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The Aging Auditory System

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This volume is dedicated to our friend and colleague, Dr. Judith A. Finkelstein, for her sustained interest in the field and her exceptionally strong support for research during her years at the National Institute on Aging (1995-2006) of the National Institutes of Health. Her efforts were instrumental in guiding new and seasoned investigators alike toward securing funding for research on age-related hearing loss and fostering communication between researchers to promote innovative scientific developments in this area. This volume showcases the work of many of the investigators with whom Dr. Finkelstein worked, either as chapter authors or as authors of hundreds of citations that are referenced throughout.

The senior volume editors also wish to express their appreciation to their spouses, Steven and Susan, for their love and support through all of the late-night experiments, the grant and paper deadlines, and travel to sometimes unusual meeting sites.

Series Preface

Springer Handbook of Auditory Research

The Springer Handbook of Auditory Research presents a series of comprehensive and synthetic reviews of the fundamental topics in modern auditory research. The volumes are aimed at all individuals with interests in hearing research including advanced graduate students, postdoctoral researchers, and clinical investigators. The volumes are intended to introduce new investigators to important aspects of hearing science and to help established investigators to better understand the fundamental theories and data in fields of hearing that they may not normally follow closely.

Each volume presents a particular topic comprehensively, and each serves as a synthetic overview and guide to the literature. As such, the chapters present neither exhaustive data reviews nor original research that has not yet appeared in peer-reviewed journals. The volumes focus on topics that have developed a solid data and conceptual foundation rather than on those for which a literature is only beginning to develop. New research areas will be covered on a timely basis in the series as they begin to mature.

Each volume in the series consists of a few substantial chapters on a particular topic. In some cases, the topics will be ones of traditional interest for which there is a substantial body of data and theory, such as auditory neuroanatomy (Vol. 1) and neurophysiology (Vol. 2). Other volumes in the series deal with topics that have begun to mature more recently, such as development, plasticity, and computational models of neural processing. In many cases, the series editors are joined by a coeditor having special expertise in the topic of the volume.

Richard R. Fay, Chicago, IL
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Volume Preface

Age-related hearing loss (ARHL) is one of the top three most common chronic health conditions affecting individuals aged 65 years and older. The high prevalence of age-related hearing loss compels audiologists, otolaryngologists, and auditory neuroscientists alike to understand the neural, genetic, and molecular mechanisms underlying this disorder. A comprehensive understanding of these factors is needed so that effective prevention, intervention, and rehabilitative strategies can be developed to ameliorate the myriad of behavioral manifestations. This volume presents an overview of contemporary research trends on ARHL from interrelated disciplines whose studies aim to meet this compelling need.

The overall objective of this volume is to bring together noted scientists who study presbycusis from the perspective of complementary disciplines for a review of the current state of knowledge on the aging auditory system. In Chapter 1, Gordon-Salant and Frisina provide an overview to the volume and put the material in the perspective of the field in general. In Chapter 2, Schmiedt presents the morphology and physiology of age-related changes in the auditory periphery, with a description of animal models that control for the effects of known acquired disorders (e.g., noise exposure and ototoxicity) on peripheral auditory system function. In Chapter 3, Canlon, Illing, and Walton describe the direct effects of biological aging at each major level of the ascending central auditory nervous system, with a focus on anatomical, physiological, and neurochemical alterations. This is followed by Chapter 4 by Ison, Tremblay, and Allen that reviews definitive evidence of ARHL in animals and compares findings with those obtained from humans, for whom control of diet, environment, genetics, and other factors is not possible. Chapter 5, by Fitzgibbons and Gordon-Salant, begins a series of chapters on behavioral manifestations of presbycusis in human listeners. Fitzgibbons and Gordon-Salant review changes in hearing sensitivity over time as well as age-related alterations in the perception of the spectral, intensive, and temporal attributes of simple and complex nonspeech acoustic signals. Results of masking and suppression studies are also presented. This is followed in Chapter 6 by Eddins and Hall who discuss binaural processing and temporal asymmetries in aging for both speech and nonspeech signals. In Chapter 7, Schneider, Pichora-Fuller, and Daneman present an integrated systems approach to explain the levels of processing required for spoken language comprehension in communication situations

encountered in daily life. In Chapter 8, Humes and Dubno review the effects of aging on speech perception, with an effort to distinguish the effects of peripheral hearing loss from those attributed to higher-level processing problems on speech perception performance of older people. The epidemiology of ARHL is presented in Chapter 9 by Cruickshanks, Zhan, and Zhong. Finally, in Chapter 10, Willott and Schacht consider chemical and environmental strategies for delaying the onset and progression of ARHL.

Although this volume focuses on hearing in aging adult humans, there are chapters in other volumes of the Springer Handbook of Auditory Research that provide additional related material. Many chapters in *Auditory Trauma, Protection, and Repair* (Volume 31, edited by Schact, Popper, and Fay) and *Hair Cell Regeneration, Repair, and Protection* (Volume 33, edited by Salvi, Popper, and Fay) consider issues of damage to hearing and to the ear and methods by which some of these problems might arise. One technical intervention for treating changes in hearing with age that is gaining momentum is fitting presbycusic listeners with cochlear implants, and these are considered in depth in *Cochlear Implants: Auditory Prostheses and Electric Hearing* (Volume 20, edited by Zeng, Popper, and Fay). Issues related to general perception sounds by humans are also considered at length in chapters in *Auditory Perception of Sound Sources* (Volume 29, edited by Yost, Popper, and Fay) and in an early volume in the series on *Human Psychophysics* (Volume 3, edited by Yost, Popper, and Fay). Other volumes with considerable bearing on this include *Clinical Aspects of Hearing* (Volume 7, edited by Van De Water, Popper, and Fay), *Speech Processing in the Auditory System* (Volume 18, edited by Greenberg, Ainsworth, Fay, and Popper), and *Plasticity of the Auditory System* (Volume 23, edited by Parks, Rubel, Popper, and Fay).

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Chapter 1
Introduction and Overview

Sandra Gordon-Salant and Robert D. Frisina

1.1 Introduction

Age-related hearing loss (ARHL) is one of the top three most common chronic health conditions affecting individuals aged 65 years and older (Pleis and Lethbridge-Çejku 2007). Applying a conservative estimate of the prevalence rate of ARHL (50%) among the population 65 years and older to US Census Bureau projections of the population, there are approximately 20 million senior citizens in the United States with significant hearing loss at present, and this number will soar to 36 million by the year 2030 (Agrawal et al. 2008; US Census Bureau 2008; note that in Cruickshanks, Zhan, and Zhong, Chapter 9, the prevalence of ARHL projected for the year 2030 is higher because it includes those aged 45 years and older). The high prevalence of ARHL compels audiologists, otolaryngologists, and auditory neuroscientists alike to understand the neural, genetic, and molecular mechanisms underlying this disorder so that effective prevention, intervention, and rehabilitative strategies can be developed to ameliorate the myriad of behavioral manifestations. This volume presents an overview of contemporary research trends on ARHL from interrelated disciplines whose studies aim to meet this compelling need. The intended audience includes advanced undergraduate and graduate students, basic and applied biomedical and communication sciences researchers, and practicing clinicians who are concerned with understanding auditory mechanisms and improving hearing health care for elderly individuals.

Historically, the term presbycusis has been used to describe hearing loss attributed to the aging process. The impetus for investigations of presbycusis was Harvard Professor Harold Schuknecht's description of four classic types of presbycusis (1955, 1974).

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In his book *Pathology of the Ear*, Schuknecht (1974) attempted to link case histories and hearing loss patterns in elderly individuals with temporal bone analyses demonstrating deterioration of specific structures in the cochlea and auditory nerve. His observations have underscored that presbycusis is a complex phenomenon that is manifested in various forms among individuals. This basic premise continues to be held today; investigators recognize that hearing abilities in advancing age result from a combination of possible factors involving morphological, chemical, physiological, perceptual, and cognitive processes. Application of sophisticated neurobiological and behavioral techniques to the study of presbycusis has led to a broader understanding of the problem. Schuknecht also recognized that the onset of presbycusis may begin during middle adulthood, with progression into advanced age, and men and women tend to exhibit different types of presbycusis. Cross-sectional and longitudinal studies in humans have clarified the nature of the onset and progression of presbycusis throughout the adult life span and underscore gender differences in behavioral manifestations (e.g., Pearson et al. 1995). The observation of gender and heritability differences also points to a genetic component in at least some cases of presbycusis. More recently, animal models have proven essential in explaining the sequence of altered morphology and subsequent physiological events that lead to hearing loss with aging when diet and environment are carefully controlled.

1.2 Overview

The overall objective of this volume is to bring together noted scientists who study presbycusis from the perspective of complementary disciplines for a review of the current state of knowledge on the aging auditory system. Schmiedt (Chapter 2) and Canlon, Illing, and Walton (Chapter 3) have a principal focus on anatomy, neurochemistry, and physiology of the aging auditory system based on animal models. Schmiedt (Chapter 2) presents the morphology and physiology of age-related changes in the auditory periphery with a description of animal models that control for the effects of known acquired disorders (e.g., noise exposure and ototoxicity) on peripheral auditory system function. Compelling evidence is presented to suggest that the principal effects of aging in a leading animal model of ARHL (the Mongolian gerbil) are morphologic changes in the lateral cochlear wall, including the stria vascularis, which degrade the endocochlear potential with age. These changes then can induce additional pathology involving damage or loss of hair cells and reduction of neurons in the spiral ganglion. Schmiedt carefully demonstrates that these changes produce patterns of sensitivity shifts in the gerbil that reflect common audiometric profiles observed with human presbycusis by considering the key roles of the cochlear amplifier, endocochlear potential, and sensorineural transduction process while signals are coded across frequency. Promising methods to halt, or even reverse, the progression of age-related hearing loss at the auditory periphery are also presented in Chapter 2.

In Chapter 3, Canlon, Illing, and Walton describe the direct effects of biological aging at each major level of the ascending central auditory nervous system, with a focus on anatomical, physiological, and neurochemical alterations. Age-dependent changes in the efferent olivocochlear system and secondary effects on the central system of alterations in the auditory periphery are also described. Research on senescent alterations in the central nuclei and pathways derive primarily from two animal models: mice and rats. Contrasts between CBA mice, which exhibit hearing loss near the end of their life span, like most humans, and C57 BL/6J mice, which exhibit early-onset, progressive hearing loss, are extremely useful for distinguishing between direct aging effects in the central pathways and derivative effects of peripheral dysfunction over time, sometimes referred to as peripherally induced central effects (Frisina et al. 2001). The other animal model of central auditory aging, the Fischer 344 rat, has been used by investigators to elucidate the multifaceted neurochemical alterations that accompany the aging process. Data presented in Chapter 3 converge on a theory of reduced inhibitory neurotransmission that is pervasive throughout the aging central auditory pathway. Evidence for age-related changes in auditory neuroplasticity and mitochondrial function and their implications for central auditory system regulation are also presented in Chapter 3. Supportive data from physiological studies of central auditory function in animal models demonstrate the consequences of morphological and neurochemical alterations with age and form a basis for understanding the mechanisms underlying some of the behavioral manifestations of human presbycusis. In particular, coding of intensive and temporal attributes of sound deteriorates in the auditory midbrain (inferior colliculus) of older animals, whereas localization appears to be less affected by age.

Ison, Tremblay, and Allen (Chapter 4) review definitive evidence of ARHL in animals and compare the findings to those obtained from humans for whom control of diet, environment, genetics, and other factors is not possible. Studies are presented in which investigators experimentally manipulated structures in the auditory periphery or the central auditory pathway of healthy animals to produce comparable anatomical changes to those observed with human aging and then to catalog the functional consequences. This strategy attempts to establish cause-and-effect associations underlying ARHL. Additionally, both behavioral data and electrophysiological data are examined, where comparable paradigms have been employed with both animals and humans. Threshold sensitivity data for pure-tone stimuli are available across the life span for monkeys, rats, gerbils, mice, and humans and show remarkably similar patterns of mean changes in audiometric thresholds over time. Similar threshold data are also available from auditory evoked potential studies (i.e., auditory brainstem responses [ABRs]), although some differences across species are noted. Comparable symptoms of ARHL are evident on ABR latency-intensity functions and otoacoustic emissions as measured in humans and animals of varying ages. Despite the correspondence in average data across species, Ison, Tremblay, and Allen are careful to highlight that individual differences in performance are a prominent characteristic of auditory aging and should be exploited for a comprehensive understanding of the aging process. Intriguing comparisons between humans and

animals in processing abilities for spectral, temporal, and binaural cues as a function of age are also presented. Overall, the findings from animal and human studies appear to converge on similar manifestations of ARHL, including variation between individuals within a group. This translational chapter therefore provides the critical link between the morphological and neurochemical findings in animal models of auditory aging reported in Chapters 2 and 3 and the psychophysical and evoked potential studies conducted in humans across the life span in the laboratory or clinical setting.

Fitzgibbons and Gordon-Salant (Chapter 5) begin a series of chapters on the behavioral manifestations of presbycusis in human listeners. In Chapter 5, changes in hearing sensitivity over time as well as age-related alterations in perception of the spectral, intensive, and temporal attributes of nonspeech acoustic signals are reviewed. Results of masking and suppression studies are also presented. Performance on basic psychoacoustic measures is thought to subsume speech processing because perception of speech requires the listener to process rapid changes in spectral and intensity cues occurring in a sequence, sometimes in the presence of an interfering background noise (i.e., masking). Thus performance deficits of older listeners on psychoacoustic measures may be useful in explaining the underlying factors related to their difficulty in understanding speech, particularly in degraded conditions such as noise or reverberation. One important issue in the investigations of aging effects on auditory behavior is the possible confounding of acquired hearing loss on performance. That is, differences in performance between young listeners (who usually have normal hearing) and older listeners (who usually have some hearing loss) could be attributed as much to the loss of sensitivity as to other factors associated with age. Chapter 5 considers alternative experimental paradigms that have been used to unravel the independent and interactive contributions of hearing loss and age to auditory performance. In general, the review of senescent changes in signal detection and discrimination presented in Chapter 5 indicates that perceptual judgments of some types of acoustic signals appear to be affected primarily by aging, with minimal impact of peripheral hearing loss. For example, age-related differences, independent of hearing loss effects, have been reported for detection of silent gaps of varying duration (i.e., gap detection) and discrimination of stimulus duration (Fitzgibbons and Gordon-Salant 1994; Snell 1997). Evidence is also presented for reduced suppression within the aging auditory system (Sommers and Gehr 1998; Dubno and Ahlstrom 2001). Such findings underscore the notion that aging produces effects on auditory processing that extend beyond those attributed exclusively to reduced signal audibility. Alterations in central auditory processes, discussed in Chapters 3 and 4, are the likely locus of this age-specific type of deficit.

Eddins and Hall (Chapter 6) review binaural processing and temporal asymmetries in aging for both speech and nonspeech signals. They present a comprehensive tutorial on temporal, spectral, and intensive cues that are necessary for sound source location in the free field. The few investigations of age-related effects on measures of source location are reviewed and indicate changes in judgments of sound localization and discrimination of minimum audible angle as a function of age (e.g., Chandler and Grantham 1991; Abel and Hay 1996). Similarly, the effects of ARHL on binaural processing under earphones are presented, with an emphasis

on studies demonstrating a performance deficit for older listeners on the processing of interaural time differences and on the binaural masking-level difference. These findings are interpreted in light of age-related changes in the morphology and neurophysiology of the central auditory system, as presented in Chapters 3 and 4. The influence of sound reflection in enclosed spaces on speech perception also point to age-related performance differences; similar age differences are suggested on measures of the precedence effect. Higher level binaural processes, such as laterality on dichotic listening tasks, also may be affected by aging, although some of the investigations reviewed are difficult to interpret because of the confounding of hearing loss and aging, as noted above. In contrast, studies of the binaural spatial release from informational masking suggest a minimal impact of age. Taken together, the analyses provided in Chapter 6 indicate that although some binaural processing abilities may be preserved in older listeners, at least some diminish with aging. Counseling older people regarding the benefit of specific hearing aid options in light of these findings is also discussed in Chapter 6.

Cognitive decline may occur in advancing age and affect an older individual's ability to perceive and respond appropriately to acoustic stimuli. However, certain cognitive abilities are well preserved in later adulthood, and plasticity may also occur in the older brain. In Chapter 7, Schneider, Pichora-Fuller, and Daneman present an integrated systems approach to explain the levels of processing required for spoken language comprehension in communication situations encountered in daily life. The contributions of sensory, perceptual, and cognitive abilities within this approach are described, with particular emphasis on the cognitive skills that are required for language processing but that may decline with age. These skills include working memory, executive function, and speed of processing. Chapter 7 reviews the age-related effects observed on a range of speech recognition measures, including source segregation, scene analysis, and release from informational masking. The findings suggest that age-related declines in central processing emerge in concert with age-related sensory limitations. However investigations that attempt to identify the independent contributions of sensory decline, cognitive decline, or interactions between the two indicate that deficits in targeted cognitive abilities can influence speech understanding performance among older listeners, even those with normal to near-normal hearing sensitivity, but the strongest effects emerge as the complexity of the listening task increases. The importance of tailoring the auditory rehabilitation process, including amplification, to accommodate the cognitive limitations of older people is also discussed.

Chapter 8 reviews the effects of aging on speech perception, with an effort to distinguish the effects of peripheral hearing loss from those attributed to higher level processing problems on speech perception performance of older people. To that end, Humes and Dubno provide considerable tutorial information on the principles of articulation index (AI) theory (French and Steinberg 1947; ANSI 1969), which quantifies predicted speech recognition performance based on signal audibility across a range of frequency bands that are important for speech, and use the AI as a framework for interpreting the speech understanding problems of older adults as assessed on a range of experimental tasks. They clearly convey the current thinking

that audibility issues primarily limit older listeners' performance for speech recognition in quiet and noise. They discuss various central-auditory and cognitive factors that may contribute to observed age-related deficits for understanding specific types of speech materials and listening conditions (i.e., time-compressed or rapid speech, speech with temporally varying noise, and dichotic speech). Chapter 8 culminates with an explanation of the issues limiting older listeners' speech understanding performance while using current hearing aid technology, again by applying principles of AI theory. Areas where further research is needed are also described.

The epidemiology of age-related hearing loss is presented in Chapter 9 by Cruickshanks, Zhan, and Zhong, commencing with a review of large, population-based studies that converge on the prevalence and incidence rates of hearing loss among men and women of advanced age from industrialized societies. Age-related hearing loss may be associated with a host of risk factors, including endogenous (genetic) factors and acquired exogenous factors. Cruickshanks, Zhan, and Zhong review epidemiological data pointing to hereditability patterns for ARHL, although specific genes have not yet been identified in humans. In contrast, numerous modifiable risk factors have been identified from epidemiological research on ARHL. Prominent among these is noise exposure because most people in industrialized societies are exposed to intense noise, either through work-related exposure (e.g., equipment noise, subway noise) or leisure activities (e.g., loud music, sporting events in public arenas, hunting). Cardiovascular disease is another documented risk factor for ARHL. There is some evidence to suggest that other lifestyle issues, such as cigarette smoking, excessive alcohol consumption, and diet, may elevate the relative risk for ARHL. Although certain medications (e.g., aminoglycosides, chemotherapeutic agents such as cisplatin, loop diuretics) have a well-known ototoxic effect, exposure to some solvents and chemicals in the environment may also cause hearing loss. In contrast, some dietary supplements appear to have a protective effect against the onset and progression of ARHL. In addition, there are comorbid medical conditions of aging that may contribute to apparent ARHL, such as Type II diabetes mellitus and hormonal changes in blood chemistry. This array of conditions that may occur over the course of adulthood, reviewed in Chapter 9 from an epidemiological perspective, underscores the observation that age-related hearing loss is a multifactorial disorder in terms of causation, and this likely contributes to the frequent report of considerable variability in the performance of older human participants in listening experiments. Congruence in causative factors of ARHL identified from animal models and epidemiological studies strengthens our understanding of key modifiable risk factors for this disorder.

In Chapter 10, Willott and Schacht consider chemical and environmental strategies for delaying the onset and progression of age-related hearing loss. Chapter 10 reviews some of the known mechanisms of ARHL in the cochlea, auditory nerve, and central auditory pathways, as discussed in Chapters 2–4, to provide a basis for evaluating the range of possible interventions that hypothetically should halt some of these progressive changes with aging. Experimental data from animal models are presented that demonstrate the benefits of the use of antioxidant therapy, hormonal therapy, dietary restrictions, repair of neural circuits in the central nervous system,

and augmented acoustic environments. However, for each of these interventions, there are also detrimental effects on auditory system function depending on the specific animal species and strain, gender, and experimental paradigm. Although many of these therapeutic approaches hold great promise for treating ARHL, at present, none of them has emerged as a strong candidate for reversing the course of presbycusis in humans, in part because of the multiple causes and etiological loci of ARHL in humans. Nevertheless, continued research with animal models is essential for accomplishing the ultimate goal of identifying chemical or environmental biomedical interventions that will relieve the extensive and diverse symptoms that characterize human presbycusis.

1.3 Future Research

Research on ARHL has advanced dramatically over the last 20 years as amply demonstrated in this volume. The impetus for these advances has derived from three sources: the support of basic research on the mechanisms of hearing loss from the National Institute on Deafness and Other Communication Disorders at the NIH that has been applied to understanding mechanisms of ARHL, the support of sensory and cognitive research from the National Institute on Aging at the NIH that has permitted extensive assessment of the consequences of aging using behavioral, neuroscientific, and molecular biological experiments, and classic literature in the 1980s and early 1990s that called for research on presbycusis to accommodate the anticipated graying of America in the early 21st century (e.g., Committee on Hearing, Bioacoustics, and Biomechanics [CHABA] 1988; Willott 1991). An extensive array of experimental paradigms has been developed to clarify the morphological changes in the periphery and CNS observed in animal models of ARHL, the manifestations of age-related changes in the cochlea, auditory nerve, auditory brainstem, and auditory cortex utilizing electrophysiological measures of auditory function, and behavioral effects on auditory sensitivity and suprathreshold auditory processing of simple and dynamic nonspeech and speech signals over time, including binaural processing in complex listening environments. The nature of cognitive abilities as people age and the impact of possible changes on speech understanding tasks have also been studied extensively. Each chapter of the present volume provides an overview of these experimental findings and their potential implications in these related areas of inquiry, and it is hoped that the critical background is provided for investigators from a variety of disciplines to identify new avenues of promising research from their own unique perspectives.

What is needed as we look toward the future of research on ARHL is a more definitive analysis of the links between the extensive anatomical, structural, electrophysiological, and molecular genetic findings in animal models and the broad range of behavioral manifestations of ARHL, in addition to formulating a better understanding of the principal sources of individual variation on auditory performance in humans, including cognitive changes with age. It is only through a

comprehensive understanding of these factors that better diagnostic procedures for distinguishing different etiologies of presbycusis will be developed and more effective biomedical therapeutic interventions will be introduced that are tailored to individual needs. Such therapeutic techniques span the range from biochemical interventions, including gene therapy and stem cell therapy, to better electroacoustic devices (hearing aids and cochlear implants designed specifically for aged persons) and behavior modification strategies. We hope that this volume provides a renewed impetus toward these visionary objectives.

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Chapter 2
The Physiology of Cochlear Presbycusis

Richard A. Schmiedt

2.1 Introduction

The effects of pure aging on the physiology and morphology of the human peripheral auditory system are difficult to study given the variability inherent in genetics and the environment with which the system must cope. Environmental exposures accumulated over a lifetime often combine mild, continuous noise exposures occurring daily, with occasional punctate episodes of very high decibel trauma associated with loud music, power equipment, and small arms fire. Moreover, the human experience includes many drugs that often have unintended side effects on the auditory periphery. Some drugs have well-known ototoxic properties; others are more insidious, like the continuous high-level use of some narcotics. Noise and drug injuries tend to preferentially damage the hair cells in the cochlea.

Genetics must then respond to an individual's environment, resulting in the very large variability present in the hearing capabilities of elderly humans. It is clear that animal models of age-related hearing loss are required to tease out the effects of aging alone from the effects of environment and genetics. Yet up until ~25 years ago, much of the research in presbycusis was accomplished by using human temporal bones and clinical data (Bredberg 1968; Schuknecht 1974; Gates et al. 1990; Schuknecht and Gacek 1993). Only in the last 30 years or so have animal models been established where the environment, diet, and genetics are strictly controlled (Keithley and Feldman 1979, 1982; Henry 1982; Keithley et al. 1989; Mills et al. 1990; Hequembourg and Liberman 2001; Ohlemiller and Gagnon 2004; for reviews see Willott 1991; Frisina and Walton 2001, 2006; Gates and Mills 2005; Canlon, Illing, and Walton, Chapter 3). Animals raised under these controlled conditions nonetheless show age-related declines in auditory function, consistent with the notion that presbycusis includes effects unique to aging and is not just the result of the combined effects of noise and other ototoxic factors over a lifetime.

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The deleterious effects of aging are often seen first in highly metabolic tissues in the body, coincident with a degradation of mitochondrial function. Mitochondrial dysfunction with age has been attributed to the buildup of reactive oxygen species (ROS), although this hypothesis still elicits controversy (Gruber et al. 2008). In the cochlea, it is the lateral wall where aerobic metabolism is extremely high because it is needed for maintenance of the K^+gradient between the endolymph and perilymph and the generation of the endocochlear potential (EP). The high K^+ and EP are both present in the endolymph of the scala media. It is not surprising then that there is now substantial evidence that age-related hearing loss uncomplicated by environmental and genetic variables is largely the result of pathologies in the cochlear lateral wall rather than just a general loss of hair cells. This chapter reviews some of the current literature on peripheral presbycusis and how lateral wall dysfunction, leading to a lowered EP, can result in audiograms in animal models that mimic those obtained from elderly humans.

2.2 Overview of Normal Mammalian Auditory Physiology

A concise yet accurate way of understanding normal cochlear physiology and how it breaks down with age is to segregate its functional aspects into three interlocking systems: the cochlear amplifier, its power supply, and the transduction mechanism. The three systems and their relationships are schematized in Fig. 2.1. The discussion here is necessarily brief and relates only to those ideas important for understanding the pathologies relating to presbycusis. Further details can be found in the cited references.

2.2.1 Cochlear Amplifier

The cochlear amplifier relies on an active process located in the outer hair cells (OHCs) to physically amplify the traveling wave vibrations along the basilar membrane (Davis 1983; Russell 1983; Cooper and Rhode 1997; Robles and Ruggero 2001). The amount of amplification is highly dependent on a potential (voltage) between the scala media and scala tympani, thereby present across the OHCs. This voltage is the EP, which is ~90 mV within the scala media when referenced to a neck muscle ground. Indeed, the amplification dependency is logarithmic-linear such that about a 1-dB decrease in amplification (corresponding to a 1-dB increase in threshold) results from a 1-mV decrease in EP (Sewell 1984; Ruggero and Rich 1991; Schmiedt 1993). The basilar membrane amplification from the active OHCs also shows a strongly compressive nonlinearity: vibrations from low-level sounds are amplified most, whereas those from intense sounds are amplified least. This compression of dynamic range at the level of the basilar membrane results in a relatively constant vibratory stimulus exciting the inner hair cells (IHCs) over a wide range of acoustic

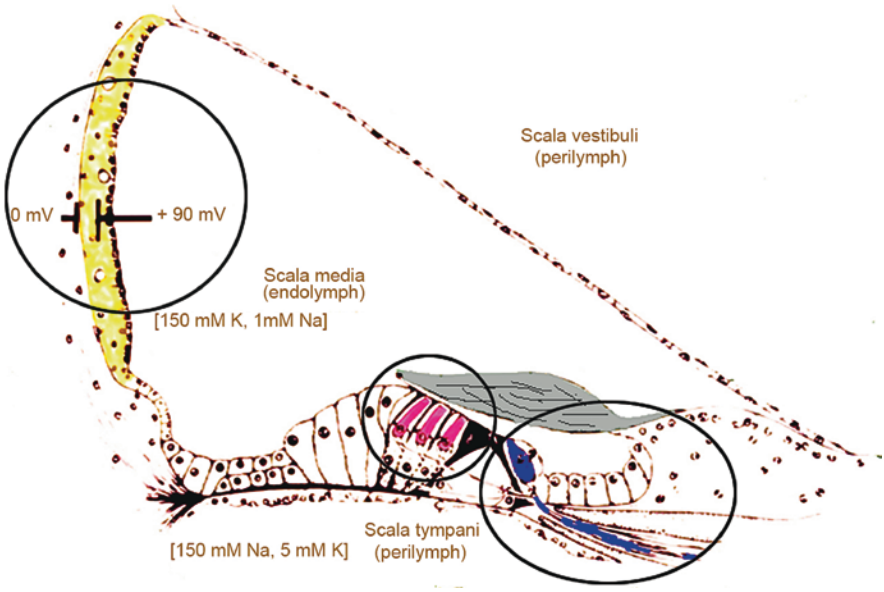

Fig. 2.1 Schematic cross section of a single turn of the cochlea. The three systems underlying basic cochlear function are outlined (circles). The left circle focuses on the lateral wall and stria vascularis and the production of the 90-mV endocochlear potential (EP) present in scala media. The middle circle centers on the outer hair cells (OHCs) and the micromechanics involved in the cochlear amplifier. The right circle is drawn around the inner hair cell (IHC) and the associated primary afferent nerve fibers that make up the transduction process where mechanical vibrations are transduced to neural impulses that are sent to the brain via the auditory nerve. (Adapted with permission from Mills et al. 2006b.)

intensities (Robles and Ruggero 2001) and is also the basis for two-tone suppression. Thus a healthy cochlea is strongly nonlinear in its response to signal intensity and multiple frequencies, resulting in various suppression phenomena and otoacoustic emissions (OAEs). (OAEs are acoustic distortion products that can be measured in the ear canal at frequencies that result when two tones are combined in a nonlinear fashion [Probst 1990]. The strongest in the ear are the cubic difference tones corresponding to frequencies of $2f_1 - f_2$.)

A final factor in understanding the normal cochlear amplifier is that its maximum gain varies along the basilar membrane. In the cochlear apex tuned to lower frequencies, the gain is only ~20 dB, yet in the base, the gain can be as high as 50-70 dB (Ruggero and Rich 1991; Mills and Rubel 1994; Cooper and Rhode 1997; Robles and Ruggero 2001; see Fig. 2.2a, b). Thus if cochlear amplification is totally lost, either from OHC loss or from a very low EP, one would expect to see the least effect at low frequencies and the most at high frequencies. This relationship is borne out in gerbil ears treated chronically with furosemide to artificially reduce the EP as well as in quiet-aged ears with a naturally reduced EP (Schmiedt et al. 2002b; Fig. 2.2c, d).

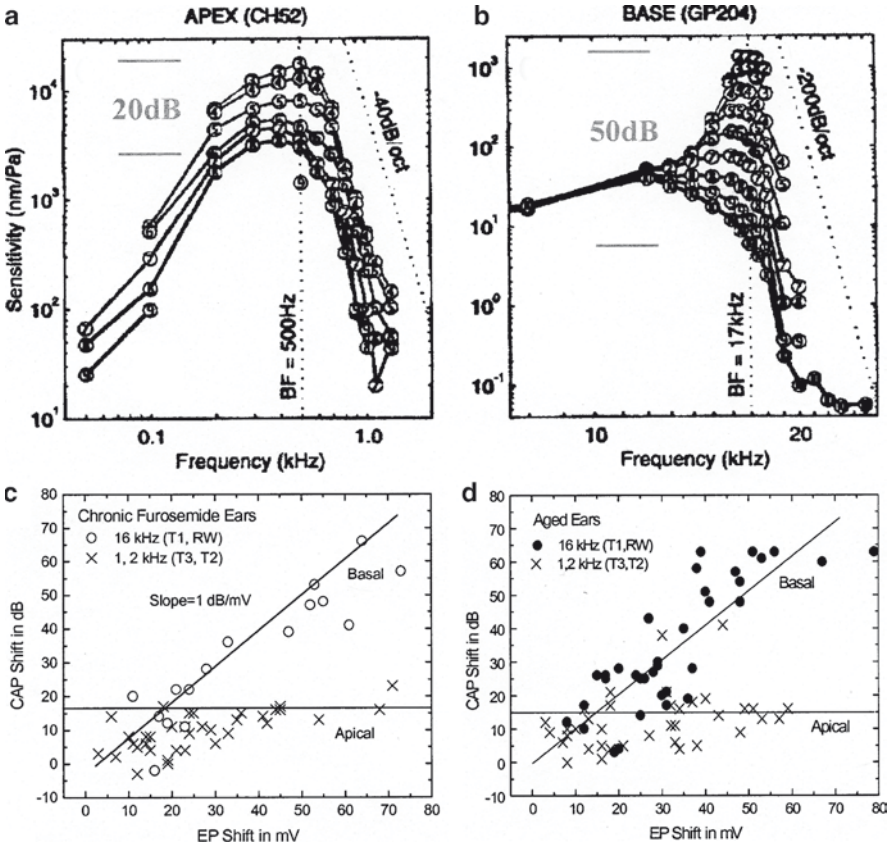

Fig. 2.2 Effects of cochlear location and condition on the vibration amplitudes of the basilar membrane in the apex of a chinchilla cochlea **(a)** and the base of the guinea pig cochlea **(b)**. Two species were used to allow the best recordings from the apex and base. The top lines were obtained first with the OHC amplifier in good condition. The bottom lines were obtained after cochlear death. Note that the apical gain from the OHC amplification is ~20 dB, whereas that from the base is 50 dB. BF, baseline frequency. (Adapted with permission from Cooper and Rhode 1997). Neural shifts in threshold derived from the compound action potential (CAP) response at 1 and 2 kHz (apical) and 16 kHz (basal) are plotted against shifts in the corresponding EP measured in gerbil ears chronically treated with furosemide **(c)** and ears aged 36 months **(d)**. Furosemide is a drug that reversibly decreases the EP and allows studying cochlear function under conditions of lowered EP but with normal hair cells and neurons in a young adult animal (see text; Schmiedt et al. 2002b). **c** and **d** emphasize the points made in a and b; i.e., the OHC amplifier gain at low frequencies is only ~20 dB, whereas at higher frequencies, it is around 50-60 dB. Additionally, **c** and **d** show that the gain in decibels is a linear function of the EP in millivolts at basal locations in the cochlea. The straight lines are not best fits but have slopes of one to show the asymptotic threshold shift for the low-frequency data and unity to show the linear relationship with EP for the high-frequency data. (Adapted with permission from Schmiedt et al. 2002b.)

2.2.2 Cochlear Power Supply

The second system is the cochlear power supply comprising the lateral wall tissues, including those of the stria vascularis where the EP is generated. This power supply is intimately related to the K^+-recycling pathway, which actively pulls K^+ back into the endolymph as it is effluxed from the hair cells into the perilymph. The pathway uses a network of supporting cells and fibrocytes (specialized cells that can turnover and often have stem cell precursors) along the basilar membrane and lateral wall, respectively, connected by gap junctions (Spicer and Schulte 1991, 1996; Marcus and Chiba 1999). A final step in K^+ recycling is the actual generation of the EP within the stria vascularis (Salt et al. 1987; Wangemann et al. 1995; Marcus et al. 2002; Wangemann 2002; Schulte 2007).

Note that K^+ recycling works against both concentration and electrical gradients: the K^+ concentration in the endolymph is ~150-170 mM compared with ~1 mM in the perilymph, and the potential present in the endolymph is ~90 mV (the EP) as compared with the 4-mV potential in the perilymph (Salt et al. 1987; Schmiedt 1996). Thus pushing K^+ along this route takes energy that is largely generated by Na^+-K^+-ATPase pumps in concert with the Na^+-K^+-$2Cl^-$ (NKCC) transporter (Wangemann 2002). The NKCC transporter is an important tool in our studies of the effects of EP changes on auditory function in that furosemide, a fairly specific, reversible antagonist against NKCC, provides a means to experimentally turn off and on the recycling pathway and subsequently the EP (Evans and Klinke 1982; Sewell 1984; Schmiedt et al. 2002b; Mills and Schmiedt 2004). Furosemide delivered either intravenously or via a round window application can reduce the EP to near 0 mV, with recovery from a single dose taking between tens of minutes to over a month if osmotic pumps are used for delivery (Sewell, 1984; Mills and Rubel 1994; Schmiedt et al. 2002b).

The EP serves as the cochlear battery. It is generated within the stria across the intrastrial space and is present in the endolymph along the entire cochlear duct (Wangemann 2002). (Note that EP generation in the stria is dependent on the ion flux provided by the fibrocytes in the lateral wall. In this context, strial and lateral wall pathologies can both result in a lowered EP.) The EP is produced largely by the stria in the basal turn where it is the highest and drops by ~10 mV in the more apical turns of the cochlea. Destruction of the stria or lateral wall in the basal turn results in a significantly lowered EP throughout the cochlear spiral, whereas destruction of the stria in the higher turns with an intact basal stria yields relatively minor reductions in the overall EP (Salt et al. 1987; Wu and Hoshino 1999). Thus apical strial pathology, as often seen with presbycusis, does not necessarily correlate with significantly lowered EP values, whereas basal atrophy is highly correlated with a reduced EP.

2.2.3 Cochlear Transduction

The third system in the transduction of cochlear vibration to neural impulses comprises the IHCs and the afferent fibers of the auditory nerve (see Fig. 2.1).

The IHCs function as passive detectors of basilar membrane vibration and excite afferent fibers via ribbon synapses around the base of the cell (Robles and Ruggero 2001). IHCs are more resistant to noise and chemical trauma than the OHCs and tend to survive with comparatively less pathology in aged ears. Even so, in animals raised their entire lives in quiet (quiet-aged ears), there is a significant loss and shrinkage of the afferent nerve fibers and their cell bodies, the spiral ganglion cells (SGCs) in Rosenthal's canal. The loss and shrinkage with age occur even with the IHCs present and seemingly normal both in animal models and in humans (Schuknecht 1974; Keithley and Feldman, 1979, 1982; Mills et al. 2006a).

In young healthy ears that have been raised in quiet, afferent fibers can be segregated into two or three groups corresponding to spontaneous rates (spont) and sensitivity (Liberman 1978; Schmiedt 1989). Typically, the most sensitive fibers have high rates of spontaneous activity (high-spont, 18 spikes/s and higher), with somewhat less sensitive fibers forming a middle group with spontaneous rates from 0.5 to 18 spikes/s (medium spont). The third group comprises the low-spont fibers with sensitivities that can be up to 50-60 dB lower than those of the high-spont group and have spontaneous rates below 0.5 spikes/s. Thus the sensitivity range of the three groups of afferents in young ears largely covers an intensity range between 0 and 90 dB SPL.

2.3 Schuknecht's Four Types of Presbycusis

Schuknecht (1974) has described four types of human presbycusis: (1) sensory, mainly affecting the cochlear hair cells and supporting cells; (2) neural, typified by the loss of afferent neurons in the cochlea; (3) metabolic, where the lateral wall and stria vascularis of the cochlea atrophy; and (4) mechanical, where there seemed to be a so-called "stiffening" of the basilar membrane and organ of Corti. To date, no real evidence has been found that the mechanical structure of the organ of Corti stiffens with age. The diagnoses of a mechanical presbycusis was derived from a flat loss of 30-40 dB in hearing threshold and was often coupled with degeneration in the spiral "ligament" along the cochlear lateral wall. The spiral ligament originally was thought to offer structural support to the basilar membrane (thus the descriptive term ligament); however, the spiral ligament is now known to consist largely of ion-transport fibrocytes involved in the recycling of K^+ efflux from the hair cells back to the endolymph. Thus it is very likely the mechanical presbycusis described by Schuknecht is simply a severe case of metabolic presbycusis. Indeed, animals with very low EP often show a flat audiometric loss of 40 dB and greater at low frequencies, similar to that ascribed to mechanical presbycusis.

In a later report, Schuknecht and Gacek (1993) described atrophy of the stria to be the predominant lesion in the temporal bones of elderly humans and sensory cell loss as being the least important cause of hearing loss in older humans, especially if the confounding factors of noise, drug exposure, and genetic defects are eliminated. The recent results of Gates et al. (2002) using distortion product otoacoustic

emission (DPOAE) and audiogram data support the conclusion that sensory loss is not as prevalent in the aging population as once thought. Indeed, Gates et al. (2002) and Gates and Mills (2005) conclude that metabolic presbycusis is the predominant cause of human hearing loss with age. Many animal models that exclude noise history or genetic mutations lend support to that conclusion. These models include chinchilla (Bhattacharyya and Dayal 1985), rabbit (Bhattacharyya and Dayal 1989), and CBA mice (Spongr et al. 1997). Even C57 and other mutant mice, if actually aged, develop strial pathologies (Ichimiya et al. 2000; Hequembourg and Liberman 2001; Ohlemiller and Gagnon 2004; Ohlemiller et al. 2008). CBA/J mice, however, seem to show only a hair cell loss with a fairly intact lateral wall with age as discussed in Section 2.4 below (Sha et al. 2008).

2.4 Sensory Presbycusis

Loss of sensory hair cells in the human aging ear is well documented (Bredberg 1968; Schuknecht 1974; Gates and Mills 2005). Indeed, morphologically, hair cell loss is one of the most apparent changes in temporal bones both in humans and in animals of advanced age (Dayal and Bhattacharyya 1989). Species studied include rabbit, guinea pig, cat, rats of various genetic backgrounds, chinchilla, mice of various genetic backgrounds, gerbil, and primate (see Willott 1991 for review). The other universally noticeable pathological change in aged temporal bones is the shrinkage and loss of SGCs in Rosenthal's canal, so it is understandable that presbycusis is commonly thought to be of "sensorineural" origin by many in the field of hearing.

When human audiograms were matched to temporal bone pathologies, it seemed clear that the high-frequency loss so often seen in presbycusis matched the OHC loss in the basal coil of the cochlea (Bredberg 1968; Johnson and Hawkins 1972; Schuknecht 1974). A caveat here is that excess noise exposure is commonplace in western society, and many people, especially men, have been exposed throughout life. Thus the underlying cause of the hair cell loss is problematic. Animals aged in quiet also lose hair cells but more at the apex than at the base of the cochlea. Thus the cochleograms often take on the shape of an inverted "U" (Dayal and Bhattacharyya 1989; Tarnowski et al. 1991). The OHC loss is typically scattered with most, if not all, the IHCs surviving. When neural or behavioral audiograms from the animal models are compared with the OHC loss, there is often a poor correlation.

Fig. 2.3 is an illustration of this last point. Shown in the four panels are the cochleograms and neural threshold shifts of four quiet-aged gerbils. The neural thresholds were obtained with the compound action potential (CAP) response. In all cases, there is a significant scattered OHC loss at the apex, with little or no IHC loss. All the threshold shifts have little relationship to the OHC loss.

Some mouse and rat models do show profound sensory losses with age. They are typically mice with a C57BL/6J background, which has a genetic mutation where hair cell loss begins a few months after birth (Spongr et al. 1997;

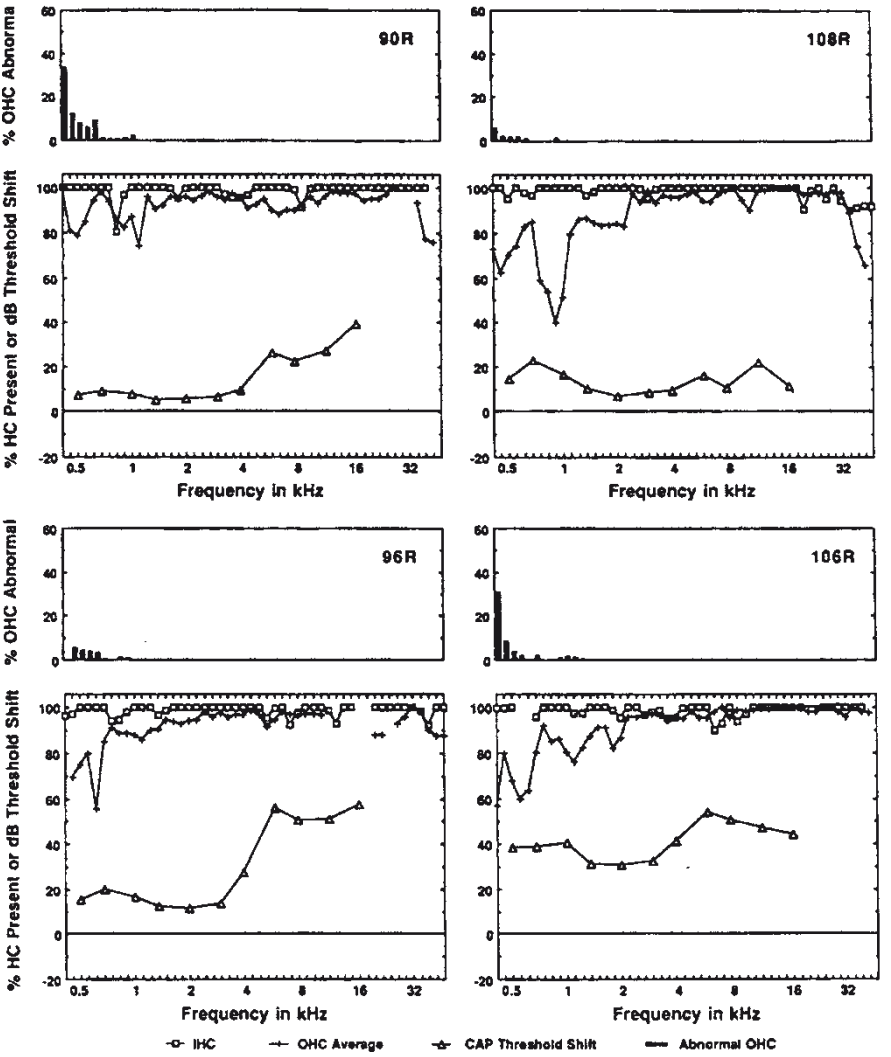

Fig. 2.3 Plots of hair cell condition, hair cell loss, and neural threshold shifts in 4 quiet-aged gerbils at 36 months of age. Percent of IHCs (open circles) and OHCs present (+) and the dB shift of the CAP (open triangles) are plotted against frequency using a gerbil frequency-distance map (Schmiedt and Zwislocki 1977). Note that OHC abnormalities and losses can be significant but are scattered and located mostly in the cochlear apex. IHCs are well preserved throughout the cochlear spiral and CAP shifts have little relationship to hair cell loss, especially with regard to frequencies above 3 kHz. (Adapted with permission from Tarnowski et al. 1991.)

Hequembourg and Liberman 2001). The OHC loss is nearly 100% and progresses from base to apex, with the IHC survival somewhat more robust than that of the OHC. The C57 mouse has been used extensively as a model for sensory presbycusis

and the genetic mutation responsible for the hair cell loss is often termed the "age-related hearing loss" mutation (Johnson et al. 1997). Although important as a model of sensory loss, the age-related hearing loss mutant is problematic with regard to being a true aging model. In the human situation, if a teenager is diagnosed with a progressive high-frequency loss caused by sensory cell degeneration, it is unlikely the condition would ever be called presbycusis.

The CBA/J mouse is a model with true sensory presbycusis (Sha et al. 2008). In this model, the sensory cells are progressively lost from the apex with some loss in the base, with little strial involvement (Lang et al. 2002). In both C57BL/6J and CBA/J mice, the EP remains normal throughout the life span of the animal, although subtle changes in the lateral wall of the C57BL/6 mice have been reported (Ichimiya et al. 2000; Hequemberg and Liberman 2001). Both these models with substantial IHC losses have neural losses with age similar to those found in other mutants without the increased IHC loss, i.e., the neural presbycusis seems not to depend directly on the survival of the IHCs. It is interesting to note that the hearing thresholds of the CBA/J model obtained from auditory brainstem recordings (ABRs) are often not well correlated with the hair cell loss, similar to findings obtained from the gerbil (Fig. 2.3). Finally, not all mice exhibit sensory presbycusis. There are some mutants, such as BALB/cj and NOD/ShiLtJ mice, that do show a decrease in EP with age (Ohlemiller et al. 2006, 2008). Given the mutant data, it is of great interest that wild-caught mice have similar patterns of hair cell loss with age as those of gerbils (Dazart et al. 1996).

2.5 Metabolic Presbycusis

2.5.1 Audiometric Data

For reference, audiograms from human subjects between the ages of 50 to more than 85 years of age are shown in Fig. 2.4. The profile of the hearing loss comprises a flat loss of between 10 and 40 dB at frequencies below ~1.5 kHz, coupled with a sloping loss at higher frequencies. In men, the high-frequency hearing loss is greater than in the women with a correspondingly steeper slope. If subjects are screened for noise history, this gender discrepancy is minimized (Jerger et al. 1993). Thus the audiograms from men are probably a mix of pure aging and cumulative noise exposure with concomitant excessive OHC loss. Note from the discussion on the cochlear amplifier that a complete loss of the OHCs in the base should lead to a flat hearing loss of between 50 and 70 dB above ~4 kHz, which is evident in the male audiograms, but not in those of the females.

The audiogram profile found in humans is also found in many animal models. Fig. 2.5 shows audiograms from an aged chinchilla, aged SJL/J mice, and three groups of gerbils raised in quiet. All show a flat loss at low frequencies coupled with a sloping loss at higher frequencies.

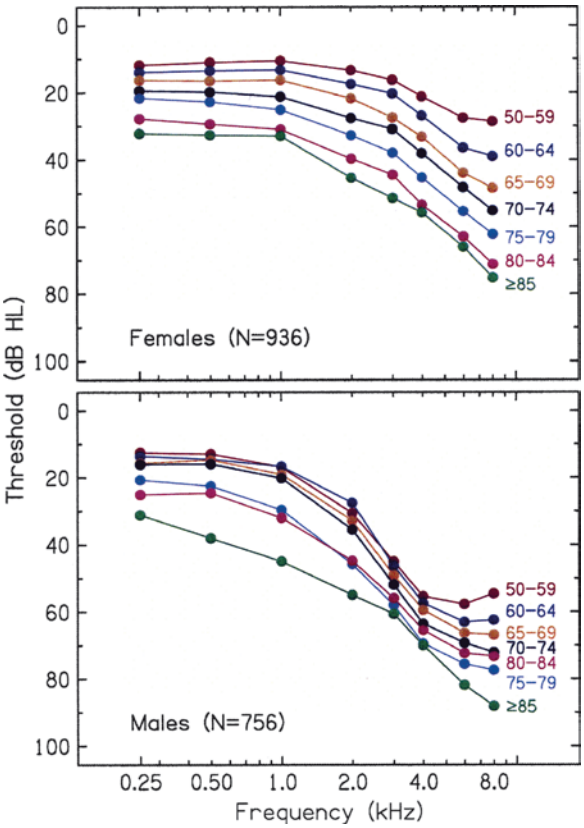

Fig. 2.4 Audiometric mean hearing losses (HL) in female (top) and male (bottom) participants in the ongoing study of age-related hearing loss at the Medical University of South Carolina (Lee et al. 2005; Dubno et al. 2008). The parameter is subject age at the time of enrollment. Note the characteristic profile of human age-related HL: a flat loss at low frequencies coupled with a sloping loss at frequencies above ~1 kHz. These subjects were not screened for noise history, and men typically show more threshold shifts at high frequencies than women, presumably from additional noise exposure (Jerger et al. 1993). Screening for noise history tends to minimize the gender difference. (Adapted with permission from Mills et al. 2006b.)

Individual hearing loss (HL) data are shown for five quiet-aged gerbils in Fig. 2.6 top. (Note that these data have been normalized to young-adult average thresholds that is represented by the 0-dB line and the 90-mV EP.) The EP decreases with age in the gerbil concomitant with a loss of strial volume and Na^+-K^+-ATPase activity along the lateral wall and stria (Schulte and Schmiedt 1992; Gratton et al. 1996, 1997; Spicer et al. 1997). Again, we see the standard presbycusic profile, which is also evident in some of the threshold shift curves plotted in Fig. 2.3. There is little or no correlation of these curves to the OHC loss in any of these animals. However, if we plot the curves with regard to the EP values found in the basal turns of the individual cochleas, a clear pattern emerges. The high-frequency loss is highly correlated with the amount of EP reduction. It is rare that the EP falls below