal eye movements with little or no roll movements. By contrast, when the same net acceleration acts on the utricles during tilting movements, the eyes counter-roll appropriate to the tilt, but do not turn horizontally as they would for an interaural translation. One way to resolve these different stimuli might be based on the frequency content. Low-frequency or static linear accelerations acting on the otolith organs might be interpreted as gravitational accelerations resulting from tilt, whereas transient linear accelerations might be interpreted as linear translations. An alternative hypothesis is that the central nervous system integrates information from the semicircular canals with information from the otolith organs to distinguish tilts (which also transiently activate canals) from translations (which activate only the otolith organs). In support of this hypothesis, experiments in rhesus monkeys in which the semicircular canals were inactivated by plugging demonstrated that in the absence of canal signals, modulation of otolithic activity by roll tilts led to eye movements that would instead be compensatory for perceived interaural translations. Thus, the brain appears to need the additional signals from the canals to distinguish tilts from translations.

Whether the brain uses the frequency content of the incoming utricular signal or the concomitant signals from the canals, the perception of a static decrease in the firing rates of utricular afferents on one side should be interpreted as tilt toward the opposite side, not translation toward the same side. From the point of view of frequency content, the static nature of the firing rate change would mimic the static (low-frequency) change due to a head tilt. From the point of view of the
Principle 11: Sudden Changes in Saccular Activity Evoke Changes in Postural Tone

Anatomic and Physiologic Basis

The saccule is almost planar and lies in a parasagittal orientation. Hair cells of the saccule, polarized so that they are excited by otoconial mass displacements away from the striola, can sense accelerations fore or aft (along the naso-occipital axis) or up and down. Most afferents from the saccule have a preferred up or down direction.97 Moreover, only the sacculus can sense linear accelerations up or down, whereas nasooccipital accelerations will activate some utricular as well as saccular afferents. Thus, the saccules have a unique role of sensing upward or downward accelerations.

When the head is upright in the gravitational field, the acceleration due to gravity (9.8 m/sec2) constantly pulls the saccular otoconial mass toward the earth. Afferents in the inferior half of the saccule, whose hair cells are excited by this downward acceleration, have lower firing rates and lower sensitivities to linear accelerations than do those afferents in the upper half of the utricle.107 The afferents in the upper half are excited by relative upward acceleration of the otoconial mass, such as might occur when the head drops suddenly, e.g., when one is falling. Thus, sudden excitation of hair cells across the saccular macula probably would be interpreted by the brain as a sudden loss of postural tone, as in falling. The appropriate compensatory reflex would be one that activates the trunk and limb extensor muscles and relaxes the flexors to restore postural tone. Accordingly, the saccular afferents project to the lateral portions of the vestibular nuclei, which give rise to the vestibulospinal tract, in contrast to the utricular afferents, which project more rostrally to areas involved in the VORs.109

Clinical Importance

Saccular excitation probably underlies the test of VEMP’s. VEMPs are transient decreases in flexor muscle electromyographic (EMG) activity evoked by loud acoustic clicks or tones applied to the ear. Sufficiently loud sounds applied to the ear excite saccular afferents.107,108 The predicted reflexive response as noted earlier would include relaxation of flexor muscles. The EMG activity averaged over multiple acoustic stimuli from a tonically contracting flexor muscle will demonstrate a biphasic short latency relaxation potential. The EMG activity can be recorded in many different flexor muscles, but the sternocleidomastoid (SCM) responses have been best described.109 Because the saccule mediates sound-evoked VEMP responses in the normal labyrinth, absence of VEMP responses may indicate saccular dysfunction. However, transmission of the VEMP acoustic stimulus is very sensitive to any cause of conductive hearing loss in the middle ear, and VEMPs are usually absent in the presence of conductive hearing loss. Interestingly, the preservation of VEMP responses in the face of conductive hearing loss implies an abnormally low acoustic impedance of the labyrinth, such as occurs in superior canal dehiscence syndrome110 or with enlarged vestibular aqueduct syndrome.111

Another example of the postural tone changes that may be related to saccular activity is the drop attack. Also known as the “otolithic crisis of Tumarkin,” the drop attack is a dramatic loss of postural tone that can occur in Meniere’s disease independent of other vestibular symptoms at the time of the fall.112 It is not clear what causes the sudden loss of postural tone, but sudden deformations of the saccular macula associated with the hydropic changes of the labyrinth have been invoked.

Principle 12: The Normal Vestibular System Can Rapidly Adjust Vestibular Reflexes in Accordance with the Context, but Adaptation to Unilateral Loss of Vestibular Function May Be Slow and Susceptible to Decompensation

Anatomic and Physiologic Basis

As emphasized throughout this chapter, the vestibular system is efficiently designed to give stereotypical motor reflex outputs that compensate for the movements of the head. Yet a stereotypical output appropriate for one context may be inappropriate for another. For example, redirection of gaze is accomplished by turning first the eyes,
then the head, toward a new visual target. During the gaze shift, there is a period during which both the eyes and head must move in the same direction. The VOR must actually be turned off during this period; otherwise, the eyes would stay fixed on the original target. This cancellation of the VOR is measurable in secondary vestibular neurons as a decrease in VOR gain when gaze is being redirected.113,114 The mechanism by which the VOR can be canceled is not clear, but secondary vestibular neurons may receive “efference copies” of the commands going to the eye muscles. These oculomotor signals may, through inhibitory connections, decrease the responses of secondary vestibular neurons participating in the VOR reflex arc.

Under other circumstances, the VOR gain may need to be increased. For example, when the eyes are verged to view a target near the nose, they must rotate through a larger angle than that fore head rotation, in order to stay on target. In fact, as head rotation brings one eye closer to the target and takes the other eye farther away from it, each eye will require a different VOR gain value. Viirre and coworkers115 showed that the VOR performs as needed under these demanding conditions to stabilize images on the retina, and it appears to do so within 10 to 20 msec of the onset of head movement—faster than could be explained by the use of any visual feedback information to correct the VOR. These investigators suggested that otolith interactions with canal signals could provide a means to constantly update an internal map of the visual target in space, allowing adjustments to the gain of the VOR for each eye.

Other contextual changes in the vestibular reflexes take place more slowly. For example, the VOR gain needs to be adjusted for changes in visual magnification when someone begins wearing spectacles. Long-term changes in vestibular reflexes, a form of motor learning, depend heavily on the cerebellum, specifically the flocculonodular lobe of the cerebellum. The basic wiring of the cerebellum as it relates to the VOR reflex arc is shown in Figure 163–31. The output of the cerebellar cortex comes from Purkinje cells, which have an inhibitory effect on their target neurons in the vestibular nuclei. Purkinje cells have two distinct patterns of activation. Simple spikes occur at high rates and are triggered by inputs from many parallel fibers. These parallel fibers arise from granule cells, which in turn receive inputs from mossy fibers. The latter convey a variety of motor and sensory signals. Input from many parallel fibers, each of which synapses weakly onto Purkinje cells, leads to a high tonic output of simple spikes from the Purkinje cells. By contrast, the climbing fibers from the inferior olive carry sensorimotor error signals—for example, retinal slip. Each climbing fiber makes numerous synapses with the dendrites of a Purkinje cell, so that one climbing fiber has a strong effect on the Purkinje cell. This effect generates complex spikes at low rates. In the classical model of cerebellar learning, repetitive and synchronous activation of climbing fiber and parallel fiber inputs causes a gradual reduction in the strength of parallel fiber synapses onto Purkinje cells—so-called long-term depression.116 In the context of the VOR, weakening the parallel fiber input would diminish the tonic inhibition of the Purkinje cells on the secondary vestibular neurons. The VOR gain would increase as needed to correct the error signal carried by the climbing fibers. It is likely that learning in the cerebellum is much more complex than this, with changes occurring at multiple synapses. An important point is that error signals such as retinal slip may be necessary to drive the motor learning that underlies some compensatory changes in the vestibular system. This phenomenon is the basis for many physical therapy interventions for loss of unilateral vestibular function.

Figure 163-31. Circuitry of the cerebellum involved in modifying the vestibulo-ocular reflex (VOR). Inputs from primary vestibular afferents and secondary vestibular neurons (VN) form mossy fiber (mf) inputs to cerebellar granule cells (gc). Parallel fibers (pf) originating from these synapse weakly with Purkinje cells (Pk), causing a highly tonic inhibitory output of simple spikes from the Purkinje cells onto secondary vestibular neurons controlling the VOR. Climbing fiber (cf) input from the inferior olive (io) carries sensorimotor error information such as retinal slip. Climbing fibers make extensive and strong synapses onto Purkinje cells. Climbing fiber activity leads to complex spikes in the Purkinje cells, which can alter the efficacy of the parallel fibers’ synapses onto the Purkinje cells—a form of learning.
Vestibular compensation requires there to be a stable (although reduced) level of peripheral vestibular function over time. The compensatory mechanisms must also be presented with sensory error signals, and their ability to sense and process these signals must not be compromised. These requirements have three important clinical consequences.

**Clinical Implications**

Vestibular compensation requires there to be a stable (although reduced) level of peripheral vestibular function over time. The compensatory mechanisms must also be presented with sensory error signals, and their ability to sense and process these signals must not be compromised. These requirements have three important clinical consequences.

**Static Loss of Vestibular Function Can Be Compensated, but Fluctuating Loss Cannot**

There are important clinical correlates to the observations that the vestibular system adapts slowly to loss of unilateral function and that changes elsewhere in the CNS or further changes in vestibular function can cause decompensation. Disease states that cause static, stable loss of peripheral vestibular function are typically much less debilitating than are losses than fluctuate over minutes to hours. When there is an acute, fixed loss of unilateral vestibular function, such as after labyrinthectomy, vestibular neuritis, or some cases of viral labyrinthitis, patients typically have several days of vertigo and nystagmus. Most patients with normal contralateral function compensate for unilateral loss remarkably well over 1 to 2 weeks. Spontaneous nystagmus resolves within a few days, although nystagmus induced by head-shaking and lateral gaze toward the contralesional side may persist longer (see Principle 9). Again, it should be emphasized that sudden, rapid head rotations to the ipsilateral (nonfunctioning) side will always cause transient failure of the VOR if there is not recovery of ipsilateral peripheral function (see Principle 6). Within 2 weeks after acute unilateral loss of function, most patients no longer have vertigo at rest, and can walk, although they may require assistance. By 1 month later, most are walking unassisted and returning to normal daily activities.

In contrast to the relatively benign and predictable course after a permanent total unilateral loss of vestibular function, the fluctuating type of loss similar to that seen in Meniere's disease and BPPV can cause intense and debilitating vertigo and nystagmus with each attack. These disorders cause a fluctuating perturbation of peripheral vestibular function on an hour-to-hour or even minute-to-minute basis. The brain simply cannot complete its compensatory work in this time frame, before peripheral function returns to normal. The compensatory mechanisms are effectively faced with a “moving target.”

Perhaps the least symptomatic loss of vestibular function occurs with the slow growth of vestibular schwannomas. As the vestibular nerves are slowly infiltrated or compressed, the brain compensates for the loss of function imperceptibly, and patients may have no symptoms save for the occasional off-balance feeling when turning the head rapidly toward the tumor side—a natural equivalent to the head thrust test. Patients with such loss of peripheral function may have little postoperative vertigo, whereas those with preserved function up until the time that one or both vestibular nerves are cut in removing the tumor often have severe vertigo, nystagmus, and the ocular tilt reaction.130

The disparity between typical responses to stable and fluctuating losses underlies the rationale behind use of ablative therapies such as intratympanic gentamicin, vestibular neuroectomy, and labyrinthectomy for intractable Meniere’s disease. After the initial period of compensation, patients who had previously suffered frequent bouts of vertigo usually have relatively few and tolerable vestibular symptoms, so long as contralateral function is intact and stable (reviewed by Blakley). The difference between stable and fluctuating losses also has diagnostic importance. Because stable vestibular deficits generally do not cause ongoing vertigo, recurrent vertigo in the setting of a well-compensated vestibular loss should be seen as a sign of further fluctuation in vestibular function. This fluctuation may be due to a reactivation of a quiescent disease process such as Meniere’s disease, or the appearance of a new labyrinthine problem. A relatively common example of the latter is occurrence of posterior canal BPPV in 15% to 30% of patients who previously had vestibular neuritis.132,133 As noted in the clinical implications of Principle 7, vestibular neuritis usually involves the superior vestibular nerve and its endorgans, sparing the saccule and posterior canal, which are supplied by the inferior vestibular nerve. It is thought that the damage to the labyrinth can cause release of otococia from the utricle, and that these otococia then settle in the posterior canal, precipitating BPPV. Typical posterior canal BPPV can develop in an ear that had vestibular neuritis even months after the onset of the neuritis.

**The Effect of Suppressive Drugs on Vestibular Compensation**

Patients with the acute syndrome of unilateral vestibular hypofunction are commonly given medications to alleviate their distressing symptoms: benzodiazepines (e.g., diazepam), anticholinergic agents (e.g., meclizine), and antiemetic agents (e.g., promethazine). Although these drugs are invaluable for the acute relief of these distressing symptoms, they can be counterproductive to vestibular compensation if continued for too long. Recall that central adaptation is partially driven by error signals, the sensory mismatch that occurs, for example, between the vestibular signals and visual signals when the VOR fails. These sensory mismatches cause a sense of vertigo in patients with recent-onset unilateral hypofunction as they begin moving once the static symptoms have abated. Suppressing this vertigo with the continued use of some medications can prolong or even prevent vestibular compensation. Studying the effects of medications on vestibular compensation after unilateral labyrinthectomy in cats, Peppard134 found that the commonly used vestibular symptom suppressants diazepam, scopolamine and dimenhydrinate could hinder the rate and extent of compensation. Meclizine probably has similar effects. Conversely, a combination of a stimulant (amphetamine) and a general antiemetic (trimethobenzamide) had a beneficial effect in enhancing compensation, perhaps because increased physical activity corresponded to more head movements that challenged the system and drove compensation.

**The Basis of Vestibular Rehabilitation**

A variety of rehabilitation regimens have been constructed around the principle that vestibular compensation is driven by sensory mismatches, particularly between the visual and vestibular systems. Not only do these mismatches drive changes in the gain of remaining vestibular reflexes, but they also engender compensatory changes in other motor systems to replace lost vestibular functions. Examples are the central preprogramming of eye movements and of postural responses, the potentiation of the cervico-ocular reflex, and modification of saccadic eye movements. Sensory substitution of visual and somatosensory cues for the lost vestibular cues may also contribute to overall compensation.135

Although controlled studies of vestibular rehabilitation are difficult to perform, these programs generally do improve the subjective sense of balance in persons with fixed loss of vestibular function and often improve their objective performance on balance tests, as well as returning them to many of their activities of daily living.136-138

**Appendix**

Experimental and clinical vestibular tests often employ sinusoidal head rotations at different frequencies as stimuli, and report results in terms of VOR gain, phase, and time constant. These terms describe the frequency response of the system. The concept of the frequency response of a system is familiar to anyone who has used a graphic equalizer on a stereo system (Fig. 163-32A). Setting the sliders determines how much attenuation of the incoming signal is applied to each frequency range. The Bode plot for a system is a graph of the magnitude of the frequency response versus frequency and is commonly used to derive the frequency response—the Bode plot—for the semicircular canal.

Equation 163-8, which describes the movement of the cupula, can be written as

\[ \Theta(t) = \frac{H(t) - B \Theta(t) - K \Theta(t)}{I} \]

Eq. 163-13
This differential equation is expressed as a function of time, or in the time domain. Although it can be solved as a function of time, our principal interest is to determine this system’s frequency dependence. Thus, it is useful to transform this equation into the frequency domain. The French mathematician Laplace (1749-1827) devised a method to transform differential equations in the time domain to algebraic equations. Transfer functions, which describe the input-output characteristics of systems across frequencies, are fundamental to the study of the auditory system in the form of a transfer function. Thus, it is useful to transform this equation into the frequency domain. Using these features, Equation 163-13 can now be written in the frequency domain:

\[ \mathcal{L} \{ f(t) \} = \int_0^\infty e^{-st} f(t) \, dt, \text{ where } s = \sigma + j\omega. \]  

Eq. 163-14

The Laplace transform essentially converts signals that vary in time into those that vary in frequency by using complex exponentials. This works because most natural signals can be represented as some combination of functions that have exponential growth or decay and sinusoidal oscillations. Equations of the form \( F(t) = Ae^{\sigma t} \) describe exponential growth or decay. Those of the form \( F(t) = Ae^{\sigma t}\cos(\omega t) \) or \( F(t) = Ae^{\sigma t}\sin(\omega t) \) describe sinusoidal oscillations, because

\[ Ae^{\sigma t} = A(\cos(\omega t) + j\sin(\omega t)). \]  

Eq. 163-15

Thus, the complex exponential term \( e^{j\omega t} \) encompasses most signals.

The following two features of the Laplace transform make it of such practical use in converting differential equations to algebraic ones. If \( L\{f(t)\} = F(s) \),

1. \[ L\{f(t) - Y(0)\} = sY(s) - Y(0) \]  

Eq. 163-16

That is, the Laplace transform of a derivative is just \( s \) times the Laplace transform of the function, minus the value of the function at time zero. The value at time zero often is 0. Thus, differentiation in the time domain becomes multiplication by \( s \) in the frequency domain.

2. \[ \mathcal{L} \{ \int_0^t Y(s) \, ds \} = \frac{Y(s)}{s} \]  

Eq. 163-17

That is, the Laplace transform of an integral is just the Laplace transform of the function divided by \( s \). Thus, integration in the time domain becomes division by \( s \) in the frequency domain.

Combining the different constants gives

\[ \frac{\Theta(s)}{H(s)} = \frac{\tau_1 \tau_2}{(\tau_1 s + 1)(\tau_2 s + 1)} \]  

Eq. 163-20

where \( \tau_1 \tau_2 = \frac{1}{K} \) and \( \tau_1 + \tau_2 = \frac{1}{I} \). Values for these time constants have been estimated at \( \tau_1 = 0.006 \) second and \( \tau_2 = 13 \) seconds.82

Note that Equation 163-20 gives the desired relationship between the motion of the endolymph (output) and the head velocity (input). This input-output relationship is the transfer function of the semicircular canal. The shown or frequency response of this transfer function relative to head velocity as given in Equation 163-20. Upper and lower corner frequencies (\( f \)) are indicated.

Figure 163-33. Gain (A) and phase (B) plots for the semicircular canal transfer function relative to head velocity as given in Equation 163-20. Upper and lower corner frequencies (\( f \)) are indicated.

That is indeed in phase with head velocity and has a constant gain over a wide frequency range, from approximately 0.012 to 27 Hz. Thus, over this frequency range, the semicircular canal approximately encodes head velocity.

Although this range encompasses most natural head movements, it should be noted that the canal is not a particularly good encoder of head velocity for very low frequency rotations. For example, whereas a slow turn at 0.02 Hz is sensed with little attenuation (1.4 dB below the...
flat midfrequency gain), the phase shift is approximately 32 degrees. This deficiency in the performance of the canals at low frequencies is improved by the central mechanism of velocity storage (see Principle 9).

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We would like to thank Dr. Philip Cremer (Sydney, Australia) for the inspiration to explain vestibular physiology with a few fundamental principles. Principle 4 is directly attributed to him. We also thank Dr. Thomas Haslwanter (Linz, Austria) for comments on the manuscript.

SUGGESTED READINGS

Books

Journal Articles
Goldberg JM, Fernández C. Physiology of peripheral neurons innervating semicircular canals of the squirrel monkey I. Resting discharge and response to constant angular accelerations. J Neurophysiol. 1971;34:635.
The Importance of Vestibular Reflexes
Crawford J. Living without a balancing mechanism. N Engl J Med. 1952;246: 458. (A classic paper describing first-hand the experience of oscillopsia from acute bilateral vestibular loss.)
Vestibular Afferent Physiology
Goldberg JM. Afferent diversity and the organization of central vestibular pathways. Exp Brain Res. 2000;130:277. (This review summarizes decades of research into mammalian vestibular afferent physiology.)
Hightstein SM, Rabbitt RD, Holstein GR, et al. Determinants of spatial and temporal coding by semicircular canal afferents. J Neurophysiol. 2005;93:2359. (This work presents a novel explanation for why some semicircular canal afferents carry head acceleration information, even though endolymph motion in the canal approximates head velocity.)

For complete list of references log onto www.expertconsult.com.

Semicircular Canals
Aw ST, Halmagyi GM, Haslwanter T, et al. Three-dimensional vector analysis of the human vestibulo-ocular reflex in response to high acceleration head rotations. II. Responses in subjects with unilateral vestibular loss and selective semicircular canal occlusion. J Neurophysiol. 1996;76:4021. (This paper lays the quantitative basis for the head thrust test.)
Aw ST, Todd MJ, Aw GE, et al. Benign positional nystagmus: a study of its three-dimensional spatio-temporal characteristics. Neurology. 2005;64:1897. (This paper provides excellent examples of eye movements in the planes of individual semicircular canals.)
Fetter M, Dichgans J. Vestibular neuritis spares the inferior division of the vestibular nerve. Brain. 1996;119:755. (Illustrating Principle 7, this paper demonstrates that the spontaneous nystagmus of vestibular neuritis suggests a predominantly superior vestibular nerve lesion.)
Robinson DA. The use of matrices in analyzing the three-dimensional behavior of the vestibulo-ocular reflex. Biol Cybern. 1982;46:53. (Robinson demonstrates how the anatomic alignment of semicircular canals and extracranial muscles simplifies the computational requirements of the angular VOR, making it the fastest reflex in the body.)

Otolith Organs
Murofushi T, Curthoys IS. Physiological and anatomical study of click-sensitive primary vestibular afferents in the guinea pig. Acta Otolaryngol. 1997;117:66. (This work provides the cellular basis for vestibular sound-evoked myogenic potentials.)
Vestibular Compensation and Adaptation
De Zeeuw CI, Yeo CH. Time and tide in cerebellar memory formation. Curr Opin Neurobiol. 2005;15:667. (This review summarizes recent insights into the molecular mechanisms of cerebellar adaptation of the vestibulo-ocular reflexes.)
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