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This book is dedicated to our families.
Even the most experienced clinical neurologist may need to take a deep breath before attempting to obtain a clear, crisp history from a patient whose chief complaint is “dizziness”. It is no secret that people with neurological symptoms have widely varying conceptions of the meaning of this word. In some patients, even providing hints or clues cannot induce the patient to express precisely the feeling experienced. It may help to suggest key words such as “off-balance”, “spinning sensation”, “light-headedness”, and “faintness”. I have actually had the experience of running through a long series of words to help guide the patient to express his symptoms precisely when, in response to a hint from me, the patient informed me that he meant that he lost his vision briefly! Taking a clear, precise history in a patient such as this is absolutely essential in order to determine whether the problem might be peripheral or central. This will help greatly in focusing the neurological examination and determining which diagnostic studies to request and how to manage the problem. Even when the clinician determines that the problem is either peripheral or central, the list of neurological disorders that might be responsible can be daunting. With all this in mind, it is a pleasure to welcome a new contribution to this interesting and challenging field in the fourth edition of the classic book, Clinical Neurophysiology of the Vestibular System. Dr. Robert Baloh, a senior clinician and renowned investigator famous for his seminal work on the interface between clinical neurology and vestibular physiology, has been an author of all of the previous volumes. He is joined in this new version of the book by Dr. Kevin Kerber, a brilliant young clinical neurologist trained in both neurology and in clinical vestibular neurophysiology.

This edition of the book is divided into four parts: 1. Anatomy and Physiology of the Nervous System, 2. Evaluation of the Dizzy Patient, 3. Diagnosis and Management of Common Neurotologic Disorders, and 4. Symptomatic Treatment of Vertigo. The current volume has been completely reorganized and expanded to cover advances over the past decade. This book includes newly described molecular mechanisms of peripheral and central processing within the vestibular system. There is a lucid, clinically practical review of the key features to assess in the clinical evaluation of the patient to determine the site of the lesion. The discussion of the differential diagnosis of dizziness is clear and complete, and I found the description of bedside tests of vestibular function to be practical and helpful. The clinical sections have been completely updated and expanded with an emphasis on evidence-based medicine, but the book is informative even for the clinical scenarios that are lacking in high-level evidence. The chapter on benign paroxysmal positional vertigo contains guides to the latest treatment maneuvers. This book also contains a strategy for deciding on which drugs to use for symptomatic control of vertigo and for designing a vestibular exercise program. This extremely valuable contribution will be useful to clinical neurologists, otolaryngologists, physiatrists, and general and emergency medicine physicians in practice as well as residents and fellows in these specialties. This book is also a comprehensive basic science source for professionals and trainees in vestibular neuroscience.

Sid Gilman, MD, FRCP
William J. Herdman Distinguished University Professor of Neurology
Director, Michigan Alzheimer’s Disease Research Center
Department of Neurology
University of Michigan
Ann Arbor, MI
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Preface

The purpose of this book is to provide a framework for understanding the pathophysiology of diseases involving the vestibular system. The book is divided into four parts: 1. Anatomy and physiology of the nervous system, 2. Evaluation of the dizzy patient, 3. Diagnosis and management of common neurotologic disorders, and 4. Symptomatic treatment of vertigo. Part 1 reviews the anatomy and physiology of the vestibular system with emphasis on clinically relevant material. Part 2 outlines the important features in the patient’s history, examination, and laboratory evaluation that determine the probable site of lesion. Part 3 covers the differential diagnostic points that help the clinician decide on the cause and treatment of the patient’s problem. Part 4 describes the commonly used antivertiginous and antiemetic drugs and the rationale for vestibular exercises.

This completely reorganized and expanded fourth edition covers the rapid advances that have occurred in the basic and clinical vestibular sciences in the past 10 years. Recent breakthroughs in our understanding of the molecular mechanisms of peripheral transduction and central processing within the vestibular system are reviewed. We discuss the differential diagnosis of dizziness of both vestibular and nonvestibular etiology and demonstrate bedside tests of vestibular function. Videos showing tests and important clinical findings are available online. The chapter on the laboratory diagnosis of vestibular dysfunction has been expanded to include videonystagmography (VNG) and vestibular evoked myogenic potentials (VEMPs). In Part 3, the chapter on benign paroxysmal positional vertigo includes all the latest treatment maneuvers. We emphasize controlled treatment trials whenever available. In Part 4 we provide a strategy for deciding on which drugs to use for symptomatic control of vertigo and for designing a vestibular exercise program for patients with different types of vestibular lesions.

We believe that this book will be useful to all physicians who treat patients complaining of dizziness. It should be particularly helpful for those in the field of family practice, internal medicine, neurology, head and neck surgery, and neurosurgery. We hope that it will encourage students (in both the clinical and basic sciences) to choose neurotology as their field of study, or at least help clinicians to enjoy the evaluation and management of patients with dizziness. Finally, we hope that the information in this book can contribute to efforts to optimize the care of patients.

K. A. K.
V. H.
R. W. B.
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Acknowledgments

Our students and colleagues in Neurology and Head and Neck Surgery provided inspiration. We are grateful to the chairmen of our departments, John C. Mazziotta and David J. Fink, and the major sponsors of our research (National Institutes of Health and Agency for Healthcare Research and Quality) for their continued support. We would also like to thank Krister Brantberg, who provided helpful suggestions for the chapter on the clinical evaluation of hearing.
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PART 1

Anatomy and Physiology of the Nervous System
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Overview of Vestibular Anatomy and Physiology

Chapter 1

PERIPHERAL VESTIBULAR RECEPTORS
Hair Cells
The Macules
The Cristae
Basis of Stimulus Specificity of the Inner Ear Receptor Organs

CENTRAL VESTIBULAR PATHWAYS
Vestibular Nuclei

VESTIBULAR REFLEXES
Horizontal Canal-Ocular Reflex
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The Ocular Tilt Reflex
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MOTION PERCEPTION AND ORIENTATION

PATHOPHYSIOLOGY OF VESTIBULAR SYMPTOMS
CENTRAL COMPENSATION FOR VESTIBULAR LESIONS
SUMMARY

The vestibular system like other sensory systems (i.e., auditory, visual, olfactory, gustatory, and somatosensory) serves the basic function of translating environmental information into biological signals. However, unlike other sensory systems there is usually no conscious awareness of it during routine activities when the system is functioning normally. In fact, the inner ear vestibular receptors were not even recognized until the seminal work of Prosper Meniere in the mid 1800s. Meniere worked in a deaf-mute institute and noticed that many of his patients with hearing loss also had vertigo. Prior to Meniere, vertigo—the most common symptom of vestibular dysfunction—was considered a cerebral symptom, similar to epileptic seizures. The semicircular canals had been identified but were considered to be part of the hearing apparatus. Meniere’s notion that vertigo could result from damage to the inner ear was met with great scepticism. The vestibular system continues to be underappreciated in most comprehensive clinical and basic science medical textbooks.

The vestibular system has a “behind the scenes” role of maintaining spatial orientation and driving reflexes that stabilize vision and balance. To do this, it transforms forces associated with head acceleration and gravity into biological signals that travel directly to motor centers for postural and ocular stability and to the cortex to aid in orientation. When the system functions normally, you have no awareness of these ongoing activities. Unlike the ability to appreciate visual, olfactory, or auditory stimuli, you do not appreciate the function of the vestibular system until something goes awry.

This is not to say that you cannot perceive motion. The vestibular system projects to many areas of the cerebral cortex but unlike other sensory systems there is no primary vestibular cortex that only receives vestibular signals. All cortical neurons that receive vestibular signals also receive other sensory signals, particularly...
visual and somatosensory. It is not possible to determine which signal is responsible for the perceived motion.

An acute malfunction of the vestibular system causes a profound inability to function, leaving one completely disabled because of severe spatial disorientation, imbalance, nausea, and vomiting during the most intense periods. These are some of the most bizarre and incapacitating symptoms in all of medicine. The patient simply cannot navigate the environment because, to the patient, the world is moving as though he is on an unremitting carnival ride. Interestingly, however, a chronic lesion—even a bilateral loss of function—leads to relatively little disability in most patients affected by it. In fact, many patients with a bilateral vestibular loss probably go undiagnosed because of few or mild symptoms that either do not lead to a medical evaluation or are not recognized by physicians. As opposed to gradual hearing loss or visual loss, a gradual vestibular loss can go virtually unnoticed.

Vestibular symptoms pose a great deal of difficulty in clinical medicine. First, patients suffering vestibular symptoms often have difficulty describing the symptoms. Many patients with a vestibular disturbance will simply report “dizziness”—a nonspecific term that can refer to symptoms stemming from cardiac disturbances, a psychological disorder, medication side effects, or many other disturbances. Second, there is much overlap among the symptoms and signs of vestibular disorders, and discriminating among vestibular lesions depends on appreciating rather subtle differences in how the eyes are moving. In fact, most of the examination of the vestibular system involves observing eye movements since the vestibular structures cannot be visualized at the bedside and the most recognizable functions of the vestibular system are manifest by the vestibulo-ocular reflex. Most physicians can recognize nystagmus—a hallmark movement of the eyes reflecting vestibular function—but most physicians do not appreciate that characterizing the pattern of nystagmus can discriminate a benign disorder from a life-threatening disorder. Physicians typically have little training in the basic science and clinical evaluation of the vestibular system, and this in turn results in overuse of tests, misdiagnosis, and underuse of effective treatments.

The purpose of this book, then, is to provide the basic science and clinical training needed to diagnose and treat vestibular system disorders. In this overview chapter, we provide the most salient information regarding the vestibular system. An overview chapter is important because it rapidly and succinctly presents the essential elements that can be periodically revisited. Whenever appropriate the reader is referred to later sections where the material is described in more detail.

PERIPHERAL VESTIBULAR RECEPTORS

The role of the inner ear vestibular receptors in maintaining orientation has remained the same from the earliest organisms in the animal kingdom. A primitive gravity-detection organ, the statocyst, appeared more than 600 million years ago in some bygastrulated animals such as jellyfish, allowing the animal to regulate its static position in space (see Fig. 2–5 in Chapter 2). With the advent of modern fish (about 100 million years ago), the vestibular labyrinth reached its peak of development, and relatively little change has taken place since that time. The basic structure of the three semicircular canals, the utricle, and the saccule is similar in all higher vertebrates. The membranous labyrinths of modern fish lie in the bony chamber of the skull directly behind the orbits. In its subsequent evolution in amphibians, birds, and mammals, the membranous labyrinth is completely surrounded by a bony labyrinth enclosing the periotic space. This space is filled with perilymphatic fluid and suspensory connective tissue acting as a shock absorber. The relative positions of the planes of the three semicircular canals vary from species to species, although in primates they are approximately orthogonal to each other. The shape of each semicircular canal also varies considerably from that of a triangle in reptiles to an ellipse in birds to an almost true circle in mammals.

Hair Cells

The basic element of the labyrinthine receptor organs that transduces mechanical force to nerve action potentials is the hair cell. Already developed in the statocysts of invertebrates, this specialized sensory cell becomes more
sophisticated in mammals. Transducer cells are surrounded by supporting cells in specialized areas in the walls of the sensory epithelium. Two types of hair cells occur in birds and mammals (Fig. 1–1). Type II cells are cylindrical, with multiple nerve terminals at their base, whereas type I are globular or flask shaped, with a single large, chalice-like nerve terminal surrounding the base. A bundle of nonmobile stereocilia protrudes from the cuticular plate on the apical end of each hair cell. The height of the stereocilia increases stepwise from one side to the other, and next to the tallest stereocilia a thicker, longer cilia, the *kinocilia*, protrudes from the cell’s cytoplasm through a segment of the cell membrane lacking a cuticular plate. The tips of the cilia are connected by *tip-links* that open and close mechanosensory channels (Fig. 1–1; also see Fig. 2–12 in Chapter 2).

The adequate stimulus for hair cell activation is a force acting parallel to the top of the cell,
resulting in bending of the cilia (a shearing force). Force applied perpendicular to the cell surface (a compressional force) is ineffective in stimulating the hair cell. The stimulus is maximum when the force is directed along an axis that bisects the bundle of stereocilia and goes through the kinocilium (Fig. 1–1, insert). Deflection of the cilia toward the kinocilium opens the mechanosensory channels at the tips causing an influx of potassium and depolarization of the resting membrane potential. This opens voltage-gated calcium channels at the base and releases neurotransmitter (mostly glutamate) activating the afferent nerve terminals. Bending of the cilia in the opposite direction produces the reverse effect (closing of the channels and hyperpolarization of the hair cells).

Much of the basic information regarding the physiological properties of hair cells and their afferent nerves has been obtained through the study of hair cell systems in nonmammalian species. Analysis of the lateral line organs of amphibians and fish has been particularly informative. The organs consist of groups of hair cells, the neuromasts, aligned in longitudinal rows on the side of the animal’s body and head. A free-standing gelatinous cupula covering the cilia transmits the force associated with water displacement into hair cell deflection, which in turn results in change in firing rate of the afferent nerve. A key observation that has been confirmed in all other hair cell systems is a continuous spontaneous activity of the afferent nerves. A small percentage of the mechanosensory channels remains open at rest, leading to the spontaneous afferent nerve discharge. Depolarization and hyperpolarization of the hair cells’ membrane potential result in modulation of this spontaneous activity (Fig. 1–2). Bending of the cilia toward the kinocilium increases the spontaneous activity, and bending of the cilia away from the kinocilium results in a decrease. The spontaneous firing rate varies among different animal species and among different sensory receptors. It is thought to be highest in the afferent neurons of the semicircular canals of mammals (up to 90 spikes per second). The Macules

The membranous labyrinth forms two globular cavities within the vestibule: the utricle and the saccule. Each cavity contains a separate macule. In the saccule, the macule is located on the medial wall in the sagittal plane; in the utricle, the macule is mostly in the horizontal plane next to the opening of the horizontal semicircular canal (Fig. 1–3C). The surfaces of the utricular and saccular macules are covered by the otolithic membrane, a structure consisting of a mesh of fibers embedded in a gel with a superficial layer of calcium carbonate crystals, the otoconia (Fig. 1–3A). The stereocilia of the macular hair cells protrude into the otolithic membrane. The striola, a distinctive curved zone running through the center, divides each macule into two parts. The hair cells on each side of the striola are oriented so that the kinocilia are in opposite directions (as indicated by the arrows in Fig. 1–3C). In the utricle, the kinocilia face the striola, and in the saccule, they face away from it. Because of the different orientation, displacement of the otolithic membrane has an opposite effect on the set of hair cells on each side of the striola.

The density of the otolithic membrane overlying the hair cells of the macules is much greater than that of the surrounding endolymph, owing to the presence of the calcium carbonate crystals. The weight of this membrane produces a shearing force on the underlying hair cells that is proportional to the sine of the angle between the line of gravitational force and a line perpendicular to the plane of the macule (Fig. 1–3B). During linear head acceleration tangential to the surface of the receptor, the force acting on the hair cells is the result of the two forces: one in the opposite direction of the head displacement and the other in the direction of gravitational pull. Recordings of afferent neuronal activity from the macules of primates confirm that the utricular and saccular macules are responsive to static tilt and dynamic linear acceleration forces (see Fig. 3–6 in Chapter 3). The Cristae

The cristae are the receptor organs of the semicircular canals. The semicircular canals are aligned to form a coordinate system. The horizontal canal makes a 30-degree angle with the horizontal plane, and the vertical canals make 45-degree angles with the frontal plane (Fig. 1–4C). At the anterior opening of the
horizontal and anterior semicircular canals and the inferior opening of the posterior canal, each tube enlarges to form the ampulla. The crista, the sensory epithelium composed of hair cells and supporting cells, crosses each ampulla in a direction perpendicular to the longitudinal axis of the canal (Fig. 1–4A). Hair cells are located on the surface of the crista, with the cilia protruding into the cupula, a gelatinous mass that extends from the surface of the crista to the ceiling of the ampulla, forming a watertight seal.

The hair cells in each crista are oriented with their kinocilia in the same direction. In the horizontal canal, however, the kinocilia are directed toward the utricular side of the ampulla, whereas in the vertical canals the kinocilia are directed toward the canal side of the ampulla. This difference in morphological polarization explains the difference in directional sensitivity between horizontal and vertical canals. The afferent nerve fibers of the horizontal canals increase their baseline firing when endolymph moves toward the utricle and
ampulla (ampullopetal flow), but the afferent nerves of the vertical canals increase their baseline firing rate with endolymph flow away from the ampulla (ampullofugal flow).

Since the cupula has the same specific gravity as the surrounding endolymph, it is not subject to displacement by changes in the line of gravitational force. The forces associated with angular head acceleration displace the cupula and bend the hair cells of the crista, however. The motion of the cupula can be likened to that of a pendulum in a viscous medium. Sudden displacement of the cupula by a step change in angular velocity is followed by a gradual exponential return of the cupula to its baseline position (Fig. 1–5). The rate of return (time constant, $T_c$) is determined by the ratio of the viscous drag coefficient of the endolymph to the elasticity coefficient of the cupula according to the pendulum model (see Chapter 2).

Precise measurements of primary afferent nerve activity originating from the cristae of animals during physiological rotatory stimulation reveal that the change in frequency of action potentials is approximately proportional to the deviation of the cupula as predicted by the pendulum model. For example, during sinusoidal head rotation in the plane of a semicircular canal, a sinusoidal change in firing frequency is superimposed on the rather high resting discharge (about 90 spikes per second in the squirrel monkey). The peak firing rate occurs at the time of maximum cupular displacement, which occurs at the time of peak angular head velocity. With small-amplitude sinusoidal rotation, the modulation is almost symmetrical about the baseline firing rate. For larger

![Figure 1–3. The macule: (a) anatomy, (b) mechanism of hair cell activation with static tilt, and (c) orientation of saccular and utricular macules. Arrows indicate the direction that the kinocilia point toward. (Adapted from Barber HO, Stockwell CW. Manual of Electronystagmography. CV Mosby, St. Louis, 1976.)](image-url)
Figure 1–4. The crista: (a) anatomy, (b) mechanism of hair cell activation with angular acceleration, and (c) orientation of the semicircular canals within the head. AC, anterior canal; HC, horizontal canal; PC, posterior canal.

Figure 1–5. Rate of return of the cupula to its initial position after a step change in angular velocity (thin solid line) and rate of decay in nystagmus slow phase velocity after the same step change in angular velocity (each blue dot represents a single beat of nystagmus). Note that the nystagmus outlasts the cupular deviation (and afferent nerve activity) due to central velocity storage.
stimulus amplitudes, the response becomes increasingly asymmetrical. The excitatory responses can increase to more than 400 spikes per second in proportion to stimulus magnitude, whereas the growth of inhibitory response is limited to the disappearance of spontaneous activity. This asymmetry in afferent nerve response partially explains the presence of a positive head thrust sign in patients with only one functioning labyrinth (see Chapter 6).

**Basis of Stimulus Specificity of the Inner Ear Receptor Organs**

The inner ear receptors all work on the same basic principal: activation of hair cells by an applied external force. The density of the otolithic membrane overlying the hair cells of the macule is greater than that of the surrounding endolymph. The hair cell cilia are embedded in the otolithic membrane and, when displaced, produce a shearing force ($F_t$) on the underlying hair cells that is proportional to the sine of the angle between the line of resulting gravitational vector and a line perpendicular to the plane of the macule. Each macule is bisected by a distinctive curved zone, the striola. Hair cells are oriented in opposite directions on each side of the striola so that displacement of the otolithic membrane has an opposite effect on the set of hair cells on each side of the striola (see Fig. 1–3C).

The hair cell cilia in the cristae of the semicircular canals are embedded in the cupula, a jelly-like substance of the same specific gravity as that of the surrounding fluids. The cupula, therefore, does not exert a force on the underlying crista and is not subject to displacement by changes in the line of gravitational force. The forces associated with angular head acceleration, however, do result in a displacement of the cupula that stimulates the hair cells of the crista in the same way that displacement of the otoliths stimulates the macular hair cells (Fig. 1–4B). However, in the cristae, all the hair cells are oriented in the same direction in the crista surface. All hair cells are either excited or inhibited by motion of the fluid in the canal, but the orientation is different in different semicircular canals.

In the cochlea, the hair cells are mounted on the flexible basilar membrane in the organ of Corti. Covering the organ of Corti and resting over the hair cells is the tectorial membrane, a relatively rigid structure attached to the wall of the cochlea. A small, acoustically induced pressure difference across the basilar membrane causes the organ of Corti and hair cells to vibrate at the frequency of sound. The motion of the basilar membrane has a different effect on the outer hair cells than on the inner. Outer hair cells have their cilia embedded in the tectorial membrane and are directly stimulated as the cilia are displaced in relation to the relatively fixed tectorial membrane, which acts as a hinge. In contrast, the inner hair cell cilia are not embedded in the tectorial membrane but are instead surrounded by endolymph. Their stimulation is produced by the dragging viscous force of the fluid on the cilia. Intracellular recordings in mammalian cochlear hair cells show a difference of phase between the receptor potentials of the inner and outer hair cells as predicted by the difference in the coupling of the cilia to the tectorial membrane. The outer hair cells respond to position and the inner hair cells respond to the velocity of the basilar membrane motion.

In all cases, the effective stimulus to the sensory cells is the relative displacement of the cilia produced by application of mechanical force to their surroundings. Since the mechanical properties of the “supporting and coupling” structures are different, the frequency ranges at which the cilia can be moved by the applied force are different. Because of the great flexibility of the basilar membrane, the range of sound frequencies to which the hair cells in the cochlea are sensitive varies from 20 to 20,000 Hz. In the macules, the otoconia are maximally displaced during constant accelerations such as those associated with steady head displacement. Owing to the characteristics of the restraining viscoelastic forces holding the otoliths to the macule, their motion rapidly diminishes if the linear acceleration changes at a frequency >0.5 Hz. The semicircular canals also respond maximally to constant angular acceleration, but they can respond to changes in angular acceleration as high as 40 to 50 Hz. This frequency limitation is due to the inertial and viscous forces restraining the displacement of fluid and cupula in the narrow semicircular canals.
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Parallel to the separation of receptor organs, afferent nerve fibers differentiate into bundles that maintain independent identity in the internal auditory canal and at the entrance to the brain stem. The afferent nerve from the utricle and horizontal and anterior semicircular canals and some of the nerve fibers from the saccule form the superior division of the vestibular nerve; most nerve fibers from the saccule and the nerve from the posterior semicircular canal contribute to the inferior branch (Fig. 1–6). The afferent fibers from the auditory organ form a separate nerve anterior and inferior to the vestibular nerve to innervate the organ of Corti, the auditory receptor organ. Together these two nerves constitute the eighth cranial nerve and, within them, a system of efferent fibers from the central nervous system (CNS) gates or modulates the activity of the peripheral organs. Phylogenetically, this neural feedback system is already present in gastropods, in which action potentials directed from the brain to the receptors have been recorded.

In comparison with the vestibular sensory organs, central vestibular connections become progressively more complex in higher vertebrates. This complexity accompanies the development of other afferent systems for the maintenance of equilibrium (vision, proprioception) and pathways for interaction of these systems with the vestibular system.

Vestibular Nuclei

The central processes of the primary vestibular neurons divide into an ascending and descending branch after entering the brain stem at the inner aspect of the restiform body (see Fig. 3–1 in Chapter 3). The ascending branch ends either in the rostral end of the vestibular nuclei or in the cerebellum, and the descending branch ends in the caudal vestibular nuclei. None of the primary afferents cross the midline. Four distinct anatomical groups of neurons have traditionally been identified: medial, lateral, superior, and inferior nuclei (Fig. 1–7).

Canal and otolith signals converge on most secondary neurons that receive primary afferent input (Fig. 1–7C). Major connections run to and from the cerebellum, particularly the so-called vestibulocerebellum (uvula, nodulus, and flocculonodular lobes) (Fig. 1–7E). The two sides are connected by reciprocal commissural

Figure 1–6. Innervation of the labyrinth.
pathways most of which originate in the medial nucleus (Fig. 1–7D). Secondary vestibular neurons project to target areas involved in stabilization of gaze and posture, vegetative regulation, and higher cognitive function (Fig. 1–7B).

Vestibular nucleus neurons receive afferent visual and proprioceptive signals in addition to primary vestibular signals (Fig. 1–7A). For example, visual and proprioceptive signals are organized such that movement of the visual surround in one direction excites and inhibits the same neurons that are excited and inhibited by movement of the head and neck in the opposite direction. The vestibular nucleus is therefore not simply a relay station for vestibular signals but rather an important sensorimotor interaction center.

VESTIBULAR REFLEXES

The basic elements of a simple vestibular reflex arc are a hair cell, an afferent bipolar neuron, an interneuron, and an effector neuron (Fig. 1–8). This simple three-neuron reflex arc is already developed in the phylum Mollusca, among which the class Cephalopoda...
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has contributed to many classic anatomic and physiologic studies of gravitational reflexes. Vestibular reflexes have developed further in vertebrates and mammals with the addition of multiple neuronal pathways.

The terminal fibers of the afferent neuron make synaptic contact with the hair cell and transmit nerve signals to neuronal sensory pools on the same side of the CNS (the vestibular nuclei) that contain both excitatory and inhibitory neurons. Besides receiving signals from excitatory first-order neurons from the ipsilateral ear, the excitatory neurons also receive signals from the inhibitory neurons of the contralateral side by way of crossed neural pathways. The output of the excitatory vestibular nuclei interneurons is transmitted to the effector motor pools, which consequently reflect the activity of both ears. The effector neuron, in turn, controls the activity in an appropriate muscle to coordinate orienting behavior.

In 1947, Sherrington noted, “The simple reflex is probably a purely abstract conception because all parts of the nervous system are connected together and no part of it is probably ever capable of reaction without affecting and being affected by various other parts.” The maintenance of body equilibrium and posture in everyday life is a complex function involving multiple receptor organs and neural centers in addition to the labyrinths. Visual and proprioceptive reflexes in particular must be integrated with vestibular reflexes to ensure postural stability. The prominent role of sensory interaction in orientation can already be appreciated in the behavior of gastropods. The invertebrate *Hermissenda* has only rudimentary vestibular and visual receptors, yet the two systems fully interact to control behavior. Afférent signals from photoreceptors in the eye and from hair cells in the statocyst converge on interneurons in the cerebrophoral ganglia, which control a putative motor neuron in each pedal ganglion. Excitation of the motor neuron produces turning of the animal’s foot in the ipsilateral direction, consistent with the animal’s turning behavior toward light. In humans, during most natural head movements, gaze stabilization is achieved by a combination of vestibular, neck proprioceptive, and visual inputs; the interaction can be synergistic or antagonistic. For example, when the vestibular induced eye movements lie in a direction opposite to that required to maintain the desired gaze position, the visual reflexes override the vestibular reflex. The kind of head rotation that would produce compensatory eye movement in the dark does not do so in the light if the subject fixates on a target moving in phase with the head (Fig. 1–9). In this simple example, failure to override the vestibular signal leads to disorientation.

**Horizontal Canal-Ocular Reflex**

The direct pathways from the horizontal canals to the horizontal extraocular muscles deserve particular attention, since the horizontal vestibulo-ocular reflex is the focus of most clinical vestibular testing (Fig. 1–10). The secondary vestibular neurons lie in the medial and lateral vestibular nuclei. The more medial group of excitatory neurons projects to the contralateral abducens nucleus, while the more laterally located excitatory neurons (in the medial part of the lateral nucleus) project to ipsilateral
Figure 1–9. Eye movement induced in a normal human subject by sinusoidal angular acceleration (0.05 Hz, maximum velocity 60°/sec) in the dark and in the light with a target moving in phase with the subject.

medial rectus motoneurons via the *ascending tract of Deiters* (ATD). The ipsilateral medial rectus neurons also receive a strong excitatory input via the *medial longitudinal fasciculus* (MLF) from interneurons in the contralateral abducens nucleus. These interneurons are excited by the same secondary vestibular neurons that excite the abducens motoneurons. The relative contributions to the horizontal vestibulo-ocular reflex of the ATD and MLF excitatory pathways is not entirely clear, but the MLF pathway seems more important since the eyes cannot adduct past the midline if the MLF is sectioned. Inhibitory secondary neurons in the rostral part of the medial vestibular nucleus run directly to the ipsilateral abducens nucleus. Contralateral medial rectus motoneurons apparently do not receive disynaptic inhibition from the horizontal semicircular canals.

In addition to the direct and indirect connection between secondary vestibular neurons and oculomotor neurons, commissural connections between the two vestibular nuclei play an important role in controlling the rotational vestibulo-ocular reflex. Through GABAergic interneurons, secondary vestibular neurons on one side inhibit their counterparts of the opposite side (see Fig. 3–4 in Chapter 3). As will be seen later, the commissural connections are particularly important after unilateral loss of vestibular function since they provide a mechanism for a single labyrinth to control the vestibular nuclei on both sides, thus maintaining a functional vestibulo-ocular reflex.

Because physiological stimuli activate both labyrinths, the horizontal vestibulo-ocular reflex is controlled by a four-way *push-pull mechanism* (Fig. 1–11). For example, physiological stimulation of the crista of the right horizontal semicircular canal excites the left lateral rectus and the right medial rectus and inhibits the right lateral rectus. Because of the symmetry between the labyrinths, the same receptor in the other ear simultaneously diminishes its afferent output, thereby disfacilitating the left medial rectus and right lateral rectus and disinhibiting the left lateral rectus. The end result is contraction of the left lateral and right medial rectus muscles and relaxation of the left medial and right lateral rectus muscles.

**Nystagmus**

When the head is rotated back and forth in the dark in the plane of the horizontal semicircular canals, compensatory eye movements are produced, with eye velocity approximately equal and opposite to the head velocity. This is easily demonstrated in lower animals such as the rabbit, who have few spontaneous eye movements (Fig. 1–12A,B). If the angle of rotation is large, such that it cannot be compensated for by the motion of the eye in the orbit, the slow compensatory vestibular-induced eye movement is interrupted by quick movements in the opposite direction. This combination of rhythmic slow and fast eye movements is called nystagmus. Because of the fast components, the trajectory of the eye motion during the slow components effectively compensates for head rotation as if the eye had unlimited range.

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**Figure 1–11.** Organization of the horizontal semicircular canal-ocular reflex. R – right, L – left.
of motion. If the fast components were removed from the tracings in Figure 1–12C,D and the slow components joined end to end, the resulting sinusoidal eye movement would be approximately equal and opposite in direction to the sinusoidal head movement just as in Figure 1–12A,B. Thus, the quick component of nystagmus is a strategy developed in the brain to increase the functional capabilities of the reflex.

Spontaneous nystagmus occurs after lesions of the labyrinth, the vestibular nerve or the central vestibulo-ocular neurons and interconnecting pathways. The driving force of the spontaneous nystagmus is an imbalance of tonic signals within the vestibulo-ocular pathways. Damage to one labyrinth or its vestibular nerve results in spontaneous nystagmus, with the slow phase directed toward the damaged side; the tonic input from the intact side is no longer balanced by tonic input from the damaged side. This spontaneous nystagmus is similar to nystagmus produced by physiological stimulation of the horizontal semicircular canals (Fig. 1–13; also see Video 6–4). The direction of nystagmus associated with lesions of the brain stem is less predictable, depending on the location and extent of the lesion. Central spontaneous nystagmus can be purely vertical or torsional, since tonic signals for vertical and torsional eye movements run in different tracts from the vestibular nuclei to the oculomotor neurons. By contrast, peripheral spontaneous nystagmus aligns with the planes of the semicircular canals, producing a combination of torsional and linear components. After a complete unilateral peripheral vestibular loss, the nystagmus is horizontal/torsional because the vertical components from the loss of vertical canal input cancel out.

Groups of neurons in the paramedian pontine reticular formation (PPRF) adjacent to the abducens nuclei fire in short bursts just before the onset of horizontal fast components. Pathways interconnect neurons in the vestibular nuclei with neurons in this region of the PPRF, and these neurons project directly to oculomotor neurons and interneurons in the abducens nucleus. Neurons in the PPRF monitor vestibulo-ocular signals and intermittently trigger bursts of firing in the opposite direction mainly based on the eye position in the orbit. During angular rotation, the fast components of the initial beats of nystagmus are larger in amplitude than the preceding slow components so that the eyes deviate in the direction of the fast components. The apparent advantage of this strategy is that the eyes are ready to follow new targets arriving in the field of vision and fixation can be maintained during the subsequent slow component. Unilateral lesions of the PPRF impair ipsilateral rapid eye movements...
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Stimuli that normally would produce nystagmus with ipsilateral fast components simply cause a tonic contralateral deviation of the eyes.

Translational Vestibulo-Ocular Reflexes

Natural head movements consist of a combination of rotation and translation. For images to remain stable on the retina, vestibular reflexes must compensate for both types of movement. Translational movements are sensed by the otolith organs of the inner ear, and compensatory eye movements are generated by the otolith ocular reflexes. Although the rotational vestibulo-ocular reflexes are highly conserved throughout evolution, translational reflexes develop later in frontal-eyed animals with foveal vision. Unlike the rotational vestibulo-ocular reflexes where an equal and opposite eye movement suffices regardless of target distance, the translational vestibulo-ocular reflexes must be scaled to viewing distance to compensate for the fact that the size of the required compensatory eye movement increases as the target moves closer, the so-called motion parallax (see Chapter 3). Furthermore, unlike the rotational vestibulo-ocular reflexes that stabilize images on the entire retina, the translational vestibulo-ocular reflexes only stabilize images on one spatial location in the visual field, usually the fovea. Not surprisingly, there is a close functional relationship between the translational vestibulo-ocular reflexes and the other foveal stabilizing systems, the smooth pursuit and the vergence systems.

The Ocular Tilt Reflex

If a subject is tilted in the roll plane (about the nasal occipital axis), there is a reflex counter-rolling and skewing of the eyes to maintain gaze stabilization (see Fig. 6–7 in Chapter 6). This represents an utriculo-ocular reflex primarily mediated by excitation of the utricle of the dependent ear with synapses in the ipsilateral vestibular nucleus and in the contralateral oculomotor complex in the rostral brain stem. Unlike the translational vestibulo-ocular reflex,
Vestibulospinal Reflexes

At least three major functional roles for vestibulospinal reflexes can be identified.\textsuperscript{49,50} The first is to maintain posture, namely, the upright position in relation to the earth vertical. Vestibular reflexes of this kind induce muscle contractions that produce negative geotropic movement or forces that compensate for steady changes in the direction of the force of gravity. If the pull of gravity on the body were unopposed by forces developed in the muscles, the body would collapse. Reflexes in this category in humans are dependent on the function of the otolith organs but not on that of the semicircular canals. The second role is to produce “kinetic,” or transitory, contractions of muscles for maintenance of equilibrium during movement. This category includes reflexes arising from both the semicircular canals during angular acceleration and the otolithic organs during linear acceleration.\textsuperscript{51} Most natural head movements contain both types of acceleration, and the vestibular reflexes act in combination to maintain equilibrium. A third role of vestibular reflex activity is to help maintain muscular tone, a role in which both the macules\textsuperscript{50} and cristae participate.\textsuperscript{52} The labyrinthine contribution to skeletal-muscle tone can be demonstrated by the change in posture that follows unilateral labyrinthectomy in normal animals.\textsuperscript{53} Tone is increased in the extensor muscles of the contralateral extremities and decreased in the ipsilateral extensor muscles. An even more striking demonstration of the vestibular role in maintenance of muscle tone is the removal of decerebrate rigidity after sectioning of both vestibular nerves or destruction of the vestibular nuclei (see later discussion).\textsuperscript{54,55} The extensor rigidity that results from transection of the nervous system at the caudal end of the mesencephalon is markedly decreased when the tonic labyrinthine input is removed.

The anterior horn cells of the antigravity muscles (extensors of the neck, trunk, and extremities) are under the combined excitatory and inhibitory influence of multiple supraspinal neural centers (Fig. 1–14).\textsuperscript{54} At least in the cat, one finds two main facilitatory centers (the lateral vestibular nucleus and rostral reticular formation) and four inhibitory centers.
(the pericruciate cortex, basal ganglia, cerebellum, and caudal reticular formation). The balance of input from these different centers determines the degree of tone in the antigravity muscles. If one removes the inhibitory influence of the frontal cortex and basal ganglia by sectioning the animal’s midbrain, a characteristic state of contraction in the antigravity muscles results—so-called decerebrate rigidity. The extensor muscles increase their resistance to lengthening and the deep tendon reflexes become hyperactive. As noted earlier, the vestibular system contributes largely to this increased extensor tone since there is a marked decrease upon bilateral destruction of the labyrinths. Unilateral destruction of the labyrinth or the lateral vestibular nucleus results in an ipsilateral decrease in tone, indicating that the main excitatory input to the anterior horn cells arrives from the ipsilateral lateral vestibulospinal tract.

In a decerebrate animal with normal labyrinths, the intensity of the extensor tone can be modulated in a specific way by changing the position of the head in space. The tone is maximal when the animal is in the supine position with the angle of the mouth 45 degrees above horizontal and minimal when the animal is prone with the angle of the mouth 45 degrees below horizontal. Intermediate positions of rotation of the animal’s body about the transverse or longitudinal axis result in intermediate degrees of extensor tone. If the head of the upright animal is tilted upward (without neck extension), extensor tone in the forelegs increases; downward tilting of the head causes decreased extensor tone and flexion of the forelegs. Lateral tilt produces extension of the extremities on the opposite side. These tonic labyrinthine reflexes, mediated by way of the otoliths, seldom occur in intact animals or human subjects because of the inhibitory influence of the higher cortical and subcortical centers; however, they can be demonstrated in premature infants.

Vestibulo-Autonomic Reflexes

The strong connections between vestibular and vegetative centers are apparent based on the prominent vegetative symptoms that accompany vestibular lesions. Nausea and vomiting, diarrhea, perfuse sweating, and fainting can be the predominant presenting symptoms of a vestibular lesion. Animal and human studies have shown that electrical or physiological stimulation of the vestibular receptors alters the activity of sympathetic efferents. Neurons in the caudal vestibular nuclei project to medullary regions known to participate in regulation of blood pressure, heart rate, and breathing; lesions in this region abolish cardiovascular and respiratory responses to stimulation of vestibular afferents. Loss of vestibulocardiac and vestibulovascular reflexes may explain the fainting and near fainting often associated with vestibular lesions. There are also connections from the vestibular nuclei to the locus coeruleus, area postrema, and more centrally to the hypothalamus, amygdale, and limbic cortex that could explain the motion sickness and symptoms of fear and panic that commonly accompany vertigo.

MOTION PERCEPTION AND ORIENTATION

Several important clinical observations support the existence of a specific vestibular sensation. Probably the most convincing is that patients without vestibular function (either on an acquired or congenital basis) do not experience a turning sensation when rotated in the dark if visual and tactile cues are eliminated. In contrast, in patients with the sensation of movement, it is not dependent on vision or associated nystagmus, since blind subjects and patients with complete oculomotor paralysis experience a spinning sensation comparable to that of normal subjects when their vestibular end organs are stimulated. Focal cortical lesions can interfere with spatial orientation and the performance of three-dimensional construction tasks, and epileptic discharges from many different areas of the cortex can be associated with a subjective illusion of movement (usually spinning). These observations imply a cerebrocortical representation for vestibular sensation.

The vestibulocortical pathway via the thalamus is concerned with the control of body position and orientation in space (Fig. 1–15). Thalamic and cortical units that receive vestibular signals are also activated by proprioception and visual stimuli. Most units respond in a similar way to rotation in the dark, or to moving
visual fields, indicating that they play a role in relaying information about self-motion. From a functional point of view, the vestibulothalamocortical projections appear to integrate vestibular, proprioceptive, and visual signals to provide one with a “conscious awareness” of body orientation. Beginning at the vestibular nuclei, a stepwise integration of body-orienting signals occurs, reaching its maximum at the level of the cortex.

**PATHOPHYSIOLOGY OF VESTIBULAR SYMPTOMS**

Much of our knowledge of labyrinthine function was accumulated at the turn of the twentieth century from clinical and experimental observations in humans and animals with unilateral and bilateral lesions of the peripheral labyrinth. At that time, a controversy existed concerning whether the symptoms associated with acute unilateral labyrinthine damage was due to irritation or paralysis of the affected labyrinth. The subsequent discovery of the continuous flow of action potentials in the vestibular nerve at baseline led to the present concept that symptoms are usually caused by an imbalance of the normal resting state activity—that is, by a unilateral decrease in activity.

Symptoms and signs after labyrinthine lesions can largely be traced to asymmetric tone or loss of function within the vestibular reflex pathways (Table 1–1). The magnitude of symptoms and signs depends on (1) whether the lesion is unilateral or bilateral, (2) the rapidity with which the functional loss occurs, and (3) the extent of the lesion. In most experimental animals, simultaneous removal of both labyrinths does not produce severe abnormalities, although vestibular reflex activity is lost and ocular and postural stability is
impaired. Similarly, patients who lose vestibular function bilaterally (e.g., secondary to gentamicin treatment) usually do not complain of vertigo, but they do report visual blurring or oscillopsia with head movements and instability when walking at night (due to loss of vestibulo-ocular and vestibulospinal reflex activity).

In contrast, animals and humans develop severe symptoms and signs following acute unilateral labyrinthectomy. Lower mammals are initially unable to walk and develop head tilt and decreased ipsilateral muscle tone. Nystagmus is prominent, with the slow component directed toward the damaged side and the fast component toward the intact side. These signs abate with time but may persist for months after surgery.

A sudden unilateral loss of labyrinthine function in humans is a dramatic event. The patient complains of severe vertigo and nausea, is pale and perspiring, and usually vomits repeatedly. The patient prefers to lie motionless but can walk if forced to (deviating toward the side of the lesion). Head and ocular tilt and changes in extremity tone occur but less frequently than in lower animals. A brisk, spontaneous nystagmus interferes with vision. These symptoms and signs are temporary, and the process of compensation starts almost immediately. Within 1 week of the occurrence of the labyrinthine lesion, a young patient can walk without difficulty and, with fixation, can inhibit the spontaneous nystagmus. Within 1 month, most patients return to work with few, if any, residual symptoms. If a patient slowly loses vestibular function unilaterally over a period of months or years (e.g., with a vestibular schwannoma), symptoms and signs may be absent.

### CENTRAL COMPENSATION FOR VESTIBULAR LESIONS

In animals immediately after a labyrinthectomy, ipsilateral secondary vestibular neurons lose their afferent input, become silent, and do not respond to ipsilateral angular rotation. At the same time, contralateral healthy secondary neurons lose their inhibitory contralateral input, and their spontaneous activity increases in comparison to normal levels. An imbalance in ocular and skeletal muscle tone takes place, resulting in the clinical signs of labyrinthectomy—nystagmus and disequilibrium. A few days after the labyrinthectomy, the previously silent secondary neurons on the damaged side recover their spontaneous activity and begin to respond to physiologic stimulation of the contralateral labyrinth, the result of their connections through the commissural pathways. Although the responses of secondary neurons on the damaged side are not as intense as those on the normal side, they are qualitatively similar. The recovery of sensitivity in the ipsilateral secondary neurons after a labyrinthectomy parallels the time course of recovery in clinical symptoms and signs.

The genesis of the renewed tonic input to ipsilateral secondary neurons several days after a complete labyrinthectomy is not entirely known. It does not come from the healthy side, since afferent activity on that side does not change. It probably results from changes in ion channels expressed in the cell membrane, from the sprouting of axons from other sources (e.g., neck proprioceptive), and from up and down regulation of synaptic receptors (particularly GABA receptors) (see Chapter 3).

#### Table 1–1: Symptoms and signs after labyrinthine lesions result from asymmetric tone and/or loss of function within vestibular reflex pathways

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Asymmetric Tone</th>
<th>Loss of Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestibulo-ocular</td>
<td>Spontaneous nystagmus</td>
<td>Head movement dependent oscillopsia</td>
</tr>
<tr>
<td></td>
<td>Ocular roll &amp; skew</td>
<td></td>
</tr>
<tr>
<td>Vestibulo-spinal</td>
<td>Head tilt</td>
<td>Imbalance worse with eyes closed</td>
</tr>
<tr>
<td></td>
<td>Lateropulsion</td>
<td></td>
</tr>
<tr>
<td>Vestibulo-autonomic</td>
<td>Nausea, vomiting, fainting, fear, anxiety</td>
<td>Resistant to motion sickness</td>
</tr>
<tr>
<td>Vestibulo-cortical</td>
<td>Illusion of movement</td>
<td>Decreased motion perception, visual dependency</td>
</tr>
<tr>
<td></td>
<td>Tilt of subjective vertical</td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY

The vestibular system transduces the forces associated with head acceleration and gravity into a biologic signal. The control centers in the brain use this signal to develop a subjective awareness of head position in relation to the environment and to produce motor reflexes for equilibrium, relating these experiences to those of other sensory systems during locomotion. The vestibular system, by means of its receptors for the perception of linear and angular acceleration, plays a central role in orientation.

Inertial guidance systems that control the trajectory of space vehicles include the same basic components: a monitor of displacement based on sensors for linear and angular acceleration, and a central processor that integrates this information, computing the coordinates of the space position. The central processor also maintains a memory of the trajectory and can therefore make appropriate adjustments in course when necessary. Here the similarities of vestibular organs to space vehicle guidance systems end, for they do not explain the complex operational capabilities of the brain in support of the sensory function of orientation. The performance of space vehicles is based upon preprogrammed strategies while the brain can resolve even the most unexpected conflicts. For example, the direction of the vestibulo-ocular reflex can be reversed (i.e., the eyes will move in the same direction as that of the head instead of in the opposite direction) if one wears glasses with reversing prisms for several days or even hours. Patients with vestibular system disorders can adapt rapidly to perturbed disequilibrium. The neuroanatomic and physiologic substrates for this capability are becoming better understood, opening new avenues of research in the study of vestibular function in health and in disease.

REFERENCES


60. Balaban CD. Projections from the parabrachial nucleus to the vestibular nuclei: potential substrates for autonomic and limbic influences on vestibular responses. *Brain Res.* 2004;996:126.


Chapter 2

The Peripheral Vestibular System

TEMPORAL BONE
Tympanic Membrane
Middle Ear
Facial Nerve
INNER EAR (LABYRINTH)
Phylogeny
Structure
Fluid Dynamics
Fluid Chemistry
Blood Supply
Innervation
Embryonic Development
THE HAIR CELL
Morphologic Characteristics
Sequence of Hair Cell Activation

Relationship between the Direction of Force and Hair Cell Activation
Mechanism of Hair Cell Activation
Hair Cell Influence on Afferent Nerve Activity
Signal Processing at the Hair Cell/Afferent Nerve Junction
THE INNER EAR VESTIBULAR RECEPTORS
Anatomy of the Semicircular Canals
Physiology of the Semicircular Canals
Anatomy of the Otolith Organs
Physiology of the Otolith Organs
PRIMARY VESTIBULAR NEURONS
Anatomy of Primary Neurons
Physiology of Primary Neurons
EFFERENT VESTIBULAR NEURONS

TEMPORAL BONE

The ear is divided into three anatomic parts: the external, middle, and inner ear. Except for the auricle and soft tissue portion of the external auditory canal, the ear is enclosed within the temporal bone of the skull.

The temporal bone contributes to the base and lateral wall of the skull and forms part of the middle and posterior fossae. It is divided into four parts: the squamous, tympanic, petrous, and mastoid areas. The petrous portion, or pyramid, contains the sense organs of the inner ear. The seventh and eighth cranial nerves enter the petrous portion through the internal auditory canal; the facial nerve exits via the stylomastoid foramen of the mastoid portion (Fig. 2–1). The internal carotid artery and internal jugular vein enter the skull through the temporal bone, their bony canals forming part of the anteroinferior wall of the middle ear.

The anatomical proximity of these major vessels to the inner ear can explain pulsatile tinnitus in a patient without vascular abnormalities.

A cross section of the temporal bone in Figure 2–2 illustrates the relationship between the three functional parts of the ear. Although the external and middle ear are auditory organs with no direct bearing on vestibular function, a knowledge of their structure, particularly those of the middle ear, is important for understanding diseases involving the inner ear. For example, infection arising in the middle ear can spread directly through its medial wall (oval and round windows) into the inner ear, or it can enter the intracranial cavity by breaking through the roof of the epitympanic recess. The aditus ad antrum interconnects the epitympanic recess with the middle ear by means of air cells throughout the mastoid portion of the temporal bone so that infection beginning in the middle ear can spread to the...