FUNCTIONAL AND HISTOLOGIC FINDINGS IN THE COCHLEA OF THE AGING CANINE WITH HEARING LOSS

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TABLE OF CONTENTS

TABLES

FIGURES

PLATES

INTRODUCTION

Over the last three decades, there has been considerable study of the biological aging of many organ systems. The auditory system undergoes senescent changes like other systems of the body,[1] and it is commonly recognized that hearing in dogs becomes less acute with advancing age.[2] The anatomic basis for this hearing loss has received little attention. It has been proposed that the senescent changes in geriatric dogs with progressive hearing loss are due to degeneration of either the receptor organ or the chain of ossicles in the middle ear.[2] Aging-associated electrophysiological and morphological changes of the auditory pathway have been extensively studied in man, however, few investigators have studied such age-related changes in the canine.

A veterinary clinician is often presented with an aging dog for which the primary complaint is reduced or absent hearing. The hearing loss can be easily confirmed electrophysiologically, using evoked response audiometry. However, the applicability of therapeutic intervention with hearing aids or other auditory prothesis will remain difficult to determine until the anatomic area(s) of pathologic change and type of hearing loss is determined.

The objectives of this study were:

1. To characterize the type of hearing loss occurring in geriatric dogs as either conductive or sensorineural.
2. To evaluate gross and histopathologic changes of selected middle and inner ear structures in older dogs with reduced or absent hearing.
3. To evaluate the alteration of the brainstem auditory-evoked response in aged dogs as a function of reduced or absent hearing.

LITERATURE REVIEW

A. Anatomy

The canine ear is composed of three parts, each possessing distinctive structural and functional characteristics. The first portion, or external ear, consists of the auricle and external auditory meatus.[3] The auricle (pinna) serves to collect and convey sound to a short conducting tube, the external auditory meatus. The external auditory meatus extends from the auricle to the tympanic membrane.

The second component, or middle ear, includes the tympanic membrane, tympanic cavity, auditory tube, and the auditory ossicles with their associated ligaments and muscles.[3,4] The tympanic membrane forms a common membranous partition between the external acoustic meatus and the tympanic cavity.[5] The auditory ossicles (malleus, incus, stapes) and their associated ligaments and muscles functionally connect the tympanic membrane to the inner ear. The ossicles extend like a chain across the tympanic cavity and articulate with each other. The manubrium of the malleus attaches to the tympanic membrane; the footplate of the stapes is held by an annular fibrous ligament in the oval window.[3] The incus lies intermediate between the malleus and stapes. The tensor tympani muscle attaches to the malleus and the stapedius muscle attaches to the stapes.[4] The auditory ossicles transmit the

vibrations of sound waves on the tympanic membrane to the inner ear fluids. The air-filled tympanic cavity communicates with the nasopharynx via the auditory tube.[3]

The internal ear is located within the petrous part of the temporal bone and consists of the membranous and osseous labyrinth. The osseous labyrinth has three incompletely divided regions: the vestibule, the semicircular canals and the cochlea.[3] The osseous labyrinth is shaped to house the smaller membranous labyrinth.

The osseous cochlea lies within the promontory and resembles a snail's shell in shape.[3] It provides a rigid protective covering for the membranous cochlea. Its base lies upon the internal acoustic meatus and its apex, or cupula, is directed laterally and ventrorostrally and ends blindly.[3] The bony cochlea makes three and one quarter turns around its axis, the modiolus.[2] The canal of the bony cochlea is partially divided by a thin projection of bone from the modiolus, called the osseous spiral lamina; it winds around the modiolus like the thread of a screw.[5] Attached to the osseous spiral lamina and outer wall of the canal is the membranous cochlea, which separates the bony cochlear canal into an upper and lower portion. The upper portion is called the scala vestibule and the lower portion, the scala tympani.[6] The two scalae communicate apically at the helicotrema.[3] The scala vestibuli opens into the vestibule at the oval window and the scala tympani

ends basally at the round window. A secondary tympanic membrane closes the round window.[3]

The internal surface of the osseous labyrinth contains perilymph which surrounds the membranous labyrinth; thus, the scala tympani and scala vestibuli are perilymph-filled spaces. Perilymph from the vestibule, cochlea, and semicircular canals communicates with the subarachnoid space via the perilymphatic duct. This duct lies in a narrow canal called the cochlear canaliculus.[5]

The membranous cochlea is attached inwardly to the osseous spiral lamina, and outwardly by the spiral ligament to the bony wall of the cochlea. The lumen of the membranous cochlea is called the scala media.[3] It is delimited toward the scala vestibuli by the vestibular (Reissner's) membrane and toward the scala tympani by the basilar membrane.[3] Reissner's membrane is attached to the inner surface of the vestibular lip of the osseous spiral lamina and extends to the outer wall of the bony cochlea at the upper end of the spiral ligament.[6] The basilar membrane extends from the tympanic lip of the osseous spiral lamina to the basilar crest of the spiral ligament. The third wall of the scala media contains the stria vascularis. It rests on the spiral ligament and runs from the attachment of Reissner's membrane to the external sulcus.[6] The stria vascularis is in intimate contact with capillaries and is believed to secrete the endolymph that

fills the membranous cochlea.[1,4,6] On the upper surface of the basilar membrane, toward the scala media side, rests the receptor for hearing -- the organ of Corti. It extends from the round window to the helicotrema. The membranous cochlea, utricle, saccule, and semicircular ducts are filled with endolymph. The endolymphatic system passes through a bony canal known as the vestibular aqueduct and ends as a blind sac within the layers of the dura mater.[5,7]

The osseous vestibule communicates with the cochlea rostrally and the semicircular canals caudally. It is separated from the tympanic cavity by the annular ligament and the footplate of the stapes. The vestibule houses two sensory areas of the vestibular labyrinth, the utricle and the saccule. The sacculus is united with the scala media by the ductus reunions.[5] Their receptors consist of maculae with neuroepithelial cells, covered by a gelatinous material, called the otolithic membrane. Concretions of calcium carbonate and protein (otoliths) are present on this membrane.[7] Otoliths are denser than endolymph, and gravitational forces can cause a shearing motion of the otolithic membrane relative to the sensory epithelium and thus excite or inhibit vestibular neurons.[1]

Three semicircular canals (anterior, lateral, posterior) lie at right angles to each other and communicate with the vestibule. The osseous semicircular canals are dilated at one extremity to form an ampulla.

Each semicircular canal contains a membranous semicircular duct and ampulla. Within the membranous ampulla is a receptor organ called the cristae ampullares.[6] The cristae ampullares is covered by neuroepithelium composed of sensory hair cells and supporting cells.[7] This neuroepithelium is in turn covered by a gelatinous cupula.[7] The cupula of the crista ampullaris detects motion of the endolymph within the semicircular ducts and excites the sensory hair cells of the crista ampullaris by displacing them. The cristae ampullares detect angular acceleration of the head.[7] The macula of the utricle detects the orientation of the head in relation to gravity, and linear acceleration or deceleration.[7] The macule of the saccule detects low frequency vibrations.[7]

The eighth cranial nerve supplies the sensory areas of the membranous labyrinth and consists of vestibular and cochlear branches. Fibers of the vestibular division arise from cell bodies in the vestibular ganglion. These fibers are distributed in two rami to the macula of the utricle and saccule, and to the cristae ampullares of the semicircular ducts.[6] The spiral (Rosenthals) canal of the modiolus contains the cell bodies of cochlear nerve fibers in the spiral ganglion.[7] Peripheral fibers pass from the modiolus through canals (foramina nervosa)in the spiral lamina, to reach the hair cells of the organ of Corti.[6] As fibers leave the foramina nervosa they lose their myelin

sheaths.[6] Axons from the spiral and vestibular ganglia form the vestibulocochlear nerve and are enclosed in a common dural sheath with the facial nerve as they pass through the internal acoustic meatus.[3] The central processes of the vestibular nerve enter the brainstem at the junction of the pons and medulla oblongata. The central processes of the cochlear nerve enter the brainstem slightly caudal to the vestibular portion of the same nerve.[3]

Central Auditory Pathway:

After entering the brainstem, the primary auditory fibers course as a large ascending and small descending branch. Descending branches pass to the dorsal cochlear nuclei, whereas the ascending branches enter the ventral cochlear nucleus.[1] The major projection of afferent input to the auditory cortex is from the ventral cochlear nuclei.[1]

Secondary fibers originating from the dorsal cochlear nucleus constitute the acoustic stria. After crossing the midline, the fibers pass via the lateral lemniscus to the contralateral dorsal nucleus of the lateral lemniscus and the caudal colliculus.[6,8] The other auditory projection, the corpus trapezoideum, arises from the ventral cochlear nucleus. Some of its fibers pass directly to the contralateral caudal colliculus via the lateral lemniscus, but other fibers are interrupted by nuclei of the superior

olivary complex or by the nucleus of the lateral lemniscus.[8] The caudal colliculi of either side is interrupted by commissural fibers and is connected to the medial geniculate body by the brachium of the caudal colliculus.[2] The final link in the auditory system is formed by the auditory radiations through which the medial geniculate is connected with the auditory cortex.[1,8] The auditory sensory cortex is located mostly in the sylvian and ectosylvian gyri.[2,9] Although the sylvian and ectosylvian gyri receive impulses from both the contralateral and ipsilateral cochlea, at the cortical level there is a predominance of contralateral representation.[2]

Parallel to the pathway from the organ of Corti to the auditory cortex, there is a chain of descending efferent neurons conducting impulses in the opposite direction. These efferent neurons pass through the same areas as do the ascending pathways and terminate in either the olivocochlear bundle or the dorsal cochlear nucleus.[10] The final link in the descending system is formed by the olivocochlear bundle which is located in the vicinity of the superior olivary nuclei. Fibers from this bundle terminate at the base of the hair cells of the organ of Corti.[10] The efferent auditory pathway is believed to exert an inhibitory influence on sensory outflow from the cochlea.[8]

In addition to a relay center for the auditory pathway, auditory cell masses in the brainstem serve as reflex centers. Thus reflex regulation of sound wave frequency occurs by way of afferent cochlear neurons and the cochlear nuclei, the superior olivary nucleus and the efferent neurons of the motor nuclei of the trigeminal and facial nerves.[1,2,8] This reflex pathway forms a link between the organ of Corti and the tensor tympani and stapedius muscles. In response to sounds of high intensity, these muscles contract reflexly and dampen the vibrations of the ear ossicles.[1]

B. Mechanism of Hearing

Sound waves, transmitted through air, enter the external auditory meatus and are conducted to the tympanic membrane causing it to vibrate. Vibrations of the tympanic membrane cause the malleus to rotate along its longitudinal axis and move the incus.[9] The movement of the incus causes the stapes footplate to move in and out of the oval window, like a piston, and impose a wave of vibration upon the perilymph of the scala vestibuli.[9] Without a middle ear mechanism about 0.1% of the energy in an air wave would be transmitted into the perilymph and about 99.9% would be reflected.[1] The ability of sound energy to be transferred from a gas phase to a liquid phase without significant energy loss is primarily attributed to the lever effect of the ossicular chain and the hydraulic effect of the middle

ear.[9] The lever effect is accomplished by the fact that the manubrium of the malleus is longer than the long process of the incus in a ratio of 1.3:1.[1,9] The hydraulic effect is achieved by the difference in diameter of the tympanic membrane compared to the oval window. The tympanic membrane being 20 to 30 times larger than the oval window.[1,9] Thus the product of the lever ratio and hydraulic ratio allows a considerable mechanical advantage.

The secondary tympanic membrane which closes the round window is also important in determining the effectiveness of sound transmission to the inner ear. In the normal ear, the intact tympanic membrane shields the round window from the direct impact of sound.[1] With a perforated tympanic membrane, the round window membrane is no longer shielded and optimum sound transmission is decreased.[1]

Acoustic vibrations continue through the endolymph of the scala media and the perilymph of the scala tympani, causing a deflection of the vestibular and basilar membranes. Upward displacement of the basilar membrane lifts the hair cells such that the hair processes undergo a shearing effect between the organ of Corti and the tectorial membrane.[11] This shearing effect between the organ of Corti and the tectorial membrane is thought to be the stimulus which triggers hair cell activity and generates nerve impulses in the cochlear nerve.[11] Acoustic

vibrations in the inner ear fluids are then released at the round window.[4]

Acoustic frequency has a spatial distribution within the cochlea due to the physical characteristics of the basilar membrane. The width of the membrane is graded along the length of the cochlea, being widest at the apex and narrowest at the base.[7] As a result of this graded width, the degree of stiffness also varies from base to apex. Increased stiffness enhances resonance mainly for high frequencies, and anatomically corresponds to the base where the membrane is the narrowest.[1,7,9] Increase in mass will improve performance for lower frequencies and is found at the apex where the basilar membrane is less stiff.[1,7,9] Different tones, representing various frequencies of sound waves, cause different portions of the basilar membrane and auditory nerve fibers to be displaced maximally. Thus, afferent nerve fibers are stimulated in a selective manner by sounds of different frequencies. The basilar membrane is therefore organized to vibrate in a tonotopic fashion, and is the basis for the frequency selectivity in the cochlea.

The range of audible frequencies in young humans is 20 to 20,000 Hz.[12] The human ear is most sensitive between 1000 to 4000 Hz, which corresponds to the frequency range important for understanding speech.[12,13] The behavioral audiogram of the dog shows maximum sensitivities between

500 to 8000 Hz.[13-15] Above 8000 Hz the canine audiogram decreases in sensitivity, with the decrease becoming relatively steep above 32,000 Hz.[15] At a level of 60 dB (SPL) the audiograms in the dog range from 67 Hz to 45,000 Hz.[15]

C. Types of Hearing Loss

The act of hearing is often described as being divided into four fundamental processes: (1) the relay of vibratory energy to the organ of Corti; (2) the conversion of this vibratory energy into a nerve impulse; (3) the relay and integration of the nerve impulse; and (4) the neural processes giving rise to cognition and association.[16] Hearing disorders can then be classified as conductive or sensorineural based on the anatomic site of pathology. By definition, conductive deafness refers to malfunction of the first fundamental process, and sensorineural deafness refers to malfunction in one or all of the last three.

Deafness in mammals can be unilateral, bilateral, partial or complete. Complete bilateral deafness is assumed to be a peripheral disorder due to the large percent of afferent fiber decussation central to the cochlear nuclei. The extensive ipsilateral and contralateral connections within the central auditory pathway also account for the fact that a small isolated central lesion would be unlikely to result in total

deafness. Also, extensive damage to both cerebral hemispheres or both sides of the brainstem would be necessary to produce a central deafness.[2]

Conductive hearing loss results from lesions involving the external or middle ear. Usually there is an abnormality of the tympanic membrane, ossicular chain or both. Causes of "pure" conductive hearing loss would include congenital anomalies of the external or middle ear, impacted cerumen within the external ear canal, perforation of the tympanic membrane, otitis media, tumors of the middle ear and otosclerosis.

Sensorineural hearing loss usually results from lesions of the cochlea and/or the auditory division of the eighth cranial nerve. Congenital/inherited degeneration of the cochlea and saccule, otitis interna, acoustic trauma and ototoxicities are examples of disorders producing sensorineural deafness.

D. Review of Etiologies

1. Conductive Hearing Loss

Aural or ossicular chain malformations have received little attention in veterinary medicine. There are many inherited syndromes in infants and children in which deafness has a confirmed conductive pathology. These frequently occur in combination with other developmental defects.

The more common causes of conductive hearing loss in animals include impacted cerumen in the external auditory meatus, ruptured tympanic membrane and otitis externa/media. Granulomatous lesions resulting from chronic hyperplastic otitis externa can partially or completely occlude the external ear canal. Neoplasms of the external ear may arise from skin, adnexa, or cartilage.[17] Several tumor types have been reported.[18] Otitis media in dogs usually occurs from extension of otitis externa.[19,20] Less frequently otitis media results from extension of bacteria from the oral cavity through the auditory tube. Inflammatory polyps, described primarily in cats, can arise from the middle ear cavity or auditory tube.[18]

Otosclerosis is a disorder of the bony labyrinth and stapes known to affect only humans.[1] It commonly produces a progressive conductive hearing loss by immobilizing the stapes with new bone growth in front of and below the oval window.[12] Typically, the conductive loss reaches a maximum and thereafter there is little change in the hearing loss.[1,12] It is usually bilateral with the onset of the hearing loss in the second or third decade of life.[1] The primary site of otosclerotic foci is the oval window.[21,22] Other areas of predilection include the round window, anterior wall of the internal acoustic meatus, and within the stapedial footplate.[1,23] Involvement of the incus is

rare.[1] Occasionally, otosclerosis will replace cochlear endosteum and can involve multiple turns.[1,23,24] This has raised the question of the relationship of otosclerotic involvement of the cochlea and sensorineural hearing loss. Some audiologists believe that otosclerosis damages the inner ear and causes sensorineural hearing loss. Pathophysiologic mechanisms proposed include toxic substances liberated from otosclerotic foci, vascular shunts between otosclerotic foci and spiral capillaries leading to venous congestion, and mechanical distortion of the cochlear capsule with relaxation of the basilar membrane.[25-27] Other investigators have failed to establish a correlation between the location and extent of cochlear otosclerosis and sensorineural hearing loss.[1,23]

2. Sensorineural Hearing Loss

a) Hereditary/Congenital deafness:

Hereditary deafness occurs in many species of mammals. Thus, considerable audiologic research deals with hereditary sensorineural deafness in animal models in an effort to gain a better understanding of human inner ear abnormalities. Hereditary deafness is frequently found in association with disorders of pigmentation and has been reported in the cat, mouse, guinea pig, mink, and several breeds of dogs.[28,29]

Cats. The association of white coat color, blue iris color and deafness in cats is widely recognized.[28-31]

Waardenburg's syndrome, the human analog of this condition, is believed to be inherited in an autosomal dominant manner.[1,12,29] It is responsible for childhood sensorineural deafness.[1,12] The histologic features, development, and pathogenesis of the inner ear degeneration in deaf white cats with blue irises have been examined by several investigators.[28,30-33] The development of the cochlea in these kittens is structurally and functionally indistinguishable from normal kittens for a short period postnatally.[31] The first histologic evidence of degeneration appears around day 5 and is limited to the scala media and saccule.[30,31] Strial atrophy and a progressive degeneration of the organ of Corti occurs from the base to the apex.[30,31] The saccule also collapses with degeneration of the macular epithelium.[30,31] The degeneration is a dynamic process and continues to progress, but the organ of Corti is already at an advanced stage of degeneration by day 21.[30] Spiral ganglion degeneration is statistically significant after 10.5 months, and the cochlear nerve appears thin.[32,33] In a study of eight cases, a reduction in cross-sectional area of neuronal cell bodies and nuclei in the medial superior olivary nucleus was found.[33] Although the time course of degeneration may vary, most authors agree that the degeneration process begins with the epithelial and sensory elements of the cochlea and progresses to the central

auditory pathways.[30-32] It has been suggested that the initial cause of the degenerative changes in the cochlea results from disorders of endolymph.[29,31] Genetic studies indicate that deafness in white cats results from a single autosomal dominant gene.[30,31,34] The deafness shows 80% penetrance for the white coat color.[34] This gene also predisposes toward blue eyes or heterochromia concomitant with deafness.[31,34]

Dogs. Deafness has been observed in several breeds of dogs, especially in those affected with the merling trait.[2,28] In this pattern, the pigment of the hair is greatly diluted in most areas, but is of full intensity in patches scattered throughout the coat.[28] The merle pattern is caused by a single dominant gene for dilution.[2,28] In heterozygotes, the amount of white in the animal's coat is increased.[35] This results in marbling in the pigmented portions of the coat, alterations in tapetal and iris pigment, and sometimes deafness.[28,35] Homozygotes are nearly completely white in color, blind and deaf.[28,35] The deafness appears to be due to a recessive factor linked with the merle factor.[28] Collies, Border Collies, English Setters, Australian Shepherds, Australian Heelers, Old English Sheepdogs, Norwegian Dunkerhounds, Great Danes, Dachshunds, Bull Terriers, and Foxhounds possess the merle color gene and are predisposed to deafness.[2,28,29,35] Other breeds in which a hereditary pattern has been

suggested include Dalmatians, Boston Terriers, Shopshire Terrier and Sealyhams.[2,29,35] Congenital deafness is seen sporadically in other breeds.

A cochleosaccular degeneration, like that found in the deaf white cat, has been reported in most of the latter breeds. Exceptions include the Shropshire Terrier, in which only scala media degeneration has been reported, and in one Foxhound in which deafness was attributed to agenesis of the cochlea.[36,37]

The Dalmatian breed typifies the cochleosaccular or Scheibe type of end organ degeneration.[1,38,39] This type of degeneration has been described in hereditary hearing loss in humans, and involves the cochlea and saccule.[1,28] Histologic studies in Dalmatians show that atrophy of the stria vascularis, collapse of Reissner's membrane, displacement and distortion of the tectorial membrane, and degeneration of the organ of Corti are advanced by 4 weeks of age.[14,38,39] Also, partial collapse of the saccule with loss of both sensory and supporting cells in the saccular macula and otolithic membrane are evident.[14,38,39] Spiral ganglion cell density is normal in young animals.[38] By 2 years of age, degeneration and spiral ganglion cell loss are notable at the junction of the upper basal and lower middle turns and increase both apically and basally with advancing age.[38] Atrophy of the saccular and cochlear nerves is also apparent in 2 year old adult dogs.[38,39]

Most authors agree that there is a definite temporal relationship in the degeneration pattern of Dalmatians.[14,38-40] The receptor organ degenerates rapidly, followed by a slower retrograde degeneration of the spiral ganglion and cochlear nerve fibers. Degeneration of the central auditory pathways has received little attention. The mode of inheritance in Dalmatian deafness is not known.

Mink. Hereditary deafness has been described in the Hedlund strain of mink which were originally bred for their white coats.[41] They had pigmented eyes and differed from other mink in being more docile and less distracted by noise.[41] Later investigators have demonstrated a cochleosaccular degeneration.[29,41,42] Collapse of Reissner's membrane and lateral saccular wall, strial atrophy, and organ of Corti degeneration are evident on the 12th post-natal day.[41,42] No lesions were recognized in the spiral ganglion or cochlear nerve in a study of 9 deaf white mink.[41] They were, however, only 6 months old at the time of examination, and retrograde degeneration may not have had time to develop. The degenerative changes are related to a marked reduction of strial capillaries with a loss of vessel patency throughout the cochlea.[29,42]

Mice, Guinea pig. In the mouse and guinea pig, hereditary deafness is often associated with motor disturbances.[1,28] Mice carry several types of genes for

hereditary deafness, and the inner ear degeneration is described as the cochleosaccular or strictly scala media type.[28,29] Some of the names given to these mutants,"Dancer", "Shaker", "Pirouetting", and "Waltzer", describe their locomotor abnormalities.[1,28] Initial reports described no peripheral vestibular abnormalities. Degeneration and loss of saccular hair cells with disruption of the otolithic membrane have subsequently been described in some strains.[29,43]

The degeneration in the Waltzing guinea pig is predominately in the scala media.[28,29,44-46] These animals tend to run in circles and are deaf. Light microscopy shows normal cochlear structures prior to birth.[44] By the 5th to 10th day postpartum, degeneration of the organ of Corti can be seen. It begins in the upper basal and lower middle turn and spreads to the helicotrema. At 90 days, degeneration of spiral ganglion cells is present, and with increasing age cochlear nerve atrophy is apparent.[44] During the degenerative process, strial atrophy is mild and patchy and is not considered to be a primary feature of the degenerative process.[44] Circling, absent caloric responses and absent righting reflexes were initially attributed to a central vestibular lesion, as no abnormalities in the vestibular endorgans were seen by light microscopy. A later investigation found ultrastructural lesions consisting of sensory hair fusion and distortion with

cytoplasmic protrusion of the cristae and maculae.[46] These findings would be consistent with a peripheral lesion causing the locomotor abnormalities.

b) Ototoxicity:

There are a number of drugs which affect the inner ear to create temporary or permanent alterations in auditory or vestibular function. Aminoglycosides, quinine and related chemicals, salicylates, ethacrynic acid, furosemide, thalidomide (toxic to embryo), nitrogen mustard, tetanus antitoxin, and cis-platinum are examples of drugs causing ototoxicity.[1,47-54] Ototoxicity from aminoglycosides has been studied from both a clinical and experimental point of view. In experimental animals, the administration of aminoglycosides either by direct infusion into the cochlear perilymph or by a systemic route is a common method of producing sensorineural deafness.[1,49-51] Based on behavioral audiometry and microscopic examination of inner ear structures in laboratory animals, aminoglycosides are concentrated in the perilymph and endolymph and initially cause a high-frequency hearing loss.[1,54] The ototoxic process begins at the basal end of the cochlea, and if treatment is prolonged the middle and apical areas may also become involved.[1]

Streptomycin has been shown to primarily affect the vestibular endorgans.[1] Studies with several animal models have found that the hair cells of the cristae are affected

most with less damage occurring in the maculae or organ of Corti.[1,55] Small doses of Streptomycin given to cats have produced vestibular dysfunction.[55] High frequency hearing loss is noted when larger doses are administered over longer periods of time.[55] When Streptomycin is injected directly into the auditory bullae of cats, severe hair cell loss develops in the cristae, macula and basal turn of the cochlea.[56] Due to its relatively selective toxic action on the vestibular system, it has been used to treat vertigo in patients with Meniere's disease which are nonresponsive to conservative management.[1,55]

In humans, the ototoxic effects of dihydrostreptomycin and neomycin are less predictable, and may be delayed for weeks or months following administration.[1] Dihydrostreptomycin given to cats, in doses ranging from 100-300 mg/kg/day and for periods of time varying from 11-60 days, produced both vestibular signs and hearing losses.[55] Histologic studies showed loss of hair cells in the cristae and utricle as well as the organ of Corti.[55]

Neomycin's toxicity is predominately cochlear with less effects on the vestibular system.[1,48,50,51] When injected directly into the perilymph of cats, it produces rapid and severe hair cell degeneration within 2 hours.[50] Twelve hours after infusion, degeneration of supporting cells and chromatolysis of spiral ganglion cells can be seen.[50] Intramuscular injections of neomycin in cats

produced hair cell degeneration within 12 days.[50] Supporting cell damage was not noted until 6 weeks post administration.[50]

The ototoxicity of systemically administered kanamycin was studied in guinea pigs.[52] Cochlear hair cell and spiral ganglion degeneration were noted after 3 months.[52] Disappearance of many myelinated fibers in the osseous spiral lamina was also seen.[52] Gentamicin has been found to damage the vestibular endorgans more than the organ of Corti in the rat, cat, dog, and guinea pig.[1]

In high doses, salicylates have been reported to produce reversible symptoms of hearing loss, tinnitus, and vertigo in humans.[1,12] Studies in monkeys, using high doses of aspirin, show a reversible hearing loss 24 hours after administration.[57] Hearing returns to normal in a few days and no cochlear or vestibular lesions are noted using light microscopy.[57] Diminished electrical activity of the cochlea and inner ear fluids in cats has been demonstrated following intraperitoneal infusion of toxic doses of salicylates.[1]

c) Intrauterine Factors:

In humans, intrauterine factors resulting in malformations of the inner ear have been attributed to several etiologies.[1,12] These factors include infection, toxic, metabolic and endocrine disorders, anoxia secondary to Rh incompatibility, and difficult delivery.[12] Many

congenital defects including cataracts, microphthalmia, patent ductus arteriosus, atrial and ventricular septal defects, hearing loss, microcephaly, dental defects, and general stunting of growth and development have been shown to result from maternal rubella infection.[1,12,58] Rubella or German measles, produces a profound sensorineural hearing loss if infection occurs during the 9th week of gestation.[12,58] A cochleosaccular aplasia has been found to be the cause of the deafness.[1,58] Middle ear anomalies such as the stapes having a thickened capitulum and crura, as well as cartilaginous fixation of the footplate are less frequent.[1]

Sensorineural deafness, hydrops, encephalopathy, hemolytic anemia, and icterus are manifestations of erythroblastosis fetalis.[1,12] Based on audiometric findings, the hearing loss is compatible with a cochlear lesion.[1] The hearing loss is bilateral and most severe for the high frequencies.[1,29] Perilymphatic hydrops was reported in one study.[1] Degenerative changes in the auditory pathway similiar to lesions of anoxia have also been described.[1,29]

Hypothyroidism during fetal life can produce a sensorineural deafness; this occurs in a goiterous mother with low iodine intake.[1,58]

d) Otitis Interna:

Otitis interna or labyrinitis is associated with sensorineural deafness if the organ of Corti is destroyed.[1,2] Infectious agents usually enter the inner ear from the middle ear or auditory tube. Frequently there is a history of recurrent or chronic otitis media. In addition to hearing loss, vestibular signs are common.

e) Age-Related Changes:

The hearing loss caused by the degenerative changes of aging is called presbycusis.[1,59,60] It is classified into four distinct pathologic types based on selective atrophy of different morphologic structures in the cochlea and distinct audiometric patterns. The hearing loss is typically bilaterally symmetric, slowly progressive, and no therapeutic intervention can alter its course.[1] Cochleas of many individuals exhibit more than one type of presbycusis, and the functional deficits from each are additive.[1]

Sensory presbycusis is widely recognized as the predominant form, and is characterized by atrophy and degeneration of the organ of Corti in the basal end of the cochlea.[1,61,62] Atrophy and degeneration of spiral ganglion cells and the cochlear nerve parallels in location and severity the changes in the organ of Corti. These are believed to be secondary changes.[63,64] Efferent fibers to the hair cells also degenerate. Loss of efferent fibers

might be due to degeneration of the superior olivary nucleus, where the cell body of the efferent fiber is located; however, it may also degenerate secondary to sensory cells if they have been lost for a considerable length of time.[65] Audiometrically, an abrupt threshold elevation for pure tones of high-frequency is present.[1,63,66]

The degenerative change usually begins in middle age and progresses very slowly. In advanced age, the lesion progresses apically but is still more severe in the basal end of the cochlea and therefore does not severely affect hearing for the frequencies of speech.[61]

Neural presbycusis is due to a loss of spiral ganglion neurons throughout the cochlea. The loss is, however, more severe in the basal turn. This type of presbycusis is considered to be rare in man.[1] Although atrophy of the organ of Corti in the extreme basal end of the cochlea may be present, loss of spiral ganglion cells predominates.[1] Auditory testing shows a severe loss of speech discrimination which is more severe than the hearing loss for pure tones.[63] Because of poor speech discrimination, patients with neural presbycusis find amplification of sound of limited value.

In metabolic presbycusis, the underlying pathological change is atrophy of the stria vascularis.[1,59,60,63] Clinically this is distinguished from other types of

presbycusis by threshold elevations for all frequencies associated with normal speech discrimination (until threshold elevation exceeds 50dB).[1,64] Patients with "pure" strial atrophy, when stimulated within their sensitivity range, respond well to amplification of sound.[1] Histologically there is patchy strial atrophy in the middle and apical turns of the cochlea.[64,66]

The stria vascularis is thought to be the site of endolymph production. Although the exact role of endolymph in the excitatory process is not known, it is thought to function as a medium for storage and transmission of energy to the organ of Corti.[64] In addition, large amounts of oxidative enzymes required for glucose metabolism are found within strial tissue.[1,64] These may be essential for energy production to support cochlear function.[1] Thus, atrophy of the stria vascularis is presumed to cause a biochemical or energy deficient state throughout the endolymph resulting in threshold elevations for all frequencies.[1]

Cochlear conductive presbycusis is due to changes in the basilar membrane and/or spiral ligament.[1,59,63] These changes are believed to interfere with the vibratory mechanics of supporting elements of the organ of Corti.[1,59-63] Threshold losses are accompanied by a descending audiometric pattern for bone conduction.[1] This type of audiometric pattern is also found in patients with

otosclerosis or otitis media.[64] Speech discrimination in this from of presbycusis is inversely related to the steepness of the threshold gradient.[1,64] Histologic studies have failed to reveal morphologic changes in the organ of Corti or auditory nerve adequate to explain the hearing loss.[1,64] The only consistent pathologic change in ears demonstrating this form of presbycusis is atrophy of the spiral ligament.[1] As the ligament shrinks, the configuration of the scala media is altered. Rupture of the cochlear duct can occur as the end result of advanced atrophy of the spiral ligament.[64] In some patients, hyalinization, calcification and increased thickness of the basilar membrane accompanies spiral ligament atrophy.[1,64]

There is no doubt that mental processes become slowed with age. Senile changes in the central auditory pathways are considered to be an important contributory factor in certain cases of presbycusis.[67,68] In a study involving elderly patients which demonstrated high frequency threshold elevations and a loss of speech discrimination, degenerative lesions in the central auditory pathways were found.[67] Decreased numbers and atrophy of neurons in the dorsal and ventral cochlear nuclei, superior olivary nucleus, inferior colliculus and medial geniculate area have been reported.[67,69] A quantitative analysis of the effects of advancing age on several regions of the cerebral

cortex showed the greatest decrease in neuron numbers occurred in the auditory cortex.[70]

f) Animal Models:

Inner ear morphological changes associated with aging have been studied in a few animal species.[1,59,60,61,71-78] Behavioral and electrophysiological testing of auditory pathway function, coupled with inner ear histology, has revealed an age-related high frequency sensitivity loss.

Cats. A high tone hearing loss has been demonstrated in aged cats using behavioral audiometry. On histologic examination, marked degenerative lesions in the organ of Corti, supporting cells, afferent and efferent nerve fibers, and spiral ganglion cells were found. The changes were most severe in the basal end of the cochlea.[59]

The labyrinths from a 19 year old cat that had a progressive hearing loss for several years showed atrophic changes in the cochlea and saccule.[71] There was a total loss of the organ of Corti in the basal 15 mm of the cochlea, and in the remaining 8 mm approximately 20% of the hair cells remained.[71] The stria vascularis was atrophied throughout the cochlea and there was a loss of 50% of the hair and supporting cells in the macula.[71]

Guinea Pig. Using behavioral audiometry, guinea pigs show a deterioration in hearing threshold sensitivity to all sound frequencies with increasing age.[72,73] In an investigation to study the normal variation in hair cell

populations in the organ of Corti of guinea pigs of different ages, a significant apical loss of outer hair cells was noted in the older animals.[72]

Histologic changes in the cochleas of older guinea pigs with diminished or absent Preyer's reflex were compared with those of younger guinea pigs. The earliest senile change was a loss of spiral ganglion cells in the apical and extreme basal region of Rosenthal's canal.[74] Although degeneration of both sensory and supporting cells in Corti's organ was noted in the region of spiral ganglion cell loss, it was not thought to be the predominate finding because spiral ganglion atrophy preceded the degenerative lesion in the organ of Corti.[73] In many specimens, no pathologic changes were found in strial tissue. When present, they consisted of atrophic changes, increased pigmentation and cystic degenerative lesions.[73] Degeneration of the stria vascularis occurred no more frequently in the senile animals than in the controls.

In a detailed study comparing the vascular anatomy of guinea pigs of different ages, no changes due to age could be found.[75]

Rats. Albino rats of the Sprague-Dawley strain have been used by several investigators as an experimental animal model for presbycusis due to their short life span. In older animals, hair cell loss was greatest at the apex and was predominately outer hair cells.[76] When inner hair

cell loss was observed, it also occurred apically.[76] These authors also noted that spiral ganglion loss was greatest at the apical and lower basal regions of Rosenthal's canal.[77]

Monkeys. The temporal bones of a 24 and 31 year old monkey exhibiting a high frequency hearing loss were examined. The histopathological changes consisted of: hair cell loss in the organ of Corti primarily at the basal and apical regions; degeneration of spiral ganglion cells in the lower basal turn; and degeneration of distal portions of cochlear nerve fibers.[61]

Dogs. Inner ear structures from a 20 year old Dachshund who suffered from progressive loss of hearing for several years and was behaviorally deaf were examined. A loss of hair cells from the organ of Corti was noted throughout the cochlea, but was more severe in the basal end.[71] Spiral ganglion cell loss was proportional to hair cell loss and considered to be of a secondary nature.[71] Sensory epithelium of the saccule was flattened and a loss of 50% of the hair cells was noted.[71] The stria vascularis and spiral ligament were normal.[71]

In another study of a 16 year old dog (hearing status not reported) complete loss of outer hair cells throughout the cochlea was present. The entire organ of Corti was degenerated in the lower basal turn. Strial atrophy was

diffuse throughout the cochlea, but again most severe in the basal turn.[60]

The cochleas of a series of dogs ranging from 6 months to 20 years of age were evaluated using light and electron microscopy. Outer hair cell loss was present in all aged dogs, but was most severe in the basal and apical coils.[78] Spiral ganglion cell losses were extreme in the basal coil and were accompanied by a corresponding decrease in nerve fiber density within the osseous spiral lamina.[78] Strial atrophy was present but varied in magnitude and location from animal to animal such that a predilection of atrophy for a particular region could not be determined.[78] A slight decrease in cellularity and hyalinization of the spiral ligament was also seen.[78]

E. Clinical Evaluation of Auditory Function

Deafness is difficult to evaluate in animals when there is an incomplete bilateral or a complete unilateral hearing loss. The total clinical examination should assess the external ear canal, tympanic membrane, and should include both behavioral and electrophysiological assessments. Skull radiographs are useful to help rule out middle ear disease, and cerebrospinal fluid analysis can be helpful if brainstem inflammation/infection or neoplasia is suspected.

Cochlear function in animals can be evaluated behaviorally, and using electrodiagnostic procedures that

selectively assess the integrity of peripheral and central nervous system structures. Electrodiagnostic methods include cochlear microphonics, brainstem auditory evoked responses, and electroencephalography alerting responses.

1. Behavioral Evaluation

A quick test for hearing loss is to observe an animal's behavioral response to sounds that are a part of its natural environment or to a spoken command of different intensities. Pets in a clinical setting are usually so apprehensive that their attentiveness to the examiner is minimal. The appropriate behavioral response is subjective and ultimately depends on the animal's level of interest, its temperament, and the presence or absence of distracting environmental factors.

Conditioned audiometry involves training an animal to show a behavioral response to a pure tone at selected frequencies which are terminated in conjunction with a mild electrical shock. Eventually the animal learns to respond to the test tone and the shock is then omitted. The intensity of the test tone is gradually decreased and the threshold for each tested frequency is the lowest tone level to which the animal responds.[14,30] An audiogram can then be constructed based on the animal's reaction to sound of varying intensities and frequencies. The disadvantages of this technique are that the conditioning procedure is

time consuming, and has proved unsuitable for young animals.[14]

2. Electrodiagnostic Evaluation

Electrophysiological recordings provide the clinician and extended measure of auditory ability, even beyond that obtained from the trained animal. Electrodiagnostic testing does not require conscious cooperation and is particularly useful in testing the very young animal in which behavioral responses to familiar or unfamiliar sounds are difficult to assess.

a) Electroencephalographic Audiometry:

Electroencephalographic (EEG) audiometry is based upon an arousal phenomenon. The EEG tracing is recorded with the animal in a relaxed state, and is then recorded with subsequent auditory stimuli. A normal response consists of an alerting response which is characterized by an increase in frequency and a decrease in voltage, in the EEG at the time of stimulus application.[79,80]

b) Auditory Evoked Response:

Evoked response audiometry is an objective, noninvasive and reliable method of assessing auditory function in humans and animals.[81-84] Its use in detection of peripheral vestibular disorders, tumors of the auditory nerve and brainstem, ototoxicity from aminoglycoside antibiotics, demyelinating or degenerative diseases, and assessment of brainstem pathology have been

reported.[51,81,85] Auditory-evoked responses are recorded from scalp electrodes and can be divided into early, middle and late components on the basis of waveform latency. The brainstem auditory-evoked response (BAER), or early latency potentials, consist of a series of 4 to 7 waves at approximately 1.0 msec intervals after presentation of sound stimuli; these waves are believed to reflect electrical activity in the eighth nerve and brainstem. The generators of the middle and late potentials are not certain, but subcortical and cortical structures have been suggested.[86] To record the BAER, the most efficient stimulus to use is the click.[81] The BAER amplitude is smaller than that of background noise and must be extracted from other electrical activity such as the EEG or myogenic artifacts by signal averaging.[81,83,85,87-89]

For the dog and cat, it is generally agreed that the generator of wave I is the distal part of the eighth cranial nerve.[90-92] The exact origins of the other waveforms are less clearly established in the dog; however, in humans based on pathological correlates and direct recordings during neurosurgical procedures, the primary anatomic locations have been suggested: wave II, proximal part of the eighth nerve; wave III, cochlear nucleus; wave IV, superior olivary complex; wave V, lateral lemniscus; wave VI, inferior colliculus; wave VII, medial geniculate.[86]

c) Cochlear Microphonic:

The electrical responses that occur in different parts of the cochlea, except in the cochlear nerve, are referred to as the cochlear microphonic.[81,86,90] The cochlear microphonic is thought to arise from the cuticular surface of the hair cells of the organ of Corti.[81,86] This wave occurs just prior to wave I of the BAER.[81] It can be distinguished from wave I by changing the polarity of the stimulus.[81,86,90] When this is done, the polarity of wave I will not change, but the polarity of the cochlear microphonic will reverse. The cochlear microphonic and BAER waveforms are not present in animals whose cochlea are lacking Corti's organ.

MATERIALS AND METHODS

A. Animal Selection

A total of 16 apparently healthy adult dogs of pure and mixed breeds were included in the study; all dogs were donated to the Department of Surgery and Medicine at Kansas State University. Nine of the dogs were suspected of having a hearing deficit and 7 dogs, without clinical evidence of hearing loss, were examined as controls. Weights ranged from 3.6 to 22.7 kg, and the dogs were from 1.5 to 17 years of age. Historical information pertaining to a dog's hearing ability was obtained from owners' responses to a questionnaire. If a dog was judged by the owner to have a hearing deficit, the date when the loss of hearing was first detected and whether it appeared to be progressive were recorded. All dogs were house pets and no hunting dogs were included. Medical records indicated that no dog had received treatment for otitis, and that none had been administered ototoxic drugs. Otoscopic examination failed to reveal abnormalities of any dog's external ear canals or tympanic membranes. Based on results of routine physical and neurological examinations, all animals were considered to be free of clinical signs of neurological disease, other than hearing deficits.

At the onset of the study, subjective tests of hearing were performed and dogs were evaluated separately. The examinations included observing for behavioral orientation

(head lifting, ear movements, head turning toward the source of the sound) to commands spoken at different intensities (whispering, normal conversation, shouting). Each dog's reactions to handclaps and high-pitched sounds (whistling) were recorded, as were sleeping dogs' responses to loud handclaps. The deaf group did not show startle or other behavioral reactions to intense sounds. The reduced hearing group showed startle and behavioral orientation to intense sound (shouting or handclaps, but did not show a response at conversational or lower intensities of sound. The normal hearing group rapidly and consistently responded to sounds at all intensities. Owner's awareness of the onset of their dog's hearing loss had been gradual, and was $\geq$ 2 years for the deaf group and $\geq$ 1 year for the reduced hearing group.

Dogs were separated into 3 groups, based on the historical and clinical impressions of their ability to hear. Group I [n=7, 1.5-8 years of age ($\bar{x}$=3.2 years)] had normal hearing. Group II [n=4, 9-14 years of age ($\bar{x}$=10.8 years)] had reduced hearing and group III [n=5, 15-17 years of age ($\bar{x}$=15.8 years)] appeared to be completely deaf. The clinical hearing assessments, ages, breeds and weights are presented in Table 1.

B. Audiometry

To minimize myographic artifacts, all dogs were anesthetized during the BAER recordings; each dog was

induced with thiamylal sodium[a] (20 mg/kg intravenously), intubated, and maintained using methoxyflurane vaporized with oxygen. Dogs were positioned in sternal recumbency and sand bags were used to position their heads. Body temperatures were maintained at 38.5 to 39.2° C by heating pads, when necessary.

Testing was performed in a quiet room. Stainless steel needle electrodes were inserted subcutaneously at three sites. A reference electrode (-)[b] was placed near the mastoid area of the ear being tested and a recording electrode (+)[b] was positioned on the vertex. The ground electrode[c] was placed dorsal to the spinous process of the axis. Electrodes were connected to the signal averaging system[d] through a preamplifier,[e] so that the recording electrode was positive relative to the reference electrode and produced an upward deflection in the tracing. In vivo electrode impedance using a 120 Hz sine wave test signal was < 3 KΩ.

A monaural mixed-frequency stimulus in the form of a click was delivered through an ear phone placed in the external auditory canal. The click was produced by a

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[a]Surital, Parke Davis & Co., Detroit, Michigan.

[b]Model MF-12, Teca Corp., Pleasantville, New York.

[c]Model RE-12, Teca Corp., Pleasantville, New York

[d]Teca-AV7, Pleasantville, New York

[e]Model PA62T, Teca Corp., Pleasantville, New York.

square-wave DC electrical pulse with a duration of 0.1 ms. The click had a center frequency of 709 Hz, and an intensity of 84 dB SL. The acoustic stimuli were delivered at 20/s in all cases.

Evoked activity was sampled during the first 10 ms after each click and recorded on an electromyograph[f] at an amplifier band pass between 20 Hz and 20 KHz. Amplification was 1 per 2.6 mm. Each ear was stimulated independently and recorded ipsilaterally. The responses to 1,024 click presentations were averaged and displayed on a storage cathode ray oscilloscope.[f] The averaged response was photographed[g] and the procedure was repeated immediately to test waveform consistency. Photographs of the averaged responses of each ear were compared visually and then superimposed with the use of a template overlay. Only responses in which corresponding waveform latencies were within 0.06 ms were considered reliable trials.

Latencies (from click onset to the positive peak of each wave) were measured to the nearest 0.06 ms using a template overlay. For broad or poorly defined peaks, latency was considered to be the point of intersection of lines extrapolated from positive and negative slopes of the waves. Amplitudes for waves I-V (measured from the peak of each wave to the nadir of the following wave) were recorded

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[f]Model M, Teca Corp., Pleasantville, New York.

[g]Tektronix C-5C, Beaverton, Oregon

to the nearest 0.01 μV using a template overlay. Differences in latencies and amplitudes for each wave between groups were analyzed using the independent sample t-test. Between right and left ears, latencies and amplitudes were compared using the paired sample t-test.

C. Tissue Preparation

Following BAER recordings, each dog was euthanized with intravenous T-61 solution,[h] and decapitated. In each dog the left middle ear and petrous temporal bone were used for histologic examination, and the right middle ear and petrous temporal bone were evaluated macroscopically. Septal tissue from the left auditory bulla of each dog was removed. The middle ear cavity and petrous temporal bones were then fixed by immersion in 10% buffered neutral formalin (BNF); the time interval between euthanasia and fixation was 20 minutes or less in all cases. Specimens remained in the 10% BNF for 10 days and were then trimmed into sections, approximately 15 mm in length, prior to decalcification in 8% sulfosalicylic acid. Time required for decalcification varied from 12-24 days. Tissues were routinely processed for paraffin embedding, and 8um serial sections were cut parallel to the mid-modiolar plane. To select optimal mid-modiolar sections from each block, unstained slide-mounted sections were examined under a dissecting microscope. From 30 to 60 mid-modiolar sections

[h]American Hoechst Corp., Somerville, NJ.

were selected and stained with hematoxylin and eosin. In all dogs, the annular ligament, footplate of the stapes, and margins of the oval window were examined for evidence of osteosclerotic foci. Crural arches of the stapes, when present in the sections, were also examined for osteosclerotic foci.

The right middle ear cavity and petrous temporal bone from each dog were isolated and surrounding soft tissue structures were removed for maceration. The maceration process began by placing each specimen in a guaze bag which was subsequently immersed in tap water at 86° C for 3 hours. The water temperature was then reduced to 24° C and the specimen remained immersed for 1 week. The specimen was then transferred to a solution of 30% peroxide for 24 hours followed by gentle rinsing with tap water. The ossicular chain and margins of the stapes footplate and oval window were examined for bony ankylosis, with a dissecting microscope.

D. Morphometric Analysis

In all specimens, mid-modiolar sections were used for determining spiral ganglion cell numbers in the apical, middle, upper and lower basal regions of the cochleas. The nuclei were counted four times in each region, on four to six consecutive sections. The average of the counts on consecutive sections was used to compare regions between groups of dogs. Only nuclei that appeared unfragmented and

whose circumference was clearly visable were counted, at a magnification of 400X using a grid reticle. In each region the average nuclear diameter, measured with a micrometer[i] was 15um and the smallest nucleus counted was 5um. The perimeter of Rosenthal's canal was traced on a drawing pad at a magnification of 125X using a drawing tube[j] attached to the microscope. The cross-sectional areas, of the same four sections where the nuclear counts were made, of each canal were measured planimetrically using a digitizing pad[k] interfaced with a IBM computer and an image analysis system.[l] Nuclear counts within each canal, and canal areas allowed the packing density to be calculated as follows:[33]

$$\text{Density} = \frac{\text{No. of nuclei counted per canal}}{\text{cross-sectional area per canal } (mm^2)}$$

Nuclear counts and cross-sectional areas of consectutive sections were used to calculate four packing densities per region. The average of these packing densities served as the comparative packing density for each region when comparing groups of dogs. Packing densities were used for regional comparisons of densities and to circumvent the difficulty associated with sectioning Rosenthal's canal in exactly the same plane in each sample. Regional

[i]Bausch & Lomb Opt. Co., Rochester, New York.

[j]Zeichentubus, Wild Co., Heerbrugg, Switzerland.

[k]Hipad Digitizing Pad, Bausch & Lomb Co., Austin, TX.

[l]Bioquant System IV, R&M Biometrics, Inc., Nashville, TN.

differences in mean canal area and differences between groups were evaluated using a One-way analysis of variance.

RESULTS

A. Auditory testing

BAER waveforms were obtained from all dogs of the normal hearing and reduced hearing groups and had 4 major positive peaks (Fig. 1). The deaf group had isoelectric tracings, and amplitude and latency measurements could not be performed. Waveform identification was primarily based on latencies, which agreed with values established for the normal canine.[3,88,93] Waveform conformation and numbers also aided in identifying waves. Recognition of waves I-IV was facilitated by identifying wave V, with its trough extending below baseline, and its latency usually in the 3.5-3.9 ms interval. Waves III and IV appeared as a single peak with a latency comparable to that reported for wave III.[88] Waves VI and VII were not consistently recorded from any dog.

Table 2 shows the mean latencies and amplitudes of the waves in the normal hearing and reduced hearing groups. There were no differences ($p \geq 0.05$) between mean latencies of waves I, II, III-IV, and V for the two groups. BAER abnormalities of the reduced hearing group consisted of amplitude reductions of waves I and II. The mean amplitude of wave I in the normal hearing group was 4.57 μV for the left ear and 4.31 μV for the right ear; the range for both ears was 2.30 to 6.20 μV. In the reduced hearing group, the mean amplitudes of wave I for the left ear and right

ear were 1.93 and 1.64 μV respectively. Ranges for both ears in the reduced hearing group were 0.63 to 3.70 μV. There was at least a 58% reduction for the left ear and 62% reduction for the right ear in mean amplitude of wave I in the reduced hearing group ($p < 0.01$). The mean amplitude of wave II in the normal hearing group was 2.60 μV for left ear and 2.22 μV for right ear; minimum and maximum values for the left or right ear were 1.30 to 4.0 μV. Mean amplitudes of wave II for the reduced hearing group were 1.37μV for the left ear and 1.23 μV for the right ear. The range for either ear was 0.63 to 1.80 μV; this corresponded to a 47% reduction for the left ear and a 44.5% reduction for the right ear in mean amplitude of wave II for the reduced hearing group ($p < 0.025$). There was no significant difference ($p \geq 0.05$) in mean amplitude of waves III/IV and V between the normal hearing group and the reduced hearing group, for either ear.

The difference in amplitudes between the right ear and left ear within either the normal or reduced hearing groups was not significant ($p \geq 0.05$). There was no difference in latency of any wave when comparing the right ear to left ear in the reduced hearing group ($p \geq 0.05$). Latencies for waves I, II and V of the normal hearing group showed no significant intrasubject (left ear vs right ear) difference ($p \geq 0.05$), but latency values of wave III were larger for the left ear ($p < 0.05$).

B. Microscopic and Morphometic Observations

In mid-modiolar sections of the normal dogs' cochleas the nuclei of the spiral ganglion cells were closely packed within Rosenthal's canal [Plate 1 (fig.1)]. The most distinctive pathologic change in both the deaf group and the reduced hearing group was a loss of spiral ganglion cells within each of the four regions of Rosenthal's canal [Plate 1 (figs.2-4), Plate 2 (figs. 5-8), Plate 3 (fig.9)]. The means, percentage differences between means, and ranges of spiral ganglion densities for each groups' four canal regions are shown in Tables 3 & 4. The mean apical packing density of the normal hearing, reduced hearing and deaf groups was 2,147, 2,074 and 1,383 respectively; the mean apical packing density for the deaf group was substantially lower ($p<0.05$) than that of either the normal hearing group or the reduced hearing group. There was no significant difference ($p\geq0.05$) in mean middle packing densities between the normal hearing group (1,763) and the reduced hearing group (1,777). Mean middle packing density of the deaf group was 974, which was significantly lower ($p<0.05$) than that of the other groups. In the upper basal region, mean packing density of the normal group was 1,875; for the reduced hearing group, 1,128; and for the deaf group, 547; a significant reduction ($p<0.05$) in spiral ganglion packing density was noted in the deaf group and reduced hearing group. Mean packing density of the lower basal region of

the normal hearing group was 1,785; for the reduced hearing group, 464; and for the deaf group, 71. A significant reduction ($p<0.05$) in mean packing densities of both the deaf group and the reduced hearing group was found upon comparison to that of the normal hearing group. In the deaf group, approximately one fourth of the cells per mm^2 remained in the upper basal and only one sixthteenth of the cells per mm^2 remained in the lower basal area. A summary of spiral ganglion densities for each region and for each group is presented in Fig. 2. To determine whether differences in canal area influenced packing density reductions, mean regional variations in canal area were analyzed. Within each region of Rosenthal's canal, the mean area ($mm^2 x 10^3$) for all groups was calculated: apical, 57.32; middle, 49.51; upper basal, 55.40 and lower basal, 68.84. Group mean cross-sectional areas for each region (Table 5) were not significantly different ($p \geq 0.05$) in the apical, middle and upper basal regions. The lower basal regions of the deaf group and the reduced hearing group showed a significant increase ($p<0.05$) in area compared to the normal hearing group.

In all areas where ganglion cell reduction was observed, it appeared to be accompanied by a loss of nerve fibers in the osseous spiral lamina. In both the reduced hearing and deaf groups, spiral ganglion cells were atrophied in all areas of Rosenthal's canal; ganglion cell

atrophy in these groups was especially extensive in the upper and lower basal regions, and cochlear nerves appeared abnormally thin compared to those of the normal hearing group.

All dogs in the study appeared to have normal stapediovestibular articulations, and annular ligaments showed no evidence of calcific fixation to the walls of the oval windows [Plate 3 (figs. 10,11), Plate 4 (fig. 12)]. The organ of Corti and other morphologic structures of the cochlear duct were not evaluated, due to disfigurement of these structures from handling during tissue preparation.

C. Macroscopic Observations

All animals were free of gross pathologic changes of the external auditory canals, tympanic membranes, auditory bulla and middle ear ossicles. In each of the macerated specimens, the ossicular chain and oval window were normal and the stapes footplate and oval window had smooth elliptical contours [Plate 4 (figs. 13-15)]. No evidence of ankylosis of the stapes footplate to the oval window or incus was found in any dog. In many macerated specimens, the stapes had fallen into the vestibule indicating pathological ossification had not caused fixation of the stapediovestibular articulation [Plate 4 (fig.16)].

DISCUSSION

One of the major applications of the BAER in veterinary medicine is the assessment of auditory function. As this technique is not affected by attention of the subject or many types of sedation, it is extremely valuable when the history or neurological examinations are inconclusive. Providing external/middle ear problems and neurological disorders have been ruled out, the BAER yields reliable information regarding the peripheral auditory system.

Cochlear nerve destruction and aminoglycoside intoxication have been shown to abolish all neural components of the BAER during ipsilateral acoustic stimulation.[51,92,94] In the present study, the reduced hearing group and deaf group were older than the normal hearing group, which is consistent with the common clinical observation of auditory dysfunction in aged dogs. The absence of recognizable recordings obtained from the deaf group is consistent with a loss of cochlear or eighth nerve function.

Normal dogs have been reported to behaviorally respond to the frequency band used in this study.[14,15] The recording of BAERs from the normal hearing group and reduced hearing group indicates the intensity of the stimulus exceeded the threshold for hearing and was adequate to trigger the BAER generators. Latency

prolongation of wave I has been reported in elderly human subjects with sensorineural hearing loss, and is believed to be due to elevations in click threshold as a consequence of peripheral auditory dysfunction.[84] In the present study, no significant differences in latencies of all waveforms were found when comparing the normal hearing and reduced hearing groups. This was surprising considering that the click intensity remained the same between groups. A difference in latency between the reduced hearing and normal hearing groups might have been seen with lower dB clicks, as has been reported in older dogs with impaired hearing.[95] The unexpected finding of significant peak III latency differences between the left and right ear in the normal hearing group was attributed to biologic variation.

Human BAER amplitudes have been shown to decrease with increasing age, presumably due to fewer fibers conducting impulses through the auditory pathways.[96] Absolute amplitudes have also been reported to be extremely variable in normal humans, making amplitude measurements unsuitable for individual clinical or pathophysiologic interpretation.[81] The fact that no increase in latencies of any waves in the reduced hearing group was noted in our study suggests that amplitude reductions of wave I and II in this group may have been the result of some nonpathologic mechanism. Variables such as head size, increased skull thickness and dehydration of any of the

fluid compartments of the skull or brain could influence the amplitude of the BAER.[84,95] These variables are not likely to be the reason for the amplitude reductions in Group II, or all waves (I-V) would have been similarly affected. As no nonpathological reason for the amplitude reductions of waves I and II was identified, we must assume that these findings could indicate a pathologic change in group II.

Hearing loss in our heterogenous canine population appeared to have a gradual onset and be coincidentally associated with aging. Reduced amplitudes of waves I and II correlated well with the dog's histories and our clinical findings of impaired hearing. From this study it appears that a reduction in amplitude of waves I and II can be used to examine groups of animals with reduced hearing. Additional studies will be needed to establish amplitude ranges for diagnosing reduced hearing in individual dogs. If age-related sensorineural hearing loss in humans resembles age-related hearing loss in the dog, a delay in latency would be expected. Prolongations of waveform latency might not be seen at high click intensity. To detect individual threshold elevations, it is recommended that any dog with impaired hearing be tested with low and high intensity clicks.

The histological results of this study indicate that hearing loss in geriatric dogs is associated with

degeneration, atrophy and loss of spiral ganglion neurons. Although a significant loss of ganglion cells were found in all areas of the cochlea, the largest reductions of the reduced hearing and deaf groups were consistently found in the upper and lower basal regions. This finding is compatable with sensorineural hearing loss, and with reports that loss of spiral ganglion cells in the basal coils is the prominent histopathological lesion in humans with hearing loss caused by the advanced changes of aging.[97,98] In our deaf group, the magnitude of spiral ganglion loss in the basal regions was higher (96%) than that reported for deaf humans (50% and 85%).[63,99] The location of cell loss in our reduced hearing and deaf groups differs from that reported in old guinea pigs with diminished or absent Preyer's reflexes, which had a 94% reduction of ganglion cells in the apex and a smaller reduction (65%) in the base of the cochlea.[74]

There were no statistically significant differences in apical, middle or upper basal mean cross-sectional areas between groups of dogs; cell packing density reductions in these regions appear to be due only to a loss of cells. The lower basal mean cross-sectional areas of the normal hearing group were significantly less than those of either the reduced hearing or deaf group, and this comparitively lessened the latter groups' packing densities in this region; however, either of these groups actually had

significantly fewer lower basal nuclei per cross-section than did dogs with normal hearing. (Several sections had to be examined in an effort to find any cells remaining in the lower basal turns of the deaf group.)

The ability to record BAERs from the reduced hearing group, in spite of degeneration and loss of spiral ganglion cells, indicates that a significant percentage of ganglion cells may be lost and electrophysiologic evidence of hearing can persist.

No evidence of ossicular chain abnormalities or otosclerotic foci involving the stapedial footplate or oval window was found in any histologic section or macerated specimens, suggesting that such abnormalities are not responsible for hearing loss in old dogs.

In areas with ganglion cell loss there appeared to be a proportional loss of fibers in the osseous spiral lamina, and the cochlear nerve was thin. Hair cell loss and other degenerative changes of the membranous labyrinth have been reported to accompany spiral ganglion cell loss in aged dogs, cats, guinea pigs, and humans.[1,59,71,72,78] Loss of spiral ganglion cells and nerve fibers in the osseous spiral lamina are probably secondary to the loss of hair cells and supporting cells in the organ of Corti. Further studies are needed to determine whether degenerative changes and loss of spiral ganglion cells in older dogs with hearing loss are changes secondary to hair cell

degeneration, or whether ganglion cells can be lost without resultant degeneration of supporting structures.

CONCLUSIONS

1. BAERs of the normal group and of the reduced hearing groupconsistently had 4 major peaks (I, II, III-IV, V) with latencies similar to those previously reported in dogs with normal hearing. No recognizable waves could be recorded from the deaf group, indicating a lack of peripheral auditory function.
2. No difference was found in mean latencies of the 4 major waveforms when comparing the normal group with the reduced group.
3. Significant reductions in mean amplitudes of waves I and II were found in the reduced hearing group.
4. Ossicular chains and stapediovestibular articulations were evaluated for evidence of bony ankylosis; no abnormalities were found.
5. Spiral ganglion packing density revealed a loss of spiral cells in all areas of the cochleas in the deaf group, and in the upper and lower basal region of the reduced hearing group. These morphological findings are consistent with a sensorineural hearing loss.

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Table 1. Hearing Assessments, Breeds, Ages and Weights

Group*	Dog Number	Breed	Age (yrs)	Weight (kg)
I	1	Mix	2.0	22.7
	2	Mix	2.0	18.0
	3	Mix	2.0	22.7
	4	Mix	1.5	22.7
	5	Beagle	3.0	12.3
	6	Mix	8.0	19.5
	7	Siberian Husky	4.0	27.3
II	8	Spitz	9.0	11.4
	9	Mix	12.0	18.2
	10	Lhasa Apso	8.0	7.7
	11	Dachshund	14.0	4.1
III	12	Mix	17.0	5.2
	13	Dachshund	16.0	6.5
	14	Pomeranian	16.0	3.6
	15	Min. Schnauzer	15.0	12.3
	16	Mix	15.0	20.5

* Group - I, normal hearing; II, reduced hearing; III, deaf

Table 2. Mean Amplitudes and Latencies of the 4 Major Waves of the BAER in Normal (Group I) and Reduced Hearing (Group II) Dogs.

Wave	Ear*	Group I (n=7) Amp (μV)	Group I (n=7) Lat (ms)	Group II (n=4) Amp (μV)	Group II (n=4) Lat (ms)
I	L	4.57±0.70	0.96±0.04	1.93±1.29**	0.99±0.12
	R	4.31±1.07	0.90±0.05	1.64±1.12**	1.14±0.24
II	L	2.60±0.66	1.82±0.56	1.37±0.33***	1.82±0.15
	R	2.22±0.46	1.82±0.05	1.23±0.42**	1.97±0.15
III/IV	L	1.30±0.36	2.58±0.21	1.23±0.36	2.32±0.05
	R	1.41±0.54	2.48±0.18	1.23±0.36	2.32±0.05
V	L	1.37±0.43	3.61±0.23	1.18±0.65	3.57±0.34
	R	1.15±0.30	3.57±0.18	1.02±0.93	3.86±0.29

* L, Left; R, Right

** $p < 0.01$ with respect to group 1

*** $p < 0.026$ with respect to group 1

Data expressed as mean ± SEM

Table 3. Group Means of Spiral Ganglion Packing Densities for each Region of Rosenthal's Canal.

Group	Apical	Middle	Upper Basal	Lower Basal
I	2,147*	1,761	1,875	1,785
(n=7)	(1,911-2,495)**	(1,558-1,910)	(1,565-2,582)	(1,343-2,917)
II	2,074	1,777	1,128***	464***
(n=4)	(2,002-2,177)	(1,497-1,953)	(680-1,578)	(119-976)
III	1,383***	974***	547***	71***
(n=5)	(1,004-1,628)	(861-1,214)	(452-735)	(17-146)

* Nuclei per mm^2

** Numbers in parentheses indicate ranges of means within each group.

*** P <0.05 with respect to group I

Table 4. Percentage Differences Between Means of Spiral Ganglion Densities by Group.

Difference between Means by Group	Apical	Middle	Upper Basal	Lower Basal
Group I and II	3%	-0.9%	40%*	74%*
Group I and III	35%*	45%*	70%*	96%*
Group II and III	32%*	45%*	51%*	84%*

* $p < 0.05$

Table 5. Mean Cross-Sectional Areas of Subdivisions of Rosenthal's Canal.

Region of Rosenthal's Canal	Cross-Sectional Areas ($mm^2 x 10^3$)		
	Group I (n = 7)	Group II (n = 4)	Group III (n = 5)
Apical	67.21±11.30	48.44±13.79	50.60±6.75
	(38.50-117.50)*	(26.50-81.75)	(35.75-62.75)
Middle	50.86±4.19	42.69±6.74	53.10±4.84
	(41.00-58.25)	(29.25-51.50)	(45.25-61.00)
Upper Basal	46.86±6.96	57.25±12.17	65.90±8.03
	(30.25-71.25)	(29.50-78.25)	(50.50-80.50)
Lower Basal	44.46±5.84	94.94±21.58**	82.10±16.05**
	(38.25-65.50)	(54.00-145.25)	(44.50-118.00)

* Numbers in parentheses indicate ranges of canal areas

** $p < 0.05$ compared to group I

Figure 1. Typical BAER from Dogs within the Normal Hearing Group (I), Reduced Hearing Group (II), and Deaf Group (III). Each Tracing is the Computer Average of 1,024 Responses Evoked at a Stimulus Rate of 20/s at an Intensity Setting of 84 dBSL. Arrow = Stimulus Artifact.

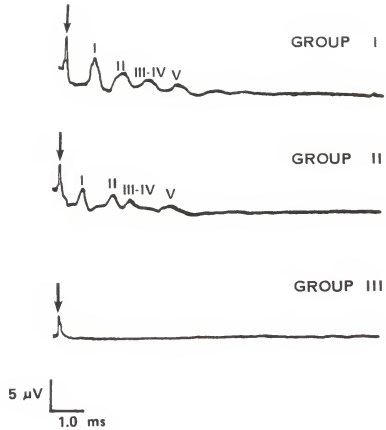

GROUP I
I
II
III-IV
V
GROUP II
I
II
III-IV
V
GROUP III
5 μV
1.0 ms

Figure 2. Plots of Mean Spiral Ganglion Densities for Regions of Rosenthal's Canal.

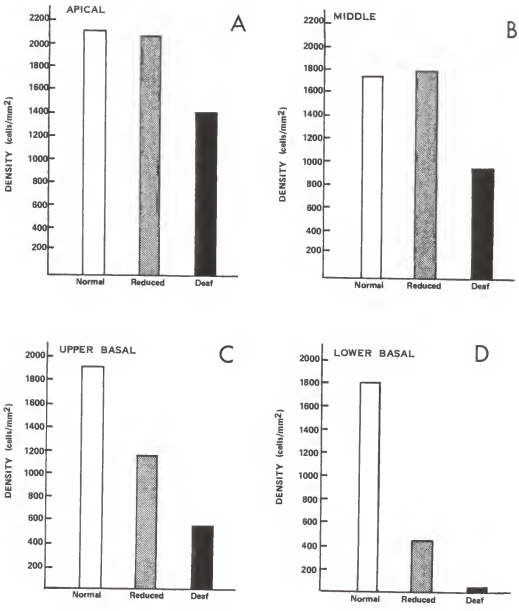

APICAL
A
DENSITY (cells/mm²)
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
Normal
Reduced
Deaf
MIDDLE
B
DENSITY (cells/mm²)
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
Normal
Reduced
Deaf
UPPER BASAL
C
DENSITY (cells/mm²)
2000
1800
1600
1400
1200
1000
800
600
400
200
Normal
Reduced
Deaf
LOWER BASAL
D
DENSITY (cells/mm²)
2000
1800
1600
1400
1200
1000
800
600
400
200
Normal
Reduced
Deaf

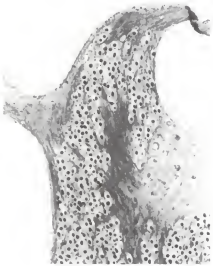
PLATE 1

Figure 1. Apical and Middle Regions of Rosenthal's Canal from a Dog in the Normal Hearing Group. HE

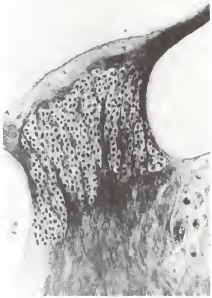
Figure 2. Apical Region of Rosenthal's Canal from a Dog in the Normal Hearing Group Showing a Normal Neuronal Population. HE

Figure 3. Apical Region of Rosenthal's Canal from a Dog in the Deaf Group Showing a Large Loss of Ganglion Cells. HE

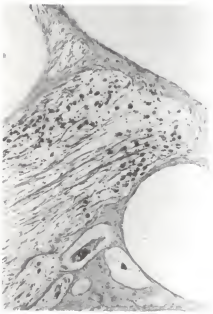
Figure 4. Middle Region of Rosenthal's Canal from a Dog in the Normal Hearing Group. Note the Large Population of Spiral Ganglion Cells. HE



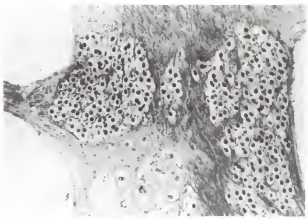
1



2



3



4

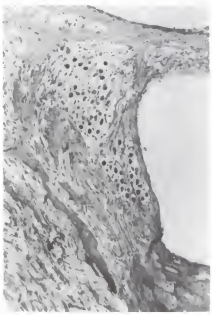
PLATE 2

Figure 5. Middle Region of Rosenthal's Canal from a Dog in the Deaf Group. Note Loss of Spiral Ganglion Cells. HE

Figure 6. Upper Basal Region of Rosenthal's Canal from a Dog in the Normal Hearing Group. HE

Figure 7. Upper Basal Region of Rosenthal's Canal from a Dog in the Deaf Group Showing a Severe Loss of Spiral Ganglion Cells. HE

Figure 8. Lower Basal Region of Rosenthal's Canal from a Dog in the Normal Hearing Group Showing a Normal Population of Spiral Ganglion Cells. HE



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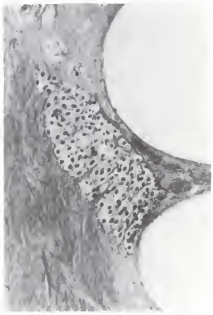

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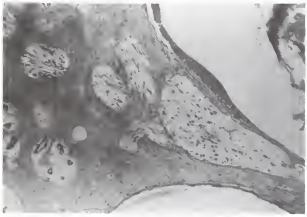

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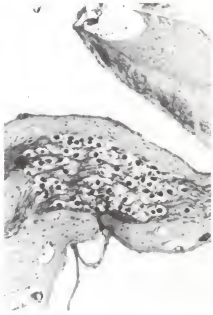

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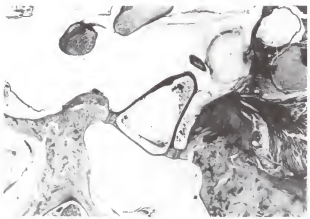
PLATE 3

Figure 9. Lower Basal Region of Rosenthal's Canal from a Dog in the Deaf Group Showing a Complete Loss of Spiral Ganglion Cells. HE

Figure 10. Entire Stapes from a Dog in the Deaf Group. Note Lack of Otosclerosis Involving the Footplate, Oval Window or Crural Arches. HE

Figure 11. Annular Ligament (arrows) from a Dog in the Normal Hearing Group. HE

9



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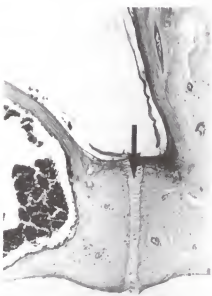

11

PLATE 4

Figure 12. Annular Ligament (arrows) from a Dog in the Normal Hearing Group. HE

Figure 13. Normal Stapes from a Dog in the Deaf Group.

Figure 14. Stapedial Footplate from a Dog in the Deaf Group. Note Smooth Elliptical Contour.

Figure 15. Smooth Borders of the Oval Window from a Dog in the Deaf Group.

Figure 16. Oval Window from a Dog in the Deaf Group. Note Stapes within the Vestibule (arrows).

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FUNCTIONAL AND HISTOLOGIC FINDINGS IN THE COCHLEA OF THE AGING CANINE WITH HEARING LOSS

by

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ABSTRACT

The middle and inner ears of 9 dogs, from 8 to 17 years of age, with differing degrees of suspected hearing loss were examined to characterize the type of hearing loss occurring in the geriatric dog. The middle and inner ears of 7 dogs, from 1.5 to 8 years of age, without evidence of hearing loss were examined as controls. Auditory function was assessed subjectively, and electrophysiologically by recording brainstem auditory-evoked responses (BAERs) to click stimuli.

Monaural clicks of alternating polarities were used to elicit BAERs. BAERs of the normal group and of the reduced hearing group consistently had 4 major peaks (I, II, III-IV, V) with latencies similar to those previously reported in dogs with normal hearing. No difference ($p \geq 0.05$) was found in mean latencies of the 4 major waveforms when comparing the normal group with the reduced hearing group. Significant reductions in mean amplitudes of waves I ($p < 0.01$) and II ($p < 0.025$) were found in the reduced hearing group. No recognizable waves could be recorded from the deaf group, indicating a lack of peripheral auditory function.

Ossicular chains and stapediovestibular articulations were evaluated macroscopically and by light microscopy for evidence of bony ankylosis; no abnormalities were found. The extent and location of cell loss in the spiral ganglia was assessed by quantitative histologic measurements of

cell numbers in the apical, middle, upper basal and lower basal regions of mid-modiolar sections of the cochleas. A determination of spiral ganglion packing density revealed a loss of spiral ganglion cells in all areas of the cochleas of the deaf group, and in the upper and lower basal regions of the reduced hearing group. These morphological findings in the aging canine are consistent with a sensorineural hearing loss.