DEAFNESS IN DOGS AND CATS

This book is dedicated to my family, each of whom has made a good life better.

Deafness in Dogs and Cats

George M. Strain
Professor of Neuroscience
Louisiana State University, USA

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CABI
Nosworthy Way
Wallingford
Oxfordshire, OX10 8DE
UK

Tel: +44 (0)1491 832111
Fax: +44 (0)1491 833508
E-mail: cabi@cabi.org
Website: www.cabi.org

CABI
875 Massachusetts Avenue
7th Floor
Cambridge, MA 02139
USA

Tel: +1 617 395 4056
Fax: +1 617 354 6875
E-mail: cabi-nao@cabi.org

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Preface

This book would not have come about without the efforts of the countless dog and cat owners and breeders who time and again encouraged me to return to the research laboratory to determine the causes of deafness in their animals and thereby improve the lives of the many dogs and cats who have been affected by this disability. The work presented in this book was not generated entirely by me – by a long shot – but deafness in animals has been my primary research emphasis for nearly 25 years. The work of others that is presented in this book is a significant part of its content, and the story would not approach completeness without their contributions. Needless to say, any errors of omission or commission in presenting that work are mine alone.

When I began my studies of deafness in the early 1980s – initially in the Dalmatian breed – deafness was mostly a briefly mentioned afterthought in veterinary medicine and veterinary neurology texts, and the number of published research studies could easily be counted. Most of the publications were histological studies in Dalmatians or white cats from a small group of researchers, pursued from the perspective of advancing understanding of deafness in people. Today the picture is quite different, with a widespread awareness of animal deafness being present in the research community, among veterinary professionals, in the dog-breeding community, and in the overall population.

There are no good measures of the overall incidence of deafness in the dog and cat populations. Although more recent registration numbers are not publicly available, individual Dalmatian registrations reported from American Kennel Club records for the years 2000 and 2001 were 3084 and 2139, respectively, and the numbers of litter registrations were 1262 and 764 (Bielski, 2002). Assuming an average litter size of eight (Treen and Treen,

1980), the estimated total registrations for the two years were 13,108 and 8251 Dalmatians. Numbers from February, 2009, show single-month registration rates of 79 dogs and 15 litters (Anonymous, 2009), which would project to 2388 Dalmatians for the year, a drop which reflects a decrease in the breed's AKC popularity ranking from 48th in 2000 to 61st in 2001 and 69th in 2010. Nevertheless, given the 30% prevalence rate (unilateral and bilateral deafness) determined for this breed in several studies in the US, it is likely that at least 3941 and 2467 deaf Dalmatians were born in 2000 and 2001, respectively, in the US. When these numbers are expanded to include the numerous other dog breeds affected by congenital hereditary deafness, expanded further to include other countries where purebred dogs are kept as pets, and then further expanded to cover non-hereditary forms of deafness, it is obvious that deafness affects an inordinate number of dogs. And there are also the cats, where we have fewer data; the numbers that we do have show a smaller, but not insignificant number of affected animals. We do not yet have all of the important answers about deafness, but perhaps the compilation in this one source of so much relevant information will provide guidance for others who are likewise dedicated to the same end of improving the lives of our pets by reducing and eventually eliminating deafness as a health problem. It is also hoped that this volume will also prove informative to those pet owners and breeders wishing to learn more about deafness.

George M. Strain
Baton Rouge, LA
September 30, 2011

Anatomy of the Auditory System

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Cathryn K. Stevens-Sparks

Louisiana State University School of Veterinary Medicine and Comparative Biomedical Sciences, Baton Rouge, Louisiana 70803, USA

The ear is the sensory organ for hearing, balance and equilibrium. This organ can be divided into the outer, middle and inner ear; all of the inner ear structures are contained within the osseous labyrinth, a series of excavations within the temporal bone of the skull. The three components of the ear provide the ability for terrestrial mammals to transform sound pressure waves, i.e. longitudinal waves, into electrical energy. Pressure waves are transformed into mechanical energy in the middle ear, then into pressure waves in the fluid-filled inner ear and into electrical energy in the organ of Corti. This electrical energy is then processed and interpreted by the central nervous system. Sound waves are captured and transmitted to the middle ear by the structures of the external ear. The components of the external ear include the auricle, or pinna, and external auditory meatus, or ear canal, which receive sound waves and guide those to the eardrum, or tympanic membrane. The tympanic membrane separates the external ear from the middle ear. Components of the middle ear include the tympanic cavity and the three auditory ossicles (malleus, incus and stapes) and their associated ligaments and muscles. Components of the inner ear include the organ of hearing, the cochlea, and the organs of equilibrium, the semicircular canal ducts, the utricle and the saccule.

Anatomy of the External Ear

The external ear is comprised of the auricle (pinna) and external auditory meatus (ear canal). The auricle of the ear is shaped like a funnel in many

mammals and its wall contains an elastic auricular cartilage as well as a hyaline annular cartilage. Both cartilages maintain the species-specific shape of the external ear and facilitate movement of the pinna by the auricular muscles. However, a small portion of the external auditory passageway exists within the temporal bone of the skull (Fig. 1.1). In most domestic species, the cartilaginous external ear canal comprises two parts – a vertical and a horizontal part (Fig. 1.2). The vertical part extends ventromedially from the external orifice of the ear and is continuous with the horizontal part, which originates where the vertical part makes a sharp medial bend. The horizontal part extends to the bony external auditory meatus of the temporal bone. The epithelial lining of the ear canal is continuous on the external surface of the tympanic membrane, which is suspended in the bony external auditory meatus by a ring of bone, the tympanic annulus. The auricular and annular cartilages form the auricle and the majority of the ear canal (Fig. 1.3). The auricular cartilage is shaped like an asymmetrical funnel, with its proximal end forming a canal. The free distal end of the cartilage forms the pinna, which serves as a funnel for capturing and concentrating air vibrations or sound waves (Fig. 1.4).

The auricle, or pinna, is the visible portion of the outer ear that varies species-specifically in shape and differs in the fibroelastic cartilage collagen/elastin composition among breeds, resulting in either an erect (small, v-shaped), a semi-erect (lobated) or a non-erect (lop-ear) appearance. The auricle is necessary in sound wave collection and sound localization and guides these pressure waves into the external acoustic meatus. The size and shape of the pinna determines which sound frequencies are collected optimally and also may reduce noise. For example, there appears to be a correlation between increased auricle size and the detection of low-frequency (long-wavelength) sounds (i.e. longitudinal waves in gas/air), allowing the animal to detect sounds from greater distances (Nummela, 2008). The external surface of the auricle is slightly convex and covered by hairy skin, while the internal surface is concave and covered by hairy skin distally. Modified hairy skin with glands that produce earwax (cerumen) is found proximally and extends into the external ear canal. The orientation of the auricle is controlled by skeletal muscles, thus allowing the 'funnel' to be oriented toward the source of sound. Unlike humans, who must turn their head toward the sound source, many mammals can move the auricle of each ear, even independently. The extensive movement of the auricle is permitted by the attachment of a complex set of auricular muscles (Fig. 1.5). These auricular muscles are often considered in groups, rather than individually – there is a rostral auricular group of muscles and a caudal group. The rostral auricular muscles rotate the ear medially and narrow the concave aspect of the erect auricle. The primary function of the caudal auricular muscles is to raise the ear, but this group of muscles also rotates the ear (Heine, 2004). A flat, boot-shaped cartilage is located just rostral and medial to the base of the auricle. This is the scutiform cartilage, which serves as an attachment for

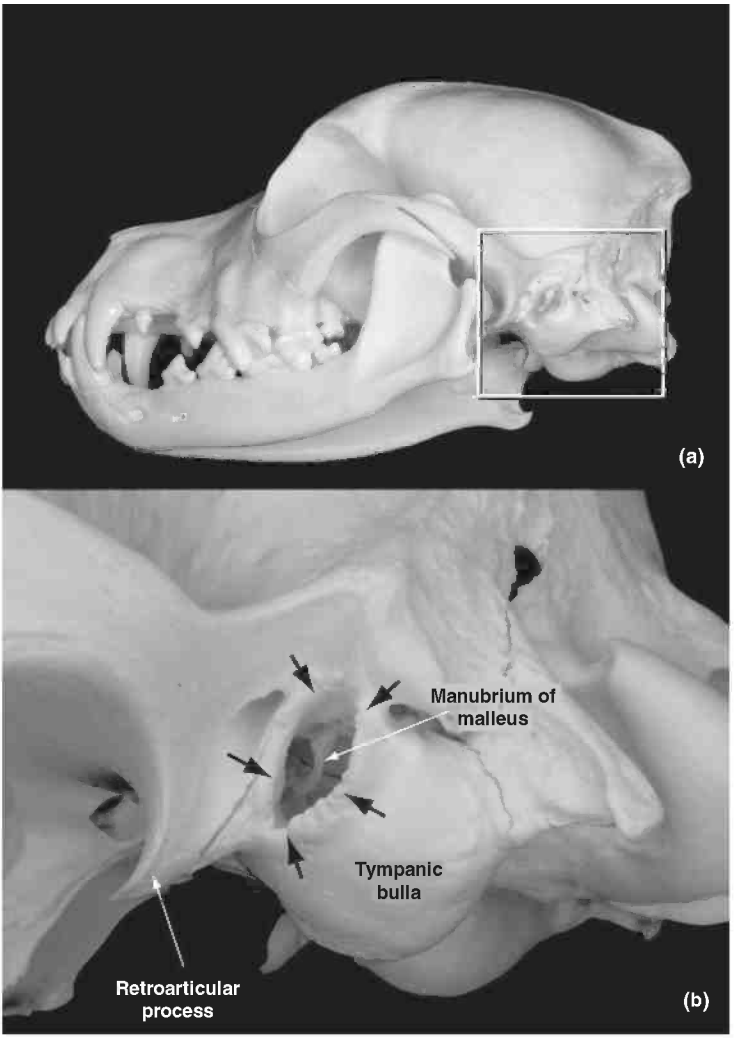


Fig. 1.1. (a) Ventrolateral aspect of the canine skull showing the osseous external auditory meatus and tympanic bulla. (b) Enlarged view of the tympanic region (boxed area in (a)). Margins of the ossified external acoustic meatus are indicated by the black arrows (images courtesy of Dr Daniel J. Hillmann).

many of the auricular muscles to the auricle (Fig. 1.3). This cartilage aids in the redirection of the pull of some of these muscles (Dyce *et al.*, 2010). In addition, a ventral muscle of the auricle pulls the pinna downwards.

The visible portion of the external ear has several regions that provide important surgical landmarks, namely the helix, scapha, anthelix, tragus and antitragus (Fig. 1.3). The helix is the rim of the auricle, whose free margins

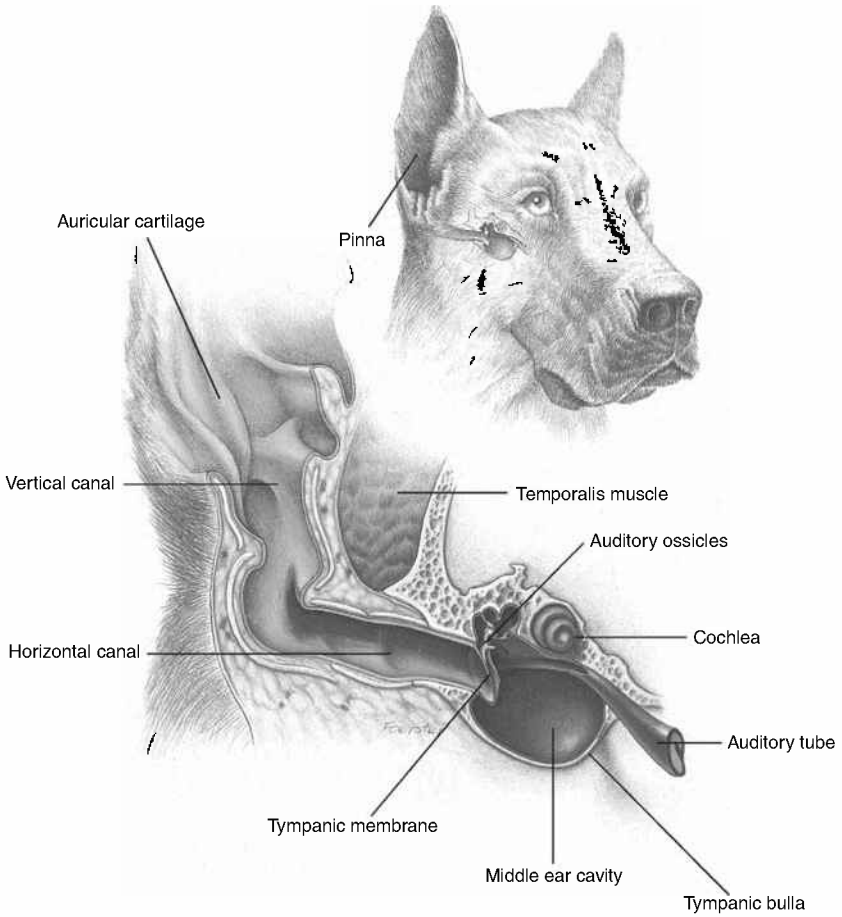


Fig. 1.2. The two components of the external ear canal in domestic species are the vertical and horizontal canals. The horizontal canal originates where the vertical canal makes a sharp medial bend and terminates at the tympanic membrane (reproduced with permission from Hill's Pet Nutrition, Inc.).

face rostrally and caudally in lobated and lop-eared breeds. In cats and dogs with erect, v-shaped auricles, the margins of the helix face cranio-medially and caudo-laterally. Dorsally, the rostral and caudal borders of the helix meet at the apex. The scapha is the triangular portion of the auricle that is bounded by the apex dorsally, the rostral and caudal margins of the helix rostrally and caudally and the anthelix ventrally. The anthelix is a transverse ridge located on the concave surface of the auricular cartilage just distal and medial to the beginning of the ear canal. Opposite to the anthelix, the lateral border of the ear canal is formed by the quadrangular-shaped tragus. A deepened groove, the tragohelicine incisure, separates the tragus from the helix rostrally. The intertragic incisure separates the caudal portion of the

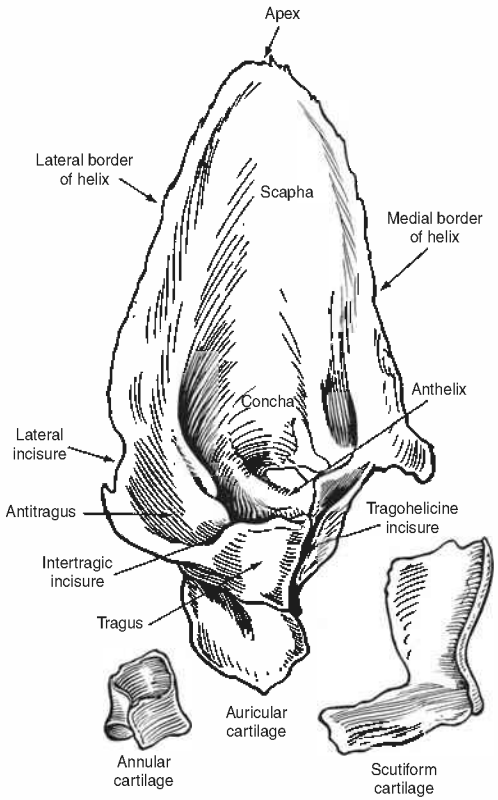


Fig. 1.3. The two main cartilages of the ear are the auricular and annular cartilages. The scutiform cartilage serves as an attachment surface for the auricular muscles. The visible portion of the auricular cartilage has several regions that provide important surgical landmarks (image from MediClip software, Williams & Wilkins Co., Baltimore, Maryland).

tragus from the antitragus. The antitragus forms the caudolateral border of the external ear canal and extends to the lateral incisure. When covered with skin, a cutaneous marginal pouch is formed at this incisure.

The expanded opening of the ear canal is called the concha. The constricted, tubular vertical ear canal continues the concha ventromedially. The vertical ear canal is continued by the horizontal ear canal where the canal makes a sharp, medial bend. Depending on their shape and dimensions, the concha and ear canal will have resonant properties that will selectively amplify certain sound frequencies before they reach the tympanic membrane and middle ear (Rosowski, 1994; Hetherington, 2008). The skin covering of the auricle extends into the ear canal and has all of the characteristics of hairy skin, including sebaceous glands and hair follicles. Ceruminous glands,

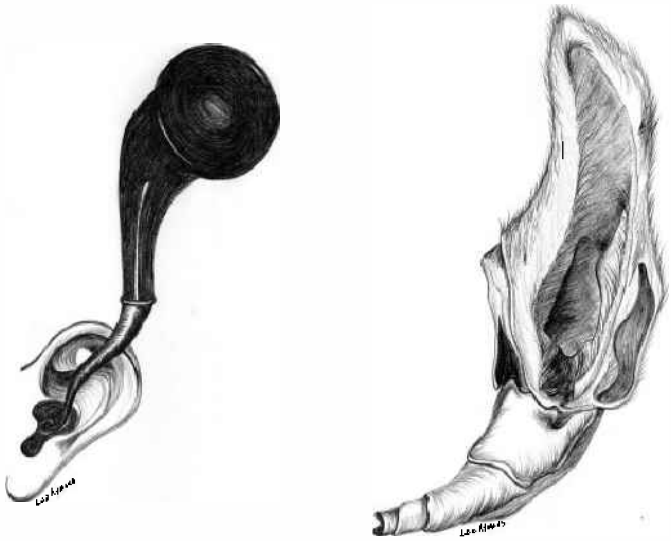


Fig. 1.4. The shape of the canine external ear cartilages can be likened to a vintage ear trumpet, a device used by humans for sound wave collection and amplification. The size and shape of the pinna determines which sound frequencies are collected optimally (drawing by Lee Aymond).

which are modified sweat glands, produce a waxy material called cerumen (ear wax), and are found only within the ear canal. The secretion of ear wax traps small particles and prevents those from gaining access to the innermost depths of the external ear canal. The most common tumors of the external ear canal arise from the ceruminous glands (ceruminous gland adenoma or adenocarcinoma), although proliferation of other cell types may also result in tumors (squamous cell carcinoma, basal cell tumor and mast cell tumor) (Fossum, 2007). Most canine ceruminous gland tumors are benign, but these are more aggressive in cats and are usually malignant (White-Weithers, 2005; Fossum, 2007). The anular cartilage connects the cartilaginous meatus to the bony external acoustic meatus. The external meatus ends at the tympanic membrane, which represents the barrier between the external and middle ear. This membrane not only functions in the transfer of sound waves to the middle ear, but also serves a protective function against pathogen invasion of the middle ear from the external environment. However, aggressive pathogenic infections can cross the tympanic membrane and gain access to the middle ear (Fossum, 2007).

Anatomy of the Middle Ear

The middle ear is located in the air-filled cavity of the temporal bone, whose only direct contact to the external environment occurs by way of the auditory

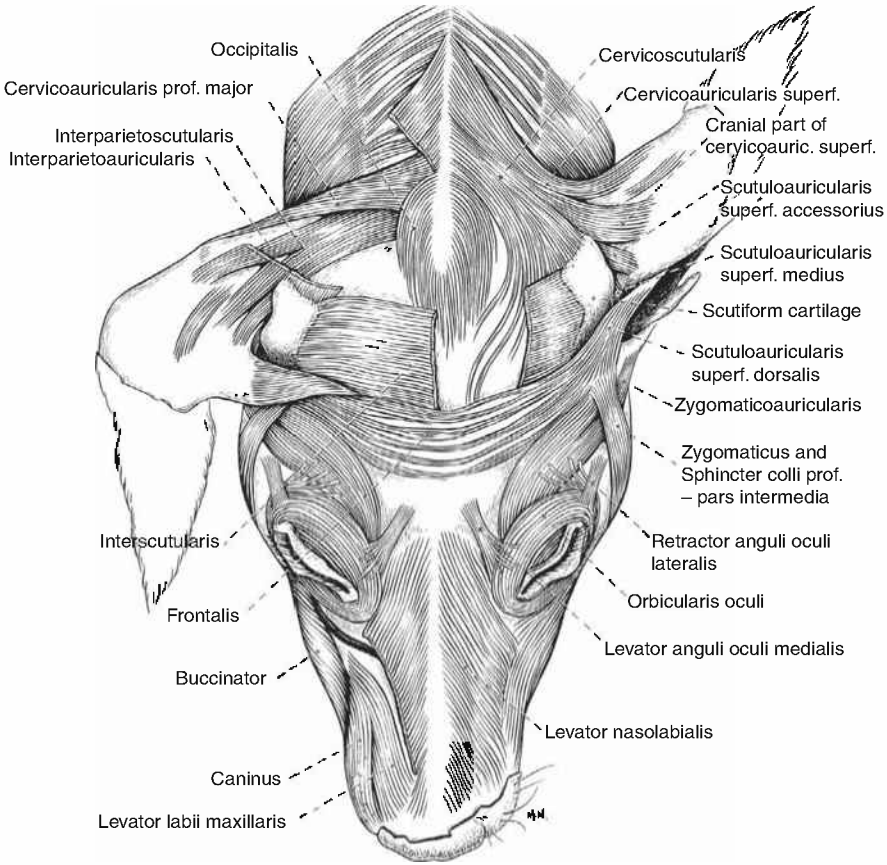


Fig. 1.5. Dorsal view of the cephalic and cervical muscles of the canine. Several muscles attach to the ear by way of the scutiform cartilage. The muscles of the ear are often considered in two groups: the rostral auricular muscles and the caudal auricular muscles (from Hermanson and Evans, 1993; reproduced with permission).

(eustachian or pharyngotympanic) tube. The middle ear is necessary for amplification of sound pressure waves to be transmitted to the inner ear. Additionally, the middle ear muscles, the tensor tympani muscle and the stapedius muscle can limit sound amplification by limiting the movement of the ossicles in order to prevent damage to the inner ear. Without the middle ear as an intermediate, many of the pressure waves being transmitted in air would be reflected at the air/fluid interface at the fluid-filled inner ear due to differences in acoustic impedance within these different media (Nummela and Thewissen, 2008).

The origin of the middle ear is demarcated by the medial surface of the tympanic membrane. The tympanic membrane has two parts, the pars tensa and the pars flaccida. The pars tensa is the tense region of the membrane that is readily visible through an otoscope. The outermost margins of the

membrane are attached to an internal ring of bone, the tympanic annulus, located just inside the margin of the bony external auditory meatus. The external surface of the pars tensa is drawn into a slightly concave profile due to the medial and central attachment of the manubrium of the malleus. The pars tensa is comprised of three layers: an outer epithelial layer, an inner epithelial (mucosal) layer and a middle layer of fibrous connective tissue. The pars flaccida is a small, triangular portion of the tympanic membrane located dorsal to the lateral process of the malleus. Medial to the tympanic membrane is the cavity of the middle ear, also referred to as the tympanic cavity, in the tympanic part of the temporal bone. The middle ear cavity has three regions, the dorsal epitympanum (epitympanic recess), the intermediate mesotympanum (tympanic cavity proper) and the ventral hypotympanum. This hypotympanum is enlarged in dogs and cats as the tympanic bulla (Fig. 1.1). The majority of the tympanic cavity is lined by simple squamous epithelium, which is continuous with the internal layer of the tympanic membrane.

The tympanic cavity houses a chain of three small bones, the ear ossicles, with associated ligaments and muscles (Fig. 1.6). The malleus is the lateral ossicle, named for its resemblance to a mallet; the incus is the middle ossicle, named for its resemblance to an anvil; and the stapes is the medial ossicle, named for its resemblance to a stirrup. The head and neck of the malleus, the incus and the stapes are located in the dorsalmost region of the tympanic cavity, the epitympanic recess. The three ossicles are articulated to each other and to the wall of the tympanic cavity by joints and ligaments. The joints between the ossicles are synovial (diarthrotic) joints. The handle, or manubrium, of the malleus extends ventrally from the neck of the malleus and attaches to the medial surface of the tympanic membrane. If the tympanic membrane is displaced by sound vibrations, the malleus will be moved, and this results in the movement of the incus, which then moves the stapes. The footplate, or base, of the stapes rests on a connective tissue membrane, which is suspended on the edge of the oval window. The base of the stapes is articulated at the oval window by a syndesmosis with the cartilage that covers the edge of the oval window (Getty *et al.*, 1956). This flexible membrane of the oval window serves as a barrier between the cavity of the middle ear and the fluid-filled cavity of the inner ear. The oval window membrane is significantly smaller than the tympanic membrane. Ratios in size of oval window to tympanic membrane range from about 1:10 to 1:60 in vertebrates (Hetherington, 2008). This difference in size allows for amplification of sound, as energy is collected over a relatively large tympanic membrane and converged onto a relatively small oval window. When the ear ossicles are moved, the footplate of the stapes reverberates the membrane covering the oval window, thus displacing the fluids contained within the inner ear.

The malleus has three main parts, the head, the neck and the manubrium (handle) (Fig. 1.6). Three distinct processes project from the neck. The muscular process extends medially from the base of the neck and serves as an attachment for the tendon of the tensor tympani muscle. The rostral process of

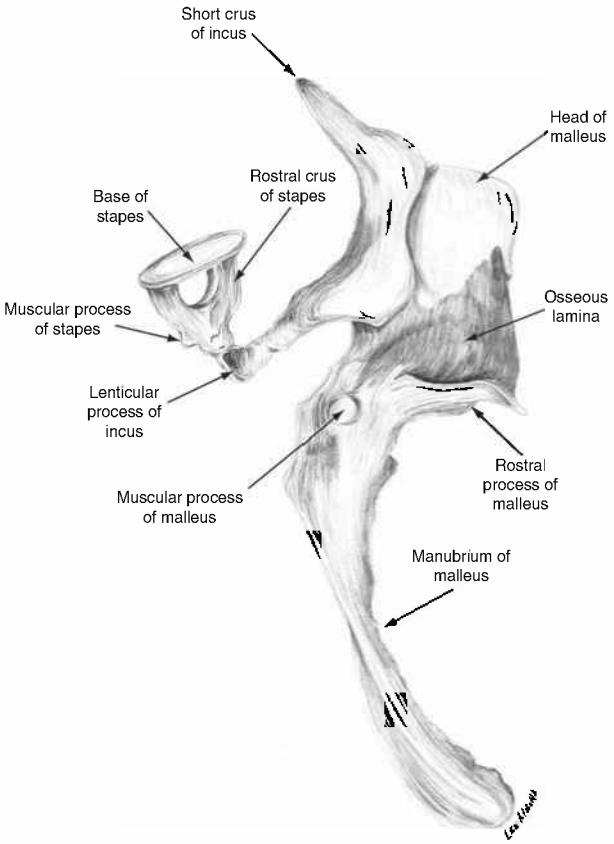


Fig. 1.6. Medial view of the isolated, articulated middle ear ossicles of the left canine ear (drawing by Lee Aymond).

the malleus is located at a 90° angle to the muscular process and serves as the attachment site of the rostral malleolar ligament, which anchors the malleus to the rostral wall of the tympanic cavity, close to the petrotympanic fissure (Fig. 1.7). It is through this fissure that the chorda tympani nerve passes on its course to unite with the lingual nerve (Cranial Nerve V). A thin lamina of bone (osseous lamina) extends between the head and rostral process of the malleus (Fig. 1.6). The lateral process of the malleus extends laterally and is located slightly ventral and at about 180° relative to the muscular process. The lateral process is the attachment site for the lateral ligament of the malleus, which connects the malleus to the tympanic notch, located at the caudodorsal margin of the tympanic annulus. The dorsal ligament of the malleus attaches the head of the malleus to the roof of the epitympanic recess.

The incus is in the middle of the chain of ear ossicles and its structure is compared to that of a premolar tooth with two roots. The body of the incus

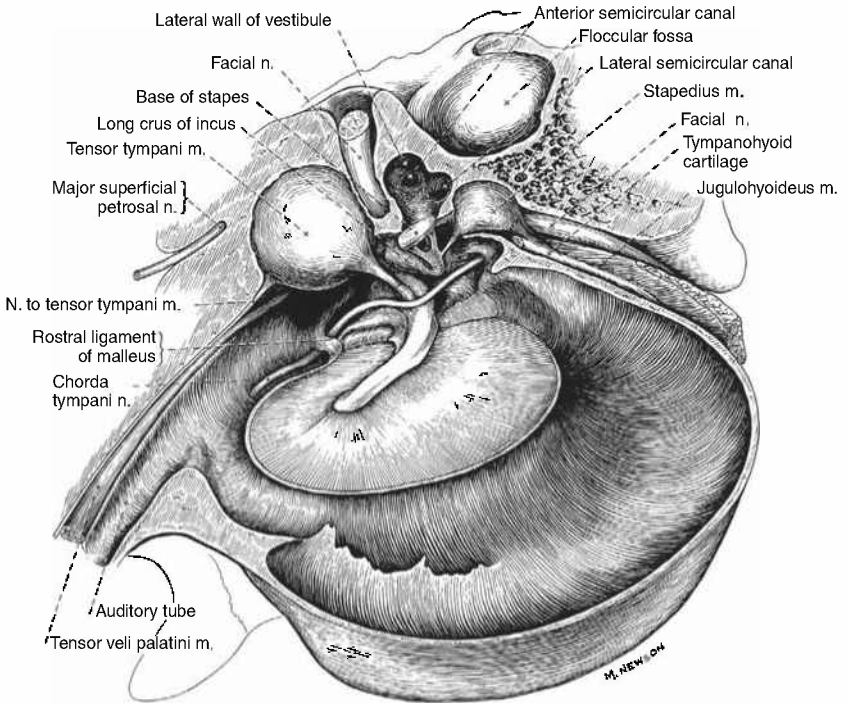


Fig. 1.7. Medial view of the right canine middle ear showing the *in situ* auditory ossicles and their muscles. The cochlea and promontory have been removed (from Evans, 1993a; reproduced with permission).

articulates with the head of the malleus. The crura, or limbs, of the incus are asymmetrical, forming a short crus and an elongated crus. The short crus is directed caudodorsally and is anchored within a fossa caudal to the epitympanic recess (fossa incudis) by the caudal ligament of the incus. The long crus is directed caudoventrally and has a medially directed lenticular process at its distal end, which articulates with the stapes. The dorsal ligament of the incus attaches its body to the roof of the epitympanic recess.

The head of the stapes articulates with the distal end of the lenticular process of the incus. The head is continued by a neck, which has a muscular process for the attachment of the tendon of the stapedius muscle (Fig. 1.7). Rostral and caudal crura extend from the neck and attach to the base, or footplate, of the stapes (Fig. 1.6). The stapes lies in a horizontal plane and its footplate projects medially toward the oval window, which is located on the dorsolateral surface of the bony promontory of the petrous part of the temporal bone (Fig. 1.8). A syndesmosis forms the articulation of the annular ligament of the footplate of the stapes with the cartilage that lines the edge of the oval window.

Atmospheric (air) pressure on each side of the tympanic membrane must be equalized in order to maintain proper tension for optimal vibration of the membrane. Atmospheric pressure is equalized by the fibrocartilaginous auditory (eustachian) tube, which connects the nasopharynx to the tympanic cavity. The left and right auditory tubes extend dorsocaudolaterally from their pharyngeal openings in the lateral wall of the pharynx to the rostrodorsal region of the mesotympanum. The auditory tube passes through a bony canal, the musculotubal canal of the tympanic part of the temporal bone, on its course to the cavity of the middle ear. The mucosal lining in the region surrounding the entry of the auditory tube into the middle ear cavity contains many mucous glands covered by a ciliated epithelium. The ducts of these glands open into the tympanic cavity. Polyps, i.e. benign proliferations of the mucosa, that form in this region can block the auditory tube opening, thereby preventing proper drainage and pressure equalization of the middle ear cavity. Running along the lateral wall of the auditory tube is the elongated tendon of the tensor veli palatini muscle and a branch of CN (cranial nerve) V, which innervates the tensor tympani muscle.

Anatomy of the Inner Ear

The structures of the inner ear are protected by the petrous part of the temporal bone. The internal architecture of the inner ear can be divided into a bony, or osseous, labyrinth and a membranous labyrinth. The osseous labyrinth is an excavation in the petrous temporal bone, which is filled with perilymph fluid. The osseous labyrinth includes the vestibule, semicircular canals and the cochlea. The membranous labyrinth of the inner ear is contained within the osseous labyrinth and is comprised of a continuous network of endolymph (a viscous fluid similar to extracellular fluid)-filled sacs and tubes. The membranous labyrinth includes the utricle, saccule, cochlear duct and semicircular ducts. The membranous labyrinth represents the structures necessary for hearing and equilibrium.

The bony promontory is the ventral expansion of the petrous part of the temporal bone and protrudes into the dorsomedial region of the tympanic cavity proper (Fig. 1.8). This promontory houses the cochlea and the vestibule and is located medial to the flaccid portion of the tympanic membrane (Getty *et al.*, 1956). The round window is an opening from the cavity of the middle ear into the cochlea that is located at the caudal end of the promontory and is covered by the membrane of the round window. The oval window, which is closed by the annular ligament attached to the footplate of the stapes, is located on the dorsolateral surface of the bony promontory and leads into the vestibule of the osseous labyrinth. The membranes that close these two windows separate the middle ear cavity from the cavity of the inner ear.

The vestibule of the inner ear can be thought of as the entryway, or foyer, of the osseous labyrinth of the inner ear. A series of canals extend from this

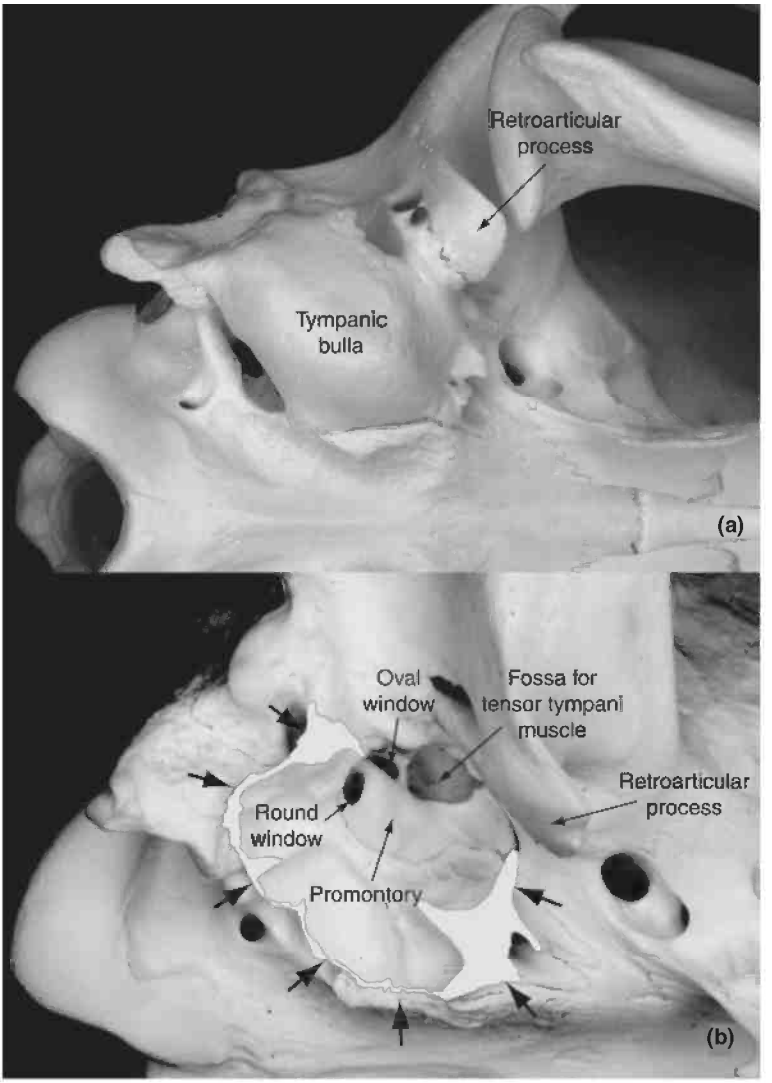


Fig. 1.8. (a) Ventral view of the intact canine right tympanic bulla. (b) Ventrolateral view of the canine middle ear cavity with the ventral part of the tympanic bulla removed, showing the promontory of the petrous temporal bone with affiliated oval and round windows. Black arrows indicate the cut margin of the bulla (images courtesy of Dr Daniel J. Hillmann).

foyer. The canal that runs medially from the central vestibule to the interior of the caudal cranial fossa of the cranial cavity is the vestibular aqueduct. The cochlea is medial and ventral to the vestibule and is directed rostroventrally and slightly lateral (Fig. 1.9). The cochlear canal is spiral in shape and is reminiscent of a snail shell, from which it derives its name (Fig. 1.10). The

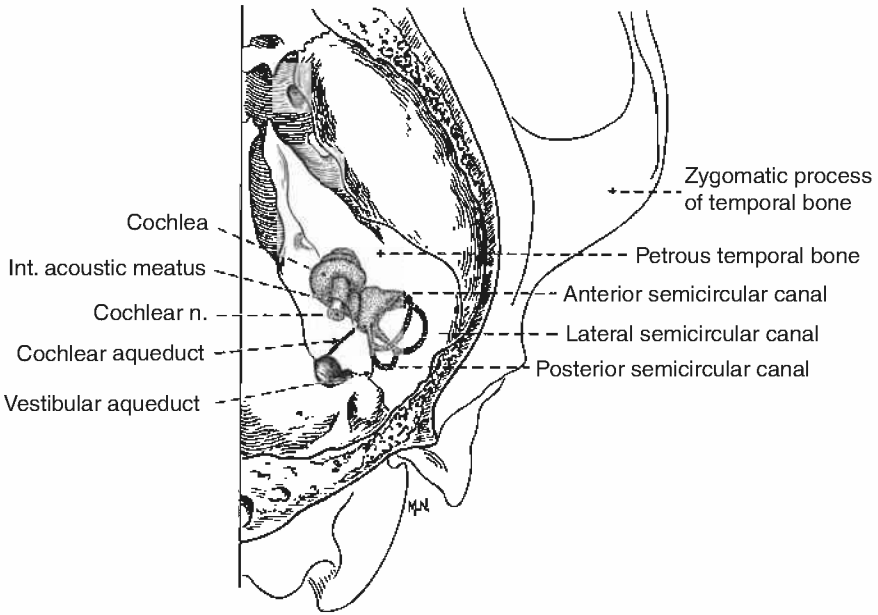


Fig. 1.9. Dorsal view of the canine cranial fossa showing the petrous temporal bone and position of the membranous labyrinth of the inner ear (from Evans, 1993a; reproduced with permission).

central core of the cochlea is supported by a hollow, bony prominence, the modiolus. A thin, hollow, continuous shelf of bone spirals around the modiolus from its base to its apex. This bony spiral lamina extends outward like a shelf from the modiolus toward, but does not completely reach, the walls of the cochlear canal. The cochlear aqueduct is a canal that leads ventrally from the perilymphatic space surrounding the cochlea to the meninges that surround the brain. This canal connects the perilymphatic space, filled with perilymphatic fluid, to the subarachnoid space, which contains cerebrospinal fluid (CSF). The perilymphatic fluid of the osseous labyrinth is absorbed into the CSF by way of this canal. Perilymphatic fluid is a filtrate produced by the periosteal blood vessels of the osseous labyrinth and has the same ionic concentration as extracellular, or interstitial, fluid (Banks, 1993). Caudal and slightly dorsal to the vestibule are three separate canals that tunnel through the petrous bone. These canals are semicircular and are located dorsally, laterally and caudally. Each semicircular canal is located in a plane approximately perpendicular to the other two. The crura are the proximal ends of each canal that communicate with the vestibule. One crus of each canal is dilated, or ampullated, where it joins with the vestibule. The non-ampullated ends of the caudal and dorsal canals form a common crus before joining caudally with the vestibule.

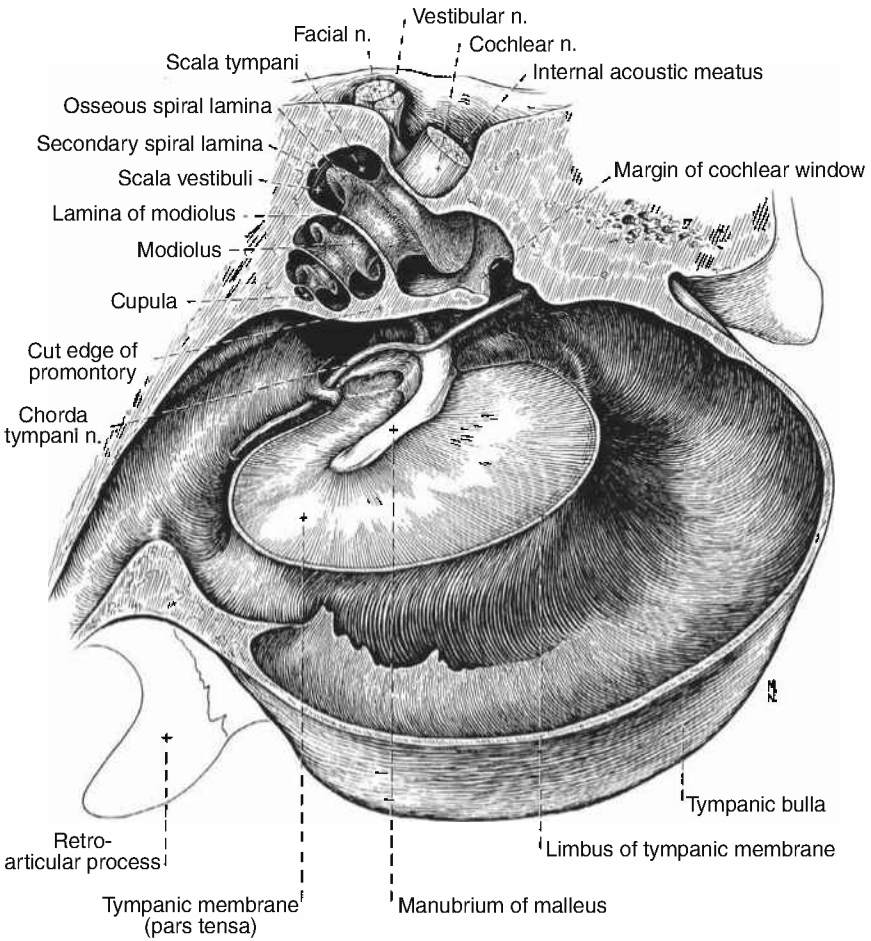


Fig. 1.10. Medial view of the right canine middle ear. The promontory has been sectioned to show the cochlea (from Evans, 1993a; reproduced with permission).

Contained within the bony vestibule are two membranous sacs, the saccule and utricle. The saccule is located ventrally within the vestibule and the utricle is located dorsally within the vestibule (Fig. 1.11). From the utricle arise three semicircular ducts, which extend into the canals of the osseous labyrinth. Endolymph is displaced within these ducts when the head is rotated. Because the three ducts are oriented in different planes, circulation of fluid within the ducts is determined by the direction of head movement. This allows for spatial orientation, and thus aids in the maintenance of balance following positional changes of the head. The sensory cells in the epithelium of the wall of the semicircular ducts are located within specialized sensory structures of the ampullae termed cristae ampullares. Two other receptor areas, the maculae, monitor the position of the head with respect to gravity.

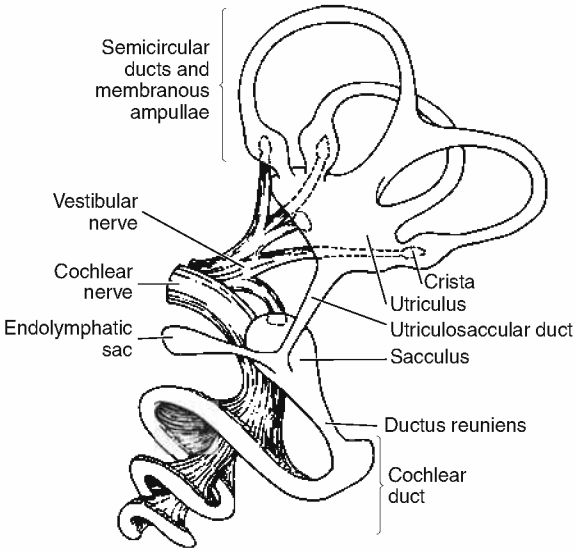


Fig. 1.11. The isolated membranous labyrinth of the canine inner ear (from Evans, 1993a; reproduced with permission).

These are represented by circumscribed areas of sensory cells within the epithelial walls of the saccule (macula sacculi) and utricle (macula utriculi). The maculae respond mainly to changes in linear acceleration, rather than to rotational movements of the head. Afferent information from the maculae and cristae ampullares is transported within the vestibular portion of the vestibulocochlear nerve (CN VIII). Two ducts that extend medially from the saccule and utricle unite and form the endolymphatic duct. The endolymphatic duct runs within the vestibular aqueduct and terminates as the expanded endolymphatic sac on the caudal, internal surface of the petrous part of the temporal bone, where it is in contact with the dura mater. Studies suggest that the endolymphatic duct and endolymphatic sac perform both absorptive and secretory (Wackym *et al.*, 1987a; Rask-Andersen *et al.*, 1991; Schuknecht, 1993; Yeo *et al.*, 1995) as well as phagocytic (Fukuzawa *et al.*, 1991) and immunodefensive functions (Wackym *et al.*, 1987b).

The cochlear duct is connected ventrally to the sacculus via the ductus reuniens (Fig. 1.11). The cochlear duct spirals within the cochlea, due to its attachment to the spiral lamina on one side and the cochlear cavity wall on the other. The duct has a wedge shape in cross-sections, with the apex of the wedge attached to the osseous lamina of the modiolus and its base forming the spiral ligament where it fuses with the periosteum lining the cochlear cavity wall. This peripheral wall of the cochlear duct is termed the stria vascularis, and is comprised of a bistratified layer of cuboidal or columnar cells that are underlain by a highly vascularized connective tissue, the spiral

ligament (Banks, 1993). Endolymph is produced by the stria vascularis, circulates within the membranous labyrinth and finally drains into the venous sinuses of the dura mater via the endolymphatic duct (Banks, 1993). Together with the osseous spiral lamina, the cochlear duct divides the cochlear space into upper and lower chambers. The upper spiral chamber is the scala vestibuli and begins at the vestibule, close to the oval window; the lower spiral chamber is the scala tympani and ends at the round window. These two chambers communicate at the helicotrema, which is located at the apex of the cochlea, rostral to the tip of the osseous modiolus. The endolymph-filled chamber of the blind-ending cochlear duct, which is wedged between the upper and lower perilymph-filled chambers, is the scala media. Reissner's membrane (vestibular membrane) separates the cochlear duct from the scala vestibuli, while the basilar membrane separates the cochlear duct from the scala tympani. The limbus occurs where these two membranes approximate each other at the spiral lamina of the modiolus.

The organ of Corti, which is the organ of hearing, is comprised of groupings of specialized sensory cells called hair cells, which are embedded within supporting cells, all of which rest on the basilar membrane. These sensory cells serve as mechanoreceptors that convert mechanical energy into electrical energy, or nerve potentials. The apical surface of the hair cells contains hair-like projections called stereocilia (modified cilia, non-motile), which project into the lumen of the cochlear duct. The stereocilia of these hair cells descend in height across the apical surface of the cell and the tips of the most elongated stereocilia are embedded within the overlying tectorial membrane. This membrane is a gelatinous structure that is secreted by specialized epithelial cells (interdental cells) located at the limbus of the spiral lamina. When activated by mechanical stimulation, deflections of the apical stereocilia result in the release of neurotransmitters from the bases of the hair cells onto afferent neuron receptive endings of bipolar cells. Bundles of afferent fibers direct impulses medially within the hollow, bony spiral lamina toward the bodies of bipolar nerve cells. The cell bodies of these bipolar neurons are located within spiral ganglia, which are located in the modiolus at the origin of the spiral lamina. Afferent axons extend from the spiral ganglia and collect centrally within the hollow modiolus, thus forming the cochlear portion of the vestibulocochlear nerve (CN VIII).

Movement of the stapes at the oval window results in the displacement of perilymphatic fluid as a transverse wave in the scala vestibuli toward the helicotrema, where this wave is continued in the perilymphatic fluid of the scala tympani. The round window is a membrane-covered opening at the caudal end of the promontory that provides a relief valve function so that when the perilymphatic fluid is compressed by inward deflection of the oval window, the membrane of the round window bulges outward. As the wave of perilymphatic fluid circulates through the scala vestibuli and scala tympani, Reissner's membrane and the basilar membrane are deflected, resulting in stimulation of the embedded hair cells with subsequent firing of afferent

cochlear neurons. The width of the bony spiral lamina decreases from the base of the modiolus to the apex, and so the width of the basilar membrane, which extends from the bony spiral lamina to the cochlear wall, increases from base to apex. Different portions of the sensory epithelium of the organ of Corti respond maximally to sound waves of specific frequencies, with low-frequency (long-wavelength) detection being greatest at the cochlear apex and high-frequency (short-wavelength) detection being maximal at the cochlear base. An extended length of the cochlear duct increases the range of detectable audible frequencies. In dogs, there are 3.25 cochlear turns and the organ of Corti is sensitive to a frequency range of 67– 45,000 Hz, compared with a range of 64–23,000 Hz in humans who have 2.75 cochlear coils (deLahunta and Glass, 2009; see Chapter 3). The cat has 3.0 cochlear spirals (Brown, 1987; Heine, 2004), with a hearing frequency range of 45–64,000 Hz.

Development of the Ear

One distinguishing feature of the development of the head region of the vertebrate embryo (Moore and Persaud, 2003; McGeady *et al.*, 2006; Sinowatz, 2010) is the formation of the pharyngeal arches, pouches and grooves. Discrete aggregations are visible as a result of the migration of neural crest-derived mesenchymal cells and proliferation of mesoderm within the developing head and neck region. These aggregations give rise to six pharyngeal arches, of which four are visible in most mammalian embryos. Externally, the arches are lined by ectoderm; internally, by endoderm. The external invaginations between subsequent arches lined by ectoderm are called pharyngeal grooves. The internal outpouchings of the primitive foregut between subsequent arches lined by endoderm are called pharyngeal pouches. Local circumscript proliferation of mesodermally and neural crest-derived tissue between the ectoderm and endoderm results in pharyngeal arch restructuring. Structures of the external and middle ear are derived from the first and second pharyngeal arches and the first pharyngeal groove and pouch.

External and middle ear

Mesenchymal tissue from the first and second pharyngeal arches proliferates and surrounds the first pharyngeal groove, forming the auricle and external auditory meatus. The auricle and ear canal are thus lined by ectodermally derived epithelium. The tympanic membrane is formed when the recess of the first pharyngeal groove and the first pharyngeal pouch excavate deeper into the mesoderm between the first and second pharyngeal arches to a face of apposition. The lateral, or external, epithelium of the tympanic membrane is derived from the deepest recess of the first pharyngeal groove ectoderm; the medial, or internal, epithelium of the tympanic membrane is derived from the

deepest recess of the first pharyngeal pouch endoderm. Between these two layers is a thin layer of mesoderm. The first pharyngeal pouch maintains its connection to the pharynx and gives rise to the auditory tube and middle ear cavity. The ossicles of the middle ear are formed by neural crest-derived mesenchyme and their affiliated muscles are formed from the mesoderm of the first and second pharyngeal arches. The malleus, incus and tensor tympani muscle are derivatives of the first pharyngeal arch. The stapes and stapedius muscle are derived from tissues of the second pharyngeal arch. The cranial nerve that supplies structures of the first pharyngeal arch is the trigeminal nerve (CN V); therefore branches of the trigeminal nerve supply the auricle, ear canal, malleus, incus and tensor tympani muscle. The cranial nerve that supplies structures of the second pharyngeal arch is the facial nerve (CN VII), and therefore branches of the facial nerve supply caudal parts of the auricle, ear canal, stapes and stapedius muscle. Nerves of the cervical plexus, which is formed by the ventral branches of cervical spinal nerves, also supply auricular structures derived from the second pharyngeal arch.

Inner ear

The development of the inner ear begins with the induction of the otic placodes, which are bilateral ectodermal thickenings located lateral to the caudal part of the rhombencephalon. These ectodermal placodes invaginate to form the otic pits, which maintain their connection for a time with the surface ectoderm. Eventually, the connection with the surface ectoderm is lost and the result is the formation of the otic vesicles. The cavity of the otic vesicle fills with endolymph, which is produced by the ectodermal epithelial cells and has a composition similar to that of intracellular fluid. Proliferation of the ectodermal cells of the otic vesicle results in the elongation of the otic vesicle and the initial differentiation into two distinct regions: the dorsally expanded utricle and the ventrally located saccule. A series of outpocketings from the utricle and saccule establishes the primordia of the semicircular and cochlear ducts. The cochlear diverticulum evaginates from the ventral portion of the saccule. As the cochlea elongates it constricts and coils, forming the cochlear duct. The connection between the cochlea and the saccule is maintained by the narrow ductus reuniens.

Blood Supply of the Ear

External ear

The main blood supply to the external ear is derived from branches of the external carotid artery, the caudal auricular artery and the superficial temporal artery (see Evans, 1993b, Fig 11.14, p. 606). The caudal auricular

artery supplies the auricle, caudal auricular muscles and the ear canal. The rostral auricular branch of the superficial temporal artery supplies the rostral auricular muscles. The caudal auricular artery arises from the external carotid artery at the base of the ear canal, deep to the parotid salivary gland at the caudal border of the masseter muscle. It courses caudally and dorsally at the base of the ear, initially deep and then superficial to the caudal auricular muscles, and sends branches distally toward the apex of the auricle. The branches of the caudal auricular artery include the lateral, intermediate and medial auricular branches to the convex external surface of the auricle and the deep auricular artery that supplies the cutaneous portions of the external auditory canal. The lateral, intermediate and medial auricular branches of the caudal auricular artery provide perforating branches through numerous foramina in the auricular cartilage to supply the concave surface of the auricle. It is these blood vessels that may be affected during head shaking and fighting, resulting in the formation of aural hematomas (Fossum, 2007). Branches of the intermediate auricular branch also supply the caudal auricular muscles. The superficial temporal artery arises and ascends dorsally from the external carotid artery, immediately rostral to the auricle. One of its branches, the rostral auricular branch, extends caudally to supply the rostral auricular muscles (Evans, 1993a; Heine, 2004).

Middle ear

The canine middle ear blood supply has not been thoroughly described and there are some ambiguities in its description among various authors. In 1943, Davis and Story provided a thorough description of the feline middle ear blood supply through investigating the carotid circulation in this species. The following description of the middle ear vasculature will therefore be based on the feline, with canine comparisons discussed where applicable.

The middle ear receives its arterial supply from branches of the ascending pharyngeal, occipital and maxillary arteries. The ascending pharyngeal artery provides a eustachian branch (ramus eustachii) that supplies the eustachian tube and accompanies it through the musculotubal canal of the temporal bone into the lateral chamber of the bulla. The vessel then ramifies over the surface of the promontory, where it anastomoses with the rostral and caudal tympanic arteries. The caudal (inferior) tympanic artery, a branch of the occipital artery, enters the skull at the foramen lacerum, where it immediately branches. The more posterior of the two branches derives several twigs that ramify either within the mucosa covering the promontory or over the posterior part of the dorsal surface of the bulla. According to Evans (1993a), the condyloid artery of the canine is synonymous with the caudal (inferior) tympanic artery described by Davis and Story (1943). The condyloid artery enters the petro-occipital fissure and passes through the petrobasilar canal, accompanied by the accessory nerve, where it dissipates in the dura at

the ventral end of the pyramid of the medulla oblongata. In its course it supplies twigs to the middle and inner ear. Ghoshal (1975) and Schummer *et al.* (1981) state that the canine caudal tympanic artery (a. tympanica caudalis) is a branch of the occipital artery-derived caudal meningeal artery. In the cat, the branches of the maxillary artery that supply the middle ear are the deep auricular (a. auricularis profunda) and rostral (anterior) tympanic (a. tympanica anterior or a. tympanica rostralis). In the dog, the deep auricular artery is not a direct branch of the maxillary artery, but is a branch of the caudal auricular artery, which is a branch of the external carotid artery. This deep auricular artery supplies the periosteum of the malleus manubrium as well as the tympanic membrane (Cole, 2009). The rostral (anterior) tympanic artery is a constant branch of the feline maxillary artery and is an important supply to the middle ear. However, in the dog, the rostral tympanic artery is described as an inconstant vessel that branches from the maxillary artery rostral and medial to the retroarticular process of the temporal bone (Ghoshal, 1975; Evans, 1993a). When present, this vessel extends caudally from its origin and enters the middle ear cavity via a small foramen medial to the temporomandibular joint, near the petrotympanic fissure. In the dog, the caudal auricular artery, a branch of the external carotid artery, provides middle ear vascularization (Schummer *et al.*, 1981). A stylomastoid branch of the caudal auricular artery enters the stylomastoid foramen and courses parallel to the facial nerve within the facial canal. This vessel gives off neural, mucosal and muscular branches to the middle ear cavity. Neural branches supply the facial nerve, while mucosal branches supply the tympanic membrane and the epithelial lining of the tympanic cavity (Maher, 1988). Cole (2009) describes a more specific branch of the stylomastoid artery, the caudal (posterior) tympanic branch, which supplies the fibrous propria (intermediate layer) of the tympanic membrane. The middle meningeal artery arises from the maxillary artery, distal to the rostral tympanic artery. It arises just prior to the course of the maxillary artery through the alar canal. Branches of the middle meningeal artery supply the tensor tympani muscle and structures within the epitympanum.

Inner ear

The main blood supply to the inner ear in dogs and cats is provided by the vertebral–basilar system (Shambaugh, 1923; Bernstein and Silverstein, 1966). The left and right vertebral arteries unite at the ventral midline at the level of the caudal part of the brainstem to form the basilar artery. The basilar artery provides bilateral branches that supply structures of the cerebellum and pons in its rostral ascent toward its confluence at the arterial circle. Caudal to the pons, the basilar artery gives off bilateral labyrinthine arteries, which course laterally toward the internal acoustic meatus of the petrous temporal bone. The labyrinthine artery can be found between the roots of CN

VII and CN VIII before these nerves enter the bony labyrinth at the internal acoustic meatus. The labyrinthine artery supplies terminal branches to the membranous labyrinth of the inner ear.

Innervation of the Ear

External ear

The external ear is supplied by both cranial and cervical spinal nerves (Evans and Kitchell, 1993). The auricular muscles are supplied by motor branches of CN VII (see Evans and Kitchell, 1993, Fig 12.19, p. 965). Muscles of the rostroauricular group are innervated by the rostral auricular nerve, a branch of the auriculopalpebral branch of the facial nerve that is located rostral to the ear base. Muscles of the caudal auricular group are innervated by caudal auricular branches that emerge from the trunk of the facial nerve caudal to the ear base. Sensory innervation of the central and caudal concave auricle and vertical ear canal is provided by sensory branches of the facial nerve: the middle internal auricular nerve, the caudal internal auricular nerve and the lateral internal auricular nerve. The rostal part of the auricle is supplied sensory innervation by the mandibular branch of the trigeminal nerve (CN V). The medial horizontal ear canal is supplied by the auriculotemporal branch of the mandibular nerve of CN V. Cervical innervation of the cutaneous convex surface of the auricle is provided by the great auricular nerve, one of the two branches of the ventral branch of the second cervical nerve (C2).

Middle ear

Innervation of the mucosal lining of the tympanic cavity is provided by the tympanic plexus; its main source comes from the tympanic branch of the glossopharyngeal nerve (CN IX). The plexus ramifies over the surface of the promontory and supplies somatic innervation to the mucosal linings of the auditory tube and tympanic cavity, including the tympanic membrane and the oval and round window membranes. The innervation of the tensor tympani muscle is provided by a branch of the mandibular nerve of CN V. This branch is closely affiliated with the long tendon of the tensor veli palatini muscle, which lies on the lateral wall of the auditory tube. As the facial nerve passes through the facial canal, it gives off a muscular branch and an autonomic branch. The muscular, or stapedial, branch is given off where the facial canal opens into the cavity of the middle ear near the vestibular (oval) window and supplies the stapedius muscle. The chorda tympani, a sensory branch of CN VII, passes through the middle ear cavity. Although direct innervation to middle ear structures is not provided by the chorda tympani,

this nerve is usually described due to its prominent course through the middle ear cavity. The chorda tympani can be seen passing ventrorostrally through the tympanic cavity proper, medial to the neck of the malleus, on its course from CN VII to the petrotympanic fissure, which lies just ventral to the attachment of the rostral ligament of the malleus. After emerging from the petrotympanic fissure, it will join the lingual branch of the mandibular nerve to provide sensory innervation to the rostral part of the tongue.

Inner ear

Innervation of the inner ear was for many years thought to be purely afferent. However, recent evidence has shown that the outer hair cells of the cochlea also have an efferent innervation (Ryugo, 1992). Sensory afferent innervation of the inner ear is provided by CN VIII, which has a vestibular and a cochlear branch. The vestibular branch is formed by the bundle of axonal processes arising from bipolar cell bodies within vestibular ganglia. The dendritic processes of the vestibular bipolar cells are distributed in the sensory epithelium of the cristae ampullares of the semicircular ducts and the maculae of the utricle and saccule. The cochlear branch is formed by a bundle of axonal processes of the spiral ganglia. Both nerve branches unite within the bony vestibule and emerge as the vestibulocochlear nerve from the internal acoustic meatus.

Physiology of the Auditory System 2

The sense of hearing, which is linked anatomically and physiologically to the sense of balance, permits an animal to monitor its external environment through the vibrations of sound in the medium in which it exists. This medium is typically either air or water, but sound can also be detected through vibrations in solid matter, including bone. Conduction of auditory stimuli through bone vibration provides a useful mechanism for differentiating between sensorineural and conduction deafness (see Chapter 6). Hearing is limited mostly to insects and the vertebrates (Shepherd, 1994).

The inner ear of mammals contains two sensory organ systems: the vestibular system and the auditory system. The cochlea is the organ of hearing. Both systems share a common embryonic origin (the otic vesicle), plus other common morphological or physiological properties such as the fluid bathing the receptor cells – endolymph; specialized sensory cells for detecting appropriate stimuli – hair cells; and both detect their appropriate stimuli by mechano-transduction. Sound is transmitted from the external medium of the body to the cochlea in the inner ear, where the vibrational energy is transduced or converted into an electrical signal in receptor cells and that signal is transmitted by the eighth cranial nerve (CN VIII) to the brainstem and higher brain centers. Perception of the sound stimulus results when the information is conveyed through neural pathways to the auditory portion of the cerebral cortex. Auditory reflexes, which include those protective against loud noises, do not require cortical involvement.

The sense of hearing plays a significant role in the daily activities of animals, and is important to both domestic and wild animals in detecting external dangers such as predators and motor vehicles, in responding to

vocalizations by conspecifics and animals from other species, in prey pursuit, in courting behaviors and in a variety of other functions. Disruption of hearing typically does not induce pain or discomfort, but can greatly impede an animal's ability to function and survive in its normal environment.

Sound

Sound is a pressure disturbance or vibration of air molecules (or molecules in other media) which spreads out from the source in waves. Sound has features of amplitude, frequency, and velocity. Sound amplitude (or loudness or pressure) is measured in logarithmic units of decibels (dB). Decibels can be defined on several different scales, the two most common being sound pressure level (SPL) and normal hearing level (nHL). The dB SPL scale is based on a physical standard where 0 dB is equivalent to 20 μPa (or $\mu N/m^2$), a level near the human hearing threshold in air, and all other values are logarithms of the ratio of the measured sound pressure divided by the baseline of 20 μPa. The dB nHL scale is also a logarithmic ratio of sound levels, but on this scale 0 dB is defined as the average hearing threshold of a group of young adult humans, a behavioral measurement. Sound intensities in dB SPL are numerically higher than the same sound measured in dB nHL. An increase in sound amplitude of 10 dB equates to a 100-fold increase in loudness. Loudness values for common environmental sounds are shown in Table 2.1.

Table 2.1. Loudness measures for common environmental sounds. Prolonged exposure to 85 dB or greater will produce gradual hearing loss (data from National Institute on Deafness and Other Communication Disorders, 2010).

Sound	Loudness (dB)
Firecracker	150
Ambulance siren	120
Chain saw, rock concert	110
Personal stereo at max.	105
Wood shop, snowmobile	100
Motorcycle	95
Power mower	90
Heavy city traffic	85
Normal conversation	60
Refrigerator hum	40
Whispered voice	30
Threshold of normal hearing	0

The frequency of sound is a measure of the fluctuations of sound amplitude per unit of time. The base unit of frequency is the Hertz (Hz), one cycle per second. The velocity of sound is a function of the medium in which the sound travels. The velocity of sound in air (20°C, 1 atm pressure, 50% relative humidity) is 343 m/s; changes in temperature, atmospheric pressure and humidity produce small changes in this value. Sound velocity in water is 1482 m/s, or about 4.3 times the velocity in air. Velocities in solid materials range from 800 to 5200 m/s, faster than in air or water.

The sounds detected by the ear are never pure tones – sine waves – because it is impossible to produce a pure tone with a mechanical device such as a speaker without introducing small distortions. Musical notes described as pure tones include harmonics superimposed on the main tone – integer and fractional multiples of the main tone. Environmental sounds – from speech, animal vocalizations, wind, vehicles, mechanical equipment – are complex mixtures of various frequencies of sound, with each individual frequency component contributing at a different amplitude. It is theoretically possible to decompose a complex sound into a series of sinusoidal pure tones at different amplitudes, a mathematical process known as Fourier analysis. As will be described later, the cochlea performs the equivalent of Fourier analysis as it detects and transduces sounds.

In discussions of sound, noise (in the most general sense) can be considered to be a sound without any informational content. In the context of audiology, white noise is a hissing sound where the signal has sound components whose amplitudes are the same across the frequency spectrum. White noise is often introduced into one ear when testing the hearing of the contralateral ear to avoid activation of the untested ear by the test stimulus.

Divisions of the Ear

The outer ear

The ear is divided structurally into three chambers connected in series (Fig. 1.2). The outer ear, which consists of the pinna (external ear) and auditory canal (external auditory meatus) down to the cone-shaped tympanic membrane, directs sound waves toward the hearing apparatus. The auditory canal in dogs and cats has an 'L' shape, consisting of a vertical canal and a horizontal canal. The pinna is highly developed in some species and not developed or modified in others. Some avian species have no pinna, while some aquatic species like the alligator have a flap over the ear canal that can be closed during submersion. The different cartilaginous structures of the pinna help direct sounds into the ear canal and assist with sound localization. Animals with muscle control of external ear orientation can improve hearing sensitivity by as much as 28 dB in the high-kHz frequency range (wavelengths that are short compared with pinna dimensions) for

sound sources in a narrow region directly in line with the axis of the pinna (Phillips *et al.*, 1982).

The ear canals of dogs and cats are not open at birth, but typically open by three to four weeks of age. Prior to opening the sounds reaching the cochlea are muffled, but animals may respond to loud sounds that penetrate the tissues. Nevertheless, behavioral testing for the presence of hearing at these early ages is not reliable. The cochlea also undergoes postnatal maturation (Strain *et al.*, 1991) and congenital deafness does not appear until three to four weeks of age, so hearing testing of animals from breeds at risk for hereditary congenital deafness is not performed until 5 weeks of age or older.

There can be variation in the amount of cerumen or wax secreted by cells lining the ear canal in dogs and cats. This tendency, and the floppy ear configuration of some dog breeds that causes poor air circulation, can dispose animals to chronic outer ear infection, or otitis externa. This condition can in turn result in calcification of the tissues lining the canal, which is painful, and may in severe cases require surgical excision of part or all of the canal. Ear canal resection does not necessarily result in deafness if middle ear structures are not damaged, but will reduce hearing sensitivity because of muffling of the sounds reaching the inner ear.

The middle ear

The middle ear is an air-filled chamber medial to the tympanic membrane that is connected to the nasopharynx by the auditory or eustachian tube. The middle ear contains three ossicles – the smallest bones in the body – that transmit the nanometer-scale sound vibrations of the tympanic membrane to the inner ear; they are constrained in place by a series of ligaments. The malleus attaches to the back of the tympanic membrane and articulates with the incus, which articulates with the stapes. The foot plate of the stapes in turn attaches to a membranous window into the inner ear, the oval window. The vibrations of the tympanic membrane are transmitted to the fluids of the inner ear through these three bones. The middle ear structures perform mechanical impedance matching between air and the cochlear fluids, and in the process amplify the sound pressure by a factor of 20. Effusion in the middle ear from infections (otitis media) can produce conduction deafness, muffling the sounds reaching the inner ear; these infections can arise through penetration of respiratory or other infections up the auditory tube. Some species have a ligament joining the malleus and the temporomandibular joint, but its functional significance is unclear. Two branches of the facial nerve (CN VII) pass through the middle ear – the chorda tympani, which conveys afferent taste information and efferent autonomic control of salivary glands, and the main facial nerve branch, responsible for motor control of facial and ear muscles.

The middle ear is also the location for the smallest skeletal muscles in the body that connect two ossicles to the wall of the middle ear – the tensor

tympani and the stapedius muscles. The tensor tympani attaches to the malleus near the tympanic membrane and is innervated by the trigeminal nerve (CN V). The stapedius muscle is attached to the stapes and is innervated by CN VII. Contraction of these muscles increases the stiffness of the ossicular chain, reducing transmission of (mostly) low-frequency sounds as a protective reflex mechanism. Contraction is elicited by loud sounds, tactile stimulation of the head, general body movement or just prior to vocalization. However, the reflex contraction in response to loud sounds is too slow (50–100 ms) to protect against damage from impulse noises like gunfire, a problem with dogs used in hunting.

The inner ear

The cochlea

The Inner ear consists of the organs of the vestibular system (balance) and the cochlea, collectively known as the membranous labyrinth; they are encased in the petrous portion of the temporal bone in what is known as the bony labyrinth, much like a hand within a glove. The placement of the cochlea within a bony structure provides protection, but also places physical limits on changes that can occur within the structure. The term cochlea comes from the Latin word *coclea* for snail shell, which describes its shape. The coiled cochlea has its broadest coil at the interface with the middle ear, the vestibule, and tapers to an apex medially. The number of coils varies among species, with 2.75 in humans, 3.0 in cats, and 3.25 in dogs. The lowest reported value is 2.0 in dolphins, and the highest is 4.0 in guinea pigs (Echteler *et al.*, 1994). In ground-dwelling mammals, the number of coils correlates with the length in octaves of the hearing range; however, the number of coils does not correlate with either the high end or low end of audible frequencies in different species (West, 1985). Variability of the hearing frequency range within a species has not been widely explored, i.e. one dog breed versus another. However, one study (Heffner, 1983) compared a single poodle, Dachshund, Saint Bernard and Chihuahua, and found little difference despite the wide range of body size (Fig. 2.1).

When a cross-section through one of the cochlear coils is examined (Fig. 2.2), it can be seen that the cochlea consists of three fluid-filled tubes – the scala vestibuli, the scala tympani and the scala media or cochlear duct. The scala vestibuli and the scala tympani are continuous at the apex of the cochlea, so in reality there are two tubes with one bent at its midpoint, and the two arms of the long tube bracket, the scala media. The foot plate of the stapes transmits sound vibrations to the cochlear fluids at the oval window, which opens to the fluids of the scala vestibuli. The vibrations travel up the scala vestibuli and back down the scala tympani to another membranous structure, the round window. The round window, like the oval window, faces the middle ear. This is necessary because the cochlea is imbedded in the bony

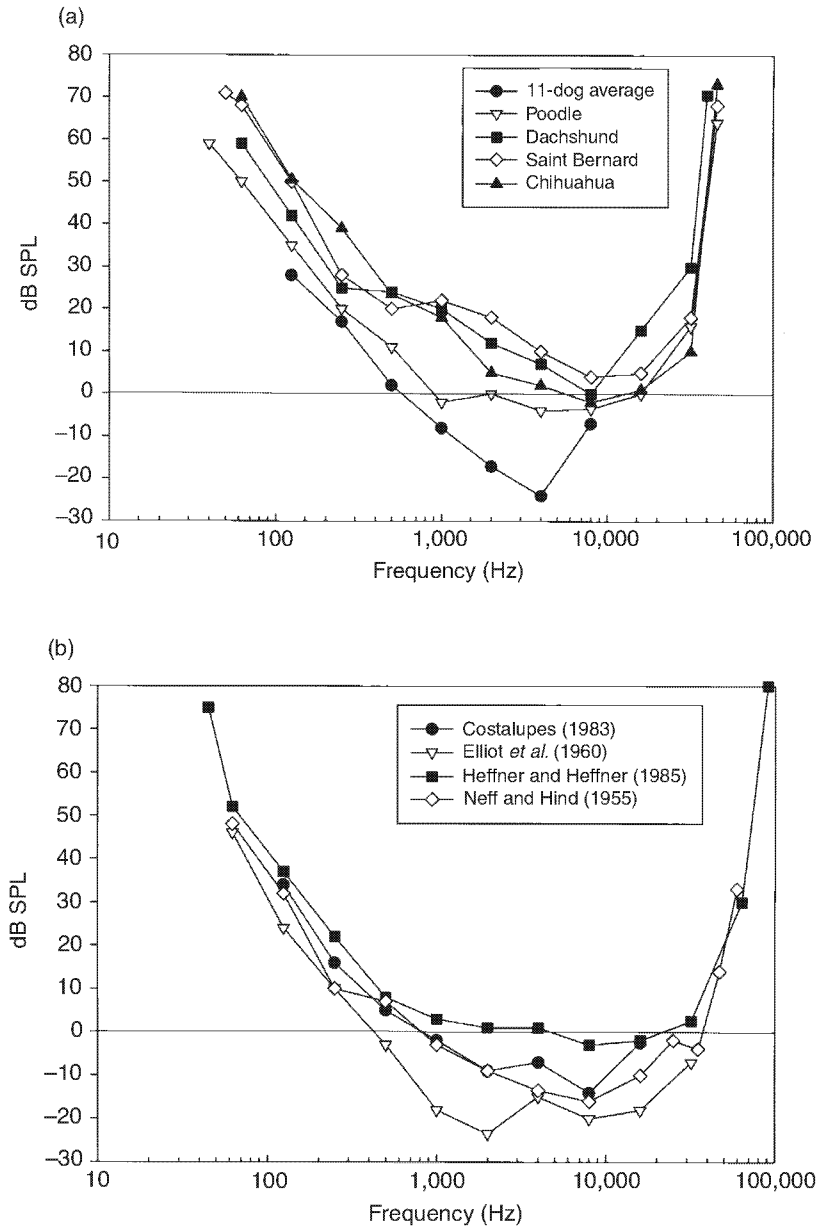


Fig. 2.1. Audiograms constructed from reports on hearing thresholds determined by operant testing. (a) Readings (average) from one study on 11 dogs (Lipman and Grassi, 1942) and from four studies on different breeds (Heffner, 1983). (b) Readings from four studies on cats (Neff and Hind, 1955; Elliot *et al.*, 1960; Costalupes, 1983; Heffner and Heffner, 1985).

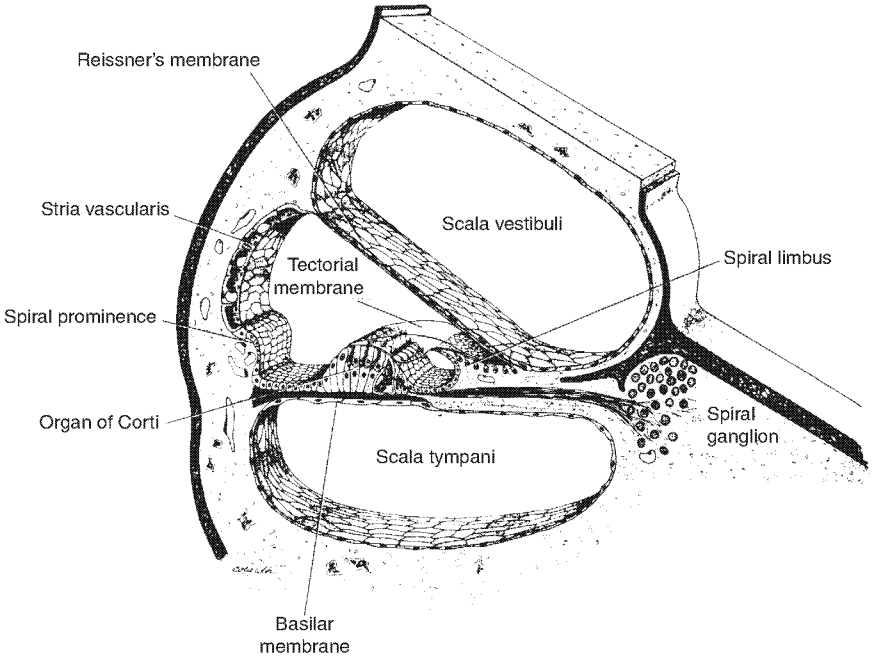


Fig. 2.2. Cross-section through the mammalian cochlea showing the three cochlear compartments, the organ of Corti, the spiral ganglion and the stria vascularis (from Bloom and Fawcett, 1975).

labyrinth. The fluids in the cochlear ducts are not compressible, so inward deflections of the oval window produced by sounds transmitted by the stapes can only occur if there is a relief structure – the round window. These two membranes operate 180° out of phase, so that an inward oval window deflection instantaneously produces an outward round window deflection.

The cochlear ducts contain fluids that differ by compartment. The scala tympani and scala vestibuli contain perilymph, which is similar to cerebrospinal fluid and extracellular fluid – relatively low in K^+ (7 mM) and high in Na^+ (140 mM). The scala media contains endolymph, which is similar to intracellular fluid – relatively high in K^+ (150 mM) and low in Na^+ (1 mM). A specialized tissue on the outer wall of the cochlear duct, the stria vascularis, actively resorbs sodium and secretes potassium against their respective concentration gradients to produce the ionic composition of the endolymph. The stria is an important target for causing several forms of deafness.

Three membranes are important in the structure of the cochlea. The wall between the scala vestibuli and the cochlear duct is Reissner's membrane (Fig. 2.2). The wall between the cochlear duct and the scala tympani is the basilar membrane; the organ of Corti sits on this structure. Sound pressure waves traveling along the scala vestibuli and scala tympani produce deflections of

Reissner's membrane and the basilar membrane, impinging into the cochlear duct. Projecting from the middle of the coil – the modiolus – toward the stria in the cochlear duct is the third membrane, the gelatinous tectorial membrane. As described below, stereocilia atop hair cells in the organ of Corti project into the tectorial membrane; deflections in the basilar membrane press the stereocilia against the tectorial membrane, bending them and producing depolarization in hair cells.

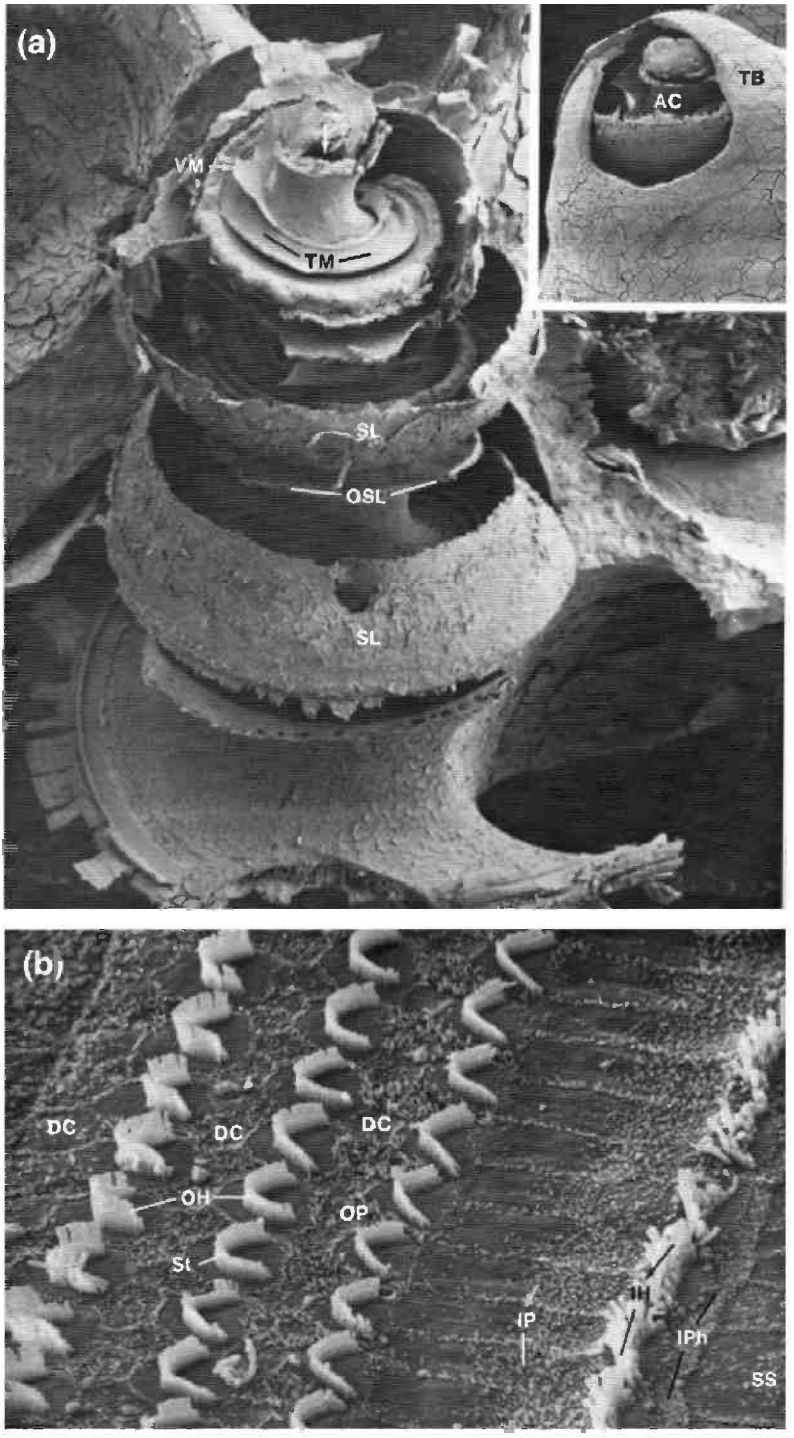
The organ of Corti

The organ of Corti, which rests on the basilar membrane, contains the receptor cells for sound transduction – the hair cells (the vestibular system also operates with hair cells). These cells are aligned in rows that spiral around the modiolus with the snail shell-like structure of the cochlea. Two types of hair cells are present – inner hair cells (IHC), numbering about 3000 in the cat, and outer hair cells (OHC), numbering about 9000 (Ryugo, 1992). There is a single row of IHC and three to five rows of OHC, depending on species (Fig. 2.3).

Each hair cell has multiple stereocilia projecting into the cochlear duct, arranged in a chevron shape that points away from the modiolus. Hair cells in the vestibular system also have stereocilia, but in addition have a larger structure at the apex of the stereocilia known as a kinocilium; cochlear hair cells lose this structure as they develop. The stereocilia tips are embedded in the gelatinous tectorial membrane so that upward deflections of the basilar membrane produce bending of the stereocilia against the tectorial membrane. Bending of the stereocilia changes the transmembrane potential of the hair cells – deflections of the stereocilia in the direction from shortest to tallest excite hair cells, while deflections in the opposite direction inhibit them.

The stereocilia tips on a single hair cell are interconnected by filaments so that deflections of the taller stereocilia away from the shorter stereocilia pull

Fig. 2.3. Scanning electron micrographs from guinea pig cochleas. (a) View of an exposed cochlea following removal of overlying temporal bone, demonstrating the curved shape of the structure. The white arrow at the apex indicates the modiolus, the central bony axis of the cochlea. The osseous spiral lamina (OSL) projects from the modiolus to support the membranes. Portions of the tectorial membrane (TM) and Reissner's (vestibular) membrane (VM) are visible near the apex. The spiral ligament (SL) is the periosteal covering of the outer wall. ×55. Inset: Partially exposed cochlea after removal of part of the temporal bone (TB), exposing the apical turn of the cochlea (AC). ×35. (b) Organ of Corti with the tectorial membrane removed, showing one row of inner hair cells (IH) and three rows of outer hair cells (OH), with stereocilia (St) projecting from the hair cells. Non-neural structural support cells include Deiter's cells, outer pillar cells (OP), inner pillar cells (IP), inner phalangeal cells (IPh), and spiral sulcus cells (SS). ×2915. (Reproduced with permission from Kessel, RG and Kardon, RH (1979) Tissues and Organs, WH Freeman).


(a)
VM
TM
AC
TB
SL
OSL
SL
(b)
DC
DC
DC
OH
OP
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IP
IH
IPh
SS

them along, amplifying the effects of the deflection (Fig. 2.4). These tip links are attached to mechanically gated K^+ channels, classified as TRPA1 channels. Tension applied to the tip links between stereocilia opens the channels. Potassium enters the stereocilia, depolarizing the cell. When the potential difference is measured between the cochlear duct and the scala tympani (the endocochlear potential), the typical value is +80 mV. The potential difference between the hair cell interior and the scala tympani is typically –45 mV. As a result, the potential driving potassium ions into the hair cell after opening of mechanically gated K^+ channels is: +80 – (–45) = 125 mV (Fig. 2.4). Depolarization from potassium influx activates voltage-gated Ca^{2+} channels, allowing Ca^{2+} influx, further depolarizing the cell and triggering neurotransmitter release from synapses of the hair cell onto the distal fibers of spiral ganglion sensory neurons. These neurons then enter the brain as a part of the cochlear branch of CN VIII and synapse on the cochlear nuclei in the brainstem. The primary neurotransmitter thought to be released from hair cells onto afferent fibers is glutamate, although others may be present, including ATP. There are approximately 50,000 myelinated axons and 2500 unmyelinated axons in the cat auditory nerve (Ryugo, 1992). These stereocilia

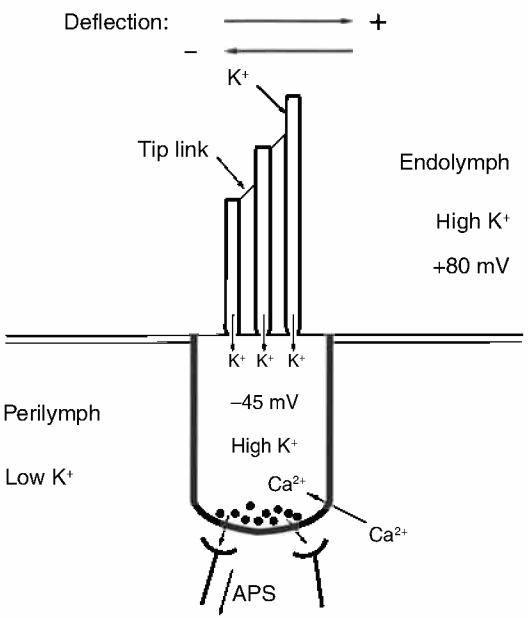

Fig. 2.4. Schematic drawing of a cochlear hair cell showing tip links between stereocilia. Deflection from left to right opens mechanically gated K^+ channels; the resulting K^+ influx opens voltage-gated Ca^{2+} channels and the Ca^{2+} influx triggers release of neurotransmitter onto postsynaptic receptors of spiral ganglion sensory afferents (from Strain and Myers, 2004). APS, action potentials.

deflection transduction processes are most relevant to IHC, which are the primary auditory sensory cells. OHC play a different role to bias the sensitivity of inner hair cells, as described below.

Hair cell innervation consists of two types of connections, afferents that send information to the CNS (central nervous system) and efferents that convey information from the brain to the cochlea. The afferents are spiral ganglion fibers projecting to the brain. Of these, 90–95% are from IHC (Type I afferents) and 5–10% are from OHC (Type II afferents). The efferents, numbering approximately 1800 in the cat, originate in the olivary nuclei and the trapezoid body. The efferents terminating near IHC are mostly presynaptic to spiral ganglion afferent terminals, while efferents to OHC synapse on hair cell somas. Olivocochlear fibers synapsing on OHC release the transmitter acetylcholine to activate nicotinic receptors.

Outer hair cells are present in greater numbers than IHC, but the IHC provide the majority of the sensory input from the cochlea. Outer hair cells instead appear to provide an amplification function whereby IHC sensitivity is increased or decreased. The OHC contain a membrane motor protein known as prestin (Zheng *et al.*, 2002), similar to myosin, which enables the OHC to rapidly shorten when activated by cell depolarization; the shortening does not use ATP as an energy source. This shortening pulls the basilar membrane toward the tectorial membrane and increases the bending of the adjacent IHC, amplifying their response. The depolarization that shortens OHC can originate from two sources: by (i) deflection of the OHC by sound waves traveling through the cochlea, which also deflect the stereocilia of IHC; or (ii) activation of brain efferents to the OHC. Efferent depolarization of OHC, independent of ICH stereocilia mechanical deflections, can function to preload the IHC stereocilia, partially deflecting them, and thereby facilitating or inhibiting IHC sensitivity.

These active OHC properties provide an explanation of an unusual phenomenon known as otoacoustic emissions (OAE), where the cochlea generates sounds by rapidly contracting and relaxing OHC. These OAE can be spontaneous or evoked in response to pure tone stimuli. Spontaneous OAE, although uncommon, can be detected by the unaided ear (Sims *et al.*, 1991). Evoked OAE can be used to assess OHC function and as a screen for functional integrity of the cochlea (see Chapter 7).

The molecular basis of auditory function still remains largely uncharted territory. Progress is being made, though, as a consequence of studies of the molecular genetics of hereditary deafness. As genes are identified as the basis for hereditary deafness, the products of those genes then become subjects of study that advance our understanding of cochlear function at the molecular level (Richardson *et al.*, 2011).

Cochlear information processing

Recordings from hair cells and spiral ganglion afferents demonstrate that for low-frequency auditory stimuli, the neurons fire in synchrony with the sound oscillations for frequencies up to about 1 kHz. At higher frequencies the cells cannot keep up with the stimuli due to the refractory period of the nerve cells. Thus, conveying information to the brain about the frequency content of sounds requires a second mechanism in addition to simple frequency following.

When sound waves enter the cochlea through the oval window, they produce deflections of hair cell stereocilia, but in a non-random pattern. Specific frequencies have regions of optimum sensitivity along the length of the organ of Corti, with high frequencies (short wavelengths) being detected at the basal coil of the cochlea and low frequencies (long wavelengths) being detected at the apical coil. This frequency sensitivity within the cochlea is known as the Place Theory. The complex mixture of frequencies of environmental sounds becomes mapped along the organ of Corti, in a manner similar to the mathematical process of Fourier analysis. Hair cells at any one position along the stretch of the basilar membrane respond optimally to a specific narrow range of frequencies. Neurons projecting into the CNS from these hair cells inform the brain that the sound input contained a frequency within the narrow range to which they respond – in addition to the frequency-following mechanism described above for low frequencies. Figure 2.5 shows this effect in the tuning curves of two adjacent hair cells that respond optimally to a range of frequencies centered around 18 kHz; the cells only respond to other frequencies when they are presented at very high intensities. The mapping of frequencies along the organ of Corti is known as tonotopic organization, a feature that is maintained as auditory information is advanced along neural pathways all the way to the cerebral cortex.

What produces this frequency selectivity? As the cochlea coils around the modiolus from base to apex, the properties of the basilar membrane change: the membrane widens by a factor of five and the stiffness decreases by a factor of about 100. As the mechanical properties of the basilar membrane change, the frequency at which that area of membrane resonates – or deflects – the greatest distance also changes. It can be helpful to think of sound traveling up the cochlea based on the wavelength of the sound: a low frequency has a long wavelength, so it will take a greater distance along the basilar membrane for that frequency to complete one wavelength, while a high frequency's short wavelength completes its wavelength in a short distance.

Information about the amplitude or loudness of a sound is conveyed by increasing numbers of activated hair cells and spiral ganglion cells that result from larger deflections of the basilar membrane with louder sounds, as well as increased numbers of action potentials per second in afferent fibers. The larger basilar membrane deflections produce greater deflections of hair cell

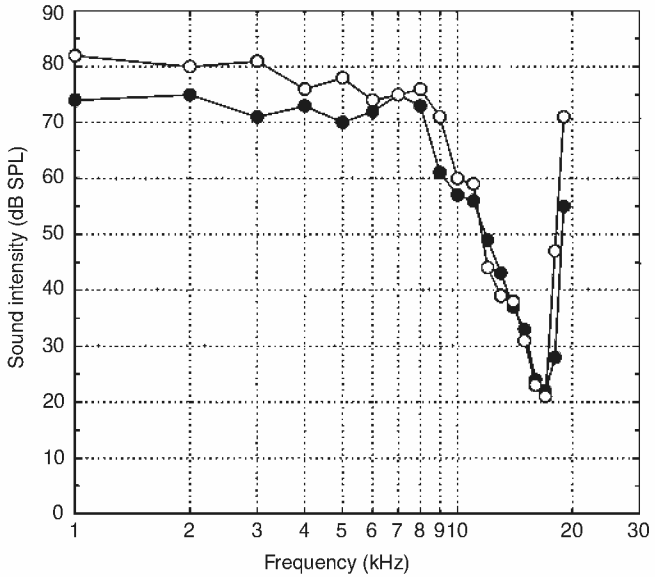

Fig. 2.5. Hair cell tuning curve, demonstrating the narrow range of frequencies to which two adjacent hair cells (○, ●) respond, in this case centered around 18 kHz (from Strain and Myers, 2004).

stereocilia, and inclusion of adjacent hair cells on the membrane. Loudness is reflected in the amount of activity in the auditory nerve.

As seen in Fig. 2.1, dogs and cats have similar audiograms: their hearing frequency range is similar, the frequency range of greatest sensitivity is similar and their sensitivities are similar. Considerable variation exists across the animal kingdom in regard to hearing ranges, as shown in Table 2.2. Reported hearing ranges are usually based on behavioral testing, where subjects are trained to respond for a reward when they detect a test tone. Since testing conditions and criteria often differed, comparisons between species should be made with caution.

Sound Localization

In addition to detecting the presence of sound, the auditory system also enables an animal to localize the source of a sound in the three-dimensional space around it. Sound localization in the horizontal plane is accomplished by the brain analysing differences in the same sounds detected by both ears. Differences between ears are compared for sound intensity and for sound

Table 2.2. Approximate frequency hearing ranges for various species (data from Warfield, 1973; Fay, 1988; and Echteler *et al.*, 1994).

Species	Approximate range (Hz)
Human	64–23,000
Dog	67–45,000
Cat	45–64,000
Cow	23–35,000
Horse	55–33,500
Sheep	100–30,000
Rabbit	360–42,000
Rat	200–76,000
Mouse	1,000–91,000
Gerbil	100–60,000
Guinea pig	54–50,000
Hedgehog	250–45,000
Raccoon	100–40,000
Ferret	16–44,000
Opossum	500–64,000
Chinchilla	90–22,800
Bat	2,000–110,000
Elephant	16–12,000
Beluga whale	1,000–123,000
Porpoise	75–150,000
Goldfish	20–3,000
Catfish	50–4,000
Tuna	50–1,100
Bullfrog	100–3,000
Tree frog	50–4,000
Canary	250–8,000
Parakeet	200–8,500
Cockatiel	250–8,000
Owl	200–12,000
Chicken	125–2,000

arrival time. Louder sounds and earlier arrival times at one ear indicate that the sound originated in the direction of that ear. Typically the animal then turns its head toward that ear until loudness and arrival time are the same – for repeated sounds. Interaural sound arrival time differences are most effective for localizing lower-frequency sounds, up to 1–2 kHz, a function of the width of the head, while interaural intensity differences are more effective

for localizing higher frequencies. Animals with muscle control of the pinna, such as cats and some dogs, can further enhance localization ability by changing orientation of the pinna; animals without such muscle control can only move their head to improve localization.

Localization of sound in the vertical plane must rely on different mechanisms, since interaural differences will not exist for sound sources that only differ in elevation. Species with an external pinna structure use reflections off the cartilaginous structures of the pinna, which will produce small differences between the arrival of direct sound waves and later reflected sound waves. In owls, which do not have a pinna, the ear canals are located at different heights on their head. Some other species, like bats, use reflections of emitted sounds in sound localization.

Sound localization in unilateral deafness is impaired, with the subject often turning toward the side of the good ear no matter where the sound's origin, but some animals adapt with time and develop better localization skills.

Central Projections

The major retrochochlear projections of the auditory system, which are complex, are shown in Fig. 2.6. Spiral ganglion fibers from hair cells enter the brain in CN VIII and synapse on the dorsal or ventral cochlear nuclei. From there, fibers project in the trapezoid body to the olivary complex. Olivary complex and some dorsal cochlear nuclei neurons project in the lateral lemniscus to the caudal colliculus, to the medial geniculate nucleus of the thalamus and finally to the auditory cortex on the temporal lobe. Not all pathways are shown, including multiple feedback paths from higher to lower centers. Fibers can decussate at the level of the cochlear nuclei/olivary nuclei and the caudal colliculus. Tonotopic organization of the sensory information is maintained all the way to the cortex. Rostral to the olivary nuclei the auditory projections on each side contain both left and right ear information. As a result, it is difficult for a lesion or damage to result in 'central' or retrocochlear deafness without significant impact on other neurologic function.

As auditory information is projected to higher centers, more complex aspects of auditory processing occur. For example, neurons in the olivary complex receive inputs from both the left and right cochlea, permitting comparisons. This is thought to be the region where localization comparisons of arrival latency and relative loudness are made. Efferent fibers to the middle ear muscles originate in the trigeminal and facial nerves; the brainstem nuclei of these cranial nerves must receive loudness information to trigger reflex contractions of these muscles in response to loud noises. While the various higher processes are neither well studied nor well understood, it is likely that they function in a manner similar to the visual system where simple features are first detected, such as the presence of edges or lines, then increasingly

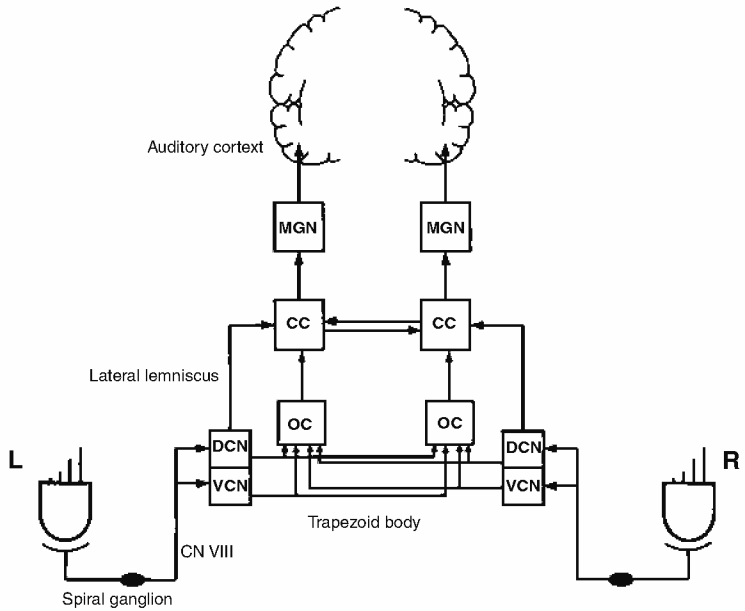

Fig. 2.6. Central auditory pathways. Spiral ganglion fibers from hair cells enter the brain in the eighth cranial nerve (CN VIII) and synapse on the dorsal (DCN) or ventral (VCN) cochlear nuclei. From there fibers project in the trapezoid body to the olivary complex (OC). OC and some DCN neurons project in the lateral lemniscus to the caudal colliculus (CC), to the medial geniculate nucleus (MGN) of the thalamus and finally to the auditory cortex on the temporal lobe. Not all pathways are shown. Fibers can decussate at the level of the cochlear nuclei/OC and the CC (modified from Strain and Myers, 2004).

more complex features are detected, such as color, transient or continued presence, movement and so on.

Upon arrival at the temporal cerebral cortex, the auditory signal is mapped by frequency, with higher frequencies projected to the medial temporal lobe and lower frequencies projected to the lateral lobe. Cortical perception is a complex process that is not well understood. Based on our knowledge about information processing in other sensory systems, the auditory information first arrives at an auditory primary cortical area on the temporal lobe, where the features of the sound are identified. That analysed information is then conveyed to an adjacent secondary cortical area where it is recognized – if familiar – or classified based on past experience. The results of this processing are then conveyed to other cortical areas for appropriate responses, such as vocalization or initiation of motor responses.

The brains of animals congenitally deaf or become deaf later in life have been shown to exhibit plasticity – a change in function. Ferrara and Halnan

(1983) reported significant auditory cortex reduction in deaf Dalmatian puppies. In congenitally deaf white cats, the area of cerebral cortex dedicated to auditory function is reduced below normal, while adjacent areas dedicated to visual function enlarge (Lomber *et al.*, 2010). The deaf cats exhibited improved localization in their peripheral visual fields and a lower visual movement detection threshold. From an efficiency perspective it makes sense that an area of the brain that is going unused – due in this case to deafness – gets reassigned to other use. Similar remodeling or plasticity has been observed for the visual cortex of blind subjects.

For more depth and detail on the physiology of the auditory system, readers are directed to references such as Pickles (1988), Geisler (1998), Jahn and Santos-Sacchi (2001) and Schwander *et al.* (2010).

Forms and Mechanisms of Deafness

3

Hearing loss or deafness can seriously impact an animal's ability to cope and survive in its environment. However, deafness is not a monolithic disorder, and knowledge of an animal's type of hearing loss and its cause is useful in understanding the limitations deafness imposes on the animal's life as well as any impact on its potential breeding future.

Classification of forms of deafness can be approached from differing perspectives, generally based on selecting between pairs of descriptors. Deafness can be unilateral, affecting just one ear, or can be bilateral. Hearing loss can be partial, where some function remains, or it can be total. Deafness can be syndromic, associated with some other phenotypic change or disease, or it can be non-syndromic. These and other descriptors that can be used to classify deafness will be considered in turn below.

Unilateral versus Bilateral Deafness

When spoken of in general terms, deafness is often assumed – unconsciously perhaps – to affect both ears. This is likely because of the fact that bilateral deafness is relatively easily recognized whereas unilateral deafness is seldom obvious from an animal's behavior and requires specialized testing to identify. However, it is possible for a single ear to be affected in a variety of forms of deafness. In hereditary deafness in dogs and cats, where the deafness is usually associated with white pigmentation, animals can be deaf in one or both ears. Based on large population studies of dog breeds affected with this disorder (Strain, 2004), there are typically two to four puppies in a litter with unilateral

deafness for every bilaterally deaf puppy. When these animals are not identified as being affected with hereditary deafness, they may end up being bred and propagating the disorder within their breed. Hereditary unilateral deafness is uncommon in humans (Dikkers *et al.*, 2005).

Various forms of non-hereditary deafness may also be expressed as unilateral or bilateral. Drug or chemical ototoxicity, unless it results from unilateral topical exposure, will usually affect both ears, as will age-related hearing loss, known as presbycusis. Otitis interna will usually cause unilateral deafness unless both inner ears are infected. Noise trauma, such as that from gunfire, will generally produce bilateral deafness.

Animals with unilateral deafness still respond to sound stimuli via detection by the unaffected ear. This condition can be difficult to detect behaviorally – the only deficit is in localizing the origin of a sound. If a unilaterally deaf puppy or kitten is presented with an auditory stimulus on the affected side but originating outside the animal's visual field, it often will turn in the direction of the good ear. Careful testing of animals away from their littermates may enable identification of affected animals, but not with reliability. The brainstem auditory evoked response (BAER) is the gold standard for objective determination, one ear at a time, of whether hearing function is present (see Chapter 6). With time, unilaterally deaf animals often compensate and develop the ability to better determine the origin of sounds, so that no obvious behavioral evidence of their disability remains. Pet owners are often surprised to learn that unilaterally deaf animals make bilateral conjugate ear movements in response to stimuli detected by the hearing ear, and bilaterally deaf animals are capable of vocalizations in the same way that pre-lingually deaf children vocalize and learn to speak, albeit often with distorted speech.

Partial versus Total Deafness

When both ears of an animal lose all auditory function it will obviously not respond to auditory stimuli unless it instead detects the stimulus or its source through its other sensory modalities such as vibration, vision, or touch. Total bilateral deafness is commonly seen with hereditary deafness. In a very small number of affected animals some hearing is preserved at very high frequencies, but it is of little value in assisting with everyday communication needs.

In most other forms of hearing loss, the deficit is partial, at least initially. This includes noise trauma, usually from gunfire (which produces cumulative damage), age-related hearing loss or presbycusis (which is a progressive disorder), and drug ototoxicity; with the latter the loss is usually far advanced before the owner is aware of it. Behaviorally, affected dogs will exhibit a reduced range at which they detect and respond to whistles or vocal signals, which can be especially evident with hunting and field trial dogs. Otherwise

the animals will become progressively unresponsive to normal auditory stimuli or cues. Owners are usually unaware of partial hearing loss unless it has progressed and the deficit becomes significant. Clinical assessment of the extent of partial hearing loss is difficult since it requires knowledge of what a normal hearing threshold should be in a species – and even in a breed within a species because we do not know whether thresholds differ between breeds – and also the current threshold in the affected animals. Threshold determination can be performed using the BAER, either for clicks or pure tone stimuli, but determination of the thresholds requires anesthesia and significant time, and these determinations are not offered clinically.

Syndromic versus Non-syndromic Deafness

In some forms of hereditary deafness, the hearing loss is accompanied by other system diseases or phenotype abnormalities. In the absence of such accompanying features, hereditary deafness is classified as non-syndromic. A listing of human syndromic and non-syndromic hereditary hearing disorders is maintained on the Hereditary Hearing Loss Home Page (Van Camp and Smith, 2011), with links to relevant publications and listings of responsible genes and gene loci. Several human syndromes that potentially have relevance to dogs or cats are discussed here, but most syndromes do not have, and are not likely to have demonstrated naturally occurring animal equivalents.

In human Usher Syndrome, a recessive disorder, affected individuals have sensorineural hearing loss or complete deafness and retinitis pigmentosa (RP), a condition causing night blindness and progressive loss of peripheral vision. There are three clinical types of Usher syndrome (Types 1, 2, 3) that differ in severity, age of onset, and presence of concurrent vestibular dysfunction. At least nine human gene defects have been identified as causing Ushers. Although some deaf dogs and cats may also develop visual problems up to and including blindness, there is no identified dog or cat equivalent of Usher syndrome. Knockout mice and zebrafish have been used as animal models for Usher Syndrome because of the relative ease of genetic manipulation in these species. Progressive retinal atrophy (PRA) in dogs is similar to human RP, and at least one syntenic gene has been shown to cause PRA in dogs and RP in humans (Tuntivanich *et al.*, 2009), but none of the various forms of canine PRA is associated with deafness. The numerous genes shown to be mutated in Usher Syndrome are important in the development and maintenance of various structural elements in the cochlea, including hair cells, and in the retina.

The human Alport Syndrome, also known as hereditary nephritis, is a kidney disorder consisting of glomerulonephritis and terminal kidney disease, accompanied by sensorineural hearing loss and occasionally by slow deterioration of vision. The disease is caused by at least three identified mutations in the genes for collagen; X-linked, autosomal recessive, and

autosomal dominant forms have been described. Canine equivalents of the renal disease component of Alport syndrome have been reported (Cox *et al.*, 2003; Davidson *et al.*, 2007), but no hearing loss was identified in the affected animals. The affected genes for this disorder are responsible for establishing the collagen network that forms the basement membranes that support cells in the cochlea, retina, and kidney.

The human Waardenburg syndrome consists of (i) dystopia canthorum – lateral displacement of the inner canthus of each eye, resulting in a widely spaced appearance; (ii) pigmentation abnormalities of the hair, skin, and iris – different-colored irises (heterochromia iridis, with one usually blue) and a white stripe in the hair and beard with premature graying are common; and (iii) sensorineural deafness. Four types of Waardenburg syndrome are recognized (I, II, III, IV), with Type III also including upper limb abnormalities and Type IV also including Hirschsprung disease, which affects the gastrointestinal system. Type II has four subtypes, and at least seven gene defects have been identified for the disorder. Most Waardenburg syndrome cases have an autosomal dominant inheritance, but a few are recessive. The genes responsible for Waardenburg syndrome are associated with either pigmentation and melanocytes or development of facial and inner ear structures.

Pigment-associated hereditary deafness is common in dogs and cats, and can also be seen in ferrets, pigs, cattle, horses, and various other mammalian species. Affected animals are often, but not always, lacking pigment in one or both irises, giving them a blue color, similar to the blue eyes in Waardenburg syndrome subjects, and they are also lacking pigment in the tapetum lucidum at the back of the eye, resulting in a red-eye appearance in photographs. However, these pigmentation patterns are not associated with visual system abnormalities, and as a result the presence of deafness with these pigmentation abnormalities is not generally spoken of as a syndrome. It is not uncommon for lay publications and websites to refer to the condition as canine or ferret Waardenburg syndrome, for example, but there is no evidence that the disorders in animals result from the same genetic defects as those seen in humans. Nevertheless, the genes shown to be mutated in the various Waardenburg syndrome types are also involved in pigmentation patterns in dogs, discussed in Chapter 4, so an association may well be established in the future.

Peripheral versus Central Deafness

Deafness may also be classified as either peripheral – involving the outer, middle, or inner ear – or central, also known as retrocochlear deafness. Central deafness is difficult to produce without other severe CNS signs, because left and right ear signals co-mingle in the brain, starting at the level of the olivary nuclei and at more rostral levels (Chapter 2). The presence of central deafness can be difficult to document clinically. When it does occur it is

likely to be the result of a space-occupying mass or stroke; in humans it can also result from demyelinating disorders. These conditions are likely to produce unilateral deafness at the cranial nerve or brainstem levels, or they may affect auditory pathways higher on the neuraxis where left and right ear information is transmitted bilaterally, which is expressed clinically as overall reduced hearing. As a result, the owner may be unaware of the hearing loss.

When auditory information reaches the cerebral cortex, it is first processed in the primary auditory cortex on the temporal lobe, and is then further processed in the adjacent secondary cortex, where recognition and other complex analyses of sound occur. In humans a condition known as auditory agnosia may occur following damage to the secondary auditory cortex. In this condition sounds are perceived but not recognized. It is unknown whether such a disorder occurs in dogs or cats.

Forms of Peripheral Deafness

When deafness or hearing loss is peripheral, it is useful for descriptive purposes to classify the loss on the basis of three pairs of descriptors. The deafness can be (i) inherited or acquired, it can be (ii) congenital or later onset, and it can be (iii) sensorineural or conductive. As a result, one type may be hereditary, congenital, sensorineural deafness and another may be acquired, later onset, conductive deafness. Examples of the types of peripheral deafness that are observed clinically in dogs and cats are summarized in Table 3.1.

Inherited versus acquired deafness

Hereditary deafness is the most common form of deafness in dogs and cats, and it is usually associated with pigmentation genes. In most dog breeds the association is with either the recessive piebald gene or the dominant merle gene; in cats it is the dominant white gene. Hereditary deafness is also observed in a few dog breeds that do not carry either the piebald or merle gene, primarily the Doberman pinscher, puli, and pointer. Although usually associated with certain pigmentation genes, hereditary deafness is not yet understood at the molecular genetic level, and even the modes of inheritance are not established. Hereditary deafness is discussed in detail in Chapter 4. With one possible exception, primary secretory otitis media in Cavalier King Charles spaniels, there are no known forms of hereditary deafness that are not congenital, so later onset deafness is assumed to be acquired. One recent preliminary report described what was suggested to be late onset sensorineural deafness in three border collie families (Chu and Schmutz, 2008), but it will be necessary to differentiate these cases from an acquired cause.

The mechanisms of inheritance of hereditary deafness in dogs and cats are not known at present, which greatly limits breeding options for breeder

Table 3.1. Classifications and examples of different types of peripheral deafness in dogs and cats.

	Sensorineural		Conductive	
	Congenital	Later onset	Congenital	Later onset
Hereditary	Pigment-associated Non-pigment-associated (Doberman, puli)	None known	None known	Primary secretory otitis media (Cavalier King Charles spaniel)[a]
Acquired	Perinatal anoxia Dystocia Intrauterine ototoxin exposure	Ototoxin exposure Otitis interna Presbycusis Noise trauma Physical trauma Anesthesia-associated Undetermined	Ear canal atresia	Otitis externa Otitis media Cerumen impaction Ear canal inflammation (awns) Ear canal foreign bodies Middle ear polyps Otosclerosis

[a]Hereditary basis suspected but not confirmed.

owners of animals with deafness or animals that have produced deaf offspring. Unilaterally deaf and bilaterally deaf animals should not be bred, since doing so increases the likelihood of producing additional affected animals; unilaterally deaf animals still have the hereditary defect. Hearing animals that have produced deaf offspring raise issues of whether they too should not be bred. The most conservative advice argues against any subsequent breeding of either the sire or the dam. At a minimum, the breeding that produced deaf individuals should not be repeated and breeding with animals closely related to the initial sire or dam should be avoided. In the absence of an understanding of how the deafness is inherited, it must be assumed that both parents contributed to causing the deafness.

Acquired deafness is any deafness that is not hereditary. Onset may be in early life, midlife, or in old age. It may be congenital or later onset, and it can be sensorineural or conductive (Table 3.1).

Congenital versus later onset deafness

Congenital literally means 'with birth,' and the term is used in practice to describe events or conditions present at birth as well as those that appear

shortly thereafter (Strain, 1999). Nearly all cases of congenital deafness in dogs and cats are hereditary. Both species are born with their ear canals still closed, with postnatal development of the auditory apparatus still underway (Strain *et al.*, 1991). Deafness in these cases actually develops at about three weeks of age, at approximately the age when the ear canals open. Hereditary congenital deafness in the Doberman pinscher, which is not pigment-associated, is usually also accompanied by vestibular system signs, primarily head tilt, circling behavior, and ataxia. The deafness is permanent, whereas the dogs in time adapt and show few if any vestibular signs.

Acquired causes of congenital deafness may include perinatal anoxia, especially with dystocia, and intrauterine exposure to ototoxic compounds distributed systemically within the dam. These causes of deafness are uncommon.

Later onset deafness describes all forms of deafness that are not congenital. These can occur in puppies and kittens any time after the immediate postnatal period of three to five weeks, but more often develop later in life. There have been no hereditary forms of late onset sensorineural deafness reported in dogs or cats. The condition of primary secretary otitis media, which occurs primarily in Cavalier King Charles spaniels (Stern-Sertholtz *et al.*, 2003), may be a form of later onset hereditary conductive deafness, since it is mostly breed-specific (also reported in one each of Dachshund, boxer and Shih Tzu), but a hereditary basis has not been confirmed. A possibly relevant mouse model of chronic otitis media with effusion has recently been reported (Noben-Trauth and Latoche, 2011). Recent studies of possible genetic mechanisms for otitis media in humans and mice (Rye *et al.*, 2011) open the possibility that some some dog breeds may likewise have a genetic predisposition to otitis media.

Sensorineural versus conductive deafness

When deafness results from the primary or secondary death of hair cells in the cochlea, it is known as sensorineural deafness. This includes the hereditary patterns of deafness described above as well as various acquired congenital or later onset forms of deafness (Table 3.1). Non-hereditary congenital causes of sensorineural deafness include perinatal anoxia, dystocia, and intrauterine exposure to ototoxic chemicals or drugs. Later onset sensorineural deafness may result from exposure to ototoxic chemicals or drugs, otitis interna, aging (presbycusis), noise or physical trauma, and anesthetic procedures. The cause of non-hereditary sensorineural deafness is often unknown.

A useful classification scheme for describing inner ear abnormalities has been proposed that is based on identified hereditary mutations observed in mice (Steel and Bock, 1983; Steel, 1995), where well over 70 identified mutations are known, as well as on observations in humans and other species that include the dog and cat. These abnormalities are classified as morphogenetic,

neuroepithelial, or cochleo-saccular. Morphogenetic abnormalities include all structural deformities of either the bony or membranous labyrinths. The causative mutations affect early development of the labyrinth, resulting in a wide range of inner ear deformations. These can include stunting or even the absence of individual vestibular semicircular canals, a reduction of the length of the cochlear duct, or even agenesis of all or portions of the labyrinth. These forms of deafness may be sensorineural, but usually they are structural disorders and are not easily classifiable as either sensorineural or conductive. There is no identified form of hereditary morphogenetic inner ear abnormality in dogs or cats, although individual cases may be observed, albeit rarely. The rarity suggests, but does not confirm, that these cases are not hereditary.

Neuroepithelial hereditary inner ear abnormalities appear at the time that the organ of Corti is ending its developmental sequence. Cochlear hair cells degenerate after following the normal developmental pattern. Reissner's membrane and the stria vascularis appear unaffected until long after the neuronal degeneration. Vestibular system function may or may not be involved, and the abnormalities are symmetrically expressed in both ears. The hearing loss appears to always be total, but this has not been investigated. In some mutations, auditory function is never present, while in other mutations there is a progressive postnatal hearing loss (at least in mice). Mechanisms for the hair cell/organ of Corti degeneration have been identified in some mouse and human mutations. Congenital neuroepithelial hereditary deafness occurs in Doberman pinschers, accompanied by vestibular dysfunction, and may occur in a few other dog breeds, but it has not been reported in cats.

The mechanisms responsible for hereditary neuroepithelial deafness are, for the most part, not known. It is now recognized that many forms of hereditary epilepsy in humans and mouse models result from mutations in the genes responsible for neuron membrane ion channels, known as channelopathies, as well as mutations in genes responsible for enzymes involved in transmitter synthesis or metabolism. One form of human hereditary deafness – autosomal dominant progressive hearing loss, DFNA2 (Van Camp and Smith, 2011) – results from a defect in one type of potassium ion channel from the K_v7 family, the $K_v7.4$ channel, also known as KCNQ (Kim *et al.*, 2010; Lv *et al.*, 2010). These channels are present in large numbers in inner and outer hair cells and spiral ganglion neurons, where they play a role in maintaining cell transmembrane potentials by regulating potassium ion movements. Mutations in $K_v7.4$ channels cause elevations in intracellular calcium levels due to inhibition of the potassium channels, triggering apoptosis-mediated cell death. There undoubtedly are other ion channel gene mutations and other neuronal gene defects that cause hereditary neuroepithelial deafness.

Cochleo-saccular hereditary inner ear abnormalities likewise appear late in the development of the organ of Corti; this form is also known as Scheibe-type degeneration (Scheibe, 1892). The primary defect is in the stria vascularis, which is responsible for maintaining the high potassium ion

concentration in the endolymph of the cochlear duct. With strial degeneration the hair cells degenerate and Reissner's membrane collapses. With time other cochlear structures collapse and spiral ganglion neurons degenerate. In some forms there is also vestibular system degeneration, but this appears to affect only the saccule, hence the term cochleo-saccular degeneration. Expression of this abnormality can be asymmetrical, with only one ear affected, or both ears can be affected. The hearing loss is usually total; in rare cases hearing at very high frequencies is maintained, but in a frequency range that has limited usefulness for everyday activities and communication.

In most instances, cochleo-saccular deafness is associated with genes responsible for white or lightened pigmentation, which produce their pigment effects by suppressing melanocytes. Melanocytes in the cochlea and eye and most other body locations originate in the neural crest during embryogenesis, then migrate to their final destination as premelanocytes that mature into melanocytes (Alhaidari *et al.*, 1999; Hornyak, 2007). In the cochlea, melanocytes are normally present in the stria vascularis, where they participate in the endolymph ion-regulating functions of that structure. By mechanisms that are not completely understood, pigmentation gene effects on melanocyte function in the stria trigger its degeneration and the subsequent cascade of effects that include deafness. This form of hereditary abnormality is responsible for the pigment-associated deafness observed in many dog breeds that include the Dalmatian, Jack Russell terrier, and bull terrier, among others, and the deafness observed in white cats. Hereditary deafness in dogs and cats is discussed in detail in Chapter 4. Neuroepithelial and cochleo-saccular forms of cochlear degeneration can also occur from non-hereditary causes.

Conduction deafness results when sound transmission to the inner ear is reduced or blocked due to problems in the outer or middle ear. The hearing loss is usually partial initially, and pet owners do not become aware of the problem until the animal's ability to cope is exceeded. In the outer ear, later onset conduction deafness may result from otitis externa (Eger and Lindsay, 1997), cerumen impaction, or inflammatory responses to foreign objects such as grass awns. It can also result from chronic otitis externa, where calcification of the canal epithelium occurs and canal stenosis reduces the access of sounds to the tympanic membrane and subsequent structures. This is usually treated by a partial or total ear canal resection (Elkins *et al.*, 1981), which usually does not cause deafness if auditory function was present prior to surgery (Krahwinkel *et al.*, 1993; McAnulty *et al.*, 1995). Middle ear causes of later onset conductive deafness include otitis media, middle ear polyps, and otosclerosis. Primary secretory otitis media, which occurs primarily in Cavalier King Charles spaniels, may be a hereditary form of conductive deafness. This condition, also known as 'glue ear,' results from the development of a solid viscous plug in the middle ear, due either to increased production of viscous mucus by the lining of the middle ear cavity or to decreased mucus drainage through the eustachian tube (Stern-Sertholtz *et al.*,

2003). Other signs may include pain, various neurologic signs, and pruritus. It can affect one or both ears and occurs with intact tympanums and in the absence of otitis externa, strongly suggesting that the pathology originates in the middle ear. The condition is not thought to be from an infectious cause, but the mechanism is not otherwise understood; possible explanations include allergic or inflammatory reactions. A recent radiologic study (Hayes *et al.*, 2010) suggested a relationship between the disorder and pharyngeal conformation, possibly from a thick soft palate and reduced nasopharyngeal aperture. Treatment consists of removal of the plug, typically through a myringotomy, and treatment with corticosteroids; this procedure may need to be repeated multiple times before it is resolved – as many as six times in some cases. Alternatively a bulla osteotomy may be performed, but repetition of this surgery is probably not advisable. Implantation of tympanostomy tubes in the tympanic membrane, similar to the procedure used for children with chronic otitis media with effusion, has been reported to be successful in a small treatment population (Corfield *et al.*, 2008). Hearing studies have confirmed that the hearing loss is primarily conductive rather than sensorineural (Harcourt-Brown *et al.*, 2011).

Other Forms of Hearing Disturbance

Tinnitus

The perception of sounds that occur in the absence of external sounds is called tinnitus (Møller, 2007). Objective tinnitus is the perception of sounds generated by the body, usually the ear. These can result from turbulent blood flow near the cochlea or can be generated by the cochlea itself, in which case they are referred to as otoacoustic emissions (see below and Chapter 7). Although usually of low intensity, they can be heard by others when in close proximity or by means of a stethoscope. Subjective tinnitus – ringing in the ears – is the perception of phantom sounds when no actual sound is present; this is the form typically meant when tinnitus is used as a term without a modifier.

Subjective tinnitus consists of a spectrum of disorders producing phantom sensory signals, some of which produce sensations so severe as to be disabling. It may appear to originate in one ear or both, or possibly in the center of the head. It may be continuous or intermittent, and may be perceived as either single or multiple pure tones, or sounds described as hissing, roaring, whistling, chirping, clicking, buzzing and other insect sounds, electric, wind, waves, or more complex sounds. Although frequently unknown, the cause of tinnitus is most often from exposure to loud noises, especially gunfire or loud music, or presbycusis. Other identified causes include ototoxic drugs such as certain antibiotics (i.e., gentamicin), diuretics (furosemide), salicylate, and quinine, meningitis, encephalitis,

stroke, traumatic brain injury, and Ménière's disease, among others. The origin of the perceived sound is frequently peripheral in the cochlea, but may also be central.

Objective tinnitus has been reported in dogs and cats, usually as a high-frequency tone that does not appear to bother the animal. Since subjective tinnitus is subjective, it is not possible to know whether dogs or cats experience it. Some dogs that develop relatively acute deafness in mid or late life exhibit anxious behavior that may indicate tinnitus, but it may also simply be a response to the loss of hearing. Typically the behavior is short-lived, suggesting that the dog adapts if it is indeed a continuing sensation.

Hyperacusis

Hyperacusis is a condition of increased sensitivity to sounds that otherwise would not be bothersome. The condition can result from peripheral auditory disorders, central nervous system disorders, and hormonal and infectious disorders, but the cause is often unknown (Katzenell and Segal, 2001). Peripheral causes include noise-induced hearing loss and damage to the facial nerve (Bell's palsy). It often accompanies tinnitus and can appear before the tinnitus (Gu *et al.*, 2010). Some dog owners report an apparent hypersensitivity to sound, but there have been no studies of this condition in dogs or cats. BAER test results with these dogs have been normal.

Otoacoustic emissions

Otoacoustic emissions (OAE) can be spontaneous or evoked in response to introduced sounds. OAE are thought to reflect the function of outer hair cells of the cochlea, which contain contractile proteins that allow the cells to shorten or lengthen at a rapid frequency. Spontaneous OAE are present in most normal ears at very low levels, and can occasionally be loud enough to be detected by the unaided listener (Ruggero *et al.*, 1984; Sims *et al.*, 1991; Burke, 1996; personal observations by the author). Evoked OAE provide a sensitive early indicator of loss of auditory function. The use of evoked OAE to assess auditory function, which has been reported in dogs (Rogers *et al.*, 1995; Sockalingam *et al.*, 1998), is described in Chapter 7.

Treatment of Deafness

In general, treatment options for sensorineural deafness are very limited, since it has not been proven possible to regenerate nerve cells in mammals at present. Avian and other lower species retain the ability to regenerate at least some hair cells, and researchers have recently grown hair cells from mouse

stem cells (Oshima *et al.*, 2010), so regenerative function may become possible at some future time. Tinnitus associated with noise trauma hearing loss can improve. Some drug companies state that ototoxicity from the antibiotic gentamicin frequently improves, but that has not been the author's observation. Recent studies in humans have shown that concurrent administration of aspirin or other antioxidant/free radical scavengers with gentamicin can reduce or prevent the ototoxicity caused by this drug (Sha *et al.*, 2006; Chen *et al.*, 2007). It is not known whether delayed aspirin administration has any protective effect.

Owners of deaf dogs and cats often ask about the use of hearing aids for deaf animals. Hearing aids at their basic level are simply amplifiers. Accordingly, an aid is of no value when an ear is totally deaf. Potential applications in dogs or cats include presbycusis or other forms of sensorineural hearing loss where some auditory function remains. A pet hearing aid developed by an anatomist and an audiologist employing human aids proved to have mixed results (Marshall, 1990). Most dogs would not tolerate placement of an aid in the ear, but placement of the aid in a collar-mounted case with an attached flexible plastic tube ending in an acoustic foam ear piece was more acceptable. These units required training of both the dog and owner, and were most successful in small breed dogs, although they were still not universally accepted by all dogs. At present there do not appear to be hearing aids for dogs or cats available commercially.

The hearing loss of presbycusis is considered to be progressive and untreatable. However, a recent study (Ter Haar *et al.*, 2010) reported improved hearing thresholds in three dogs after implantation into the middle ear of an electrical vibrating transducer through a lateral tympanic bulla surgical approach. This device, the Vibrant Soundbridge®, is used for people with age-related hearing loss who do not obtain improved hearing with conventional hearing aids. Costs and practicality of these units are yet to be determined.

An implantable device has been used in humans – the Baha® implant – to treat conductive deafness, mixed sensorineural/conduction deafness, and unilateral deafness (Håkansson *et al.*, 1994). A titanium anchor screw is implanted in bone behind the ear and an electronic sound processor is attached to the external portion of the screw. Sounds are converted to vibrations, applied to the screw, and then conveyed through bone to the inner ear. Dogs have been utilized experimentally to evaluate system improvements (Sommerlad *et al.*, 2007), but the devices do not appear to have been tested for clinical application. Complications with the use of these devices include implant site infections, implant extrusion by bone growth, and mechanically dislodged implants, which is probably a serious factor arguing against their use in dogs. Device costs are approximately $4000 plus associated surgical implantation and other ancillary medical expenses.

Cochlear implants are increasingly being used to treat both post-lingual and pre-lingual sensorineural deafness. According to the National Institute on Deafness and Other Communication Disorders, the cost of this procedure

in the United States, including evaluation, surgery, device, hospitalization, and rehabilitation can run to $60,000. Congenitally deaf white cats were used as a deafness model for humans in the development of these devices (Kretzmer *et al.*, 2004; Ryugo *et al.*, 2005), but because of cost they are not available clinically for dogs or cats.

Conductive deafness can be treated by resolving the obstruction source in the outer or middle ear: treatment of the infections of otitis externa or media, cleaning the ear canal of excess cerumen or foreign objects, surgical repair of stenosis secondary to chronic otitis externa, or myringotomy, implantation of tympanostomy tubes, or bulla osteotomy for primary secretory otitis media.

Where deafness cannot be treated, primarily instances of sensorineural deafness, owners can be advised to provide a safe home environment by eliminating exposure to undetected dangers such as motor vehicles, to protect people from reflexive startle-induced bites, and in regard to methods for training in alternative communication techniques. This is discussed in more detail in Chapter 8.

Hereditary Deafness

4

Inheritance is by far the most frequent cause of deafness in dogs and cats. In most, but not all cases, the deafness is associated with the genes that cause white or lightened skin and hair (Strain, 2011a). Both the neuroepithelial and cochleo–saccular forms of hereditary inner ear pathology are observed (the latter more so), as described in Chapter 3. Later onset hereditary deafness has been identified in humans (Van Camp and Smith, 2011), but no later onset hereditary deafness has been confirmed in dogs or cats at this time. Thus, congenital deafness in dogs and cats is assumed to be hereditary and any later onset deafness is assumed to be acquired, although this may be shown in the future to not be true.

Dogs

Congenital deafness in dogs is usually, but not always, associated with white pigmentation (Strain, 2011a). This condition has been reported in 92 breeds (Box 4.1), but it must be noted that the deafness has not been shown to be hereditary in most of the listed breeds.

Determination of the presence of bilateral deafness in a puppy or kitten is complicated by the postnatal development pattern of their auditory systems and the time course over which deafness develops; it is also complicated because deaf young animals cue off of the behavior of their littermates, masking the deficits. Unilateral deafness can only be reliably determined by electrodiagnostic testing. The onset of behavioral responses to sounds in dogs and cats does generally not occur until opening of the ear canals, which

Box 4.1. Dog breeds with reported congenital deafness (Strain, 2011b). Dogs of any breed can be affected from a variety of causes, but breeds with white pigmentation are most affected.

Akita
American bulldog
American Eskimo
American hairless terrier
American Staffordshire terrier
American–Canadian shepherd
Anatolian shepherd
Australian cattle dog
Australian shepherd
Beagle
Belgian sheepdog/ Groenendael
Belgian Tervuren
Bichon Frise
Border collie
Borzoi
Boston terrier
Boxer
Brittany spaniel
Bull terrier
Bulldog
Canaan dog
Cardigan Welsh corgi
Catahoula leopard dog
Catalan shepherd
Cavalier King Charles spaniel
Chihuahua
Chinese crested
Chow chow
Cocker spaniel
Collie
Coton de Tulear
Dalmatian
Dappled Dachshund
Doberman pinscher
Dogo Argentino
English bulldog
English cocker spaniel
English setter
Fox terrier
Foxhound
French bulldog
German shepherd
German shorthaired pointer
Great Dane
Great Pyrenees
Greyhound
Havanese
Ibizan hound
Icelandic sheepdog
Italian greyhound
Jack/Parson Russell terrier
Japanese Chin
Kuvasz
Labrador retriever
Löwchen
Maltese
Miniature pinscher
Miniature poodle
Mongrel
Newfoundland Landseer
Norwegian Dunkerhound
Nova Scotia duck tolling retriever
Old English sheepdog
Papillon
Perro de Carea Leonés
Pit bull terrier
Pointer/English pointer
Presa Canario
Puli
Rat terrier
Rhodesian ridgeback
Rottweiler
Saint Bernard
Samoyed
Schnauzer
Scottish terrier
Sealyham terrier
Shetland sheepdog
Shih Tzu
Shropshire terrier
Siberian husky
Soft-coated Wheaten terrier
Springer spaniel
Sussex spaniel
Tibetan spaniel
Tibetan terrier
Toy fox terrier
Toy poodle
Walker American foxhound
West Highland white terrier
Whippet
Yorkshire terrier
(n = 92)

happens at approximately 5 days in cats and 12–14 days in dogs (Foss and Flottorp, 1974), although behavioral responses to loud noises can be evoked before ear canals open. Hearing thresholds become mature postnatally by 20 days in dogs (Strain, *et al.*, 1991) and 30 days in cats (Buchwald and Shipley, 1986) based on BAER measurements. Deafness in dogs and cats does not develop until after the first few weeks of life (Pujol and Hilding, 1973). In the

Dalmatian, postnatal auditory function development proceeds normally through the first three weeks, then the stria vascularis rapidly degenerates, proceeding to deafness. Histologic studies of deaf Dalmatians reported that signs of degeneration were present as early as one day after birth, and were clearly evident histologicly by four weeks (Johnsson *et al.*, 1973), although there was no way to be certain whether an ear studied early would have actually gone deaf. Degeneration begins in the middle coil of the cochlea, followed by the basal and then apical coils (Anderson *et al.*, 1968). Patterns of degeneration in other dog breeds with piebald are similar (Coppens *et al.*, 2000, 2003a); degeneration in dog breeds with non-pigment-associated deafness does not include degeneration of the stria vascularis (Coppens *et al.*, 2001, 2005). Immunohistochemical markers are available that permit distinguishing of different cell types in the stria for assessing the absence or presence of stages of strial degeneration in neonatal dogs (Coppens *et al.*, 2003b).

Pigment-associated deafness

Piebald

One of the earliest studies of deafness in animals was in Dalmatians, published more than a century ago (Rawitz, 1896). Until recently, most studies examined either Dalmatians or white cats (Lurie, 1948; Hudson and Ruben, 1962; Bosher and Hallpike, 1965; Anderson *et al.*, 1968; Suga and Hattler, 1970; Igarashi *et al.*, 1972; Johnsson *et al.*, 1973; Mair, 1973, 1976; Branis and Burda, 1985; Hiraide and Paparella, 1988). In dogs, most hereditary deafness is associated with one of the recessive alleles of the *S* pigment gene series. The dominant allele *S* (for self) produces solid color, while three recessive alleles are expressed with increasing amounts of white in the coat and skin: Irish spotting (s^i, Basenji, Bernese mountain dog), piebald (s^p, English springer spaniel, fox terrier, beagle), and extreme white piebald (s^w, Dalmatian, bull terrier, white boxer) (Little, 1957; Sponenberg and Rothschild, 2001; Karlsson *et al.*, 2007). Because these alleles are recessive, white dogs must be homozygous. The proposed molecular structures of the recessive alleles of the piebald gene are discussed below.

The overall incidence of deafness in dogs is not known. A retrospective review of records from 14 US veterinary teaching hospitals, covering 1.1 million canine visits over 10 years, reported an incidence of 2.56 cases per 10,000 (Hayes *et al.*, 1981), and a survey in Australia found 12 canine cases during one year from 37 veterinary practices, or an incidence of 0.32 cases/practice/year (Johnston and Cox, 1970). These assessments very likely underestimated deafness incidence, and also reflect both hereditary and acquired deafness cases.

Efforts to assess the prevalence of deafness in affected dog breeds began in the early 1990s (Holliday *et al.*, 1992; Strain *et al.*, 1992) and continue to the

present (Strain, 2004; Wood *et al.*, 2004; Platt *et al.*, 2006; Strain *et al.*, 2009; Di Risio *et al.*, 2010). Prevalence rates in the US range from 30% deafness (unilateral and bilateral) in Dalmatians to 1.3% in colored bull terriers (Strain, 2004). Data from European countries have reported lower prevalence rates for Dalmatians (Wood and Lakhani, 1997; Muhle *et al.*, 2002), possibly due to the disallowance of blue eyes in the Dalmatian breed standard of most European countries. Efforts to breed away from blue eyes reduced deafness prevalence in Dalmatians in Norway (Greilbrokk, 1994). Deafness prevalence rates for several dog breeds that have been studied are summarized in Table 4.1.

In the absence of an identified gene responsible for deafness, studies have examined phenotype traits for association with deafness in the hope of establishing indicators that could be used to reduce deafness prevalence. In a study of 1031 Dalmatians (Strain *et al.*, 1992), associations with deafness were examined for sex, hair coat color (black, liver, lemon, tri), pigmentation of eye rims, nose, and ears, presence of a patch, spot size and spot density, presence of pigmentation in the iris and retinal tapetum lucidum, and parent BAER hearing status. No associations were seen for sex, hair coat color, pigmentation of eye rims, nose, or ears, or spot size or density. There was a positive association between deafness and the presence of one or two blue irises, and the absence of pigment on the tapetum; the association between blue eyes and deafness has been shown for other dog breeds (Strain, 2004) and is also recognized in white cats (Delack, 1984). There was a positive association between deafness and unilateral or bilateral deafness in either or both parents. There was a negative association between deafness and patch: dogs with a patch were less likely to be deaf than dogs without a patch. (In Dalmatians, a patch is a solid-colored area of hair and skin – black or liver – present at birth when the hair of the rest of the puppy is still white.) The amount of white on an animal's body may, but does not always correlate with deafness. White bull terriers have a greater deafness prevalence than colored bull terriers (which still display considerable white color), parti-colored English cocker spaniels have a much higher prevalence than solid-colored dogs (Table 4.2), and percentage of white had a significant association with deafness in Jack Russell terriers (Comito *et al.*, 2011). However, the amount of black versus white on the ears of Dalmatians was not associated with deafness (Strain *et al.*, 1992), and long-held beliefs by breeders about distribution of white on the head and ears in various affected breeds have not been validated.

Some studies have found an association between deafness and sex in Dalmatians (Holliday *et al.*, 1992; Greilbrokk, 1994; Wood and Lakhani, 1997, 1998; Famula *et al.*, 2001), but several studies with very large subject databases have not (Hayes *et al.*, 1981; Strain *et al.*, 1992; Famula *et al.*, 2000), including one with 5333 dogs (Strain, 2004). Authors on both sides have argued that the others' results could be the result of sample bias, but no one has been able to provide a biological explanation of why there could be a gender difference, and many researchers accept that there is no difference.

Table 4.1. Breed-specific deafness prevalence rates for dogs.

Breed	*n*	Bilaterally hearing[a]	Unilaterally deaf	Bilaterally deaf	Totally deaf
Dalmatian	5638	70.0 (3971)	21.7 (1226)	7.8 (441)	29.6 (1667)
Border collie[b]	4143	97.6 (4043)	2.0 (84)	0.4 (16)	2.4 (100)
English setter	3656	92.1 (3368)	6.5 (236)	1.4 (52)	7.9 (288)
English cocker spaniel	1511[c]	94.2 (1423)	5.0 (76)	0.8 (12)	5.8 (88)
parti-colored	1425	94.1 (1341)	5.1 (72)	0.8 (12)	5.9 (84)
solid	76	98.7 (75)	1.3 (1)	0.0 (0)	1.3 (1)
Bull terrier	681	88.5 (603)	10.3 (70)	1.2 (8)	11.5 (78)
white	360	79.4 (286)	18.3 (66)	2.2 (8)	20.6 (74)
colored	312	98.7 (308)	1.3 (4)	0.0 (0)	1.3 (4)
Australian cattle dog	442	85.5 (378)	12.0 (53)	2.5 (11)	14.5 (64)
Australian stumpy-tail cattle dog[b]	315	82.2 (259)	12.4 (39)	5.4 (17)	17.8 (56)
Catahoula leopard dog[d]	162	59.9 (97)	15.4 (25)	24.7 (40)	40.1 (65)
Jack/Parson Russell terrier[d]	158	91.8 (145)	4.4 (7)	3.8 (6)	8.2 (13)
Jack Russell terrier[b]	1009	95.9 (968)	3.6 (36)	0.5 (5)	4.1 (41)
Havanese[d]	140	100 (140)	0	0	0
Whippet[d]	116	98.3 (114)	0.0 (0)	1.7 (2)	1.7 (2)
Boston terrier[d]	104	91.4 (95)	3.9 (4)	4.8 (5)	8.3 (9)

[a]Percentage (*n*).
[b]Data from Sommerlad *et al.* (2010) and De Risio *et al.* (2011); all other data from Strain (2004, 2011b).
[c]*n* values for color varieties do not sum to the *n* values for all dogs in a breed due to missing data.
[d]Insufficient numbers of animals tested for percentages to be reliable.

The association between deafness and parent hearing status is not surprising, given that the deafness is hereditary; this finding in fact supports the hereditary basis. An explanation for the other associations can be posited based on the effects of the pigment genes present in Dalmatians (see Schmutz and Berryere, 2007, for a review of canine pigmentation genes). Dalmatians have an underlying coat color of black (*B*, dominant) or liver (*b*, recessive). This color is covered up by the effects of the extreme white piebald allele; piebald is recessive, so Dalmatians are homozygous for s^w. Finally, the dominant ticking gene (*T*, Cargill *et al.*, 2005) acts to punch holes through the white to show the underlying coat color. The negative association with spot size or spot density is logical since it is controlled by *T*, not s^w. The remaining associations can be explained by how strongly s^w is expressed in a given dog. If s^w is weakly expressed, a patch results and deafness is unlikely (but still occurs, at a much lower prevalence rate). If s^w is strongly expressed, (i) pigmentation is suppressed in the iris, giving blue eyes; (ii) pigmentation is suppressed in the tapetum lucidum, giving a red eye in flash photography because retinal blood vessels are unmasked by the absence of normal pigments; and (iii) pigmentation is suppressed in the stria vascularis, causing deafness. The determinant for how strongly the piebald gene is expressed is at present unknown.

Because not all dogs with the piebald alleles are deaf or have blue eyes, it can be argued that this variable outcome is either the consequence of incomplete penetrance of a causative gene, or that one or more additional genes regulate the expression of the pigment gene. Support for the latter is suggested by the argument above where strong gene expression results in blue eyes and deafness, and weak expression results in the failure of the piebald gene to suppress melanocytes in areas of normally white skin, as seen in the Dalmatian patch.

The various alleles of the piebald gene series have been reported to be mutations of the gene *MITF* (microphthalmia-associated transcription factor) on dog chromosome 20 (CFA20; Karlsson *et al.*, 2007). *MITF* regulates the gene *tyrosinase*, which encodes for the rate-limiting enzyme in the synthesis of the pigment protein melanin. Karlsson *et al.* (2007) identified two mutations of *MITF* associated with piebald alleles, located in a 3.5 kb region upstream of the M promoter region of the gene. The first was a SINE (short interspersed element) insertion that was present in all piebald and extreme white piebald breeds, but missing in Irish spotting and solid dogs. The second mutation was a unique polymorphism – shortening of the promoter region – present in solid dogs. The s^i dogs lacked the SINE but had a longer variant at the promoter region. Dalmatians, which are s^w, were found to have the SINE insertion but a short allele at the polymorphism site, which suggested a unique mutation. However, other investigators have been unable to duplicate all of these findings (Schmutz *et al.*, 2009; Stritzel *et al.*, 2009) and another group is investigating an association between Irish spotting and the gene *KITLG* (c-Kit ligand) on CFA15, which plays a role in melanogenesis (Starr *et al.*, 2010). No

study has yet suggested an explanation for the association between the *MITF* mutations and deafness, although Stritzel *et al.* (2009) reported a significant association between *MITF*-associated microsatellite markers and deafness in Dalmatians.

The genetics of deafness in dogs is poorly understood. Studies of inheritance in Dalmatians and other breeds with piebald-associated deafness show that its inheritance is not straightforward. A recessive inheritance can explain deaf puppies that result from breeding two hearing dogs, but getting bilaterally hearing puppies from breeding two bilaterally deaf Dalmatians, observed in the author's laboratory, is harder to explain. Understanding the inheritance of deafness is complicated by its variable expression: dogs can be deaf in one or both ears, and it may even be that some dogs are genotypically deaf without expressing the deafness phenotype at all (see cryptic merles, below).

Most studies of canine deafness inheritance have employed complex segregation analysis, a statistical technique used to determine the pattern of inheritance of a trait, based on multi-generation pedigrees containing affected and unaffected subjects (Distl, 2007). In one Dalmatian study, analysis indicated that a single gene allele affected deafness prevalence but that the locus could not completely explain the inheritance (Famula *et al.*, 2000). A second study identified a single biallelic major locus where a recessive allele with incomplete penetrance best fit the data (Muhle *et al.*, 2002). Analysis in a third study indicated that the data best fit a monogenic–polygenic model with a recessive major gene (Juraschko *et al.*, 2003). A fourth study stated that the evidence for the presence of a single major gene affecting deafness was not persuasive (Cargill *et al.*, 2004). A study of Jack Russell terriers (which also carry piebald) from the same group found that a single locus model for deafness inheritance was not supported (Famula *et al.*, 2007). Finally, a recent study with Australian stumpy-tailed cattle dogs found support for an incompletely penetrant autosomal recessive model (Sommerlad *et al.*, 2010), and the authors reported mapping the deafness gene to CFA10 in the vicinity of a candidate gene known as *Sox10* using a whole genome screen with microsatellite markers. The *Sox10* gene plays a role in regulating *MITF* and mutations in it are associated with the pigment-associated human deafness syndrome known as Waardenburg type IV, which is autosomal recessive; a mutation in *MITF* is associated with Waardenburg syndrome type II, which can be either recessive or dominant (Van Camp and Smith, 2011). Clearly, the inheritance of deafness associated with the piebald alleles is not yet settled, and the complexity of the genetics of pigmentation provides numerous target genes for mutation (Steel and Barkway, 1989; Steel, 1995; Alhaidari *et al.*, 1999; Steingrímsson *et al.*, 2004; Hornyak, 2007).

Merle

The second canine pigment gene associated with deafness is known as merle (*M*), the dominant allele of the *SILV* locus, also known as *Silver* in mice. Merle

produces a pattern of random patches of diluted pigmentation alternating dark versus light over an underlying uniform coloration. This coat color pattern is called merle and is known as dapple in some breeds. Heterozygous merle (*Mm*) in an otherwise black dog produces a blue merle, and in an otherwise brown dog produces a red merle. Dogs heterozygous for the recessive allele (*mm*) have uniform color (except where acted on by other unrelated pigmentation genes that will not be discussed here). Homozygous merle carriers have been reported to be prone to both auditory and visual system disorders and even heterozygous dogs can be deaf. The merle pattern is seen in the collie, Australian shepherd, Shetland sheepdog, Catahoula leopard dog, Cardigan Welsh corgi, Dachshund, and Great Dane breeds, and less commonly in the Chihuahua, American pit bull terrier, American Staffordshire terrier, Beauceron, border collie, Koolie, poodle, Pyrenean shepherd, Old English sheepdog, American cocker spaniel, Pomeranian, Hungarian Mudi, Norwegian Dunkerhound, and others.

Few studies of the merle phenotype have been published. Among these is a study involving auditory function from a research colony of Dachshunds (*Tekels* in German) maintained in Hanover, Germany (Reetz *et al.*, 1977), with measurements taken from 38 dogs: 11 double merles (*MM*), 19 single merles (*Mm*), and 8 non-merles (*mm*). The authors reported hearing loss – slight to total, unilateral, or bilateral – in 6 (54.6%) of the double merles, in 7 (36.8%) of the single merles, and in none of the non-merles. Hearing was tested using the BAER, determining the threshold to click stimuli under sedation. Any threshold above 20 dB was considered to be abnormal, not because that is an accepted standard, but because one of the non-merle dogs had a 20 dB hearing threshold. Only one dog – a double-merle male – was totally deaf in both ears (threshold > 90 dB) and none of the dogs was totally deaf in only one ear (unilaterally deaf). Looked at this way, true bilateral deafness occurred in 9.1% (1/11) of the double merles and 0% of the single merles. The findings in this study were limited to a small, established population of one breed and have, unfortunately, been extrapolated to all breeds having the merle allele. The study was published in German with only an English abstract, and many who have cited the paper may have not read the entire article.

The high prevalence rates reported by Reetz *et al.* probably reflect their inclusion of dogs with partial hearing loss. Pigment-associated deafness typically presents as total deafness in one or both ears, so the reported partial hearing losses seem unlikely to be genetic or associated with the merle gene. Instead, they most likely reflect a combination of limited aural hygiene and otitis media, both of which cause conductive hearing loss, and otitis interna and noise-induced hearing trauma, both of which cause sensorineural hearing loss. The noise levels in institutional kennels are high, regularly exceeding 100 dB (Coppola *et al.*, 2006) and exposure to high noise levels produces cumulative hearing loss with time. Dogs in large kennels also do not often receive regular ear cleaning, leading to build-up of excessive cerumen,

and develop infections, due to humid environmental conditions and the use of hoses to clean facilities in kennel colonies. Floppy-eared breeds like the Dachshund also have inherent ear problems from poor air circulation. Both excessive cerumen and otitis externa or otitis media muffle sounds reaching the inner ear. Interestingly, of the 15 'hearing impaired' ears with thresholds between 25 and 50 dB in the Reetz study, only 3 were in males. Differences in kennel housing for females may have exposed them to greater noise levels in the whelping kennels.

Platt *et al.* (2006) BAER tested 2597 border collies in the UK; the total deafness prevalence the reported was 2.3% (unilateral) and 2.2% (bilateral). The authors found a significant association between deafness and dogs with merle or excess white coat pigmentation. Because genotyping was not performed, it is not known whether the dogs with excess white pigmentation were double merles or whether the pattern reflected the influence of a coexisting piebald gene. All border collies are thought to be homozygous for one of the piebald recessive alleles, and it is unknown what interaction may occur between merle and piebald.

We recently studied 153 merle dogs of different breeds and both sexes (Strain *et al.*, 2009), genotyping the dogs as single merles (*Mm*) or double merle (*MM*) using a DNA test (Clark *et al.*, 2006). Overall deafness prevalence in the merles of this study was found to be 4.6% (7/153) unilaterally deaf and 4.6% (7/153) bilaterally deaf (Table 4.2). These overall values are similar to those reported for dogs homozygous for the various alleles of the piebald gene: greater than those of the English cocker spaniel but comparable to or less than those of the Dalmatian and bull terrier (Strain, 2004). There was a significant association between hearing status and heterozygous versus homozygous merle genotype. In the single merles, 2.7% (3/113) were unilaterally deaf and 0.9% (1/113) were bilaterally deaf. In the double merles, 10% (4/40) were unilaterally deaf and 15% (6/40) were bilaterally deaf. There was no significant association with eye color or sex. The lack of eye color association may reflect the small sample size, since only 8 of the 14 hearing-affected dogs of this study had identified eye color, and 7 of them had blue eyes. The impact of the merle allele on auditory function appears to vary by breed (which is also the case for piebald breeds), as indicated by the differences between Catahoula leopard dogs (5.6% affected, 1 unilateral and 2 bilateral deaf out of 54, all three being *MM*) and Australian shepherds (18.8%, 6 affected dogs out of 32). Based on unpublished observations by the author, the collie-type breeds with merle (collie, Shetland sheepdog, border collie) appear to be more affected by deafness than some other breeds such as the Catahoula. However, larger numbers of BAER-tested and genotyped subjects will be required to determine whether significant breed differences exist.

The genomic location and sequence of the merle gene was recently identified and characterized on dog chromosome ten (CFA10) (Clark *et al.*, 2006) as a mutation in the dominant allele of the *SILV* pigment gene, shown in humans to encode for melanocyte protein Pmel17, which plays a role in

Table 4.2. Deafness prevalence in heterozygous and homozygous merle dogs (data from Strain *et al.*, 2009).

		Hearing[a]								
		All merle dogs			+/M			M/M		
Breed	*n*	B	U	D	B	U	D	B	U	D
Catahoula	54	51	1	2	25	0	0	26	1	2
Australian shepherd	32	29	1	2	26	1	0	3	0	2
Chihuahua	18	18	0	0	18	0	0	–	–	–
Collie	15	13	2	0	12	0	0	1	2	0
Shetland sheepdog	9	7	1	1	7	1	0	0	0	1
Cardigan Welsh corgi	8	7	1	0	7	0	0	0	1	0
Great Dane	6	4	1	1	4	1	0	0	0	1
Border collie	5	5	0	0	5	0	0	–	–	–
Dachshund	4	4	0	0	4	0	0	–	–	–
Cocker spaniel	1	0	0	1	0	0	1	–	–	–
Mix	1	1	0	0	1	0	0	–	–	–
	153	139 (90.8%)	7 (4.6%)	7 (4.6%)	109 (96.5%)	3 (2.7%)	1 (0.9%)	30 (75.0%)	4 (10.0%)	6 (15.0%)

+/M, heterozygous merle; M/M, homozygous merle.
[a]B, bilaterally hearing; U, unilaterally deaf; D, bilaterally deaf.

pigmentation patterns. The mutation responsible for merle is a 253 base pair SINE retrotransposon insertion just before Exon 11 that also includes a polyA tail (multiple adenine repeats). Expression of the merle phenotype requires the polyA tail of the SINE to be 90–100 adenine repeats in length. The same *SILV* mutation was confirmed to be present in dogs from 11 different breeds that carry merle except for a single point mutation in two breeds (Clark *et al.*, 2006).

Dogs having the merle genotype but not expressing the merle phenotype are known as cryptic merles (represented here by *M**). The SINE insertion that causes merle patterning contains a polyA tail. If the tail is truncated to ≤ 65 adenine repeats the dog does not express the merle phenotype, even though it carries the SINE insertion (Clark *et al.*, 2006). Two Australian shepherds genotyped in the study of Strain *et al.* (2009) illustrate this situation. A tested sire was a single merle, while the dog's tested daughter was a double merle. The daughter's dam (not genotype tested) was described by the owner as a black tricolor without any merle pattern. When bred, the daughter produced both merle and tricolor phenotypes. Because the daughter was a double merle but produced phenotypically non-merle pups, one of her merle alleles must have contained a truncated polyA tail. The black tricolor dam must have been a cryptic merle to explain a daughter that is a double merle, and the tricolor offspring of the daughter must also have been cryptic merles because they could only have inherited a normal merle allele or a cryptic merle allele from her. A heterozygous cryptic merle (*M*m*), when bred to a heterozygous normal merle (*Mm*), can produce heterozygous cryptic merles (*M*m*), heterozygous normal merles (*Mm*), non-merles (*mm*), and homozygous merles (*M*M*), the last displaying the phenotype of a heterozygous merle. The merle genotyping in the Strain *et al.* (2009) study did not specifically assess polyA tail length, but if it were severely truncated it would have been detected when the SINE insertion was identified. No heterozygous cryptic merles were included in the study because all dogs exhibited the merle phenotype; some of the genotyped double merles could have carried one cryptic merle allele, including the daughter described above. It is not known to what extent cryptic merles are present in merle breed populations.

Harlequin

A gene frequently associated with merle is harlequin (*H*), which produces ragged areas of color surrounded by clear white, as opposed to merle, which dilutes pigment (Sponenberg 1985; O'Sullivan and Robinson, 1989; Sponenberg and Rothschild, 2001; Clark *et al.*, 2008). It is most often associated with the Great Dane breed, but can also occur in other breeds like the Australian shepherd, collie, and Shetland sheepdog. Harlequin is a dominant modifier of merle that converts the dilute background into white; its phenotype is not present in dogs that are not carrying merle. Homozygous harlequins (*HH*) are thought to be prenatally lethal, as this genotype is not observed in live puppies. The harlequin gene locus has been localized to CFA9,

in a region where no other known pigmentation genes are located (Clark *et al.*, 2008). Since the harlequin phenotype is not seen in the absence of the merle gene, it is not surprising that no association between harlequin and deafness has been identified to date; deafness occurs in harlequin Great Danes, but the concurrent presence of merle in those dogs suggests that merle is the cause.

Pigment-associated deafness summary

The piebald gene is *MITF* on CFA20, although s^i may instead be *KITLG* on CFA15, and the merle gene is *SILV* on CFA10. These genes are responsible for their associated pigmentation pattern, but multiple genes have been shown to be involved in their regulation (Bondurand *et al.*, 2000) and studies to date have not been able directly to link deafness to *MITF* or *SILV* or a variety of other candidate genes (Brenig *et al.*, 2003; Rak *et al.*, 2003; Schmutz *et al.*, 2003; van Hagen *et al.*, 2004; Rak and Distl, 2005). Sommerlad *et al.* (2010) identified a locus for deafness on CFA10 in the vicinity of a candidate gene known as *Sox10*, and the *Sox10* gene plays a role in regulating *MITF*. It is unclear whether *Sox10* also plays any role in the regulation of *SILV*. It is becoming increasingly evident that many hereditary diseases are not monogenetic, but instead result from defects in any one of a number of interacting genes that form a network. Our understanding of polygenic disorders has had to expand to take these networks into account. At the current rate of studies on hereditary deafness, it is likely that clarification of this question will soon be available.

Sommerlad *et al.* (2010) reported the inheritance of deafness in Australian stumpy-tail cattle dogs to be incompletely penetrant autosomal recessive. Muhle *et al.* (2002) and Juraschko *et al.* (2003) suggested a similar mechanism in Dalmatians, while others (Famula *et al.*, 2000, 2007; Cargill *et al.*, 2004) found the mechanism to be more complex. Hopefully this question too will be resolved soon.

Dobermans

A condition of vestibular disease accompanied by congenital deafness in Doberman pinschers was first described by Chrisman (1980) and Skerritt (1983); Wilkes and Palmer (1992) later studied it in detail. Puppies developed head tilt, ataxia, and circling behavior between birth and 12 weeks of age, but usually adapted largely or completely to the vestibular signs. The earlier reports were unclear on the consistent presence of deafness, but all affected dogs in the latter study (Wilkes and Palmer, 1992) were bilaterally deaf by BAER tests at ages of three weeks or older. Unaffected litter mates had no vestibular signs and had normal hearing. Histologic study showed the neuroepithelial pattern of cochlear pathology, with loss of hair cells and with later loss of spiral ganglion cells but no abnormalities in Reissner's membrane or the stria vascularis. Hair cell loss was initially in the middle coil of the

cochlea, followed by the basal and apical coils. Pedigree analysis of 13 affected litters indicated a simple autosomal recessive mode of inheritance.

Similar patterns of congenital deafness with vestibular deficit have been reported in the beagle and Akita (de Lahunta, 1983), and possibly in Tibetan terriers (Bower, 1983) and Shropshire terriers (Igarashi *et al.*, 1972). No studies have yet identified a genetic basis for the disorder.

Pointers

In the mid 1960s, a female champion field trial pointer experienced what was described as a nervous breakdown. Investigators in Arkansas used her as the foundation stock in a breeding program to enhance the anxious behavior (Steinberg *et al.*, 1989, 1994), which resulted in an animal research model for anxiety disorders in humans (Klein *et al.*, 1988; Malloy *et al.*, 1992). This behavior emerged between three and nine months of age, and consisted of excessive timidity, elevated startle response, reduced exploratory activity, catatonic immobility, and cardiovascular changes in response to the presence of humans and other stimuli (Steinberg *et al.*, 1989); dog behavior was normal in the absence of these stimuli. In the process of developing this line of animals it was noticed that many of the anxious dogs were also deaf (Klein *et al.*, 1988; Steinberg *et al.*, 1989, 1994), with the BAER absent by approximately 100 days of age (Henthorn *et al.*, 2006). The majority of anxious dogs were bilaterally deaf, but not all, so the deafness was not completely penetrant. Pedigree analysis suggested an autosomal recessive mode of inheritance, but the authors pointed out that other modes of inheritance could not be ruled out due to the extensive degree of inbreeding in the colony (Steinberg *et al.*, 1994). Because this hearing disorder developed in the process of developing an inbred line of pointers, it is not clear whether pointer dogs in general are at risk of deafness.

Histologic studies indicated that the cochlear pathology of this disorder was of the neuroepithelial type (Coppens *et al.*, 2005). None of the BAER-tested anxious dogs had unilateral deafness, consistent with this type of hereditary deafness (Steel and Bock, 1983). A whole genome scan of DNA from affected pointers found linkage between deafness and several markers on CFA4 that flank the location of the syntenic human locus for cadherin-23 (*CDH23*) (Henthorn *et al.*, 2006), which is associated with mutations for a human recessive non-syndromic deafness (DFNB12) and for Usher's syndrome type 1D (USH1D), which is also recessive (Van Camp and Smith, 2011). Cadherin 23 is a protein component of the tip links between hair cell stereocilia (Siemens *et al.*, 2004; Müller, 2008). Sequencing of a portion of the *CDH23* gene in one dog identified a mis-sense substitution of proline to serine in the open reading frame of the gene, and the mutation was confirmed to be present in over 80 other affected dogs.

Cats

Deafness in blue-eyed white cats is perhaps one of the most widely recognized animal neurologic disorders in the public mind (Strain, 2007). This condition, which is linked to the dominant *W* gene, was described as early as 1829 (Bree, 1829; Chelsea, 1829) and mentioned in Darwin's *Origin of Species* (Darwin, 1859). Early descriptions stated that all blue-eyed cats were deaf, but this is now recognized not to be the case. This condition has been highly studied in the intervening years (Bamber, 1933; Wolff, 1942; Wilson and Kane, 1959; Bosher and Hallpike, 1965; Bergsma and Brown, 1971; Mair, 1973; Mair and Elverland, 1977; Pujol *et al.*, 1977; Rebillard *et al.*, 1981a, b; Saada *et al.*, 1996; Ryugo *et al.*, 1998, 2003).

White

The primary gene responsible for white pigmentation in cats is designated *W* (Searle, 1968; Vella *et al.*, 1999). It is dominant over other colors, so white cats can be either *Ww* or *WW*; cats that are *ww* express pigmentation patterns determined by other genes. There do not appear to be health problems beyond deafness in homozygous white cats the way there can be with homozygous merle dogs, and there are no vestibular abnormalities (Mair, 1973). Cats carrying the *W* gene are not always solid white, often having a colored spot on the head that may fade or disappear with age. Cat breeds carrying the *W* gene are listed in Box 4.2, but the list is likely incomplete. Whether the genotype is *Ww* or *WW*, the blue eyes and deafness have incomplete penetrance. Longhaired cats have been suggested to have a higher prevalence of blue eyes and deafness than shorthaired cats (Mair, 1973), but this has not been confirmed.

The cochlear pathology of the deaf white cat appears to have been first described in 1900 (Alexander, 1900) and subsequently in a variety of other studies (Wilson and Kane, 1959; Bosher and Hallpike, 1965; Suga and Hattler, 1970; Mair, 1973; Mair and Elverland, 1977). The pattern is that of cochleo–saccular degeneration, with degeneration of the stria vascularis, starting in the upper half of the basal coil, and collapse of the cochlear duct. However, other patterns of cochlear degeneration have also been reported (Rebillard *et al.*, 1981b; Ryugo *et al.*, 2003). Ryugo described two patterns beyond cochleo–saccular: excessive epithelial growth within the bony labyrinth, and excessive epithelial growth at the apex and a collapsed Reissner's membrane at the base (Ryugo *et al.*, 2003). In addition, partial deafness was observed in some ears of affected cats, suggesting that the pathology did not completely deafen all ears (Rebillard *et al.*, 1981a), but hearing thresholds determined by serial BAER recordings in another study did not change over time (Ryugo *et al.*, 2003), so the deafness is not progressive.

Box 4.2. Pure cat breeds carrying the *W* gene (Gebhardt *et al.*, 1979; Cvejic *et al.*, 2009; Strain, 2011b).

American shorthair
American wirehair
Balinese
British shorthair
Cornish rex
Devon rex
European white
Exotic shorthair
Foreign white
Highlander
Maine coon
Manx
Norwegian forest
Oriental shorthair
Persian
Ragdoll
Scottish fold
Siberian
Turkish angora
Turkish van
White

Based on these reports, the mechanisms of deafness in white cats are more complex than those in piebald dogs.

Studies of the prevalence of deafness in white cats mostly focus on domestic white cats rather than pure breed cats because of the greater availability of the former. Three contemporaneous studies examining a total of 256 white cats (Bosher and Hallpike, 1965; Bergsma and Brown, 1971; Mair, 1973; reviewed by Delack, 1984) found 12.1% to be unilaterally deaf and 37.9% to be bilaterally deaf, or a total of 50% affected. White cats that were the offspring of two white cats had prevalence rates of 52%, 89.3%, and 95.8% in the three studies. Crosses between white and pigmented cats produced 24.6–27.4% affected animals. A recent study of a colony of white deaf cats maintained at the University II of Frankfurt/Main in Germany analysed data on 104 white cats (Geigy *et al.*, 2007): 67% were bilaterally deaf and 29% were unilaterally deaf, or a total of 96% affected. Because the cats of this colony were inbred for purposes of generating deaf white cats – as were the cats of the studies of Bosher and Hallpike (1965), Bergsma and Brown (1971), and Mair (1973) – it cannot be said that these values reflect the prevalence of deafness in the general domestic white cat pet population. The heterozygous or homozygous genotype of the cats in these studies was often deduced from breeding records, but in some cases was unknown, somewhat clouding the data.

Data on prevalence of deafness in pure-bred white cats is limited. Included in the Geigy study (Geigy *et al.*, 2007) was the report of hearing prevalence data for three specific pure cat breeds – Norwegian forest, Maine coon, and Turkish angora – with deafness prevalence rates of 18%, 17%, and 11%, respectively, based on 329, 134, and 474 subjects. Analyses of iris and coat color were not reported, but the subjects included both white and pigmented

variants, so the deafness prevalence among the whites was likely similar to the approximate 50% that was reported for mixed-breed white cats, belying the assertion that deafness prevalence rates are lower in pure-bred white cats (Pedersen, 1991). The data also were probably underestimates because some were based on behavioral assessments instead of the more reliable BAER. However, they still represented some of the first published data on pure-bred cats instead of the usually mixed-breed cats of the Geigy colony and earlier studies. A more recent study assessed deafness prevalence in 84 client-owned pure-bred white cats by BAER for pre-breeding evaluations (Cvjec *et al.*, 2009). The authors reported 9.5% unilateral deafness and 10.7% bilateral deafness, or a total of 20.2% affected overall. Rates for individual breeds (with N values from 31 to 1) ranged from 0% up to 66.7%.

Blue eyes are one of the hallmarks of deafness in white cats, and it is common lore, but false, that all blue-eyed white cats are deaf. Bergsma and Brown (1971) and Mair (1973) examined the effect of blue eye color on deafness in their colonies. They reported finding (respectively) a prevalence of deafness (unilateral and bilateral combined) of 85% and 64.9% in cats with two blue eyes, 40% and 39.1% in cats with one blue eye, and 16.7% and 22% in cats with no blue eyes. So, not all white cats are deaf and not all blue-eyed white cats are deaf, but a great many of them are indeed affected.

Geigy *et al.* (2007) investigated whether a single gene could influence the two phenotypic traits of deafness and blue eyes using complex segregation analysis. Their analysis supported a pleiotropic gene, with heritability coefficients of 0.55 for deafness and 0.75 for blue eyes, but their data best fit a mixed inheritance (polygenic) model. A genomic location for *W* has not yet been identified.

White spotting

A dominant piebald gene (*S*), also known as white spotting, is also found in various cat breeds (Searle, 1968; Pedersen, 1991; Vella *et al.*, 1999). The phenotype can vary from a few white areas to nearly all white and can be highly variable; the pattern does not include spots, but areas of white. Some websites claim an association between *S* and deafness, but it is not clear whether a distinction between *S* and *W* has always been made, leading to confusion; there have, however, been no reports of deafness associated with its presence. Studies have identified a locus for *S* on feline chromosome B1, near the location for the pigment-associated gene *KIT* (Cooper *et al.*, 2005; Bach *et al.*, 2006). It has now been confirmed that the Birman white gloving pattern, which is produced by *S*, results from two adjacent mis-sense mutations in *KIT* and that there is no association with deafness (Lyons, L.A., personal communication, 2010); further, mutations for *W* were not found in the coding sequence for *KIT*, which supports that *W* and *S* are different genes.

Siamese and blue-eyed albino dilution

Cats carrying the underlying recessive c^s Siamese or c^a blue-eyed albino dilution pigment genes often have blue eyes, but without deafness, and it is not clear whether deafness is associated with these alleles at all. It has been suggested that the presence of c^s explains why purebred white cats are less often deaf than mixedbreed white cats (Pedersen, 1991), but no studies have provided support for this assertion about prevalence, which would seem unlikely. The feline C gene series, sometimes called the albino alleles, is a dilution gene, and includes the recessive alleles, with decreasing dominance, of Burmese dilution (c^b), Siamese dilution (c^s), blue-eyed albino (c^a), and albino (c). The dominant allele (C) produces full color (Vella *et al.*, 1999).

Albino

Albino cats are uncommon, and do not appear to be examples of true albinism (Vella *et al.*, 1999). Cats that are c^ac^a or cc are all white and only differ in having blue (c^ac^a) or pink eyes (cc); both are missing tapetal pigment. Iris color in this series progresses from blue in c^s, to pale milky blue in c^a, to pink in c. Deafness does not appear to affect cats with these alleles.

In true albinism in humans, affected individuals have hypopigmentation or absent pigmentation and may have other visual problems such as light sensitivity. It was originally thought that all albinism resulted from mutations in the tyrosinase gene (*TYR*), but this has been disproven. Human albinism is divided into oculocutaneous albinism (OCA) and ocular albinism (OA); the latter only affects pigmentation in the eye, while the former affects the eye, hair, and skin. Twelve genes have been identified as responsible for OCA in humans, and one gene is responsible for OA (Oetting *et al.*, 2003). All forms of OCA are autosomal recessive, while OA is X-linked recessive. None of these gene mutations is associated with deafness. However, at least two syndromes link deafness and albinism: the Tietz syndrome (hypopigmentation/deafness), which is autosomal dominant and caused by a mutation in *MITF* (Smith *et al.*, 2000), and the X-linked albinism–deafness syndrome (ADFN) (Shiloh *et al.*, 1990).

Later Onset Deafness 5

In addition to hereditary deafness, there are a variety of other deafness causes, as described in Chapter 3. The more common causes are discussed in detail below.

Ototoxicity

A large number of drugs and chemicals have been identified that can produce sensorineural hearing loss – over 180 compounds and classes of compounds have been identified as ototoxic (Govaerts *et al.*, 1990; Mansfield, 1990; Pickrell *et al.*, 1993; Merchant, 1994). Not all are equally toxic – in some cases the ototoxic effects are reversible if caught early, as with the salicylates, but in most instances the deficit is permanent by the time of discovery. Broadly speaking, ototoxic agents may also affect vestibular function. Effects can be auditory or vestibular or both, unilateral or bilateral, and may result in partial or total functional loss.

Toxicity may result from parenteral or topical application, and can result from both long-term and acute exposure (Gooi *et al.*, 2008). Penetration of topically applied ototoxic agents into the inner ear is enhanced by tympanic membrane rupture or drug carriers that enhance membrane permeability through the tympanum and oval and round windows; permeability may vary between species (Harada *et al.*, 1986). There may be synergism between the effects of ototoxic agents and other forms of hearing loss, such as presbycusis and noise trauma, or between two concurrent ototoxic agents (Xu *et al.*, 1993). There may be developmental differences in toxic effects, as young

kittens have been shown to be less susceptible to aminoglycoside antibiotic ototoxicity than older cats (Shepherd and Martin, 1995).

The list of agents that are reported to be ototoxic in animals is shorter than the list for humans, in large part due to the greater number of drugs available for human use. Nevertheless, many of these drugs are potentially toxic to animals and there is a need to be aware of which drugs may create problems. Toxic effects may be due to direct damage of hair cells or indirect effects through damage to the stria vascularis. Once within the perilymph, a drug has exposure to both cochlear and vestibular cells due to the continuity of the perilymph between the two systems.

The clinical signs of ototoxicity may include vestibular signs such as head tilt, circling, nystagmus, strabismus, and ataxia, but signs accompanying the loss of hearing are usually not present until well advanced. There may be increased vocalization, possibly reflecting the animal's perception of tinnitus, as well as reduced responsiveness to auditory stimuli and failure to waken to sound. Hunting dogs will display a reduction in the distance at which they respond to auditory cues such as whistles.

The drugs and chemicals that are, or have potential to be ototoxic can be classified into broad groups: antibiotics (aminoglycosides and others), loop diuretics, antiseptics, antineoplastic agents, and miscellaneous agents. A compilation of known and potential ototoxic agents is shown in Box 5.1.

Aminoglycoside antibiotics

Probably the most common ototoxic agents affecting animals are the aminoglycoside antibiotics, especially gentamicin (Hawkins and Lurie, 1953; Webster *et al.*, 1971; Clark, 1977; Morgan *et al.*, 1980; Göttl *et al.*, 1985; Elidan *et al.*, 1987; Xu *et al.*, 1993; Strain *et al.*, 1995; Uzuka *et al.*, 1996; Gookin *et al.*, 1999). The aminoglycosides display both nephrotoxicity and ototoxicity, effects that were recognized as soon as streptomycin was first isolated in the 1940s; the renal damage may recover but the auditory and vestibular damage is permanent. Despite the known potential toxicity of gentamicin, it is still said to be the most commonly utilized antibiotic for topical treatment of otitis externa, in part because of its high efficacy, broad spectrum of Gram-negative activity, and low cost. Incidence of toxic side effects for gentamicin in humans ranges from 6 to 16% for cochlear toxicity and 9 to 15% for vestibular toxicity, and one study reported a cochlear toxicity incidence (but not total deafness) of over 80% for kanamycin (Schacht, 1998). True incidence is difficult to determine and usually underestimated.

This class of drugs destroys hair cells and supporting cells of the organ of Corti, starting with the base of the cochlea, impairing high-frequency hearing, and progressing to the apex. The various aminoglycosides may preferentially affect auditory or vestibular function, and they vary in toxicity within the drug group: neomycin and streptomycin are the most toxic and

Box 5.1. Proven and potentially ototoxic agents (data from Mansfiled, 1990; Pickrell *et al.*, 1993; Merchant, 1994; Strain, 1996).

Antibiotics – aminoglycosides
- amikacin
- dactimicin
- dibekacin
- framycetin
- gentamicin
- hygromycin B
- kanamycin
- neomycin
- netilmicin
- paromomycin
- ribostamycin
- sisomicin
- streptomycin
- tobramycin

Antiseptics
- benzalkonium chloride
- benzethonium chloride
- cetrimide
- chlorhexidine
- ethanol, other alcohols
- iodine, other iodophors

Antibiotics – other
- amphotericin B
- ampicillin
- bacitracin
- chloramphenicol
- chlortetracycline
- colistin (polymyxin E)
- erythromycin
- griseofulvin
- minocycline
- polymyxin B
- tetracyclines
- vancomycin

Loop diuretics
- bumetanide
- furosemide
- ethacrynic acid
- torsemide

Antineoplastic agents
- actinocycins C and D
- cisplatin
- nitrogen mustard
- vinblastine
- vincristine

Miscellaneous agents
- acetic acid
- arsenical compounds
- ceruminolytic agents
- cyclophosphamide
- danazolol
- dapsone
- detergents
- digoxin
- dimethylsulfoxide
- diphenylhydrazine
- gold salts
- insulin
- lead
- mercury
- potassium bromide
- prednisolone
- propylene glycol
- quinine
- quinidine
- salicylates
- triethyl and trimethyl tin

netilmicin is the least toxic. Gentamicin and tobramycin are the two preferentially vestibulotoxic agents that are most commonly used in humans, and neomycin, kanamycin, and amikacin are the preferentially cochleotoxic agents most commonly used (Matz, 1993); these listings of preferential toxicity may not transfer to animal applications, as gentamicin appears to be primarily cochleotoxic in dogs and cats.

Studies in recent years have shown the sequential mechanisms of aminoglycoside ototoxicity to be iron chelation, followed by free radical formation, and then caspase-dependent apoptosis (Schacht, 1998; Rizzi and Hirose, 2007). The understanding of these mechanisms has advanced to the point of showing that the apoptosis is mediated by a mitogen-activated protein kinase (MAPK) pathway through the upregulation of the preapoptotic factor *Harakiri (Hrk)* (Kalinec *et al.*, 2005).

The development of toxicity with these drugs is not predictable on a body weight dosage basis, making it difficult and frustrating to have a rational approach to utilizing the drug's therapeutic value while simultaneously

minimizing the potential for toxicity. One human pharmacology text reported that serum gentamicin levels must exceed a 2 µg/ml threshold level for over 10 days to produce toxicity (Sande and Mandell, 1990), but the statement was not linked to a published study and is not present in later editions. Further, it is known that cochleotoxicity has resulted from single doses.

In one dog study (Strain *et al.*, 1995), healthy retired racing greyhounds were treated in one intact ear twice daily with gentamicin (7 drops of 3 mg/ml gentamicin in a buffered aqueous vehicle) for 21 days, then the same treatment was applied to the opposite ear after bilateral myringotomy, using an opposite ear vehicle control in both cases. No hearing loss was observed under either treatment by BAER testing, and no vestibular effects were seen in neurological exams. It may be that the presence of infection increases the permeability of the tympanum, oval, and round windows to the actual drug being used to treat the infection. It is not uncommon for severe otitis externa to be accompanied by rupture of the tympanum, which would also increase access of the drug to the cochlear and vestibular hair cells. It is advisable that auditory and vestibular function be assessed closely and frequently when high doses of aminoglycosides must be used, so that treatment can be discontinued if toxicity is detected early in the treatment. Drug companies have advised veterinarians and pet owners that aminoglycoside-associated hearing loss may or will recover with time, but that has not been the author's experience.

Because it recognized that formation of free radicals is a step in the mechanism of toxicity of gentamicin, studies have sought to prevent toxicity by use of free radical scavengers and antioxidants (Song and Schacht, 1996). A clinical study in humans reported that co-administration of gentamicin and therapeutic levels of aspirin prevented the development of ototoxicity in patients undergoing dialysis, where long-term gentamicin treatments are used to prevent infections (Sha *et al.*, 2006; Chen *et al.*, 2007); the aspirin did not interfere with the antibiotic effects of gentamicin. Other agents have also been shown to have protective effects, including the micronutrient L-carnitine (Kalinec *et al.*, 2005), the iron chelators deferoxamine and dihydroxybenzoate (Song and Schacht, 1996), and other antioxidants and free radical scavengers like alpha-tocopherol (Fetoni *et al.*, 2004), sodium thiosulfate (Hochman *et al.*, 2006), D-methionine (Campbell *et al.*, 2007), and *N*-acetylcysteine (Feldman *et al.*, 2007). It is not known whether post-exposure use of aspirin or these other agents would provide any protective benefit, although post-exposure use of A_1 adenosine receptor agonists has reduced noise-induced hearing loss (Wong *et al.*, 2010). Clinical studies of aspirin use with gentamicin in veterinary populations, either concurrent or post-exposure, have not yet been reported. Although not yet proven, it might be prudent to consider co-administering aspirin at therapeutic levels in cases where high gentamicin doses must be used, if preservation of cochlear function is a concern and the use of aspirin is not otherwise contraindicated.

Loop diuretics

Loop diuretics inhibit sodium and chloride absorption in the ascending loop of Henle of the kidney, promoting excretion of sodium and, along with it, water. They are used clinically to treat hypertension and edema associated with heart failure and for rapid diuresis in pulmonary or cerebral edema, especially in patients with impaired kidney function. Ototoxicity associated with these drugs is exhibited as tinnitus, hearing loss or deafness, and vertigo (Rybak *et al.*, 1991; Rybak, 1993). The hearing loss is acute in onset and usually reversible, although permanent deafness has been reported. Toxicity is most common with rapid IV administration and least common with oral administration (Jackson, 2001). Ethacrynic acid is said to be more toxic than furosemide, but furosemide is the most commonly used drug in veterinary medicine, so it may be the drug responsible for the most incidents. Bumetanide exhibits approximately 10–15% of the relative ototoxic potential of furosemide in dogs and cats (Brown, 1981). Synergism in producing ototoxicity is seen between the diuretics and aminoglycosides, cisplatin, or NSAIDs (Jackson, 2001).

The mechanism of loop diuretics has been shown to be the inhibition of the family of transport proteins called Na-K-2Cl cotransporters (Ikeda *et al.*, 1997), and it is assumed that the mechanisms of ototoxicity and nephrotoxicity involve similar inhibition of ion transporters that regulate fluid balance. The cochlear target is the stria vascularis, which develops edema, and possibly the stereocilia of outer hair cells (Rybak *et al.*, 1991). Because the toxic effects are acute and usually reversible, the urgency of the medical circumstance requiring the use of a diuretic may be the driving factor in a decision of whether to discontinue the diuretic. Switching from an IV to an oral route of administration may also be considered.

Antineoplastic agents

Antineoplastic agents by their very nature are toxic. Cisplatin is a chemotherapeutic agent typically used in treating solid tumors such as ovarian, testicular, cervical, lung, head and neck, and bladder cancers. It exhibits a wide range of toxicity, the most significant of which is nephrotoxicity. However, it also exhibits ototoxicity (Barabas *et al.*, 2008; Rybak *et al.*, 2009), which is manifested as a bilateral and irreversible hearing loss that especially effects the human pediatric population; tinnitus is also common in humans. The loss initially affects high frequencies and is dose-related and cumulative; hearing loss may develop long after treatments end, although effects more typically appear within hours to days of treatment. The major metabolite cisdiamineaquachloroplantinum (II), produced by hydrolysis in the blood, is the cytotoxic agent. It is taken up into cells by transporters, where reactive oxygen species (ROS) are generated (Rybak *et al.*,

2009). Toxicity results when the generated free radicals overwhelm the cells' antioxidant enzyme systems, leading to cell injury and apoptosis. Affected tissues include outer hair cells and the stria vascularis, the spiral ligament, and spiral ganglion cells.

A variety of antioxidants/free radical scavengers have been tested to protect against cisplatin ototoxicity (Rybak *et al.*, 1999, 2009), but none have moved into clinical use; saline diuresis is used to prevent nephrotoxicity (Barabas *et al.*, 2008). It is unclear how frequently cisplatin ototoxicity occurs in dogs or cats, but is thought by oncologists to be of low incidence. There are no veterinary clinical studies of hearing loss with cisplatin use, but the drug was evaluated in one laboratory study (Sockalingam *et al.*, 2002).

Antiseptics

A variety of antiseptics and disinfectants have been reported to be ototoxic, including chlorhexidine, cetrimide, iodines, and alcohols. This effect is unfortunate because these compounds have been used as components of otic cleaning agents. Chlorhexidine was at one time a component of commercially available otic cleaning formulations, but US federal regulators mandated removal because of the reports of toxicity (Igarashi and Suzuki, 1985; Gallé and Venker-van Haagen, 1986; Igarashi and Oka, 1988; Perez *et al.*, 2000). In the interests of economy, some practitioners have diluted dermal antiseptics or disinfectants containing chlorhexidine, which are still approved for labeled applications, resulting in additional cases of ototoxicity (Willoughby, 1989). Neuronal cells show severe degeneration in both the cochlea and vestibular organs after topical application of 2% chlorhexidine gluconate in the middle ear in cats (Igarashi and Suzuki, 1985; Igarashi and Oka, 1988), but the mechanisms of toxicity are not known. Benzalkonium chloride and benzethonium chloride produce similar effects. One study of topical ear canal application of 0.2% chlorhexidine acetate found no evidence of ototoxicity in dogs with either intact or excised tympanums (Merchant *et al.*, 1993), so toxic effects may be dose-dependent.

A study in rats compared the ototoxicity of 0.5% chlorhexidine gluconate, 70% ethanol, and 10% providone–iodine (equal to 1% iodine in aqueous solution) applied in the middle ear (Perez *et al.*, 2000). Chlorhexidine functional toxicity was complete and equivalent to that of gentamicin, ethanol only affected some rats, and providone–iodine had no vestibular effects and only minor auditory effects. The authors concluded that providone–iodine was preferable for disinfecting ears with a perforated tympanic membrane. A separate study with guinea pigs found middle ear exposure to iodine or iodophore in 70% ethanol produced a dose-dependent pattern of cochlear and vesibular damage, but iodine or iodophore in an aqueous solution produced no damage (Aursnes, 1982), implicating the ethanol carrier.

A number of commercial ceruminolytic agents have been evaluated for ototoxicity in dogs following transtympanic injection, based on the clinical observation that the tympanum is ruptured in 50% of all dogs with chronic otitis externa (Mansfield *et al.*, 1997). Various degrees of middle ear inflammation and hearing loss were documented. The hearing loss may have been conductive, produced by middle ear inflammation, but may also have been sensorineural, supporting a warning to exercise caution in using these agents when tympanic rupture is present or, if the tympanic membrane cannot be visualized, represents a possibility.

Presbycusis

The loss of hearing function with aging is a phenomenon familiar to most people. This disorder occurs in animals in the same way that it does in people, where it is much more recognized and studied in dogs than in cats. Although presbycusis, also known as presbyacusis and age-related hearing loss (ARHL), is frequently thought of simply as an elevation of hearing thresholds, it can also include a reduction in middle ear sound conduction and a decline in processing of sound information at higher neural levels. Willot (1991, pp. 2–3) has proposed a working definition for presbycusis as 'the decline of hearing associated with various types of auditory system dysfunction (peripheral and/or central) that accompanies aging and cannot be accounted for by extraordinary ototraumatic, genetic, or pathological conditions. The term "presbycusis" implies deficits not only in absolute thresholds but in auditory perception, as well.' That being said, clinically recognizable ARHL in animals appears to be primarily from reduced peripheral sensorineural function. It is undoubtedly true, though, that the central effects of general aging as well as other disorders like canine cognitive dysfunction can be exacerbating conditions in elderly dogs.

In general, presbycusis is a progressive disorder for which there is no known treatment or cure. It is generally bilaterally symmetrical and usually affects higher frequencies before lower frequencies, often going unrecognized in people for years while it slowly progresses. Among humans, males are more affected, and the deficits can be exacerbated by noise-induced hearing loss. The loss can be accompanied by tinnitus, and hypertension and diabetes can be contributory factors (Gates and Mills, 2005). The hearing loss eventually results from a cumulative loss of cochlear hair cells, but the mechanisms are multifactorial, including genetic, extrinsic (noise, ototoxins), and intrinsic (systemic disease) causes (Liu and Yan, 2007). Early studies of human temporal bones led to classifications of ARHL that included independently occurring degeneration of the organ of Corti, ganglion cell loss, and atrophy of the stria vascularis, known respectively as sensory, neural, and strial forms of presbycusis, as well as a number of other subtypes (Schuknecht, 1964; Liu and Yan, 2007). Since it is nearly impossible in humans to separate

environmental causes from genetic origins, there has been considerable focus on animal models (Ohlemiller, 2009; Bielefeld *et al.*, 2010), where noise and drug exposure, nutrition, systemic disease, and other possible contributors can be eliminated or controlled. While a variety of mechanisms and origins exist for presbycusis, a consensus appears to be developing that degeneration of the stria vascularis and the lateral wall of the cochlea is the major contributor (Liu and Yan, 2007). Studies have shown a clear hereditary component in humans (Gates *et al.*, 1999), but oxidative stress from age-related build-up of free radicals is also a causative factor. No genetic studies of presbycusis have been performed in dogs or cats.

In addition to peripheral changes with aging, there are aging changes in central auditory pathway structures. The best studied is the cochlear nucleus, where reductions in neurons and their output fibers have been documented (Shimada *et al.*, 1998; Frisina and Walton, 2006).

Since presbycusis is associated with aging and geriatrics, it is useful to provide guidelines for classifying animals as geriatric. Goldston (1989) provided data on the average ages at which dogs and cats are considered to be geriatric or are most likely to start having diseases associated with aging (Table 5.1). Since life expectancy in dogs is a function of the breed body size, the geriatric ages were distinguished for small, medium, large, and giant body size based on weight. Other factors that can affect when an animal becomes geriatric include (i) genetics – mixed breeds live longer than pure breeds; (ii) nutrition – obesity and high-fat and/or low-fiber diets decrease life expectancy; and (iii) environment – outdoor animals have a shorter life expectancy than indoor animals, neutered animals live longer than non-neutered animals, and rural animals possibly live longer than urban animals.

Several laboratories have examined the cochlea in dogs with ARHL (Knowles *et al.*, 1989; Shimada *et al.*, 1998; Ter Haar *et al.*, 2009). Findings included reductions in outer hair cells, inner hair cells, and spiral ganglion cells, reduction in stria vascularis volume, and thickening of the basilar membrane. Changes were initially seen at the basal turn of the cochlea,

Table 5.1. Average age at which dogs and cats are considered to be geriatric or most likely to start showing diseases associated with aging (data from Goldston, 1989).

Category	Weight (lb)[a]	Geriatric age (years)
Small dog	0–20	11.48 ± 1.85
Medium dog	21–50	10.90 ± 1.56
Large dog	51–90	8.85 ± 1.38
Giant dog	> 90	7.46 ± 1.94
Cat	–	11.88 ± 1.94

[a]Pounds: 1 lb = 453.6 g.

associated with high frequencies, and progressed toward the apical cochlea, associated with low frequencies.

Changes in the BAER in aged dogs were examined in one study (Knowles *et al.*, 1988) using a single, high-intensity stimulus (84 dB SL), but since hearing thresholds were not determined there was limited evidence of effects of aging. No differences in BAER peak latency were seen, but the amplitudes to peaks I and II were reduced in the reduced-hearing animals.

Pure-tone audiograms determined under anesthesia are shown in Fig. 5.1, comparing responses from a control group of young adult animals with those of four dogs that met the Goldston (1989) geriatric criteria (Smith, A.H. and Strain, G.M., unpublished observations). Hearing in the high-frequency range was most affected, although there was significant between-dog variability, while limited change in low-frequency thresholds was observed. A more extensive study by Ter Haar *et al.* (2008) examined toneburst-derived BAER thresholds in medium-sized dogs, including a longitudinal study that followed some dogs for seven years. They reported increased thresholds starting at 8–10 years of age that were progressive, being most pronounced in what they described as the middle to high frequency range of 8–32 kHz and expanding to the entire frequency range with aging. The hearing losses seen in both studies reinforce the pattern of loss experienced by people.

Although ARHL is considered to be progressive and irreversible, efforts have been made to identify approaches to preventing its development

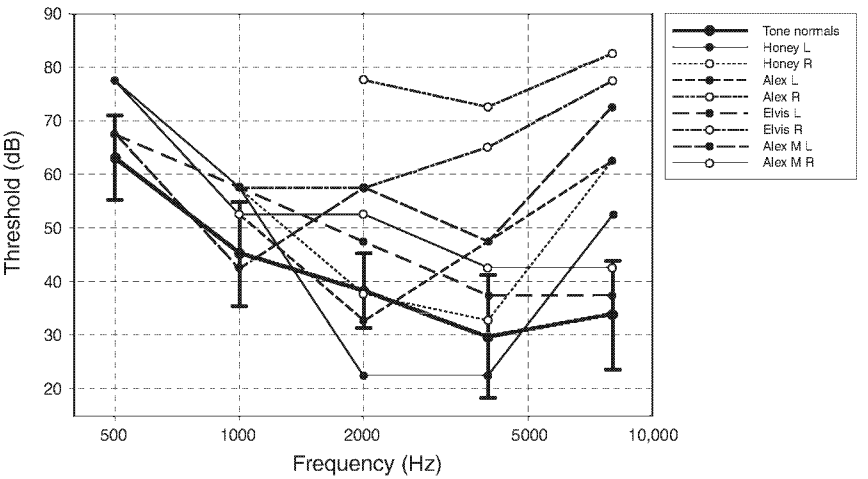

Fig. 5.1. Pure-tone audiograms recorded from left (L) and right (R) ears of four geriatric pet dogs (Honey, Alex, Elvis, and Alex M) compared with norms for a population of young adult dogs (Smith, A.H. and Strain, G.M., unpublished observations). High frequencies were most affected while low frequencies differed little from normal values.

(Bielefeld *et al.*, 2010), including reduced-noise environments, increased endogenous and exogenous antioxidants, caloric restriction, and even the use of salicylates, which can themselves be ototoxic. Surgical implantation of a human middle ear amplifying device known as a Vibrant Soundbridge has been reported in three dogs (Ter Haar *et al.*, 2010), but the probable costs and delicacy of the operational procedure raise questions as to the potential for widespread application of the device.

Noise Trauma

Noise trauma, or noise-induced hearing loss (NIHL) is an increasing problem in the human population, but one that also affects animals. It affects hunting dogs, especially Labrador retrievers, where the hunter utilizes personal hearing protective devices but nevertheless shoots firearms over the dog's head without protection, military dogs that may be repeatedly exposed to loud percussive sou nds, and it may even affect animals shipped by air due to high sound levels in airplane shipping compartments. Protective reflexes exist whereby middle ear muscles contract in response to loud sounds to reduce sound levels reaching the inner ear, but the reflexes are not fast enough for percussive sounds such as gunfire and only provide limited protection against very loud noises.

The primary damage in NIHL is to hair cells, but extreme noises can also rupture the tympanum and damage the ossicles. Hearing loss from exposure to loud noise is a cumulative process, where both the noise intensity and the duration of exposure are determinant factors. Low-frequency noise is less damaging than mid-frequency noise, so noise measurements and standards use loudness units that are A-weighted (dBA), where mid-range frequencies are given increased weight. In humans the hearing loss from noise is centered near 4 kHz, in the frequency range most critical to speech perception, but spreads with continued exposure to higher and lower frequencies (Peterson, 1980). Not all individuals are equally susceptible to NIHL. Ambient sound levels in animal shelters and kennels regularly exceed 100 dBA and frequently approach 120 dBA (Coppola *et al.*, 2006), indicating that hunting dogs are not the only animals exposed to damaging sound levels that will impact hearing. Caretakers in shelters and kennels wear ear protection to protect their hearing, but consideration is usually not given to the effects on the animals.

Both temporary and permanent hearing losses result from exposure to noise. Gradual recovery may occur with some exposures if they are brief (temporary threshold shift), but repeated or continued exposures result in permanent hearing loss, also known as a permanent threshold shift. The United States and international regulatory agencies have established regulations for allowable human noise exposure, combining noise level and duration of exposure. The US Occupational Safety and Health Administration

(OSHA) regulations (OSHA, 1971, 1974) are based on the assumption that exposure at 90 dBA for eight hours every working day is not likely to cause significant hearing loss. Higher exposure intensities are permitted if they are for shorter time periods; a 2-to-1 reduction in permissible exposure time is allowed for each 5 dB increase in loudness. Exposure times under these regulations are shown in Table 5.2. The regulations also limit continuous noise exposure of any duration to a maximum level of 115 dB, and limit exposures to impulse or impact noise to 140 dB peak SPL, not to exceed 100 impulses per day (Peterson, 1980). The intensity of impulse sounds, which would include gunfire, can be difficult to quantitate. The equivalent international standard is ISO/R 1999:1975, 'Assessment of Occupational Noise Exposure for Hearing Conservation Purposes' (International Organization for Standardization, 2011).

Age and genetics affect the impact of noise, with greater losses occurring in older people and animals. A number of mouse strains differ in their susceptibility to NIHL (Ohlemiller, 2008), indicating a genetic component to noise damage susceptibility, although it is not known whether there are canine or feline breed differences. Damage occurs to the organ of Corti, spiral ganglion cells, the stria vascularis, and the spiral ligament. The mechanisms of temporary threshold shift appear to be the result of actions on the lateral wall of the cochlea – the stria vascularis and spiral ligament, while permanent threshold shift results from effects on hair cells (Ohlemiller, 2008). Hair cell effects include macromolecular disruption of stereocilia and cuticular plates, generation of ROS, disruption of cell–cell gap junctions, and apoptosis and necrosis (Lim, 1986; Henderson *et al.*, 2006; Ohlemiller, 2008).

Dogs are more frequently affected than cats. Behaviorally, dogs with NIHL gradually develop a reduction in the distance at which they will respond to

Table 5.2. Permissible occupational noise exposures in US workplace settings (OSHA, 1974, Table G-16).

Duration (h/day)	Sound level (dbA, slow response)
8	90
6	92
4	95
3	97
2	100
1.5	102
1.0	105
0.5	110
≤ 0.25	115

auditory cues. Because the loss is cumulative and usually gradual, the affected dog is able to compensate until some critical point is reached where compensation is insufficient and the loss becomes apparent to the owner. This pattern is similar to that of animals with presbycusis, and an animal's hearing loss may actually reflect a combination of NIHL and ARHL. Animals may develop tinnitus, based on human experience, but the dog does not otherwise suffer from the condition. Precautions must be taken to protect the animal from undetected dangers like motor vehicles, and cautions must be exercised to avoid startle-triggered reflex bites.

As described above for other forms of hearing loss, various therapeutic agents have been investigated for prevention of NIHL by concurrent administration with noise exposure (Ohlemiller, 2008). In particular, N-acetylcysteine has shown protective effects in both animal and human studies (Kopke *et al.*, 2007; Lin *et al.*, 2010; Wu *et al.*, 2010). Post-exposure use of A_1 adenosine receptor agonists has been reported to reduce noise-induced hearing loss in humans (Wong *et al.*, 2010).

Anesthesia-associated Deafness

A recently identified type of acquired deafness is anesthesia-associated (Stevens-Sparks and Strain, 2010), where dogs and cats awaken from general anesthesia with bilateral deafness that appears to be permanent. Most cases are seen following procedures involving the head, especially dental cleaning or ear cleaning, suggesting compromised blood flow (i.e., Billett *et al.*, 1989), metabolic changes, or mechanical disruptions as potential causes. Both sensorineural and conductive deafness cases have been identified, but insufficient affected animals have been examined to ascribe predominance to either type. A review of 63 cases found no relationship between deafness and dog or cat breed, gender, anesthetic drug used, or dog size (Stevens-Sparks and Strain, 2010). Geriatric animals appeared more susceptible, which may have reflected sampling bias since dental cleaning is more commonly performed on older animals.

Conduction Deafness

A number of causes can be responsible for conduction deafness, but otitis externa, either acute or chronic, and otitis media are the most common. As shown in Fig. 5.2, inflammatory exudate in either the ear canal or the middle ear dampens the transmission of sound waves to the inner ear. Resolution of the infection or cleaning of the ear canal can be expected to lead to recovery of hearing. In chronic otitis externa, hyperplastic tissue changes in the canal cause stenosis; calcium deposition that accompanies the hyperplasia results in pain upon touch of the pinna or surrounding areas, which may require

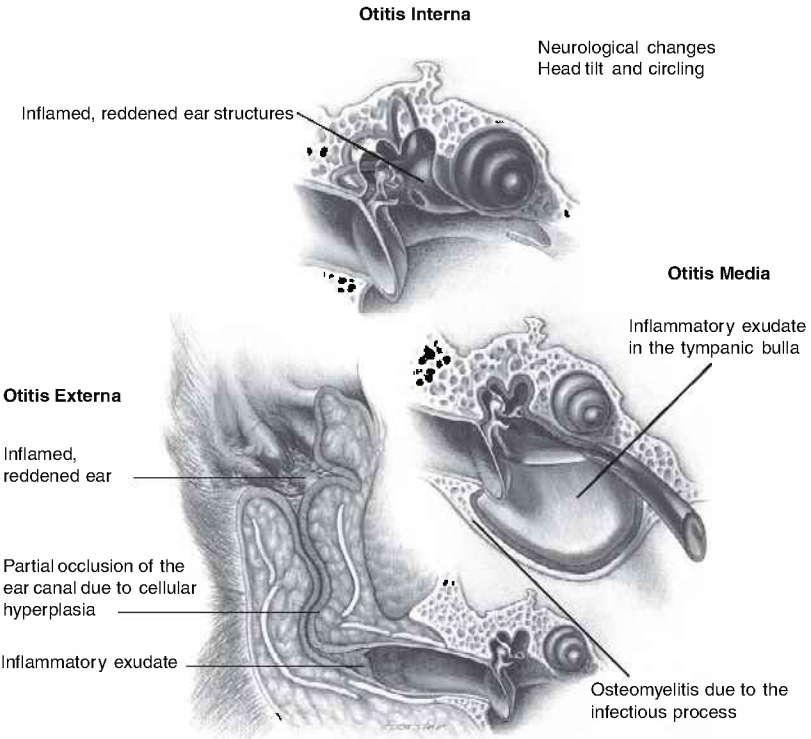

Fig. 5.2. Infectious causes of hearing loss: otitis externa, otitis media, and otitis interna (used with permission from Hill's Pet Nutrition, Inc.).

partial or total ear canal resection in severe cases. Otitis interna does not affect sound transmission, but leads to neuronal cell death in both the cochlea and the contiguous vestibular structures.

The condition of primary secretory otitis media or 'glue ear' has been discussed in Chapter 3.

Otosclerosis has been suggested as a cause of conductive hearing loss, where abnormal bone growth near or in the middle ear can produce conductive and/or sensorineural loss. However, no clear evidence for this condition in dogs has been reported (Ardouin and Wegmann, 1961; Sørensen *et al.*, 1991).

Brainstem Auditory Evoked Response (BAER)

6

Pet owners and breeders are likely to seek hearing assessment for several possible reasons. Young animals may have congenital sensorineural deafness, especially those from breeds with white pigmentation genes (piebald and merle in dogs, white in cats). Breeders may seek certification of hearing status prior to sale of puppies and kittens or for adults prior to breeding. Adult animals may have conductive deafness from excess cerumen production (especially in long-eared breeds), from residual mucopurulent discharge secondary to otitis media, or from ear canal ossification and hypertrophy secondary to chronic otitis externa. Older and aged animals may have sensorineural deafness secondary to otitis interna, exposure to ototoxic drugs or chemicals, trauma, cumulative noise exposure (percussive sounds such as firearm discharge), presbycusis, or combinations thereof.

Behavioral assessment of auditory function is a standard component of the basic neurological exam, and it is the only option available in most veterinary practices. A noise is produced outside the animal's visual fields and the animal is observed for a response to the sound: a Preyer reflex, the backward pinna movement in response to a sudden loud sound, or an attempt to orient the head to the origin of the sound. However, behavioral testing is problematic when used for anything more than determining the presence or absence of auditory function. Unilateral deafness, which is present in large numbers of dogs, generally cannot be detected by behavioral testing, and partial hearing loss in one or both ears cannot be assessed. Unilaterally deaf animals will still produce conjugate bilateral ear movements in response to sounds. Hearing animals may fail to respond to auditory stimuli because of apprehension in the clinical setting, and deaf animals may respond because

of detection of visual cues, vibrations, or air movements. If behavioral auditory testing is necessary, it is important to blindfold the animal or otherwise insure that test sounds are generated outside of the animal's visual field. Whistles or jingling keys are better stimuli than hand claps or items dropped on the floor because of the likelihood of miscues. This testing can at best demonstrate bilateral deafness or the presence of at least partial unilateral hearing, but with marginal confidence. More objective assessment of auditory function requires electrophysiologic assessment, since behavioral audiometry using operant conditioning is not practical. The most commonly utilized test is the brainstem auditory evoked response (BAER), also known as the brainstem auditory evoked potential (BAEP) or the auditory brainstem response (ABR). Clients may specifically request the 'bear test.' A variety of other testing methods have been proposed in the past (Rose, 1977a–g), but were usually beyond the capacity of general practices. Performance of the BAER test and the factors affecting its utility will be presented in this chapter. Other tests of auditory function will be covered in Chapter 7.

Biophysics of BAER Recordings

Electrophysiologic signals are described as either near field or far field. Near field responses are recordings where the signal source is in close apposition to the recording electrode, such as a peripheral nerve response to electrical stimulation. Far field responses are obtained from relatively distant structures, as with the BAER. The recorded amplitude from an event decreases with the distance from the signal source by the inverse of the distance squared, so far field responses are usually smaller than near field responses (Strain, 1997a, b).

Physiologic potentials result from ionic currents from membrane potential changes in excitable cells (Geddes and Baker, 1968; Strong, 1970). At the electrode–tissue interface the ionic current is converted to an electron current (by a series of chemical reactions), which results in the development of another potential, the offset potential, due to the build-up of charge on the metal surface; the magnitude of the offset potential for any metal/electrolyte interface can theoretically be calculated. Use of two electrodes of the same metallic composition should cancel each DC offset potential in a differential amplifier, but the actual value can frequently differ significantly from the theoretical value. As a result it is necessary to use AC amplifiers and differential recording for biological signals. Movement of the electrode mechanically disturbs the layer of charges at the electrode surface, generating artificial potentials – noise or artifact. Even without movement, microchanges in the chemical environment can produce artifacts.

The interface layer of charge also accounts for much of the capacitance of the electrode–tissue interface. This capacitance is proportional to the electrode surface area in contact with body fluids, while the resistance of the electrode–tissue interface is inversely proportional to the electrode surface

area. The resistance and capacitance are electrically in series, which produces a filtering effect on the transmitted signals. Because of the capacitance, part of the signal is passed as a capacitive current, which is less electrochemically demanding on the electrode metal surface than the faradic current.

Recording and stimulating electrodes are typically made of stainless steel or alloys of noble metals. Needle electrodes typically have slightly higher electrode impedance compared with surface disc electrodes (about 7 kΩ compared with about 5 kΩ), but disc electrodes are difficult to use on the hairy skin of animals. Needle electrodes are not more artifact prone than disc electrodes, as is occasionally reported. For evoked potential applications, stainless steel needles are satisfactory because they are strong, do not corrode, and are comparatively cheap, but they have inferior electrical characteristics compared with other metals. Platinum is preferred because it is a good electrical conductor, inert, and strong if alloyed with iridium; platinum electrodes are also less prone to movement artifact, so the higher cost is generally justifiable and electrodes are usually reused in animal applications. The impedances of the tissues and electrode wires are small compared with those of the electrode tip and the input to the amplifier. These two impedances act as a voltage divider, splitting the voltage detected at the electrode–tissue interface. Since it is desired that most of this signal be seen by the amplifier and not dissipated across the electrode impedance, the electrode impedance should be kept small compared with that of the amplifier. Amplifier input impedances range from 100 kΩ to several hundred MΩ, so-designed in part to accomplish this desired effect. High-input impedance increases the common mode rejection ratio (see below), while high-electrode impedance increases amplifier noise and external interference. Balanced impedance for the two electrodes (active and reference) reduces artifact. Currently available instrumentation provides built-in impedance testing, which should be routinely used. Impedances for evoked potential recordings should be below 5–7 kΩ. Impedance should not be tested with volt-ohm meters, since these utilize a DC testing current which polarizes the electrodes, degrading their surface and increasing artifact.

Grounding is important for good-quality recordings to reduce sources of artifact, but also for the safety of the subject and tester in the event of internal instrument damage that connects power to the metal of the instrument case. If recordings must be performed in older facilities with poorly shielded power lines or near other major sources of 60 Hz noise (50 Hz in some countries), a shielded Faraday cage may be necessary for its reduction. Electrodiagnostic instruments typically have notch filters (narrow band-exclusion filters) to reduce 60 Hz noise, but this frequency is within the range of biological significance, so some distortion of the response recorded may occur when it is used.

Commercial electrodiagnostic systems use differential amplifiers: one input (G2, reference) is subtracted from another (G1, active), and the difference is amplified. Any signal common to both inputs (60 Hz noise, offset

potentials, and distant muscle artifacts that affect both electrodes equally) is eliminated or reduced, depending on the relative amplitudes at the two inputs. The ability to ignore a common input, known as common mode rejection ratio (CMRR), is one of the specifications of an amplifier: the greater the CMRR the better the system. The polarity of the output signal is not consistent between machines or even for different test protocols from the same machine. The reason is historical: early systems produced an upward deflection for negative signals because electronic amplifiers inverted the amplified signal. Most computer signal averagers are wired or programed so that positivity is upward at the output when input G1 is greater that input G2 (or upward in response to a relative positivity at G1 and downward in response to a relative positivity at G2). However, machines capable of performing multiple tests may also be wired or programed for certain tests (e.g., EMG), so that relative positivity at input G1 deflects downward because of accepted convention. Many machines permit the user to select the convention; if not, reversing the inputs has the same effect. It is important to determine, based on a calibration signal or instrument documentation, the convention of the instrument and test protocol under use or response peaks may be misidentified. It is also important to indicate polarity on printed tracings of responses for the benefit of others viewing the record. Newer electrodiagnostic systems perform signal averaging of waveforms using digital computer processing of signals that have undergone analog-to-digital conversion, where samples of the analog voltage signal are repeatedly collected at very short intervals. This sampling frequency (the Nyquist frequency) needs to be twice the highest frequency of interest in the biological signal to avoid incorrectly representing the original source. Digital filtering and more sophisticated post-processing can be performed on digitized data with appropriate software. Periodic system calibration is important to enable reliance on amplitude measurements. Most instruments provide internal calibration features, but external calibration systems are also commercially available.

Electrophysiologic signals contain information of biological origin that nevertheless is not of interest in performance of specific tests, in addition to the noise and other artifacts that can obscure the desired information. Filtering of the source signal is used to reduce or eliminate this undesired activity. Low-pass filters eliminate frequencies higher than the numerical filter value, while high-pass filters eliminate frequencies lower than the filter value; when used together they act as a band-pass filter, allowing only a range of frequencies to pass. The values chosen for various electrodiagnostic tests are not written in stone, but have empirically been selected based on past experience or the actual analysed frequency content of the signal under examination. For example, the frequencies in muscle action potentials range from 10 Hz to 5 kHz; typical recording protocols use filter settings of 20 Hz to 5 kHz. Frequency spectra for other neurophysiologic responses are intracellular microelectrode recordings: 1–10,000 Hz, evoked potentials: 1–3000 Hz, EEG: 0.5–100 Hz, and ERG: 0.05–20 Hz.

Sources of artifact and noise in addition to the movement artifact and 60 Hz power lines mentioned above are legion. Motors, electric heating pads, and other electric and electronic equipment generate high-frequency noise in addition to 60 Hz noise. Electrical noise is inherent in amplifiers themselves. Defective apparatus introduces difficult-to-explain artifacts due to broken wires, bad solder joints, defective components, bad electrode connectors, or broken electrode wires. Bad electrode wires or absent ground lead wires introduce noise in part because the wires can actually act as antennae for 60 Hz and radiofrequency electromagnetic radiation. Biological artifacts result from the ECG, respiration, ballistocardiographic motion (pulsations in blood vessels), eye movements, any type of body movement, and electrophysiologic activity from neural tissue not under investigation (EEG, EMG, ERG, etc.) When both the active and reference electrodes are positioned over tissues that generate electrical activity, the amplified signal includes non-common activity present at both electrodes as well as activity generated in intervening tissues. Truly inactive cranial or extracranial electrode placement sites are difficult to locate because of activity in nearby brain regions, eye, muscle, peripheral nerve, and heart.

Overview of the BAER

The BAER has been described in numerous general sources (Glattke, 1983; Spehlmann, 1985; Hood and Berlin, 1986; Hood, 1988; Legatt, 1999) as well as in reports specific to dogs and cats (Barry and Barry, 1980; Kay *et al.*, 1984; Sims and Moore, 1984a; Bodenhamer *et al.*, 1985; Marshall, 1985; Sims, 1988; Venker-van Haagen *et al.*, 1989; Shiu *et al.*, 1997; Strain *et al.*, 1998; Ter Haar *et al.*, 2002; Wilson and Mills, 2005). The BAER is a noninvasive far field recording of activity in the peripheral and brainstem auditory structures in response to the onset of a sound stimulus, usually a click. The response is a series of peaks (labeled I–V) at approximate 1 ms intervals beginning approximately 2 ms after stimulus onset (Fig. 6.1). Peaks labeled VI and VII are identified in humans, and in many animals peak IV is not obvious, probably merged with peak V. The first peak is generated by the eighth cranial nerve (CN VIII). Although some uncertainty exists as to the exact origin of later peaks in the response, peak II is thought to be generated in proximal CN VIII or the cochlear nucleus, wave III is thought to be generated in the lower pons, possibly the superior olivary complex, and waves IV and V are thought to be generated in the mid or upper pons or inferior colliculus (Chiappa and Hill, 1997).

The BAER is recorded from scalp electrodes, usually subdermal needle electrodes. Response amplitudes are in the microvolt range, whereas electroencephalographic activity (EEG), electromyographic activity (EMG), and other irrelevant coexisting signals can be in the millivolt range, with the result that the BAER is buried under this other activity. In order to expose the

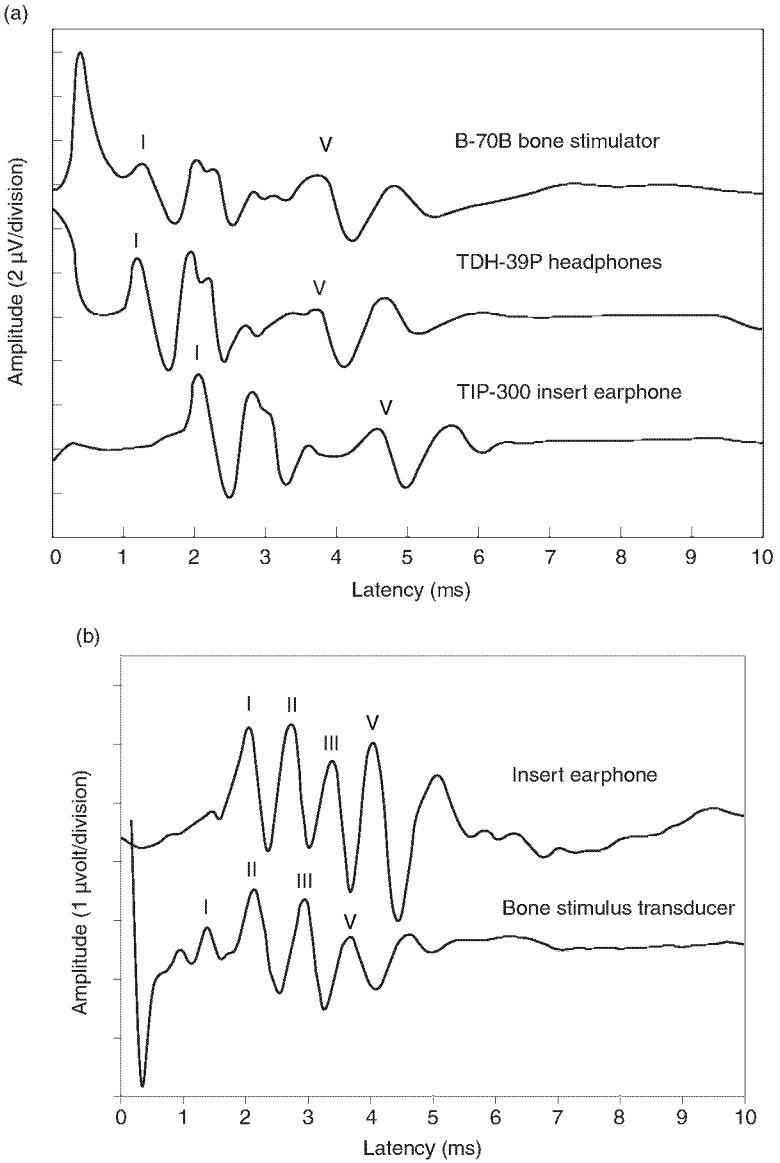

Fig. 6.1. BAER recordings from dogs and cats evoked by differing stimulus transducers. (a) Canine BAERs in response to a bone stimulus transducer, headphones, and insert earphones (reproduced with permission from Strain *et al.*, 1993). (b) Feline BAERs in response to insert earphones and a bone stimulus transducer (reproduced with permission from Strain *et al.*, 1998). Peaks in the response labeled I, II, III, and V are described in the text. Responses from insert earphones were delayed approximately 1 ms due to sound travel time in the tubing from the transducer to the insert tip.

biological response (presumed to be invariant) from within the total signal present at the tissue–electrode interface, multiple responses to the same stimulus are averaged by the recording system. Theoretically, the signal-to-noise ratio is improved by the square root of the number of averages (Sgro *et al.*, 1997), so that increasing the number of responses averaged increases the clarity of the response. In practice there is a finite limit to the improvement that can be obtained, and a large movement artifact recorded late in the averaging process can still produce major distortion in the average. As a result, 1000 responses are typically averaged in recording the BAER, but averaging may be stopped after as few as 500 responses if an unambiguous tracing is present, or may be increased to 2000 responses with unclear recordings. It is good practice to collect two recordings to confirm repeatability if there is any question as to the identity of the response peaks observed (or not observed).

Mechanics of recording the BAER

Step-by-step instructions for BAER testing for screening purposes are presented below. These are based on the author's experience and preferences, and may not be appropriate or optimum for other recording systems and operator preferences, but include suggestions that can be used by the beginner or to improve testing by experienced testers. Operating procedures vary widely among the available commercial testing systems. These directions assume that the subject is a dog, but apply for the most part to cats also. Cats are usually tested in a restraint bag that leaves only the head exposed, protecting the tester from claws. Feline skin is usually thicker than canine, requiring more force to insert the needle electrodes.

Gentle restraint must be used to insure subject relaxation – to minimize anxiety, muscle tension, and movement artifact resulting from trembling or panting. High-quality recordings can be obtained without sedation or anesthesia if patience is observed. Forcibly restraining the subject generates excessive muscle and other artifact and can actually prolong testing time. The external portion of the ear canal can actually be collapsed under pressure, resulting in a deaf response due to the imposed conductive hearing block. It is preferable to avoid chemical restraint for subject safety, as well as reducing cost and testing time. Taking the time to calm the subject is a worthwhile investment.

Developing a standardized sequence of steps in testing an animal is useful – always testing the left ear first, for example. The tester should optimize the layout of the test environment – seated at a chair next to a grooming table with the test machine at the same level works well. Having the tester at the same level as the subject produces less anxiety than looming from above, which is threatening. The owner or assistant should gently hold the dog in place and hand-muzzle the head while the electrodes are inserted. If a puppy or small adult persistently tries to move away, it can be lifted by a hand under

the belly so that none of the feet contact the table surface; when it is unable to get traction against a surface it will usually stop attempting to get away. Animals can also be calmed by gently blowing in their face.

Electrodes are inserted by grasping a pinch of skin between the thumb and forefinger and inserting the needle with a jab into the pocket of skin created by the pinch. To the extent possible, avoid having electrode wires dangling in the animal's face, which can be irritating. Once all electrodes are inserted, the grasp on the animal can be relaxed somewhat, but some control must be maintained to prevent the animal from moving enough to dislodge the electrodes. The assistant should be in a comfortable position to avoid movements that can in turn encourage the subject to attempt movement. Electrode impedance should next be checked to insure that the electrodes are correctly inserted; in long-haired dogs the needle may appear to be subcutaneous, when it actually is just in hair at the skin surface.

With the transducer box grasped in the palm and the insert foam plug held between the thumb and forefinger of the same hand, the plug should be positioned at the opening of the ear canal and held against the inner aspect of the pinna with the thumb, directed toward the ear canal, and against the outer aspect of the pinna with one or more fingers in a gentle pinch. With this placement, the insert plug will not be dislodged if the animal moves its head; keeping the transducer in the palm prevents its weight from pulling the plug away from the ear canal. The opposite hand operates the controls on the BAER machine, although an experienced assistant can provide both restraint and stimulator plug placement, freeing the tester to operate the machine.

The first test run on the first ear is next initiated, followed by a retest to confirm waveform repeatability. When the machine settings are changed to proceed from the first ear to the second, dexterity permitting, it seems to help to keep the ear plug placement unchanged until the operator is ready to start testing of the second ear, so that the operator's hands remain a presence near the animal's head. Once the operator is ready to test the second ear, change is then made to the opposite stimulator transducer and ear plug, and the second ear is tested twice.

When both ears have been satisfactorily tested, all electrodes can be removed by pulling the bundle out at one time. A small drop of blood may appear at an electrode site if a small vessel has been penetrated; wiping with an alcohol swab is normally sufficient to clean the site and stop any bleeding.

A report for both the client and patient files should be generated, with a specific conclusion noted. Conclusion phrases such as 'bilaterally hearing,' 'unilaterally deaf' and 'bilaterally deaf' are useful because they avoid the need to explain what 'normal' should be in a screening evaluation. Statements such as '25% hearing loss' or '30 dB hearing loss' should be avoided because such statements cannot be backed up without having determined the hearing threshold for that specific animal as well as the group mean threshold, determined in the lab performing the test, for that breed or species. It is useful at a minimum to identify peaks I and V on the waveform portion of the report.

If bone stimulator testing is indicated, based on a deaf response to an air-conducted click stimulus and a recent history of otitis externa or media or other indicators, both ears should be first tested with air-conducted stimuli, as the pressure of the bone transducer against the skull can be uncomfortable and make the subject less cooperative. Bone stimulation BAER testing is described below and by Strain *et al.* (1993, 1998).

If threshold determinations to either click or tone stimuli are to be performed, anesthesia is indicated to eliminate movement artifacts that frequently make recordings near threshold impossible. Thresholds are determined by identifying peak V, the last peak to disappear at threshold, as stimulus intensities are reduced. Issues related to frequency testing are discussed below and by Uzuka *et al.* (1998), Poncelet *et al.* (2002), and Ter Haar *et al.* (2002).

Analysis

Once the BAER is recorded, the results must be interpreted. If the recordings are being performed as a screen for pigment-associated deafness, the presence of a repeatable waveform demonstrating all or most of peaks I, II, III, and V in response to suprathreshold stimuli is sufficient to certify that the ear can hear. This requires familiarity on the part of the tester with the normal morphology of the BAER as well as its variability, and the reference (expected) latencies for response peaks.

More precise analyses evaluate a number of attributes of the response (Hood and Berlin, 1986; Chiappa and Hill, 1997):

- Peak latencies (I, II, III, V). Latency to peak I reflects cochlear alterations; increases in later peaks can be the same, indicating a peripheral lesion, or greater, indicating a central lesion. Reference values established in the test laboratory are necessary to know normal variability.
- Inter-peak latencies (I–III, III–V, I–V). For increased latencies in later peaks, these measures provide some localizing information based on the knowledge of putative peak-generating sites in the brain.
- Peak amplitudes. Amplitude is probably the least useful attribute due to the variety of non-pathologic factors that can affect amplitude. These include asymmetrical ear electrode placements, detritus in the ear canal, and greater movement during recording of one ear versus the other.
- Interaural latency differences (peak V). Useful in distinguishing between systemic and lateralized lesions, such as unilateral hearing loss following otitis interna versus bilateral hearing loss from presbycusis.
- Latency–intensity function (graph of peak V latency as a function of stimulus intensity). This can help distinguish between conductive, cochlear, or retrocochlear lesions (Poncelet *et al.*, 2000a).

- Peak V:I amplitude ratio. In humans a peak V:I amplitude ratio < 1.0 is associated with retrocochlear lesions, but this has not been examined systematically in dogs or cats.
- Thresholds. Determination of thresholds to click or tone stimuli can permit quantitation of hearing loss. Tone thresholds especially can identify losses over specific frequency ranges, such as with presbycusis, but testing is time-consuming and requires anesthesia.

What to do when it doesn't work

Failure of the electrodiagnostic instrument to operate or provide satisfactory recordings frequently is merely the result of technical factors (often operator error). The first consideration when a response cannot be recorded is to determine whether it results from a lesion or technical error. A systematic approach in these circumstances can be helpful.

1. Are all connections (including power cords) intact and properly connected? Is the power switch turned on? If fused, is the fuse blown?
2. Are all stimulators functioning and selected for the right modality, intensity, and other parameters? Can you detect the stimulus? If appropriate, is the stimulator synchronization pulse reaching the averager? Many an apparently deaf dog appeared that way because of reversal of left and right ear electrodes, or testing the left ear with the right ear stimulator.
3. Has the right test been selected from the menu?
4. Is the signal reaching the amplifier? If the averager has the option of displaying the input instead of the accumulating average, check the input signal. Does the signal look appropriate, or is it all noise and artifact? Has an electrode fallen off of the subject? Are the gain and filter settings correct? If artifact rejection is an option, is it inappropriately rejecting all responses? Stop the recording and perform a calibration test. Is the averager appropriately set for internal or external stimulus synchronization?
5. Was the memory from a previous trial or subject not erased?
6. For the future, develop and maintain contacts with others in your area using the same equipment and who may have experienced similar difficulties.
7. If all else fails, contact your institution's technical support/repair unit or the manufacturer's technical support service.

Extrinsic Factors Affecting the BAER

A variety of factors, both extrinsic and intrinsic, can affect the recorded BAER, separate from any existing pathology (Hood and Berlin, 1986; Chiappa, 1997; Chiappa and Hill, 1997; Strain, 1997a, b; Legatt, 1999). An understanding of these factors allows the tester to optimize recordings and to

avoid or minimize artifacts and errors. Extrinsic factors include electrodes, stimulators and stimulation parameters, and recording parameters. Intrinsic factors include age, gender, temperature, and drugs that may affect responses.

Electrodes

The recording of the BAER requires a low-impedance connection between the recording electrodes and body tissues so that most of the signal voltage drop occurs across the input impedance of the recording amplifier and not the electrode–tissue interface. Typically it is a goal to have the electrode impedances fall below 5–7 kΩ, and most instruments have a build-in impedance testing function whereby this can be measured.

In human applications it is most common to use precious metal disc recording electrodes, adhered to the skin with collodion adhesive or tape, and with a conductive paste between the metal and skin. However, because of the hairy skin on the head of animals it is usually not possible to secure a low-impedance connection without closely shaving the skin, an action usually unacceptable to owners. Alligator clips can be used, but they can be painful to the animal, may not produce a sufficiently low-impedance connection, and may be prone to movement artifact.

As a result of the above the most commonly used electrode type in animal BAER recordings is the subdermal needle electrode. These are typically 27–30 gauge and 10–12 mm in length, with an integrated lead wire that plugs into the machine input box. Impedance for needle electrodes is slightly higher than for disc electrodes – about 7 kΩ compared with about 5kΩ. For evoked potential applications, stainless steel needles are satisfactory because they are strong, do not corrode, and are comparatively low cost, but they have inferior electrical characteristics compared with other metals. Platinum is preferred because it is a good electrical conductor, inert, non-toxic, and strong if alloyed with iridium; platinum alloy electrodes (e.g., Grass Technologies Inc., West Warwick, Rhode Island) appear to also be less prone to movement artifact, so the higher cost is generally justifiable. Because the market for electrodes is driven by human medicine, electrodes are individually packaged and intended to be disposable, but their cost for single use cannot be justified in veterinary applications, so needle electrodes are frequently reused, with antiseptic cleaning between uses, until they lose their sharpness.

While needle electrodes are painful to humans if one becomes stuck, dogs almost always show no aversive response to their use; on occasion a cutaneous pain nerve may be directly struck, eliciting a yelp, but otherwise dogs show no evidence of being bothered by their use other than the irritation of wires dangling in front of the face. Needle insertion is accomplished by gently grabbing a pinch of skin between the thumb and index or middle finger, lifting the skin slightly, and then inserting the needle between and just below the pinching fingers. The entire needle should be inserted to maximally

reduce the electrode impedance. Use of needle electrodes with cats is more of a challenge due to the greater toughness of cat skin, requiring the use of somewhat greater force for insertion. For this reason, and the hazards of cat claws, it is advisable to use a restraint bag when recording from cats.

Electrode montage

Placement of electrodes for recording the BAER varies among testers, but two montages are the most common. In montage one, the active electrode is placed at the vertex (C_z under the International 10–20 nomenclature) – on the midline of the skull, approximately midway between the eyes and nuchal crest – and the reference electrode is placed at the tragus, just rostral to the opening of the ear canal of the stimulated ear (A_1, left ear; A_2, right ear); the ground electrode is placed over an 'electrically inactive' site, such as on the dorsal neck, or on the contralateral ear. Montage two consists of the active electrode at the vertex, the reference electrode over the first thoracic vertebra, and ground on the contralateral mastoid. Montage two maximizes the appearance of peak V, which is useful in determining the hearing threshold to stimuli of decreasing intensity, while montage one maximizes peak I, which is useful in screening for congenital sensorineural and conductive deafness (Holliday and Te Selle, 1985). Montage two requires contralateral masking noise to prevent stimulus detection by the ear not under test, since this electrode placement does not otherwise distinguish which ear hears the stimulus. Montage one is the preferred placement.

Stimulus transducer

Several types of auditory stimulus transducers are available. The most common type sold with evoked potential systems is the binaural audiologic headphone, where a cup-like flexible cover excludes much of the external environmental sound and perforations in the center direct sounds generated within the headphone into the ear canal. Left and right stimulators are attached to each other by a curved headband that places a slight pressure holding the cup against the external ear. Headphones are difficult to use with animals because the headband is not designed for animal head dimensions. Each ear cup can be detached from the headband and manually held in place, but it is hard to direct the generated stimulus sound into the ear canal and it is even possible to collapse the ear canal by hand pressure, which provides a test result indicating hearing loss or deafness.

Insert earphones (Fig. 6.2) were initially designed for intraoperative monitoring of humans during surgeries where potential damage to auditory function was anticipated. A flat transducer box generates the stimulus sound, which then travels down a flexible rubber tube to a terminal foam ear plug.

Fig. 6.2. Auditory stimulus transducers used to elicit the brainstem auditory evoked response (BAER). Headphone cups can be removed from the headband and held over the ear canal opening. Insert earphones can be inserted into the ear canal, but are usually held at the canal opening. The bone stimulus transducer is held against the skull over the mastoid process.

Rolling the foam plug between two fingers reduces its diameter for insertion into the ear canal, where it quickly expands back toward its original diameter, holding it in place; pediatric- and adult-diameter foam plugs are available. Insert earphones are the most commonly used form of stimulus transducer in animal applications, but the foam plug is usually held outside the ear canal opening rather than being inserted, because it is possible to inadvertently direct the opening of the foam plug into a dead-end cartilage pocket and greatly reduce the sound intensity reaching the tympanic membrane. The foam plugs are disposable, but for economy purposes they are commonly reused. Holding the plug at the opening of the ear canal also reduces the likelihood of transmitting parasites or pathogens between subjects when reusing them. The time for the stimulus sound to travel from the transducer to the foam plug is approximately 0.9 ms, depending on the length of the tube, which results in longer peak latencies in the BAER when compared with headphones. Many BAER test systems provide an option to correct this by subtracting the stimulus latency delay from the displayed numerical results. Individual labs should determine normative values for animals with intact hearing with the equipment and accessories in that lab rather than relying entirely on published values.

The signal produced by the transducer mechanism within headphones or insert earphones is constrained by the mechanical properties of the devices. As a result, a square wave voltage, used to generate a click sound, or a sine wave voltage, used to generate a tone, do not faithfully reproduce the voltage

signal. Frequencies higher than 4 kHz are attenuated (Fig. 6.3), but this is an unavoidable factor. A graphical representation of the frequency response of a headphone or insert earphone is generally provided with its purchase.

When differentiating between sensorineural and conduction deafness, a bone stimulation transducer is used (Fig. 6.2), which produces vibrations instead of air-conducted sounds (however, the device also produces air-conducted sounds that can be easily heard). When held against the head at the mastoid process behind the ear, the transducer's vibrations are transmitted through bone to the cochlea, which is buried in bone, bypassing the outer and middle ear (Strain *et al.*, 1993, 1998); the mandible and zygomatic arch are alternative placements (Fig. 6.4). Peak latencies are shorter with a bone stimulation transducer than uncorrected latencies with insert earphones (Fig. 6.1), but inter-peak latencies do not differ. Bone stimulation latencies are slightly longer than headphone latencies or corrected insert latencies. Bone stimulation BAER testing is only performed

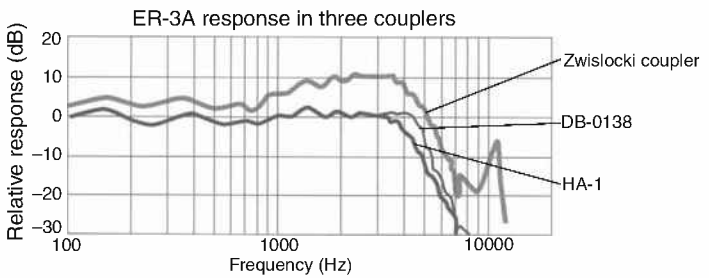

Fig. 6.3. Frequency response of an insert earphone transducer measured with different available acoustic couplers. Frequencies above 4 kHz are increasingly attenuated, but lower frequencies are faithfully produced.

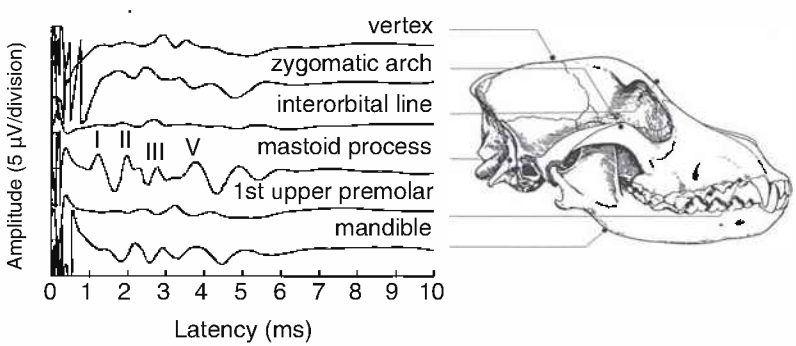

Fig. 6.4. BAERs recorded from different application sites on the canine skull. Optimum responses were recorded from placement on the mastoid process (reproduced with permission from Strain *et al.*, 1993).

when air-conducted BAER results show deafness and patient history, such as a recent ear infection, suggests possible conduction deafness.

The quality of recording with the bone stimulation transducer is a function of the quality of energy transfer from transducer to skull, so the transducer must be held firmly against the head, which can be uncomfortable for the animal. Assessment of bone-conducted BAERs is more subjective for than air-conducted BAERs. When opting to use a bone transducer, the tester is advised to test both ears with air-conducted clicks first, as the discomfort associated with the bone stimulator may reduce subject cooperation. Commercial bone transducers come with a spring-tension headband, but this does not provide adequate mechanical energy transfer, so hand-application is best.

Bone transducers are usually optional accessories on BAER systems, and their relatively high price often deters purchase. However, it is possible to purchase the transducer directly from the source used by virtually all system manufacturers at about one fifth the commercial cost (Etymotic Research Inc., Elk Grove Village, Illinois) and wire it to an appropriate electrical connector using wiring connections that can be obtained from the system manufacturer. It is important when purchasing a transducer to correctly specify the device impedance (10 Ω or 300 Ω) used by that system.

Stimulus parameters

Stimuli used in BAER testing are either clicks or tone bursts. Clicks are used when screening for hearing loss, while tone bursts are used to investigate hearing changes at specific frequencies and allow construction of an audiogram for the animal being tested (Fig. 2.1).

Stimulus type

The click is the result of a voltage square wave of 100 μs duration applied to the transducer. The resultant sound includes a broad range of frequencies up to about 8 kHz, with the higher frequencies attenuated (Fig. 6.3). This frequency range is sufficient for human testing, effectively stimulating most of the cochlea, but does not stimulate basal areas of the dog or cat cochlea where the hearing range exceeds that of humans. Despite this limitation, click stimuli are routinely used in animal BAER testing. A small number of dogs that test as deaf with the BAER may nevertheless retain very high-frequency hearing that can be demonstrated with a silent whistle; these cases are rare.

Tone burst stimuli are – at least on commercial systems – sounds generated at a discrete set of frequencies that may range from 250 Hz to 8 or 16 kHz; custom-built systems can provide more test frequencies. The stimulus duration differs depending on the type of tone stimulus utilized; commercial systems usually offer several. One type is a tone of fixed duration where the amplitude of a set frequency sine wave is ramped up over 10 ms, maintained at a plateau for 30 ms, then ramped down to zero over 10 ms, for a total

duration of 50 ms. The drawback to this stimulus type is that the number of sound oscillations striking the tympanic membrane during a stimulus will vary significantly for a 250 Hz stimulus compared with an 8 kHz stimulus. Another type of stimulus instead specifies ramp, plateau, and fall phases in cycles of the sine wave frequency instead of times; these stimuli may be called pips. A 202-tone pip stimulus will have a two-cycle rise, a zero-cycle plateau, and a two-cycle fall, and a 212-tone pip will have a two-cycle rise, a one-cycle plateau, and a two-cycle fall. Total stimulus duration will depend upon the frequency of the stimulus since cycle length is inversely related to frequency. A discussion of the relative merits of these and other frequency-specific stimuli is beyond the scope of this book.

Stimulus polarity

Click and tone stimuli both produce sound waves where the initial force on the tympanum either deflects them toward the cochlea or away from it. These stimulus polarities are referred to as condensation or rarefaction, respectively. Rarefaction stimuli are most frequently used, and the peaks of the BAER produced are of a slightly shorter latency than with condensation stimuli; peak amplitudes may be slightly larger, but no further advantage is obtained from either. BAER systems allow choice of either or alternation between the two. Alternating polarity stimuli can be useful to reduce stimulus artifact where it is a problem.

Stimulus rate

Recordings of the BAER are averages of responses to multiple stimuli. The rate at which these stimuli are presented varies widely among systems and tester preferences. Rates that are integral factors of the 60 Hz power frequency (10, 15, 20, 30/s) are best avoided to prevent aliasing, an inadvertent contamination of the recording with a time-locked artifact from nearby electrical devices; values such as 11.33 stimuli per second are chosen for this reason. Some references state that as the stimulus repetition rate is increased above about 30/s, peak latencies increase (inter-peak latencies are largely unchanged), amplitudes decrease, and repeatability and clarity are reduced as well. However, a recent study has shown that stimuli at rates as high as 91 clicks per second do not significantly degrade responses in dogs (Wilson *et al.*, 2011), which permits more rapid collection of responses in studies involving multiple recordings.

Stimulus intensity

As stimulus intensity increases, BAER peak latencies decrease and peak amplitudes increase. When the BAER is being used to screen subjects for the presence of pigment-associated deafness, where an ear is generally either deaf or normal, suprathreshold stimuli are used (e.g., 95 dB nHL) to take advantage of the improved clarity of the response at high intensities. Most animals are not bothered by the loud clicks, and some puppies actually doze off.

As stimulus intensity decreases, peak latencies increase and peak amplitudes decrease with both click and tone stimuli (Fig. 6.5). Near the hearing threshold the last peak in the response to disappear is peak V, so the stimulus intensity at which peak V is no longer produced is used to define the hearing threshold. A typical strategy is to start at a moderate intensity and in subsequent recordings reduce the intensity in 10 dB steps until the response disappears, then increase intensity by 5 dB to identify where in the last 10 dB range the actual threshold occurs. Smaller intensity increments can be utilized but the additional precision in determining the threshold is offset by the additional time required. Near-threshold responses are very sensitive to biological and other artifacts, so threshold determinations are usually performed under anesthesia or sedation, while screening testing can easily be performed without chemical restraint.

Masking noise

When one ear is tested, the stimulus sound is also available to the contralateral ear through air and bone conduction, at an intensity 40–50 dB less than for the stimulated ear (Chiappa, 1997). In dogs and cats this results

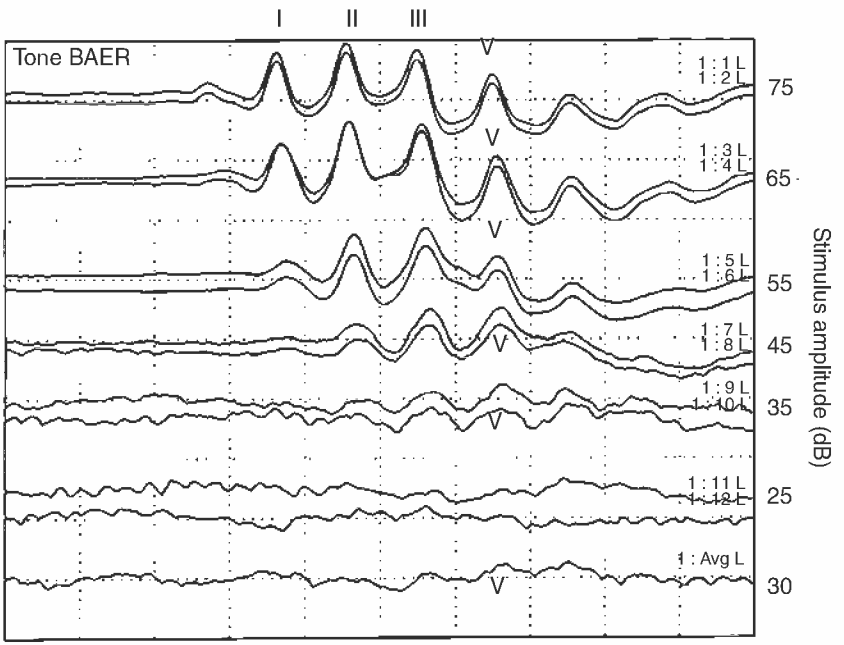

Fig. 6.5. BAER threshold determination in an adult dog using 1000 Hz 212-tone pip stimuli. Stimuli amplitudes were decreased in 10 dB steps until no peak V was present in the response, then increased by 5 dB to confirm that a peak V was present at the intermediate intensity. Threshold for this dog was 32.5 dB.

in the presence of peak V of the BAER when testing a deaf ear in a unilaterally deaf animal, due to detection of the stimulus by the contralateral hearing ear. This is not a problem in screening animals for pigment-associated deafness because the presence of peak V in the absence of earlier peaks should still be recognized as a deaf response. However, if it is desired to eliminate this possible confounding factor, the non-tested ear is masked with white noise at an intensity of 30–40 dB below the click stimulus.

Recording parameters

Most BAER test systems permit the user to adjust several controls that affect the recorded response. Changing these can at times help reduce artifact or more clearly expose specific features in the response that may be of special interest.

Duration

The duration of the acquired response is typically 10 ms, which includes all of the peaks normally identified in the BAER. Shorter durations can be used if there is interest in early events of the response, such as the cochlear microphonic. Longer durations may be useful when testing with tone-burst stimuli that have a longer duration than the click stimulus.

Filtering

Amplifiers have three types of filter that can pass or exclude portions of the signal that is of interest. Loss-pass filters allow through frequencies below the filter setting and exclude frequencies above the setting. High-pass filters allow through frequencies above the filter setting and exclude frequencies below the setting. The precision of the actual pass/exclude frequency or the sharpness of the cut-off is a function of the filter's design. A low-pass filter combined with a high-pass filter creates a band-pass filter, where each end of the frequency band can be varied independently. For BAER recordings the high-pass filter is usually 50–150 Hz and the low-pass filter is 3000 Hz, giving a band pass range of 100–3000 Hz. Reducing the high-frequency setting of the band pass, e.g., to 1500 Hz, smoothes out sharp peaks by reducing the high-frequency components of the response and slightly increases peak latencies, but may be necessary to eliminate or reduce noise. Increasing the high-frequency setting is likely to include high-frequency noise. Increasing the low-frequency setting, e.g., to 300 Hz, slightly distorts the waveform by removing slower components, while lowering it introduces slow baseline changes. Analog filters introduce shifts in peak latencies because of phase shift; digital filtering does not introduce this artifact, and most currently used systems utilize digital filtering.

The other type of filter available on BAER systems is a notch filter, designed to only exclude a very narrow range of frequencies centered around

the mains frequency of the electrical system: 60 or 50 Hz, depending on country. The notch filter can exclude some of the mains frequency artifact, but not all of it. If the recording environment consistently has high levels of 60 Hz noise, an alternate recording location should be considered if the source of the noise cannot be located and eliminated.

Number of averages

The small size of the BAER signal in comparison to other coincident signals such as EEG and muscle artifact requires averaging responses to multiple stimuli; it is typical for 1000–2000 responses to be averaged. Theoretically the signal-to-noise ratio improves with the square root of the number of averages (Sgro *et al.*, 1997), but improvement is usually small beyond 1000–2000 averages, and a late-occurring movement artifact can still significantly degrade the average. With experience, a tester will often be able to recognize the presence of the BAER response pattern with 500 or even fewer averaged responses, especially with a cooperative subject. It is good practice to perform the test twice to confirm repeatability of the response. This is especially helpful with unclear or atypical responses.

Display gain and amplification

Display gain refers to the display of the acquired average on the system display. It should be adjusted so that the averaged response falls well within the bounds of the top and bottom of the display area; if the peak-to-peak signal extends beyond these bounds it is difficult to distinguish a normal response from artifacts. Typically the vertical display amplitude is 0.5 μV/division, or a total range of 5 μV. The BAER amplitude is 0.1–0.5 μV, so the signal at the electrodes must be amplified significantly, usually by a factor of 100,000–150,000.

Intrinsic Factors Affecting the BAER

Several biological, non-disease-related factors have also been shown to affect the recorded BAER. The tester should be aware of these so as to avoid misinterpretations of test results.

Age

The BAER shows a postnatal development pattern in dogs and cats. Responses in precocial species like the cow and horse are essentially mature at birth, while altricial species like human, dog, and cat change after birth by decreases in peak latency and increases in peak amplitude (Jewett and Romano, 1972; Strain *et al.*, 1991; Kuse and Okaniwa, 1993; Poncelet *et al.*, 2000b, 2002;

Fig. 6.6). Clear BAERs cannot be recorded from dogs or cats prior to the opening of the ear canal, which occurs at about 14 days in dogs and 5 days in cats, but responses to very loud stimuli (100 dB nHL) can still produce responses. BAERs are fully mature by postnatal day 40 in the dog (Strain *et al.*, 1991) and by day 20 in the cat (Javel *et al.*, 1986). Hearing thresholds to click stimuli are mature by postnatal day 20 in both species (Fig. 6.7). Peak I matures first and peak V matures last, a reflection of the fact that the brain progressively matures from the brainstem to the cortex.

In geriatric subjects with presbycusis, there is an elevation of hearing thresholds, initially at high frequencies and later spreading to lower

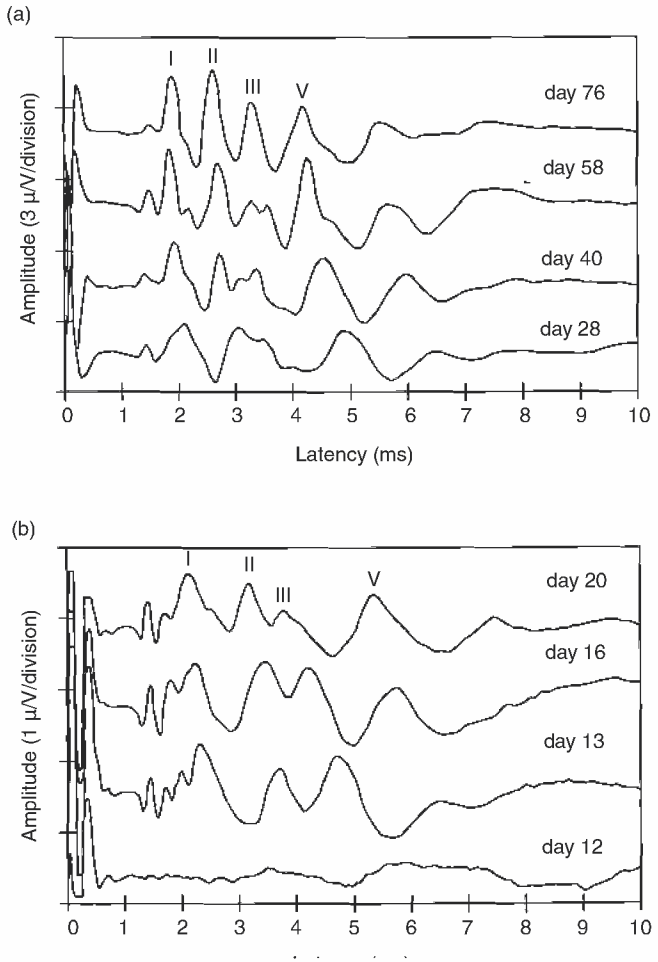

Fig. 6.6. Postnatal development of the BAER in the dog from 12 to 76 days of age. Response peak amplitudes increased and latencies decreased with maturation; adult responses were present before age 76 days. Note amplitude scale differences between (a) and (b) (reproduced with permission from Strain *et al.*, 1991).

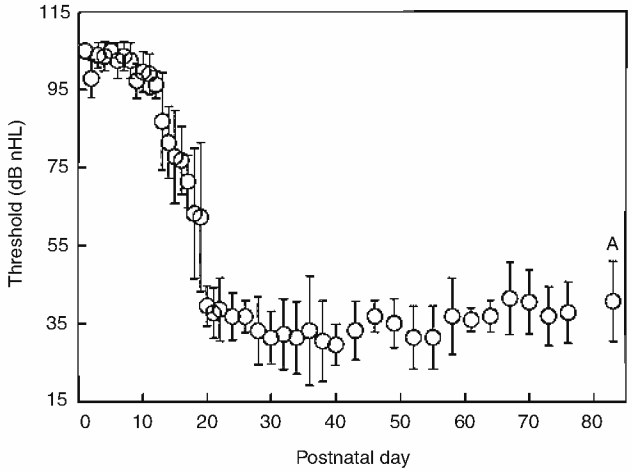

Fig. 6.7. Postnatal maturation of the threshold to BAER click stimuli; thresholds reached adult levels by day 20. A, adult (reproduced with permission from Strain *et al.*, 1991).

frequencies. With threshold elevation there is a reduction in perceived sound loudness. As a result, it can be anticipated that hearing loss associated with aging will affect BAERs by increasing peak latencies and decreasing peak amplitudes.

Head size

Pook and Steiss (1990) examined the relationship between head dimensions and body weight with peak and inter-peak latencies. The head dimensions and body weight correlated with peak V latency and the I–V inter-peak latency, but there was no correlation with the peak I latency. Meij *et al.* (1992) found similar correlations, but Munro *et al.* (1997) failed to find significant correlations when comparing Dalmatians and Jack Russell terriers. However, any variations are probably not great enough to be meaningful in clinical applications. Ear placement on the head appears to have some effect also. The author has observed shorter peak I latencies in many English cocker spaniels, which have lower-set ear canal openings, when compared with adult dogs of other breeds. Most studies have not looked at correlations between head size and peak amplitudes because of their high variability. However, mature responses in beagle puppies were larger than those of adult beagles (Strain *et al.*, 1991), and amplitudes in small breeds are often larger than in large breeds. This is not surprising since the recording electrode locations in adults would be farther from the response generator sites and potentials decrease in

amplitude with the square of distance from the source. For this reason, BAER peak amplitude comparisons have limited meaning unless taken from dogs from the same breed, or at least similar head sizes and shapes.

Gender

In humans it is well established that females have shorter absolute and inter-peak BAER latencies than males, although there are no gender differences in newborns and young children (Chiappa, 1997), an affect usually attributed to differences in head size. However, studies in dogs have found no significant gender differences (Pook and Steiss, 1990; Meij *et al.*, 1992; Munro *et al.*, 1997).

Body temperature

Within a narrow physiologic range (37.0–39.5°C), body temperature has no noticeable effect on BAER responses. With hypothermia, peak latencies (absolute and inter-peak) increase with decreasing temperature, and the response disappears in mammals at temperatures near 20°C. In humans it has been reported that the peak V latency increases 0.17 ms per degree centigrade drop in temperature (Stockard *et al.*, 1978). BAER changes associated with hypoglycemia and certain anesthetic drugs most likely result from hypothermia (Chiappa, 1997). Hyperthermia in rats (rising from 37.0° to 41.5°C) produced decreases in peak and inter-peak latencies and in peak amplitudes (He *et al.*, 2003), but it is not clear that typical changes seen with fever would significantly affect BAER responses.

Drugs

Omitting ototoxic drugs, discussed in Chapter 5, the drug classes of greatest interest are the anesthetics and sedatives. It is recognized that the state of arousal does not affect the BAER – sleep, coma, narcolepsy, or attention level – and likewise most CNS acting drugs have limited effect. Most sedatives, muscle relaxants, barbiturates, and anesthetics are without effect (Cohen and Britt, 1982; Hood and Berlin, 1986; Tokuriki *et al.*, 1990; Chiappa, 1997; Wilson and Mills, 2005) except possibly at drug levels producing very deep coma. One study (Myers *et al.*, 1985) found prolongation of peak latencies with 3% methoxyflurane anesthesia in dogs, while halothane (Sanders *et al.*, 1979) and isoflurane (Stockard *et al.*, 1977) had no effect in humans. Alcohol intoxication had a small effect on peak latencies, but this was attributed to hypothermia caused by the alcohol (Jones *et al.*, 1980).

Artifact

The various sources of artifact in BAER recordings have been discussed above. Of these, muscle artifact may be the greatest problem because its amplitude is often 1000 times the amplitude of the desired signal. Averaging eliminates some of the artifact, and many systems have an artifact reject function that excludes from averaging any response whose amplitude is greater than some preset level. Muscle artifacts can especially be a problem with low-priced testing units that do not permit changes in display amplification. When peaks exceed the peak–peak display, it is nearly impossible to distinguish artifact peaks from true BAER peaks. It is for this reason that the unit's display should be set so that the entire response takes up no more than half of the vertical display. If muscle artifact continues to be a problem in an individual animal despite averaging and artifact rejection, it may be necessary to employ anesthesia.

Clinical Applications of the BAER

Clinical uses of the BAER can be loosely separated into audiologic applications – those dealing with peripheral auditory structures – and neurologic applications – those dealing with central auditory pathways. The latter are more common in human medicine than in veterinary medicine, but with time their value in evaluating neurologic function may increase.

Audiologic applications

The earliest clinical veterinary applications of the BAER were in assessing the presence of deafness in dog breeds with pigment-associated deafness (Sims and Shull-Selcer, 1985; Marshall, 1986), although cats were used in early studies for understanding the BAER for human application (e.g., Jewett and Romano, 1972). Sample recordings are shown in Fig. 6.8, demonstrating BAERs recorded from bilaterally hearing, unilaterally deaf, and bilaterally deaf Dalmatian puppies. Early studies reported results for small numbers of animals, while later studies, attempting to determine associations with phenotypic correlations with deafness such as iris color, patch, gender, and coat colors, reported data for cohorts in excess of 1000 (Holliday *et al.*, 1992; Strain *et al.*, 1992; Platt *et al.*, 2006; De Risio *et al.*, 2011); one study included 11,300 dogs (Strain, 2007). Other applications included assessment of conductive hearing loss (Steiss *et al.*, 1990; Wolschrijn *et al.*, 1997), ototoxicity (Morgan *et al.*, 1980; Merchant *et al.*, 1993; Strain *et al.*, 1995; Uzuka *et al.*, 1996), and presbycusis (Ter Haar *et al.*, 2008). These studies have been discussed earlier in this book.

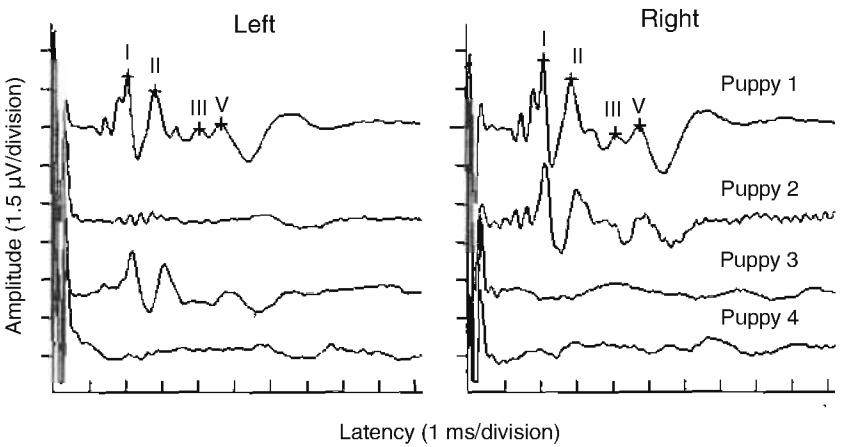

Fig. 6.8. BAER recordings from four Dalmatian puppies from the same litter. Puppy 1 was bilaterally hearing, puppies 2 and 3 were unilaterally deaf, and puppy 4 was bilaterally deaf (reprinted with permission from Strain, 1991).

Neurologic applications

The BAER has proven more useful to date in human than in veterinary applications (Starr and Achor, 1975; Hood, 1988; Chiappa and Hill, 1997; Legatt, 1999). There have been numerous studies, but useful findings have been reported to be most often seen with cerebellopontine angle tumors, demyelinating diseases, brainstem lesions, tumors, infarctions, and hemorrhages, especially those impacting the brainstem (Chiappa and Hill, 1997); and in evaluating the mechanisms of coma, localization of midbrain and brainstem tumors and demyelination of the brainstem, and the presence of diminished brainstem circulation (Starr and Achor, 1975). Neurologic uses of the BAER, in both human and veterinary neurology, are somewhat hindered due to the limited anatomic localizing precision of the test.

Two retrospective publications have addressed the use of the BAER in veterinary neurologic disease. Steiss *et al.* (1994) reported BAER results in 14 dogs with brain lesions confirmed by necropsy or biopsy. The pattern of abnormalities observed included absence of some or all of peaks I–V, increased peak latencies, especially peak V, and reduction in the peak V:I amplitude ratio. As might be expected, lesions or space-occupying masses that impacted the brainstem altered BAER responses. Disorders included brainstem/cerebellar and forebrain tumors, brainstem trauma, hydrocephalus, granulomatous meningoencephalitis, and meningoencephalitis.

Another study evaluated BAER responses from 26 dogs with intracranial neoplasias (Fischer and Obermaier, 1994). Abnormal responses were seen in dogs with cerebral (1/7), cerebellar/brainstem (4/4), brainstem (5/5), and

multifocal tumors (4/5). Since cerebral and multifocal tumors are less likely to impinge on the brainstem areas responsible for the BAER than are brainstem and cerebellar tumors, the lower correlation of BAER abnormalities with the presence of a tumor is to be expected until tumor mass becomes large.

Other neurologic applications have included studies of dogs with vestibular disorders or seizures (Myers *et al.*, 1986) and dogs with several forms of hereditary retinal degeneration (Acland *et al.*, 1985). In addition, a dog with disseminated protothecosis (systemic infection secondary to ingestion of green alga) and clinical signs of blindness and deafness showed an absent BAER, which was confirmed by histologic examination to result from extensive damage to the organ of Corti and tectorial membrane; any effect on the BAER due to diffuse brain lesions was obscured by the cochlear effects (Cook *et al.*, 1984).

Other Tests of Auditory Function 7

Although the BAER is by far the most commonly used auditory function test in veterinary medicine, a number of additional tests are available for specialized applications. The endocochlear potential and electrocochleogram (EcoG) are auditory measurements of function prior to transmission to the central nervous system. Acoustic impedance, tympanometry, and acoustic reflex tests assess middle ear function and brainstem reflexes. The distortion product otoacoustic emission (DPOAE) is an alternative to the BAER for diagnosis of deafness. The middle- and long-latency evoked responses and the auditory steady-state response are extensions of the BAER. Finally, the vestibular evoked myogenic potential (VEMP) is an electrodiagnostic test of some functions of the vestibular system that uses an auditory stimulus. Of these, the DPOAE may show the greatest potential value in veterinary applications. Brief descriptions and clinical applications are described below.

Endocochlear Potential

The endocochlear potential is a positive DC voltage of 80–100 mV recorded from the endolymph of the cochlea relative to the rest of the body; it is not present in the endolymphatic spaces of the saccule, utricle, or semicircular canals. The endocochlear potential is a cochlear resting potential, present in normal ears in the presence or absence of stimuli. This potential results from the high K^+ concentration in the endolymph, generated by the stria vascularis, and acts as a physiological indicator of the integrity of that structure and more commonly the cochlea *in toto* (Hibino *et al.*, 2010). The

potential acts as a battery, driving ions across the hair cell stereocilia membrane when deformation opens mechanically gated ion channels. Measurement requires surgical exposure of the bony labyrinth, and as a result it is primarily a research tool.

Cochlear Microphonic and Summating Potential

The cochlear microphonic (CM) and summating potential (SP) are stimulus-dependent potentials, present in the cochlea in response to stimuli but otherwise absent (Glattke, 1983). The CM is an AC signal in the μV to mV range (depending on recording location) that faithfully follows the stimulus waveform, including the phase of the stimulus: reversing the stimulus polarity reverses the polarity of the CM also. Clinical recordings of the CM are made with an electrode near the cochlea, usually on the wall of the middle ear cavity or on the tympanic membrane, but the response amplitude on the tympanic membrane is in the μV range and requires intense auditory stimuli. Early applications used a needle that penetrated the tympanum, but that approach is now considered too invasive in humans. Unlike the BAER, the CM does not increase in latency as stimulus intensity decreases. The CM is primarily generated by outer hair cells, so it indicates a response to sound stimuli prior to the first peak in the BAER. However, the response is dominated by hair cells close to the recording electrode, limiting the extent of cochlea evaluated by the recording. If a CM is present when no BAER peak I is present, it indicates that the lesion is in the cochlear nerve rather than the cochlea. The DPOAE provides similar information.

The summating potential is a DC potential that serves as a baseline shift upon which the CM rides; it is also seen as a 'shoulder' on the onset of peak I of the BAER. It consists of a 0.05–0.50 μV negative shift in a normal ear. Like the CM, the SP is only present when a stimulus is present and does not adapt during the duration of the stimulus; unlike the CM, the SP does not duplicate the stimulus waveform. The SP is also thought to originate in cochlear hair cells, especially outer hair cells, but its origin is not totally understood. The SP is recorded in the same way, and usually at the same time as, the CM. In human neurology the CM and SP are largely restricted to neuro-otology practices, especially in the diagnosis of Ménière's disease, and they have found no application at present in veterinary medicine.

Electrocochleogram

The electrical activity of the eighth cranial nerve (CN VIII) in response to activity generated in the cochlea can likewise be recorded. Typically this whole nerve action potential (AP), the synchronous firing of distal afferent nerve fibers, is recorded from the same location and with the same methods as

the CM and SP (Glattke, 1983). Taken as a group, the recording of the CM, the SP, and the AP is known as the electrocochleogram, or EcoG. The EcoG represents stimulus-related activity in the peripheral portion of the auditory system. The ratio of the SP amplitude to the AP amplitude (SP/AP ratio) is used to identify normal or abnormal function, and is considered to be abnormal if it exceeds 30–50%, depending on author. In addition to its use in the diagnosis of Ménière's disease in humans, the EcoG has been used to identify temporary threshold shift following noise trauma (Nam and Won, 2004). The AP is identical to peak I in the BAER, which has supplanted the EcoG in most applications.

Acoustic Impedance, Tympanometry and the Acoustic Reflex

Acoustic impedance does not evaluate auditory sensitivity, but instead indicates the integrity of the tympanic membrane and middle ear by tympanometry and the function of auditory reflexes that operate through the brainstem and CN VII and VIII (Martin, 1986). The reciprocal of acoustic impedance is acoustic immittance; at present immittance units (mhos) are more commonly used than impedance units (ohms). Acoustic immittance is a measure of the transfer of energy from the outer ear, through the tympanum and ossicles into the inner ear. The ideal condition exists when this energy transfer is optimized, and that occurs when the pressure is equal on both sides of the tympanic membrane. This pressure equalization is maintained through the connection of the eustachian tube to the nasopharynx, which opens the middle ear to atmospheric pressure. When the pressures are equal on both sides there is optimum transmission of sound into the middle ear.

Tympanometry

The equipment for performing tympanometry consists of an ear plug that can seal the ear canal and includes a sound source of fixed intensity and frequency (typically 226 Hz), a microphone to measure the loudness of the sound reflected off of the tympanum, and an air pressure source to vary the air pressure in the ear canal. Air pressure is varied, typically from −300 to +200 mm H_2O (decaPascals, daPa), and the reflected sound loudness is measured. The results are presented graphically, with the air pressure on the X-axis and the immittance (or compliance) of the tympanic membrane on the Y-axis. The result for an ideal normal response curve has a maximum immittance at 0 mm H_2O and declining admittance values at both lower and higher air pressures; the graph looks like a tent held up by a center pole, sagging to either side.

Tympanogram results are classified using the Jerger system into five main groups (Jerger, 1970; Campbell and Mullin, 2011), as shown in Table 7.1.

Table 7.1. Jerger (1970) system of tympanogram types and associated middle ear conditions.

Type	Pressure peak (daPa)	Immittance (mmho)	Condition
A	0	1.0–1.5	Normal middle ear pressure and compliance
As (shallow)	0	< 0.2	Normal middle ear pressure, low compliance
Ad (deep)	0	> 1.5	Normal middle ear pressure, high compliance
B	No peak	Low or not measurable	Otitis media, canal occlusion, or perforated tympanic membrane
C	Negative	1.0–1.5	Normal compliance, significant negative pressure

A type A tympanogram has its peak at 0 daPa with an immittance value of 1.0–1.5 mmho. A reduced immittance (type As, shallow) suggests low compliance (or high impedance), which implies stiffness in the middle ear system from middle ear effusion, otosclerosis, or scarring of the tympanic membrane. An elevated immittance (type Ad, deep) suggests ossicle disarticulation or a flaccid tympanum. A normal tympanogram pattern shifted left to negative pressures (type C) indicates a negative middle ear pressure, usually due to dysfunction in the eustachian tube. A flattened tympanogram (type B) can be the result of otitis media or ear canal occlusion, or a ruptured tympanic membrane; further testing is required to differentiate these possibilities.

Acoustic reflexes

Acoustic reflexes are the contractile response of the stapedius muscle in the middle ear to loud stimuli. The afferent branch of the reflex travels in CN VIII to the ventral cochlear nucleus, to the motor nucleus of CN VII, and then the efferent branch travels in both the left and right CN VII to the stapedius muscles, causing them to contract in both middle ears – ipsilateral and contralateral responses. The contralateral response anatomical pathway also includes transfer from one ventral cochlear nucleus to the opposite through the trapezoid body. Induced contraction to a loud stimulus produces a measureable change in immittance. Reflex thresholds are determined at a specific frequency, determining the lowest stimulus intensity that will trigger the reflex. Tests may be performed at just one frequency – typically 1000 Hz – to determine the integrity of the pathway. More detailed examinations determine thresholds at a variety of stimulus frequencies, ranging from 500 to 4000 Hz. Typical threshold intensities are 70–100 dB SPL for ears with

normal hearing; thresholds are elevated with conductive hearing loss, while sensorineural loss may or may not affect thresholds (Campbell and Mullin, 2011). Use of tympanometry and acoustic reflexes in dogs has been reported (Penrod and Coulter, 1980; Cook *et al.*, 1984; Forsythe, 1985; Sims, 1988), but these methods have not achieved very wide application, in part due to the need to purchase an additional piece of instrumentation.

Middle- and Long-latency-evoked Responses

A brief suprathreshold acoustic stimulus produces a series of vertex-positive peaks over a time period of several hundred milliseconds; those occurring during the first 10 ms are known as the BAER. A later set of peaks, occurring between 8 and 40 ms, is known as the middle latency response (MLR) (Sims and Moore, 1984b; Sims, 1988). This response consists of a series of negative and positive peaks (N_0, P_0, N_a, P_a, N_b, and P_b) that are thought to originate in the thalamus and cortical areas rather than the brainstem (Kaga *et al.*, 1980). The MLR correlates well with auditory threshold determinations and can provide some localization information about lesions (Musiek *et al.*, 1984), but because it is affected by certain anesthetics (Sims, 1988) its use in dogs or cats has limited potential.

A variation of the MLR is the 40 Hz response, where stimuli are presented at 40 Hz instead of the maximum 10 Hz stimulus rate of the MLR (Tiitinen *et al.*, 1993). The most prominent peak of the MLR, P_a, occurs at 25 ms in humans, so stimuli presented at 40 Hz (i.e., once every 25 ms) produce a response consisting primarily of P_a peaks that looks like a sine wave. The 40 Hz response is one of a group of auditory responses known as steady-state responses, where the stimulus is continuous instead of transient like the BAER. The 40 Hz response can be recorded in a shorter time than the MLR, but it is affected by sleep and attention levels, thus limiting its applicability.

Another steady-state response, the auditory steady-state response (ASSR) uses a stimulus that is a continuous tone (the carrier) which is amplitude-modulated at frequencies from 80 to 100 Hz, and the response assesses the brain's ability to follow the modulation (Stach, 2002; Picton *et al.*, 2003). The ASSR has been used in dogs for hearing threshold determination (Markessis *et al.*, 2006).

Auditory responses at latencies beyond those of the MLR are known as long-latency responses. These responses are most often used to assess cognitive function, and rely on an unexpected stimulus or 'oddball' stimulus presented randomly in a series of regular stimuli; the averaged response to the regular stimuli is subtracted from the response to the oddball stimulus to assess the ability to attend to different stimuli (Squires *et al.*, 1975; Goodin *et al.*, 1978). Because of the need for the subject to attend to the stimuli and await the appearance of the oddball stimulus, these would appear to have no application in animal subjects.

Distortion Product Otoacousic Emissions

Several authors have reported detection of sounds spontaneously generated from within the ear of animals (Ruggero *et al.*, 1984; Sims *et al.*, 1991; Burke, 1996), a phenomenon known as an otoacoustic emission (OAE). Spontaneous OAEs also occur in humans, and are not thought to reflect any pathology. It has also been shown that it is possible to evoke an OAE by introducing a sound stimulus into the ear canal and recording the response with a microphone, the evoked OAE. Since the input sound is brief and the elicited sound is brief, these are also known as transient EOAE (TEOAE). The TEOAE has been described in the dog (Sims *et al.*, 1994). The various OAEs are thought to reflect the function of outer hair cells and provide a sensitive early indicator of loss of auditory function.

The EOAE that has proven most useful in human studies is the distortion product (DPOAE), where two pure tones (f_1 and f_2, $f_2 > f_1$) are introduced into the ear canal and a resultant pure tone, the distortion product, is recorded in response at a frequency of $2f_1 - f_2$, which is a frequency lower than either f_1 or f_2. The frequency span of the cochlea is tested by varying f_1 and constraining the frequency ratio to $f_2/f_1 = 1.21$, a ratio proven to produce the strongest response (Lonsbury-Martin *et al.*, 1993). Full-range testing with hand-held devices can be completed in less than 30 s. DPOAE are used to screen hearing in newborn humans and to assess other audiologic conditions; failed responses are referred for further testing, including the BAER, a test that in the dog can take 20–30 min. Rogers *et al.* (1995) and Sockalingam *et al.* (1998) have described the DPOAE in dogs, and Sockalingam *et al.* (2002) have used the test in toxicology studies, but it has not been adopted into clinical use.

Earlier DPOAE studies utilized systems with the ability to widely vary stimulus and recording parameters, which can be cumbersome in clinical testing. A low-cost, hand-held automated device has become available that allows rapid performance of both DPOAE and TEOAE testing without the need for special facilities (OtoRead Clinical OAE Test Instrument; Interacoustics, Eden Prairie, Minnesota). We have evaluated this unit in comparison with standard BAER testing in screening dogs for the presence of hearing (McMillan, C.L. and Strain, G.M., unpublished observations). Results with a similar portable unit have also recently been reported in puppies (Schemera *et al.*, 2011). Performance of the DPOAE test is accomplished by inserting the tip of an L-shaped probe into the ear canal, with an appropriately sized rubber tip cover that allows formation of a seal around the tip. The tip contains a sound tube for introducing the stimuli and a microphone for recording the response. The test sequence is then initiated, which involves (i) determination of the adequacy of the seal; (ii) measuring background noise levels (in dB); (iii) injecting paired tones (at intensities of 65 (f_1) and 55 (f_2) dB SPL) into the canal at discrete frequencies that span most of the audible hearing range (2–12 kHz); and (iv) measuring the loudness of the distortion product sound

(in dB). Stimulus durations at each frequency can be set at either 1 or 2 s. Signal-to-noise ratios are graphed versus stimulus frequency, and any response signal exceeding the noise by 4 dB or more is considered a passing response; the operator determines how many passing responses from the total number of frequencies tested constitutes an acceptable response for the ear.

Figure 7.1 shows average DPOAE measurements from puppies drawn from three litters of different breeds presented for BAER testing that also

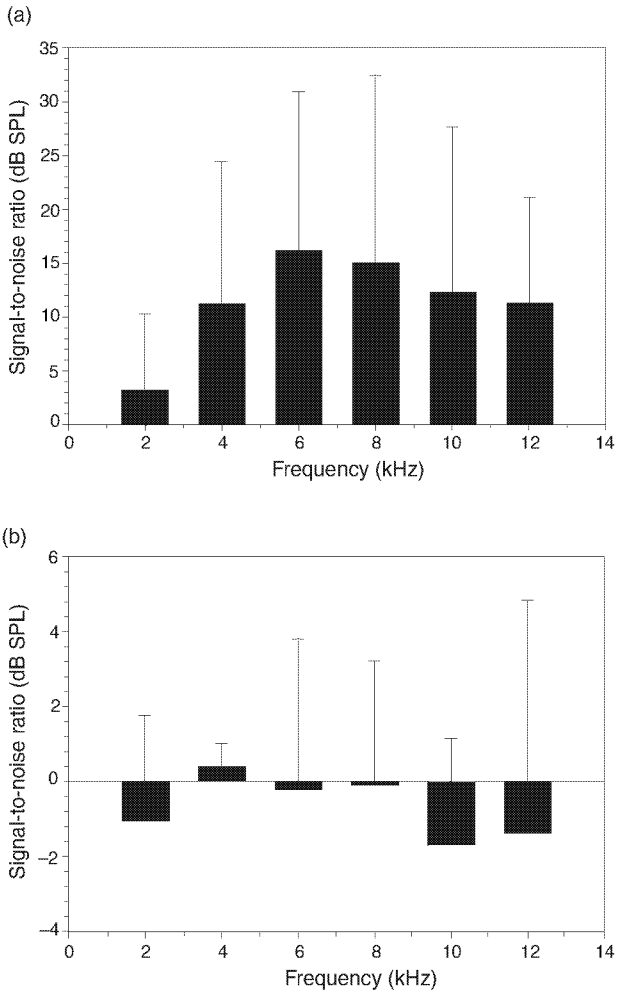

Fig. 7.1. DPOAE responses from puppies, tested at frequencies of 2, 4, 6, 8, 10, and 12 kHz (McMillan, C.L. and Strain, G.M., unpublished observations). Responses from hearing ears (a) and deaf ears (b) confirmed by BAER. Responses in hearing ears exceeded the threshold signal-to-noise value of 4 dB. Note different vertical scales.

received DPOAE testing with the hand-held device. Figure 7.1a shows responses from ears of puppies that were determined to be hearing by BAER, with DPOAE responses at all frequencies exceeding the 4 dB signal-to-noise ratio threshold. Figure 7.1b shows responses from ears shown to be deaf by BAER. Hearing ears and deaf ears could clearly be distinguished. Results from testing adult hounds from a teaching colony were identical in appearance to those in the upper graph of Fig. 7.1.

The adult subjects were tested under two conditions: under IM medetomidine (0.025 mg/kg) and butorphanol (0.2 mg/kg) sedation, and while awake. DPOAE were successfully recorded in both sedated and non-sedated dogs. Recordings of acceptable responses was more difficult in awake than in sedated subjects due to movements and reactions to the test stimuli. Subject movements increased the need for repetition, extending the total time to complete an exam. The L-shaped probe design made insertion and completion of a mechanical seal difficult and visibly uncomfortable for the dog. Results could be measured without a seal, but were considered less reliable. In addition, the seal-testing process typically triggered swallowing or other movements, which generated artifacts that obscured response detection. A custom-designed, straight-line probe proved somewhat more tolerable to the dogs but still took patience to use.

Despite the challenges seen with the DPOAE test, it still provides an alternative to BAER testing for screening purposes, as long as BAER testing is available as backup. The price of the hand-held DPOAE device at approximately $6000 US makes it an attractive alternative to BAER test equipment, which costs approximately $25,000 US.

Saccule- and Vestibular-evoked Myogenic Potentials

Recordings from humans with profound deafness have nevertheless demonstrated a small vertex-negative response (the N3 potential) to high-intensity acoustic stimuli that occurs at a latency of 3–4 ms, despite the absence of a BAER (Nong *et al.*, 2000). Similar responses have been described in deaf dogs and cats at a latency of 2–3 ms (Bianchi *et al.*, 2006). In humans the origin of the response has been attributed to the saccule, which through evolution has evolved from detecting sound to detecting acceleration. This possible origin was questioned in dogs and cats, since most were genetically deaf through the actions of the piebald, merle, or extreme white genes that produce the cochleo-saccular form of deafness that includes degeneration of the saccule (Bianchi *et al.*, 2006). However, the saccule does not always degenerate in these animals (Coppens *et al.*, 2003a) and no systematic study has been performed to determine the pattern of complete versus partial saccule degeneration in canine or feline hereditary congenital deafness, so this structure may still be the origin of the response. The presence of the N3

potential is not normally detected in hearing animals because it is obscured by the BAER.

A possibly related test is used in human neurology to evaluate vestibular function, specifically that of the saccule, by applying a loud acoustic stimulus and recording a reflex contraction of the sternocleidomastoid muscles; this recording is known as the vestibular-evoked myogenic potential (VEMP) (Colebatch *et al.*, 1994; Welgampola and Colebatch, 2005; Strain, 2010), and it is best elicited in prone subjects holding their head off of the support surface. The response is thought to reflect activation of the saccule by the loud auditory stimulus for the same reasons suggested for the N3 potential. The longer latency of the VEMP would be explained by the conduction time from the saccule to the vestibular nuclei and to the innervation of the neck muscle. The VEMP has yet to be successfully developed in dogs or cats.

Living with a Deaf Dog or Cat 8

Living with and training a deaf dog or cat can be a greater challenge than is the case with their hearing brethren. The experience is easier with animals that lose hearing after normal postnatal auditory development has occurred than it is with animals with congenital deafness. Several resources have been published for owners of deaf pets that provide advice in dealing with the issues that these animals raise (Becker, 1997; Eaton, 2005; Senechal, 2009). People choosing to adopt a pet that is deaf will benefit from an understanding of the behaviors that might be anticipated and with guidance in the life course that their pet will follow.

Behavior of Deaf Animals

Congenital deafness

The normal early development of behavior (Beaver, 1990; Landsberg, 2001) and neurological function (Kornegay, 1990; Hoskins, 2001) is well documented for puppies and kittens. The same development that occurs in unaffected animals also occurs in congenitally deaf animals, and identification of a deaf animal within a litter can be surprisingly difficult. There have been no reports of delays in the opening of the ear canal, which happens at approximately 5 days in cats and 12–14 days in dogs (Foss and Flottorp, 1974), or of the eyelids in affected animals. In dogs with congenital hereditary deafness there is normal development of the cochlea until a postnatal age of 2–3 weeks, when the stria vascularis degenerates and hair

cells die as a secondary effect (Johnsson *et al.*, 1973; Pujol and Hilding, 1973). Deafness in cats presumably demonstrates a similar but shorter time course. In the absence of sensory input to the auditory portions of the cerebral cortex, adjacent cortical regions expand to take advantage of the 'unused' cortex, resulting in some enhancement of other sensory modalities; evidence for this has recently been documented for deaf cats, where visual areas of the cortex were enlarged (Lomber *et al.*, 2010). Bilaterally deaf animals show no evidence of other neurological dysfunction or diminished mental capacities, any more than the average deaf or blind human has diminished mental capacity.

Puppies and kittens typically function within a pack, whether sleeping, feeding, or playing. Bilaterally deaf animals don't stand out as different because the jostling of littermates awakens or alerts the deaf animal, and they key their behavior off of that of their littermates. It is only through isolation from the rest of the litter and close observation that the deaf animal can be identified behaviorally. Experienced breeders from breeds with well-recognized hereditary deafness problems often develop home techniques for assessing hearing in their litters. These techniques, however, are not absolutely reliable, and BAER testing is recommended for objective identification of affected animals.

Unilaterally deaf animals only exhibit a deficit in localizing the source of a sound, which is not apparent without careful behavioral testing and cannot be confirmed with confidence without BAER testing. Many of these animals appear to compensate for the loss of localizing ability over time, making them even less likely to be identified based on behavior. As a result, unilaterally deaf young animals are less often identified than bilaterally deaf animals and are thus more likely to be bred and perpetuate the genetic defect in their descendants. Unilaterally deaf dogs and cats with the muscular ability to move their ears in localizing sound will produce conjugate movements of both ears in response to a sound, even when only one ear detects it.

Young deaf animals do not waken in response to loud sounds, but they are sensitive – when awake or asleep – to stimuli affecting other sensory modalities, so responses to visual or floor vibration cues can be misinterpreted as hearing responses. Play behavior with littermates may be more aggressive because of the absence of the vocalizations from littermates that normally indicate that the play has become too rough and that it is time to stop. Vocalizations of deaf animals may be louder than normal. Those in deaf cats are twice as loud as those from hearing cats at ages as late as 3 years, suggesting that auditory feedback plays a role in regulating vocalizations (Shipley *et al.*, 1988). Due to the dependence of deaf animals on the presence of their littermates, deaf individuals can be very vocal when isolated, but this has not been assessed to see whether the behavior differs from isolated hearing animals.

As congenitally deaf animals mature, especially dogs, problem behaviors may develop and liabilities can become a concern. Deaf animals are easily

startled, and it is not uncommon, especially in dogs, for the animal to bite as a reflex response, despite normally being gentle natured. As a result it is wise to take special care with these dogs when infants, toddlers, and strangers are present. Some dogs – probably as a result of frequently being startled – may develop an anxious behavior pattern, and others may become aggressive. The number of animals that develop these behaviors is small, although the number has never been quantified, but they do occur based on communication that the author has had with individual owners who have sought information and advice. Some advocates for deaf dogs argue that aggression is no more common in deaf dogs than in hearing dogs. While it is certainly true that hearing dogs can also develop anxious or aggressive behavior, the socialization and training experiences that mitigate against these behaviors do not occur as readily in the deaf. An owner who chooses to keep a deaf dog as a pet should recognize that in the event of a bite of a person from outside the household by that dog, there would be little legal recourse against a lawsuit due to the owner knowingly keeping an animal that could legally be considered 'dangerous,' even though the risks of such a bite might be small.

Deaf dogs can be trained (Senechal, 2009), although it takes more dedication than with hearing dogs. Deaf dogs and cats can learn to respond to a vibrating collar, and cats have been trained to return home after nightfall in response to a flashing porch light. Deaf dogs are very attentive because of their natural reliance on visual and other sensory cues in the absence of hearing; this is probably why it often seems that the deaf dogs are the smartest within a litter. Dogs quickly learn to respond to simple hand signals and even to more complex signs based on American Sign Language (ASL); training them to these signals is accomplished in the same way as training any other dog to master a desired behavior, and the deaf subjects are usually eager to comply. Deaf dogs can also be very child-like in strategy: admonishing a deaf dog that has misbehaved in some way only works if the dog's visual attention is captured by the owner, and deaf dogs who recognize that they've broken a rule will avoid looking at the owner: if they don't see the admonition, it must not have happened. Deaf animals respond to body language, so speaking to a pet as if it can hear is still a useful means of communication because they are often able to extract simple messages in the context of the owner's overall body language. Little has been published on training of deaf cats, but successful attempts to train cats are not commonly pursued beyond training the elimination behavior of kittens.

Concern must also be taken to protect animals with deafness. Dogs and cats that are not house-only pets are at some jeopardy if they roam freely outdoors, because of their inability to detect dangers such as motor vehicles and potential predators. It is not unusual for deaf animals to be struck by cars and it is not uncommon for them to become lost and unable to find their way home. A death due to a motor vehicle incident can be doubly traumatic when it is caused by the vehicle of the owner, as is often the case (Houpt and Beaver, 1981). The best advice is for deaf dogs to be on a leash or in a fenced yard if

they are allowed outdoors, and for cats to be kept indoors, since a fence is seldom a successful deterrent for cats determined to roam.

The quality of life for deaf pets, especially dogs, is not always good. A percentage of them end up in pounds or animal shelters, either from becoming lost or from owners who have given up in frustration from failed training attempts. Because of this and the liabilities discussed above with keeping deaf dogs, and in an effort to reduce hereditary deafness prevalence in affected breeds, some breed organizations and many breeders advocate that bilaterally deaf puppies should be euthanized by breeders prior to and instead of placement in homes. An example is the Dalmatian Club of America. None advocate for euthanizing unilaterally deaf puppies, but many breeders sell the unilaterally deaf with spay/neuter contracts or limited registration to reduce the possibility that affected animals will be later bred. None of these groups advocate for euthanasia of bilaterally deaf puppies after they have been placed in pet homes. There is a natural reticence to euthanizing bilaterally deaf puppies or kittens in the absence of a visible defect. However, in the absence of a reliable genetic test for carriers of the gene or genes responsible for deafness, the only means of reducing deafness prevalence is to remove affected animals from the breeding pool.

Unilaterally deaf animals make excellent pets and they usually present no behavioral evidence of their deficit. Problems arise when bilaterally deaf animals end up unknowingly as household pets, since owners quickly develop attachments with the animal. Recognition that the animal is deaf is often devastating to the new owners, and they become confronted with a difficult decision. With cats this does not present too many issues, since cats are frequently indoor animals only. Keeping a deaf puppy can be harder: they can be difficult to train and safety issues arise if there are children in the household. Ethical breeders will usually take back an animal with a genetic defect and provide a replacement puppy or a refund. Not all will do this, however, or no replacement may be available. There are no easy answers for the new owner: options include euthanasia, surrender to an animal shelter (which often means euthanasia but the owner becomes somewhat removed from the act), finding a new home willing and able to work with a deaf pet, or taking on the task of raising and training the animal. It can be helpful in the last case to connect the owner of a deaf dog with an experienced obedience trainer, most of whom can provide valuable assistance in getting the dog to an acceptable level of behavioral control and establishing methods of communicating the owner's wishes to the dog.

The human deaf community understandably finds the idea of euthanasia of dogs abhorrent, equating it with extreme eugenics movements in the past that sought to eliminate humans perceived to be defective. Many in the deaf community consider deafness to simply be a difference and not a deficit or handicap. This is an emotion-laden topic for which it is often difficult to find common ground. I have been approached numerous times by deaf individuals seeking a deaf dog for a pet. I can understand the

motivation for such a wish, especially for a child, but I do not assist in such placements due to concerns that doing so would increase problems in the life of a deaf individual.

Later onset deafness

Dogs and cats that develop deafness later in life often fare better than animals with congenital deafness. They've developed a relationship with their owner and are house-trained, and dogs have usually achieved some level of obedience training. There seem to be few or no problems with developing abnormal behaviors. The hearing loss can be acute or gradual. Acute onset – over a period of hours to days – can follow severe acoustic trauma, physical trauma, anesthesia, ototoxicity, or otitis. Behaviorally, the animal no longer responds to voice commands, door-opening sounds, sounds associated with feeding, and the like. Gradual onset is seen with presbycusis, noise trauma, and some ototoxins. Deafness due to progressive processes, such as presbycusis, may appear to the owner to have an acute onset, which reflects the fact that the animal is able to compensate and cope with the loss up to some critical point, after which its behavior clearly reflects reduced hearing, and this appears as an acute onset. Louder voice commands are necessary to elicit a response, the animal may appear confused – which must be differentiated from canine cognitive syndrome in geriatric dogs, and it may fail to awaken in response to sounds that would normally have aroused it. Animals exposed to repeated loud sounds, such as dogs used for hunting that are exposed to gunfire, will exhibit a reduced distance at which they will respond to voice or whistle commands. This is commonly seen with Labrador retrievers, but certainly affects other breeds used in hunting.

Some dogs, while deafness is developing or has recently developed, may exhibit head shaking, pawing at the ears, or sensitivity to touch around the ears. This can be a reflection of otitis media or interna, but it may also be a reflection of the presence of tinnitus (ringing in the ears); humans, while developing deafness, often experience tinnitus. This is a subjective sensation, so it is not possible to know whether dogs also experience tinnitus. Whether or not tinnitus is indeed the cause of the behavior, dogs usually appear to adapt and it ceases with time.

Hand Signal Training

It is clear that people and animals respond to the body language of other people, even when they cannot hear what is said. This has led to the development of a number of hand signals for communicating with deaf animals using a combination of standard obedience hand signals and variants of ASL. A variety of these are described in Table 8.1 (Becker, 1997; Eaton, 2005; Senechal, 2009); however, variations exist for many of them.

Table 8.1. Hand commands for communicating with deaf animals.

Command	Action
Come	Hold open hand vertically in front of you and pull toward your chest; or point both index fingers forward and move them back to point at self (ASL)
Stay	Hand flat, palm facing the dog at an angle, move forward a few inches; or hand held facing down with thumb and little finger out, move down and forward (ASL)
Sit	Starting with arm at your side, move your open hand toward your chest, palm up; or place the index and middle fingers of the right hand over the same fingers of the left hand, then move them downward (ASL)
Heel	Tap your leg on the side of the body you want the dog to come to
Stop	Left hand flat upward, chop with open right hand (ASL)
Down	Motion toward the floor with your open hand, palm down; or point the right index finger down and move it down slightly (ASL)
Lie down	Right hand palm down, move toward floor (similar to Stay)
Go/fetch	Point index finger at intended direction, move forward a few inches.
No	Bring the thumb, index, and middle fingers together (ASL); may be preceded by shaking a pointing finger at the dog
Yes/OK	Fist with the thumb pointed upward; or the OK sign with thumb and index finger forming a circle with the remaining three fingers pointing upward
Good dog	Left hand flat and facing up at waist level, fingers of right hand flat over the lips, then move them down into the left hand; or with the right hand closed move the thumb along the jaw line from ear to chin; or thumbs up (ASL)
Bad dog	Hand facing outward, bend the fingers over like a claw (ASL)
Quiet	Index finger over pursed lips
Look at me	Raise the open right hand and position it to the side of the eye
Door	Open palms facing outward, thumbs together, separate hands
Walk	Index and middle fingers pointing downward; move as if fingers are walking
Outside	Roll both hands around each other in front of body.
Car/drive	Both hands moving an imaginary steering wheel (ASL)
Drop	Open clenched fist facing downward
Toy	Index and middle fingers pointed upward, wiggle
Ball	Left and right fingers and thumb curved to meet in the shape of a ball (ASL)
Done	Wipe right palm over left palm as if brushing off
Eat	Hold fingers together as if holding food, bring to lips
Hello/greeting	Wave
I love you	Thumb, index and little finger pointing while the other two are folded into the palm (ASL)

ASL, American Sign Language.

It is also possible to use ASL alphabet letter signs as shorthand for names of the dog, the owner, and family members, typically using the first letter of the dog or person's name. The ASL alphabet letter signs and ASL dictionaries can be found on numerous Internet websites. Non-English speaking countries have their own versions of ASL, which of course are likely to be more appropriate to a deaf dog in a household or country using that language, since the commands in their own language will be easier for the owners to remember. It is common for drug-detecting dogs that received their training in European countries to continue to rely on vocal commands in their language of origin.

Counseling For Owners/Breeders of Deaf Animals

Breeders of dog or cat breeds known to have a problem with hereditary deafness are stymied at present due to the lack of a DNA test for carriers of whatever genetic defect is responsible for the disorder, and the absence of understanding at present of how the deafness is inherited in most breeds. If a deaf animal is from an affected breed, it must be assumed to have hereditary rather than acquired deafness; once an ear has gone deaf it is usually not possible to demonstrate that the deafness resulted from non-hereditary causes. It is understandable for a breeder to look for other explanations when puppies or kittens turn out to be deaf from a desire to protect the reputation of his or her breeding line; however, heredity is nearly always the explanation if the animal is from an affected breed. Animals that are deaf in both ears as well as animals deaf in just one ear should not be bred: unilateral deafness still results from the same genetic disorder and these animals will produce increased numbers of affected offspring if bred. Unilaterally deaf animals, if sold or placed as pets, should go with limited registration and/or a spay/neuter contract to reduce the likelihood that they will be bred. In addition, the following advice provides the best chance of reducing the future production of additional affected animals (see Chapter 4 for details):

- Do not repeat a breeding that produced deaf, or greater than normal numbers of deaf offspring (varies by breed).
- Avoid breeding the dam or sire to animals closely related to the opposite in the breeding that produced deaf offspring. It must be assumed that both the sire and dam contributed to the deafness by their genes, so breed away from the opposite's line.
- Avoid line-breeding of males or females that have produced deaf animals.
- Avoid breeding of dogs or avoid breeding to dogs (and in some cases cats) with blue eyes; blue in the iris of one or both eyes is significantly associated with deafness. This does not appear to be true for cats with blue eyes from the Siamese dilution (c^s) or blue-eyed albino (c^a) pigmentation genes, but does hold for cats with the dominant W gene.

- In the Dalmatian breed, do not completely breed away from patches, since a patch reflects weak expression of the piebald gene; patched Dalmatians are significantly less likely to be deaf than non-patched dogs.
- Avoid breeding merle to merle; the products of these breedings in most breeds with the merle gene have a significantly higher likelihood of deafness and other disorders.
- Always BAER test animals prior to breeding in those breeds with this problem, and BAER test puppies (or kittens if deaf kittens have been observed) in litters from affected breeds to avoid placing deaf or unilaterally deaf animals.

A breeder who discovers a deaf animal in a litter, especially a puppy, should carefully consider what action to take in light of the issues discussed above. When placing a unilaterally deaf animal in a home, the breeder should be honest about the animal's condition and explicit about the expectation that the animal should not be bred. If placing a bilaterally deaf animal is contemplated, it is imperative that the new owner understands the challenges.

Dog breeders should also be encouraged to register their animals with the various hearing registries that have been established, such as those of the Orthopedic Foundation for Animals and the English Setter Association of America; check with your breed club to see whether it has a hearing registry. Participation in these registries generates data that may be helpful in determining the mechanism of inheritance of the disorder, and it increases acceptance of being open about the presence of deafness in the various lines within a breed. Secrecy about the appearance of deaf animals is counterproductive to advancing an understanding of the condition and moving toward a future solution, and can actually lead to increased prevalence of deafness in the breed.

Those who have a deaf dog can work to make life better and safer for it. It should by all means be protected from unperceived dangers: do not allow free roaming, keep dogs in a fenced yard or linked to a stake and lead, and on a leash elsewhere when outdoors. When possible, approach from the front so that the dog sees you and is not startled. Initiate contacts between the animal and new people cautiously, allowing the stranger to pass the dog's 'sniff' test. Teach children how to interact with and behave around deaf dogs. Develop hand sign communication techniques so that you can appropriately guide the dog's behavior. Work to desensitize the dog to startle using rewards. Train the animal using positive reinforcement: aggressive behavior in both deaf and hearing dogs often results from punitive physical acts, especially when frequently applied. When available, seek guidance from obedience trainers who have experience with deaf dogs.

Many owners have had rewarding relationships with deaf pet dogs and cats. The major key to success is investing the necessary effort and time. The Internet can be a useful source of guidance.

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