6
Age-Related Hearing Loss and Its Cellular and Molecular Bases

Kevin K. Ohlemiller and Robert D. Frisina

1. Introduction

Age-related hearing loss (ARHL, or presbycusis) affects most people age 65 and older and represents the predominant neurodegenerative disease of aging. Despite decades of research, there remains disagreement as to how many forms of ARHL exist and what the environmental and genetic risk factors are. Nor are there any widely accepted prevention or treatment strategies. Age-related changes in hearing reflect alterations in both the peripheral and central auditory systems. Changes in the periphery are typically degenerative, and include cell loss in the organ of Corti, spiral ganglion, and stria vascularis. Perceptual correlates of these alterations include reduced sensitivity, reduced sharpness of tuning, loss of compression, and reduced signal-to-noise ratios. Some age-related pathology of the central auditory system appears secondary to degenerative changes in the periphery. Other central pathology occurs independently, and includes reduced connectivity and alterations in synaptic chemistry. (Central consequences of cochlear trauma are detailed in Chapter 9 by Morest and Potashner.) Central physiological effects of ARHL that have no significant peripheral origin include reduced temporal fidelity and weakened suppressive effects of olivocochlear efferent activation on cochlear processing. Perceptually, these may result in degraded signal-to-noise ratios and impaired speech perception.

Application of mouse models to the study of ARHL is promoting rapid advancement in this area. Compared to other models, mice offer a shorter natural lifespan, genetic homogeneity, and the potential for genetic engineering approaches. Nevertheless, their value for understanding human ARHL must follow establishment of common pathology and common genetic and environmental bases for disease. This chapter addresses the history, epidemiology, and current status of understanding of both peripheral and central ARHL, and attempts to identify major unanswered questions as a basis for future research. Recent findings in mice are emphasized, yet not to the exclusion of other models, and only insofar as they complement clinical findings.

2. History and Epidemiology

Historical accounts of research in ARHL are given by Gilad (1979a,b), by Schuknecht (1993), and more recently by Schacht and Hawkins (2005). The first presentation of ARHL as a distinct pathology at a scientific meeting may have been by S.J. Roosa to the American Otological Society in 1885, where he introduced the term *presbycusis*. It was not until the 1930s that Guild, and also Crowe and colleagues, associated hearing loss in aging with specific cochlear structures. von Fieandt and Saxen (1937), (cited in Schacht and Hawkins [2005]) coined the terms *senile atrophy* of auditory neurons and *angiosclerotic degeneration*, the latter term foreshadowing decades of speculation about the role of microvascular pathology in ARHL. Crowe (1934) and Saxen (1937) are credited with the initial division of ARHL into forms emphasizing pathology of organ of Corti versus afferent neurons. Glorig and Davis (1961) and later Nixon and Glorig (1962) argued for nondegenerative pathology of the mechanical structures of the inner ear, later supported by Schuknecht as inner ear conductive ARHL. Schuknecht, in a series of papers beginning in 1953, expanded the number of posited forms to include ARHL characterized by pathology of stria vascularis, and began evaluating temporal bones in terms of putatively independent pathology of organ of Corti, afferent neurons, stria, and spiral ligament. To the present day, there is no clearly superior competing paradigm for understanding ARHL.

Figure 6.1 shows the average progression of ARHL across the span of life (Glorig et al. 1957). The common pattern is one of progressive loss of sensitivity to high frequencies, with relatively little change below 2 kHz to about age 40. Ages 40–60 are characterized by further erosion of high-frequency hearing, typically accompanied by flat losses at low frequencies. After age 60, the entire audiogram may indicate increased hearing loss, such that more than 40% show a clinically significant hearing loss (generally taken to be greater than 25 dB at any frequency) by age 60. Between ages 70 and 80, the prevalence of ARHL exceeds 50%. Nevertheless, the tendencies graphed in Fig. 6.1 obscure a highly skewed character of the underlying distributions, particularly at advanced ages. The rate of hearing decline is quite individualized, so that among those 60 years of age or older will be people with near-normal hearing, sometimes referred to as “golden ears.” Debilitating hearing loss is not an inevitable part of aging, and if understood well enough, may be avoidable. Interindividual differences must reflect different environments and experiences, as well as differences in genetic makeup, predisposing some people to cellular damage from health habits or events that would be benign to others. Also not evident in Fig. 6.1 is the fact that different cochlear cells and structures are affected in different people, so that an unknown number of distinct conditions have been combined.

The pattern of sound frequencies affected by ARHL depends on gender, albeit in a complex manner. Figure 6.2, based on a summary of USPHS surveys by Jerger et al. (1993), shows that men and women have comparable hearing thresholds at 0.5 kHz up to about age 50. After that, thresholds in women deteriorate more rapidly than in men at this frequency. By contrast, above

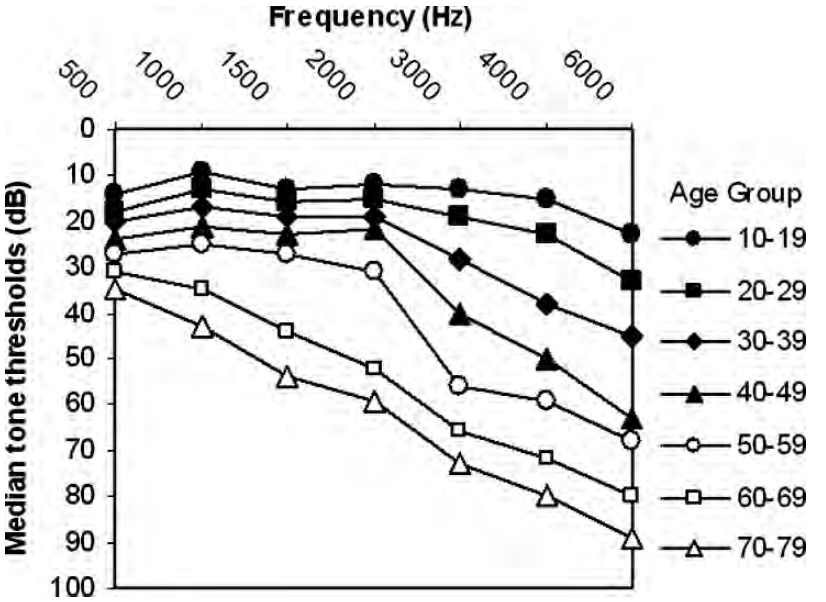

FIGURE 6.1. Median thresholds in dB SPL for men by age group. (Adapted from Glorig et al. 1957.)

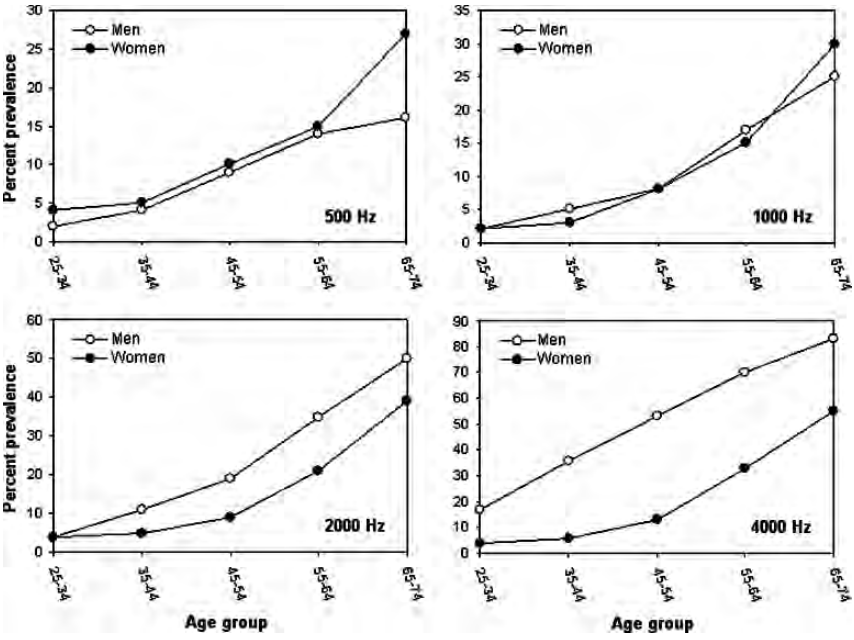

FIGURE 6.2. Prevalence of clinically significant hearing loss (>25 dB above norms) versus age for men and women at 500, 1000, 2000, and 4000 Hz. (Data are taken from a 1975 USPHS National Health Survey, and adapted from Jerger et al. 1993.)

2–4 kHz women hear better than men after about age 35. If subjects are separated into groups with a known history of noise exposure and those without, threshold disparities at high frequencies between men and women are revealed to largely reflect permanent noise-induced hearing loss (NIHL) in men (Fig. 6.3). However, the overall frequency pattern by gender is retained. The role of noise injury in ARHL and possible reasons for gender effects are considered in later sections.

Subdividing ARHL in a way that is diagnostically and prognostically meaningful has remained elusive. While the most dramatic impact of ARHL on hearing ability typically reflects auditory peripheral pathology, the auditory central nervous system (ACNS) ages in characteristic ways and differentially

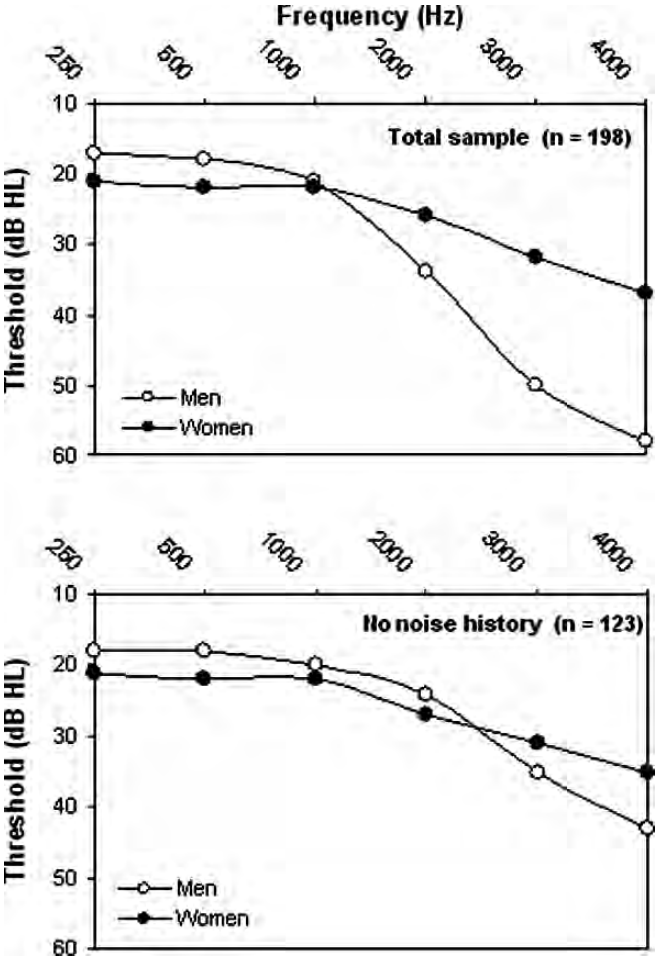

FIGURE 6.3. Hearing thresholds at six test frequencies in men and women 50–89 years of age, separated by noise exposure history. (Adapted from Jerger et al. 1993.)

impacts hearing. Separating peripheral and central pathology is therefore appropriate, and one of the organizing principles of this chapter.

3. Peripheral Aspects of ARHL in Humans

In attempting to impose some kind of typology on ARHL, one might take one of the following approaches: classifying ARHL by its clinical characteristics, by cause, or by the cell type(s) affected. Clinical measures of age-at-onset, severity, laterality, stability, and audiogram shape (see later) are not reliably diagnostic of any particular ARHL type. They are, of course, quite useful for distinguishing other forms of inner ear dysfunction from ARHL, as it is generally symmetrical and nonfluctuating. An elevated "notch" in the audiogram at 4–6 kHz may be useful in separating hearing loss that is principally noise-related from ARHL (e.g., McBride and Williams 2001). Absent any clear indications of causes other than aging, the "cause" of ARHL is the very goal of much current basic research, not a clinical tool. The single current diagnostic for a particular type of ARHL (noted later) is that speech perception in noise may be impacted, even when hearing sensitivity remains normal. To approach the cell biology of ARHL, it has proven more useful to classify cases according to the pattern of cells affected. Classifications made this way unfortunately arrive too late to help the donors of temporal bones, but thus far so have any real cures.

3.1 Classification by Affected Cochlear Structure and Cell Type

The presently dominant framework for classifying of ARHL using histopathology is one championed by Schuknecht in a series of papers written over 40 years, and in his classic book *Pathology of the Ear* (Schuknecht 1953, 1964, 1993; Schuknecht et al. 1974; Schuknecht and Gacek 1993). From his studies of a modest collection of human temporal bones, Schuknecht was struck by cases of relatively isolated degeneration of organ of Corti, afferent neurons, and stria vascularis. He proposed that these represent distinct types of ARHL: *sensory* ARHL (hearing loss due principally to organ of Corti pathology), *neural* ARHL (hearing loss reflecting primary loss of neurons despite the presence of inner hair cells), and *strial* ARHL (hearing loss due mainly to strial degeneration and reduction of the endocochlear potential). Other forms proposed included *mixed* ARHL (multiple apparent contributors), *cochlear conductive* ARHL (possible nondegenerative changes in passive mechanics), and *indeterminate*. Isolated occurrences of delimited pathology of organ of Corti, afferent neurons, and stria were taken to demonstrate the potential for independent degeneration of these structures, and for the existence of environmental and genetic risk factors specific to each. Dysfunction of any one structure/population was further posited to impact independently hearing ability and the shape of the audiogram.

Completely isolated pathology of any cochlear structure is the exception rather than the rule, and most cochleae will show a mixture of pathologies encompassing many cell types. The prevalence of mixed pathology is not really surprising, given that hair cell, neural, and fibrocyte loss increases steadily with age in human temporal bones (Fig. 6.4) (Bredberg 1968; Wright and Schuknecht 1972; Otte et al. 1978). Recognizing this, Schuknecht sought in each case to identify the major contributing degeneration(s) to ARHL. Such a process may seem arbitrary, but is less so than one might expect. Hearing sensitivity is well correlated with outer hair cell (OHC) loss (e.g., Hamernik et al. 1989), but appears surprisingly resistant to loss of afferent neurons and reduction of functional strial epithelial area (Pauler et al. 1986, 1988). In principle, it should be possible to separate the contributions of organ of Corti, afferent neurons, and stria to hearing loss, assuming the surviving cells are functional. Against a backdrop of gradual loss of many cochlear cell types with age, the specific cell types that show accelerated loss and become limiting for hearing will determine the form of ARHL diagnosed. So-called *mixed* ARHL may occur by coincidence of independent causes, or because of genetic or environmental factors that promote broad cochlear degeneration. Both of these conditions probably apply.

Consideration of Figs. 6.1 to 6.4 may raise questions about the distinctness of ARHL from other problems of aging. If one lives long enough, odds are that he or she will experience clinically significant hearing loss as part of a broad spectrum of age-related dysfunctions, one of which ultimately becomes fatal. The goal of responsible aging research is not to overthrow this ultimate limitation. Rather, it is "healthy aging"—to maximize the quality of life up to the immutable limits of the lifespan. Unless one steps in front of an unheard bus, ARHL is not often fatal. Hard limits on longevity will typically be imposed by age-related dysfunction of cardiovascular, pulmonary, or neuroendocrine systems. One's "true age" must be that of the organ system(s) whose age-related failure is life-ending. Accordingly, aging researchers have sought "biomarkers" for aging, metrics that predict longevity (Harper et al. 2003, 2004). Several good candidates have emerged spanning multiple organ systems. The possibility of such markers permits—at least conceptually—refinement of when ARHL is accumulating more rapidly than other age-related pathologies, and when it is just one facet of healthy aging. Assuming an appropriate biomarker were to be sampled in a patient, one may ask, "Is hearing loss progressing at the rate predicted from the marker, or more rapidly?" If the former applies, the ARHL may reflect broad aging processes applicable to a host of tissues, and good preventive strategies might be those shown to delay aging of the whole organism (e.g., caloric restriction). Genetic or environmental factors that promote this "biological-age-synchronous" ARHL would be expected to accelerate a host of age-related pathologies. In the latter case, the ARHL may reflect progressive failure of cochlea-specific cells, or vulnerabilities unique to the cochlea based on its mechanics or metabolic demand. Genetic and environmental risk factors that promote this "accelerated" ARHL might be expected to exert their effects principally on the cochlea, and not other organs. Optimal therapies might be aimed at replacement of lost cells, compensating for missing repair mechanisms,

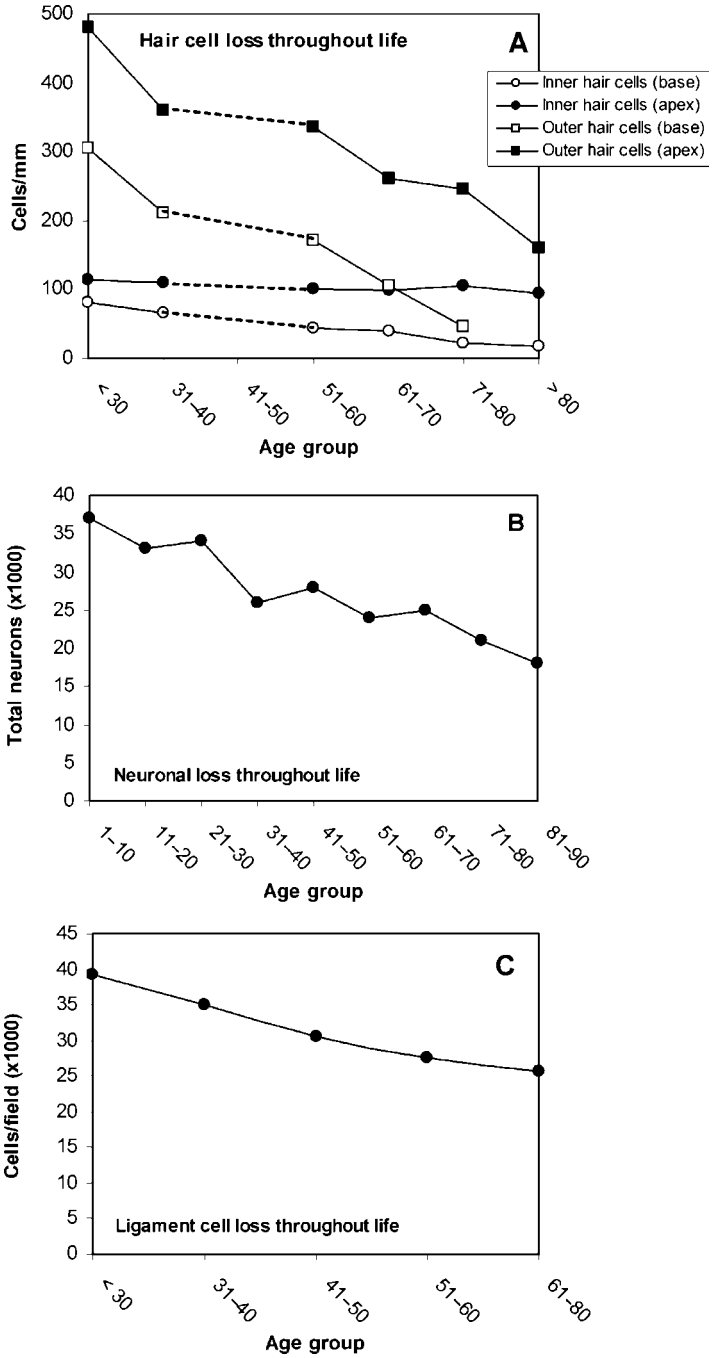

FIGURE 6.4. (**A**) Inner and outer hair cell density versus age in the basal and mid-to-apical cochlea. Data were pooled across subjects of varying hearing ability. (Adapted

or gene therapy to replace nonfunctional genes. Note that the pattern of cell loss or mechanisms of cell death need not differ between these general forms of ARHL. All ARHL is, of course, worth understanding and treating, yet the perceived seriousness of the problem will be greater if the rate of ARHL greatly outpaces overall biological age and singularly impinges on quality of life.

3.1.1 Sensory ARHL

As defined for humans, sensory ARHL refers to degeneration of the organ of Corti that extends at least 10 mm from the cochlear base, that is, into the region serving speech reception. Although most studies have emphasized hair cell loss, Schuknecht included other types of changes in the organ of Corti. Pathology principally of the basal organ of Corti would result in an audiogram that is abnormal only at the highest frequencies. Schuknecht felt that sensory ARHL was the least common form, with an incidence of less than 10% of all cases, although this seems likely to be a considerable underestimate. As hair cells degenerate, secondary neuronal degeneration eventually follows, so that some have recommended the term "sensorineural" ARHL. Among primates at least (including humans), secondary neuronal degeneration may be delayed for years after loss of hair cell targets (with favorable implications for cochlear implants). Sensory ARHL is particularly difficult to distinguish from injury due to noise or ototoxins, as these also often mainly affect the basal organ of Corti. Accordingly, it may be the form most closely associated with injury, and may in fact be mechanistically and anatomically indistinguishable from certain forms of noise or ototoxic injury.

3.1.2 Neural ARHL

Neural ARHL refers to loss of radial afferent neurons that project to inner hair cells (IHCs). Schuknecht estimated the incidence of neural ARHL at 15% to 30% of all cases. As shown in Fig. 6.4, loss of afferent neurons progresses slowly with age in most people, so that clinically significant neural ARHL means unusually rapid loss that becomes limiting for hearing, and is not secondary to loss of IHCs. In Schuknecht's sample, neuronal loss typically appeared evenly distributed along the cochlear spiral, although some studies have indicated greater loss in the extreme cochlear base and apex (Felder and Schrott-Fischer 1995). The severity criterion for this classification is taken to be a total loss of 50% or more of nerve fibers, based on the extent that may lead to impaired word discrimination. Losses up to 50% may produce few clinical signs (Pauler et al. 1986). Even

FIGURE 6.4. (continued) from Bredberg 1968.) (**B**)Total spiral ganglion cells versus age. (Adapted from Otte et al. 1978.) (**C**) Density of fibrocytes in the cochlear spiral ligament versus age. Subjects had no known hearing impairment. (Adapted from Wright 1972.)

more remarkably, significant changes in the audiogram may not occur before nearly 90% of neurons are lost. The fact that speech discrimination and threshold sensitivity are very different in their imperviousness to neuronal loss suggests that redundancy of neurons is far more important for perception of complex stimuli than for simple detection. It is highly fortunate for the operation of cochlear implants that loss of even half of all neurons may have modest consequences.

The existence of neural ARHL is controversial. Some (e.g., Starr et al. 2001) have suggested it merely represents delayed auditory neuropathy, not an explicitly age-related condition. One complication for its diagnosis and study is heterogeneity of form (e.g., Zimmermann et al. 1995; Felix et al. 2002; Chen et al. 2006). In some cases, the most obvious anomaly is loss of dendritic processes from the osseous spiral lamina, while the density of cell bodies in Rosenthal's canal may appear near normal. In other cases dendrites, cell bodies, and presumably their central projections are lost. Most likely, both observations reflect a "dying back" process, whereby dendrites are lost first, followed by cell bodies and axons. The surprising retention of cell bodies that have lost their distal processes has important implications for the success of cochlear implants, as these cells appear "drivable" by electrical stimulation. It may also have physiological implications, given evidence that cell bodies in the spiral ganglion may become commonly ensheathed in myelin and electrically coupled (Felder et al. 1997). This may still allow neurons that have lost their inner hair cell inputs to be excited acoustically.

Neither noise nor ototoxins typically produce a cochlear state resembling neural ARHL, although evidence from animals (see later) suggests that noise exposure at a young age may cause primary neural loss. One proposed mechanism (Pujol et al. 1991, 1993) assigns a significant causal role to excitotoxicity, a process whereby excessive glutamate release from IHCs promotes injury to afferent dendrites. Although excitotoxic injury after noise exposure and pharmacologic manipulations appears reversible, prolonged excitotoxic stress could lead to permanent loss of dendrites, and eventually entire neurons. Some observations indicate that some neuronal loss may follow subtle pathology of pillar cells and other supporting cells within the organ of Corti (Suzuka and Schuknecht 1988). Thus, some loss that would be superficially considered "primary" (since the hair cell targets are still present), may actually be secondary to subtle degeneration in the organ of Corti. Because there is no physiological test that is specific for IHCs and no assay for their trophic influence on neurons, apparent neural ARHL may often have its origin within the inner hair cell.

3.1.3 Strial ARHL

Strial ARHL denotes hearing loss caused by degeneration of the stria vascularis, usually in the mid-cochlear to apical regions, with presumed reduction in the endocochlear potential (EP) that is taken to be the proximate cause of hearing loss. The stria-generated EP provides a significant portion of the driving force for hair cell receptor currents, and reduction of this driving force would be expected to cause elevated hearing thresholds. The hearing loss may be "flat" at lower

frequencies, with sloping threshold elevation at higher frequencies. Because differences in the EP from base to apex are typically modest, larger sensitivity losses at high frequencies probably reflect greater dependence of the cochlear base on active mechanical processes that are "fueled" by the EP. Prevalence of strial ARHL was estimated by Schuknecht at 20% to 35% of cases.

The cochlea appears surprisingly tolerant to degenerative changes in the stria. Up to 30% to 40% of this structure may degenerate all along the cochlear spiral before changes in the audiogram occur (Pauler et al. 1988). Schuknecht noted that strial ARHL tends to occur earlier in life than other forms, and shows a stronger familial component. This has received support from inheritance studies Gates et al. (1999). Studies by Jerger et al. (1993), showing flat hearing loss at low frequencies and differences by gender (Figs. 6.2 and 6.3), have led to the interpretation by some that strial ARHL disproportionately affects women, and may reflect gender differences in microvascular pathology (Gates and Mills 2005). A causal role for microvascular disease in strial ARHL has been proposed (Hawkins et al. 1972; Johnsson and Hawkins 1972), but was not supported by Schuknecht, based on his own observations. The most subtle pathology he noted more often involved marginal cells; moreover, strial capillary anomalies he observed did not appear associated with abnormalities of strial cells. No causal link between strial degeneration and microvascular disease has been demonstrated in humans, nor have any genes that predispose individuals to strial ARHL been identified. Noise and ototoxins can cause strial injury (e.g., Ulehlova, 1983; Garetz and Schacht 1996; Hirose and Liberman 2003), but they rarely promote permanent EP reduction or produce strial pathology resembling effects of aging. Although human and animal studies have tied strial pathology to that of adjacent spiral ligament, Schuknecht saw little connection, and did not include spiral ligament in the hallmarks of strial ARHL.

3.1.4 Cochlear Conductive ARHL

Cochlear conductive ARHL remains unproven. This classification was created to cover cases showing linearly descending audiograms (greater than 50 dB decline overall) that appeared unexplained by obvious degeneration of any cochlear cells or structures (about 15% to 22% of cases). Schuknecht suggested that in some individuals subtle changes in the passive mechanical properties of the organ of Corti, basilar membrane, or adjacent spiral ligament may interfere with transduction, even without notable cell loss. Although this form of ARHL seems plausible, some have questioned its validity, pointing out that detailed cellular/molecular analysis would probably reveal pathology to sensory cells (Gates and Mills 2005).

3.1.5 Mixed ARHL

Mixed ARHL was taken by Schuknecht to be present when multiple forms of degeneration were found, each of which seemed likely to contribute to hearing loss. The shape of the audiogram was suggested to be consistent with the sum of

their effects. Mixed ARHL might arise by coincidence, because a single process common to multiple cell types is impaired, or because of the interdependency for survival among cell types. Schuknecht classified about 25% of cases as mixed, and guessed that the pathologies were often linked.

3.2 The Status of Schuknecht's Framework

Although Schuknecht was not the first to propose all the above categories, his synthesis remains today the most comprehensive. The framework has many limitations. First, its formulation was subject to problems often posed by human temporal bones. These are best interpreted in light of life history, yet health records often paint an incomplete picture of recreational and occupational noise, and ototoxin exposure. Frequently mediocre preservation of samples forced an emphasis on cell numbers rather than cell appearance for evaluation and classification. The framework also has an ad hoc character, perhaps attempting to "shoehorn" cases into too few categories. Up to 25% of cases were considered indeterminate, showing no apparent relationship between histopathology and the appearance of the audiogram. Many have expressed doubt regarding the diagnostic value of the shape of the audiogram (e.g., Chisolm et al. 2003). Even if pathologies of different structures or cells independently contribute to the audiogram, many possible combinations may yield a particular shape. The framework is also incomplete. Details that did not seem to fit anywhere included occasional atrophy of Reissner's membrane, degeneration of spiral limbus, and variable patterns in the loss of fibrocytes from the spiral ligament.

Despite its deficiencies, the core assertion of Schuknecht's framework—independent pathology of organ of Corti, afferent neurons, and stria vascularis—has appealing clarifying power and testability. If each of these structures/cell types possesses distinct environmental and genetic risk factors for age-related degeneration, then identifying these risk factors is an important research goal. Although Schuknecht's scheme has been criticized, it has not been replaced or greatly refined. Observations in humans and animals have largely provided general support, yet few studies have been directed at testing its foundations. The alternative is a murkier and unproductive notion of ARHL, whereby multiple pathologies with multiple causes invariably coincide, and may be inseparable.

4. Central Auditory Aspects of Human ARHL

Relative to the burgeoning reports on the neural and molecular bases of presbycusis from animal models, little is known about anatomical and structural changes in the human ACNS. In considering age-related pathological changes taking place in the brain, two broad etiologies present themselves (Frisina et al. 2001). Some changes, particularly those at the level of the cochlear nucleus, for example, are driven by the declines in peripheral cochlear inputs that occur with age, typically starting with the high frequencies (Frisina and Walton 2006). These

cochlear-driven changes with age are sometimes referred to as "peripherally induced central effects." In contrast, some anatomical or functional changes in the ACNS of old humans and animals appear to occur somewhat independently of the periphery, and may reflect "true aging" neurodegenerative changes in the brain. These may share some similarities or common mechanisms with other central nervous system conditions of the aged such as Alzheimer's and Parkinson's diseases.

4.1 Structural Changes in the Central Auditory System

Several noteworthy studies of structural changes with age have been performed, and what is known is generally consistent with animal model results presented below. Konigsmark and Murphy (1970, 1972) found age-dependent declines in the volume of the human ventral cochlear nucleus (VCN), while Seldon and Clark (1991) observed VCN neuron size reductions. In neither case was a change in the number of VCN neurons with age noted, but increased lipofuscin deposits and declines in capillary density were found.

Higher in the human brain stem at the level of the lateral lemniscus, which is the major ascending input tract for the inferior colliculus (IC), Ferraro and Minckler (1977) examined the anatomy of 15 brains, from persons ranging in age from birth to 97 years. They reported a significant decline in the number of lemniscal nerve fibers with age. In one of the first neurochemical studies of the ACNS, foreshadowing later animal work presented later in this chapter, McGeer and McGeer (1975) reported that the postmortem presence of glutamic acid decarboxylase (GAD), the primary synthetic enzyme for the main inhibitory neurotransmitter of the inferior colliculus, γ-aminobutyric acid (GABA), decreased with age. At the level of the auditory cortex, Brody (1955) reported a striking negative correlation ($r = -0.99$) for age and the number of neurons in the human superior temporal gyrus. This reduction was much greater than for neighboring cortical regions such as the inferior temporal cortex, striate (visual) cortex, and pre- and postcentral gyri (sensorimotor).

4.2 Functional Declines with Age

One tactic for teasing out age-related brain-specific changes from peripherally induced central effects is to perform behavioral or physiological experiments that assess some aspect of central auditory processing in human or animal subjects that have relatively good hearing. For instance, Frisina and Frisina performed the SPIN test (*S*peech *P*erception *I*n *N*oise) on young adult and old human subjects with good peripheral hearing to assess speech perception problems in background noise that might have central auditory brainstem or cortical components (Frisina and Frisina 1997). Old subjects having audiograms in the normal range nevertheless performed worse on the SPIN test, requiring a stronger speech signal and higher signal-to-noise ratio for a particular speech recognition criterion. SPIN tests performed while simultaneously assessing brain

activity in a positron emission technology (PET) scanner (Frisina 2001; Salvi et al. 2002) revealed changes in brain activity of old subjects with normal audiograms and 50% correct speech recognition performance level. Specifically, the old subjects had less brain activity in the auditory midbrain/thalamus regions, and in some of the auditory/visual processing areas.

Event-related potentials have also been utilized to assess central auditory functional changes with age. For example, the amplitude and latency of the P3, or P300, an event-related potential that marks an updating of our current sensory environment in working memory, has been employed as a probe to the aging brain. Polich's lab found that the auditory P3 amplitude declines, and the latency increases with age (Polich et al. 1985). Frisina, Walton and co-workers confirmed this basic finding, and extended it to musical stimuli (Swartz et al. 1994). Interestingly, when early Alzheimer's patients were compared to young adult and old controls on these musical P3 auditory tasks, even Alzheimer's patients who could not make an overt behavioral response to the musical stimuli displayed significant processing of music as indexed by the P3 (Swartz et al. 1992).

It has been known for some time from psychoacoustic experiments on young adults that there is a link between auditory temporal processing and speech perception capabilities. Consistent with this, Fitzgibbons and Gordon-Salant (1996) and Snell and Frisina (2000; Snell et al. 2002) discovered an age-related decline in temporal processing related to speech perception. It is interesting to note that even subjects with good peripheral hearing, i.e., audiograms in the normal range, experience problems with gap detection and speech recognition in background noise as they proceed through middle age into old age.

Jerger and his colleagues pioneered investigation of central auditory processing problems of presbycusis while taking into account cognitive factors (for a review see Martin and Jerger 2005). Interactions between cognitive slowing and auditory processing deficits of aging are still controversial given the difficulty in equating for age-related hearing loss in assessing language processing abilities in the elderly (Pichora-Fuller 2003). Human neurophysiological studies shed some light on auditory temporal dysfunction at cortical levels. For example, Pekkonen (2000) utilized the mismatch negativity to demonstrate that aged subjects exhibited deficits in processing sound duration, but not frequency, in the auditory cortex.

5. Peripheral Aspects of ARHL in Animal Models

Age-related cochlear pathology has been examined in aging chinchillas, guinea pigs, primates, dogs, and rodents (e.g., Covell and Rogers 1957; Keithley and Feldman 1979; Bohne et al. 1990; Tarnowski et al. 1991; Shimada et al. 1998). These models show the range of cochlear pathologies noted for humans (organ of Corti, neural, strial), but they have not typically been analyzed in terms of whether they would meet human criteria for sensory, neural, or strial ARHL.

Whether the relationship between measures such as neural loss and threshold elevation, or between percentage of strial impairment and EP reduction, is the same as for humans has not been examined in all models, but has received support (Schulte and Schmiedt 1992). Particularly valuable—albeit rare—animal models are those that exhibit relatively isolated forms of ARHL, allowing these to be studied with minimal confounds. Currently the best example is the gerbil, which compellingly models strial ARHL (Schulte and Schmiedt 1992; Gratton and Schulte 1995; Gratton et al. 1996, 1997; Schmiedt et al. 2002; Spicer and Schulte 2002, 2005). For the majority of animal models showing a complex mix of cochlear pathologies, there is unfortunately no way to separate these (or at least see if they can be separated). Such is possible only if there exist multiple varieties of highly inbred subpopulations of a species, allowing comparison of their aging characteristics and the possibility of segregating traits in genetic crosses. So is revealed the value of mouse models. One can raise an "old" mouse in 2 years and examine multiple genetic variants. As will be expanded upon, there are many strains of mice that show ARHL. Most are not well characterized, and only some of these will ultimately be found to be useful models of human ARHL. Like other animals, the mouse ARHL models show a mix of pathologies, and attempts to separate these are not well advanced. Nevertheless, mouse models have emerged that mirror the defining characteristics of human ARHL.

5.1 Sensory ARHL in Animals

Nearly all animal models characterized to date most resemble sensory ARHL, and studies of these have used hair cell loss as their primary metric. The best characterized mouse ARHL models, including C57BL/6 (B6), BALB/c (BALB), CD-1, 129S6/SvEv, and SAMP-1, show degeneration of the organ of Corti, and also variably include some degeneration of afferent neurons, stria vascularis, and spiral ligament (Mikaelian et al. 1974; Henry and Chole 1980; Saitoh et al. 1995; Willott et al. 1998; Hequembourg and Liberman 2001; Wu et al. 2001; Ohlemiller 2002; Ohlemiller and Gagnon 2004b). For ages up to which hearing loss is pronounced, the EP appears normal in these models, and changes in the organ of Corti can account for most hearing loss. A rapidly expanding collection of genes, collectively termed *ahl* genes (e.g., Johnson et al. 2006), have been identified that account for the hearing loss in some of these strains. The *Cdh23*^{ahl} allele, which is common to B6, BALB, and several other strains (Johnson et al. 2000), is the most intensively studied and most used to extract principles of cochlear aging. This locus codes for cadherin 23 (or otocadherin), believed to be a component of stereocilia (Siemens et al. 2004). Most strains that carry this allele show a mix of pathologies that bear no obvious relation to stereocilia function (e.g., Figs. 6.5 and 6.6), and understanding whether and how these are related may be important for how mixed ARHL occurs. The contribution of *Cdh23*^{ahl} to age-related pathology in B6 mice can be isolated by examination of the congenic B6.CAST-*Cdh23*^{CAST} line. These mice show organ of Corti degeneration in the cochlear base and high frequency hearing loss

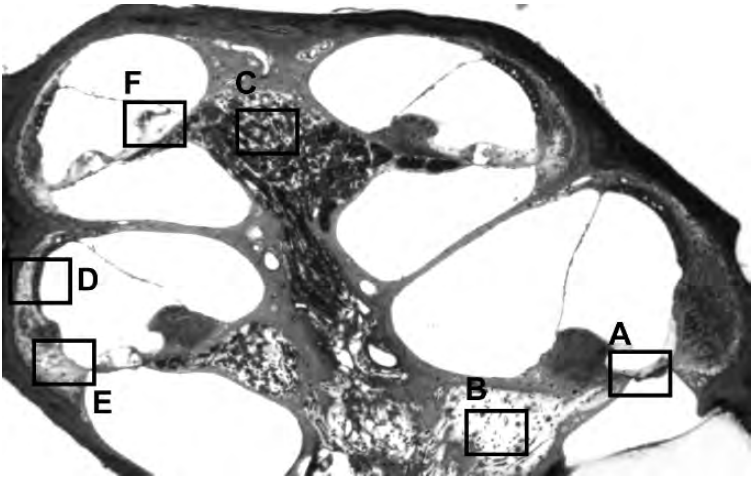

FIGURE 6.5. Mid-modiolar section from an 18-month-old female C57BL/6 mouse cochlea illustrating many types of cochlear changes found in aging. Cochlear pathology includes hair cell loss, organ of Corti anomalies, neuronal loss (probably both primary and secondary), strial degeneration, and loss of fibrocytes in spiral ligament and limbus. The animal had almost no hearing, but a normal endocochlear potential (110 mV). C57BL/6 mice carry an allele (*Cdh23*^{ahl}) that promotes sensory ARHL-like pathology. Other pathology may be related to additional unknown genes.

beginning after 1 year of age (Keithley et al. 2004), presumably reflecting the presence of additional alleles that promote ARHL. As might be expected from its gene product, *Cdh23*^{ahl} promotes cochlear pathology that appears most similar to sensory ARHL. Notably, this allele also promotes NIHL (Erway et al. 1996; Davis et al. 2001), suggesting a connection between noise injury and this ARHL form. Although the role of otocadherin is not known, it interacts with known components such as the plasma membrane Ca^{2+}-ATPase, and thus may impact processes that regulate hair bundle integrity (Davis et al. 2003). There are many processes that, if impaired, could render the organ of Corti more vulnerable to injury, so that a general link between injury and sensory ARHL seems plausible. At present, at least six loci with alleles known to promote sensory ARHL-like pathology also promote NIHL (Ohlemiller 2006). A cautionary note is in order here in that the *Cdh23*^{ahl} allele might be a confounding factor, i.e., it is a modified gene, and these mice may not reflect "true" age-related hearing loss in most human clinical cases.

5.2 Neural ARHL in Animals

Although primary loss of afferent neurons is frequently observed in animal models, whether such observations usefully model neural ARHL has remained unclear. At least three quite different "knockout" mutations (KOs, engineered

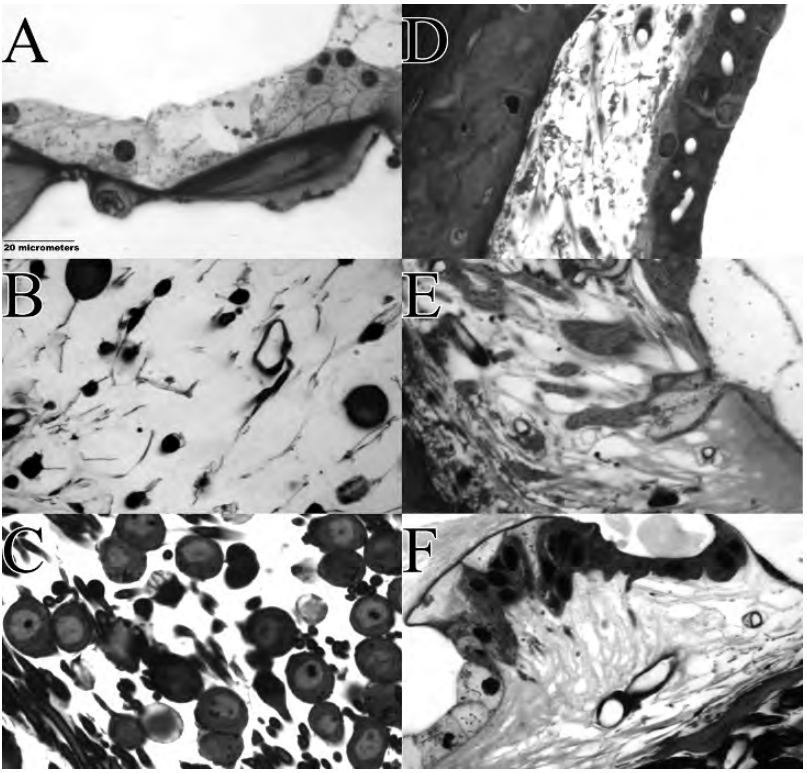

FIGURE 6.6. Enlarged view of boxed regions from Fig. 6.5. (**A**) Loss of hair cells and most recognizable cell types in organ of Corti of the lower basal turn. (**B**) Loss of spiral ganglion cells and their projections to hair cells in the lower base. Much of this loss may be secondary to hair cell loss. (**C**) Apparent primary loss of spiral ganglion cells in the upper apical turn. (**D**) Loss of type I fibrocytes in spiral ligament behind stria vascularis in the upper basal turn, along with thinning and disorganization of the stria. Overall strial degeneration is modest and may not be indicative of the kinds of cellular changes that occur in strial ARHL (see text). (**E**) Loss of type II and IV fibrocytes in the lower spiral ligament of the upper basal turn. (**F**) Loss of fibrocytes from the spiral limbus of the upper apical turn.

inactivating mutations of specific genes to test their role) promote accelerated neuronal loss, and thus point to specific genes and pathways as causes of this condition. The first is a knockout of the gene locus encoding Cu/Zn-superoxide dismutase (SOD1), a key antioxidant enzyme (Keithley et al. 2005). This suggests a role for oxidative stress and possible gene–environment interactions in neuronal survival. The second is a KO of the β_2 subunit of the nicotinic acetylcholine receptor (Bao et al. 2005), suggesting a trophic influence of lateral efferent neurons, which form synapses with afferent dendrites. In the third KO model, nuclear factor κB (NF-κB), a stress-activated transcription factor, was inactivated

by elimination of the p50 subunit (Lang et al. 2006a). Transcription factors trigger the "reading" of whole families of genes related to particular functions. NF-κB is activated by stress-related increases in intracellular calcium, and may be important for preventing excitotoxic injury to afferent neural dendrites. Compared to wild-type controls, NF-κB knockout mice exhibit greatly increased neuronal dendrite and perikaryal loss with age, plus increased signs of excitotoxic injury. They may also be more vulnerable to NIHL. These mice support the proposal that some neural ARHL results from interplay between the environment and genes that regulate afferent synaptic function or glutamate transport. In a potentially related finding, Kujawa and Liberman (2006) reported in mice an interaction between the age at which noise exposure occurs and apparent primary age-related neuronal loss. (See Borg 1983 for potentially related findings in rats.) When CBA/CaJ mice were exposed to noise at 1.5 months of age (young but sexually mature), the resulting hearing loss increased with age along with neuronal loss, despite a stable inner hair cell population. Taken together, findings in NF-κB knockout mice and young noise-exposed mice raise the possibility that early noise exposure alters the developmental program for afferent synaptic function or calcium homeostasis.

The presence of IHCs does not ensure that they function properly, or exert necessary trophic influences on afferent dendrites. Apparent primary neural loss could result from abnormalities of hair cells, neurons, efferent innervation, or some more global factor such as perilymph oxygenation, pH, or ion content. Aging B6 mice show widespread neuronal loss that has been generally assumed to be secondary to loss of IHCs due to *Cdh23*^{ahl}. However, quantitative ultrastructural studies have shown that the withdrawal of dendrites from inner hair cells in B6 mice precedes any obvious anomalies of the hair cells, so that a general process not involving *Cdh23*^{ahl} may be at work (Stamataki et al. 2006). Extension of this approach to other strains or the B6.CAST-*Cdh23*^{CAST} line may help place this finding into a broader context. Schuknecht suggested that some apparent primary cochlear neural loss was actually secondary to subtle pathology of IHCs or supporting cells. Ohlemiller and Gagnon (2004a) demonstrated that primary loss of afferent neurons in the cochlear apex of several mouse strains (B6, BALB, CBA/J, and 129S6) was correlated with degenerative changes in pillar cells and (puzzlingly) Reissner's membrane. They proposed that a common factor local to the apex underlies these changes, and that the causes of primary neuronal loss may depend on basal–apical location.

5.3 Strial ARHL in Animals

Age-related strial degeneration has been described in chinchillas, guinea pigs, and rodents. Common strial changes include thinning of the strial epithelium and capillary loss and occlusion. Because EP decline is taken to be the most significant result of strial degeneration, it is important to understand which cellular changes and what degree of strial involvement indicate that the EP is likely to be reduced. Only in mice and Mongolian gerbils have anatomical

changes and EP recordings been measured as a function of age. The gerbil appears to model strial ARHL in several respects. Age-related strial degeneration and EP reduction may drive most of the observed hearing loss in these animals (Schulte and Schmiedt 1992; Gratton and Schulte 1995; Gratton et al. 1997; Schmiedt et al. 2002; Spicer and Schulte 2002, 2005). The strial pathology is manifested as strial thinning and degeneration, followed by ligament degeneration. While the pathology in gerbils was initially interpreted as having a microvascular origin, more recent observations attribute the initial pathology to strial marginal cells. With time, other cells of stria, then spiral ligament, become affected.

Because marginal cells house ion transport systems that play a central role in EP generation, a marginal cell origin for strial ARHL makes sense from the standpoint of metabolic rate and oxidative stress. But what might be the basis of the suggested heritability of strial ARHL in humans? Because gerbils cannot be drawn from many different inbred strains, they do not readily facilitate genetic analysis. Use of mice could solve this problem, but application of mouse models to strial ARHL has been slowed by the near absence of mouse models that show significant late-onset EP reduction. B6 mice show many age-related features of the cochlear lateral wall that have been associated with strial ARHL, such as strial thinning, ligament thinning, loss of capillaries, and loss of fibrocytes (Figs. 6.5 and 6.6) (Ichimiya et al. 2000; Di Girolamo et al. 2001; Hequembourg and Liberman 2001). Yet these mice lack the key hallmark of this condition, showing little or no EP decline by 2 years of age (Lang et al. 2002). Cable et al. (1993) showed that about half of mice carrying the *Tyrp1*$^{B-lt}$ allele, which affects melanocyte function, undergo EP reduction by 22 months. No clear morphological correlate was identified. A mouse lupus model, MRL-*Fas*^{lpr}, shares characteristics with strial ARHL that merit mention. These mice hear as well as controls in their first months, but thereafter show progressive threshold elevation, strial degeneration, and EP reduction (Ruckenstein et al. 1999a,b). Strial pathology in MRL-*Fas*^{lpr} initially impacts strial vasculature and neighboring intermediate cells. As claimed for human strial ARHL, the pathology is more pronounced in females than in males (Trune and Kempton 2002). In general, autoimmune disease impacts principally females, so that some strial ARHL may possess an autoimmune component. The MRL-*Fas*^{lpr} model may be found to have implications for how some human strial ARHL arises.

Ohlemiller (2006) found moderate EP reduction beginning at 19 months in BALBs, even though the stria and adjacent ligament showed only modest changes. The contrast between BALB mice and B6 mice (which undergo more striking changes in the spiral ligament than do BALBs) presented an opportunity to isolate the major contributors to age-related EP decline in BALBs. In each strain, EP was compared with a host of factors previously associated with strial ARHL including fibrocyte density in spiral ligament, strial cell density (basal, intermediate, and marginal cells), strial thickness, ligament thickness, plus strial capillary density, diameter, and basement membrane thickness. Among all measures, only marginal cell density and ligament thickness were correlated with the EP in BALBs. B6 mice showed little age-related loss of marginal cells and

little reduction in ligament thickness, even though there was significant fibrocyte loss. Neither strain revealed any predictive value of changes in strial microvasculature. Observations in BALB mice and gerbils therefore support a marginal cell origin for some strial ARHL, specifically the form described in human temporal bones. A mouse strial ARHL model may promote identification of the underlying genes. Consideration of alleles common to B6s and BALBs, plus additional strain comparisons in the Ohlemiller et al. study permitted elimination of the *Cdh23*^{ahl} locus and loci involved in melanin synthesis as a genetic basis for the findings in BALBs. Both BALB mice and gerbils share an important feature in that only about half of animals show EP decline. Because inbred mice are essentially genetically identical and gerbils used for research are highly inbred, this suggests substantial environmental modulation of the genetic tendency toward age-related EP decline.

Accumulating evidence from animals undermines an obligate role for microvascular disease in strial ARHL. Studies using the mitotic tracer bromodeoxyuridine (BrdU, commonly used to detect new cell division) indicate that some cells in spiral ligament and stria vascularis are replaced over time (Conlee et al. 1994; Yamashita et al. 1999; Lang et al. 2003; Hirose et al. 2005). Net loss of marginal cells in BALB stria could therefore reflect either an abnormally high rate of cell death, or impaired replacement.

Findings in mice have also helped clarify the relationship between age-related degeneration of stria vascularis and spiral ligament. Schuknecht and colleagues (Wright and Schuknecht 1972; Schuknecht and Gacek 1993) treated these structures as independent, and did not include ligament pathology in the hallmarks of strial ARHL. Spicer and Schulte (2002) proposed a sequence in gerbil whereby strial pathology spreads to ligament. Certainly, the potential exists for dependence of ligament on the stria. In keeping with the notion of K^+ recycling from the organ of Corti, through ligament, and back to the stria (Wangemann 2002; see also Wangemann, Chapter 3), strial dysfunction could promote toxic K^+ accumulation in ligament. This relationship may not work in reverse, however. Mice carrying a single functional copy of *Brn4*, an X-linked transcription factor, and homolog of human *DFN3* (Minowa et al. 1999; Xiu et al. 2002) develop pathology of spiral ligament and Reissner's membrane, and EP reduction. Similarly, mice deficient in otospiralin, a protein normally present in fibrocytes of the ligament, show ligament pathology (Delprat et al. 2005). Notably, neither of these models shows strial degeneration, supporting relative insulation of the stria from moderate ligament pathology.

6. Central Auditory Aspects of ARHL in Animal Models

In the above consideration of age-related changes in the human ACNS, a distinction was made—insofar as possible—between those intrinsic to the ACNS and those that result from peripheral degeneration. Animal models permit better

separation of these, especially mice and rats, wherein strains with differing degrees of age-related peripheral pathology can be compared.

6.1 Cochlear Nucleus

6.1.1 Structural and Neurochemical Alterations in Cochlear Nucleus

Studies led by Willott were among the first to exploit differences in age-related cochlear pathology to isolate peripheral influences on the aging ACNS (Willott 1991). Unlike B6 and some of the other strains introduced in the preceding text, CBA mice (both CBA/J and CBA/CaJ) lose hearing sensitivity slowly, at a rate comparable to the slowest progression rates of human ARHL, normalizing for lifespan. Willott's group examined the neuroanatomical aspects of these peripherally induced central effects. In B6 mice, neuron size, number, and packing density decline in the VCN, in concert with the loss of high-frequency inputs from the cochlea. Changes of this nature rarely occur in very old CBAs (Lambert and Schwartz 1982; Willott et al. 1987). Neurons of the VCN in aging B6 mice also show an increase in lipofuscin deposits, nucleoplasm pathologies, and nuclear invaginations (Briner 1989). These were most pronounced in high-frequency (dorsal) regions of the VCN, and more in multipolar cells than in bushy cells. In the dorsal cochlear nucleus (DCN), only layer III, which receives direct inputs from the auditory nerve, showed significant aging declines in B6, while the CBA mice DCN was relatively stable (Willott et al. 1992).

The DBA mouse strain shows even faster age-related peripheral hearing loss than B6, presumably due to a greater number of progressive deafness alleles (Erway et al. 1993). As one might predict, neuronal declines in the anteroventral cochlear nucleus (AVCN) occur faster in DBA than in B6 (Willott and Bross 1996). In a light microscopic investigation of octopus cell region of the VCN in CBAs and B6s, Willott and Bross (1990) observed significant age-related declines in octopus cell number, number of primary dendrites, and octopus cell volume. Increases in glial cell packing density were also noted.

Age-related neuronal changes do not always take the form of degradation. In a neuroanatomical investigation of the VCN in aging rats, Keithley and Croskrey (1990) observed that axonal terminations may become larger and more complex in nature, perhaps in an attempt by the system to compensate for the decline in neuron numbers with age.

In an ultrastructural examination of age-related changes in the AVCN of Fischer-344 rats (which show good preservation of hearing with age), Helfert and coworkers (2003) observed that the synaptic terminal specializations of distal dendrites of both excitatory and inhibitory neurons (likely glycinergic) decreased in both size and length. Age-related declines in glycine receptors therefore appear associated with reduced size of synapses. In contrast, the number of dendrites and density of synapse decline with age in the IC, but not in the AVCN. In experiments involving expression of α- and β-glycine receptor subunits in the AVCN of young adult and old rats, Helfert's group uncovered age-related

changes in the subunit gene expression. The α_1 and β subunits declined with age, while α_2 increased, thus altering the overall glycine receptor functionality (Krenning et al. 1998).

6.1.2 Physiological Alterations in Cochlear Nucleus

For animals with fairly good hearing late into life such as the CBA mouse and Fischer-344 rat, neural coding of sounds does not appear to change drastically with age. By contrast, B6 mice show age-dependent tonotopic map plasticity in the central nucleus of the IC and auditory cortex. Willott et al. (1991) compared aging physiological responses of neurons in the cochlear nucleus for B6s and CBAs. The slow, progressive hearing loss in CBAs was associated with minimal change in ventral cochlear nucleus thresholds for simple sounds such as pure tones. In contrast, AVCN neuron responses in B6s showed major changes in regions representing high frequencies (peripherally induced central effect) due to the loss of inputs from the cochlear base with age. In B6 mice, DCN cells showed much less drastic changes with age, in response properties such as tuning curves and response areas, most likely due to the significantly higher proportion of their inputs that come from noncochlear sources.

Age-dependent declines in cochlear outputs can also drive aging changes at the synaptic level in the AVCN. Using brain stem slice electrophysiology, Wang and Manis (2005) measured pre- and postsynaptic potentials for the AVCN end-bulb synapses in young adult and aging DBA and CBA mice. Both pre- and postsynaptic mechanisms were altered in aging DBAs showing severe peripheral hearing loss. Presynaptic changes included reduced transmitter release probability. Postsynaptic deficits included declines in mEPSC frequency, speed and amplitude (Fig. 6.7). Apparent synaptic abnormalities were not observed in young adult mice of either strain, or in old age CBAs with relatively good hearing.

Milbrandt and Caspary (1995) performed biochemical investigations of the glycine inhibitory system in the cochlear nucleus of Fischer-344 rats. They found evidence of age-related impairment of this inhibitory system, including reductions in binding properties of glycine receptors in both the AVCN and the DCN. The posteroventral cochlear nucleus (PVCN) did not manifest age declines, as the levels of glycine receptors in young adult rats were already low. Willott et al. (1997) performed similar studies in mice, utilizing immunocytochemical and biochemical techniques, and also found reductions in glycine-based inhibitory synaptic transmission in the DCN. For example, in 18 month old B6s with severe high-frequency hearing loss the number of glycine immunoreactive neurons and strychnine-sensitive glycine receptors declined significantly relative to younger B6s and old CBAs with good hearing. Caspary et al. (2005) delineated the functional effects of age-related reductions in the glycinergic inhibitory system in rats. Responses attributed to fusiform principal neurons were altered, such that rate-intensity functions grew at a faster rate in old rats. This finding is consistent with an age-related deficit in vertical cell on-best frequency inhibitory inputs to fusiform cells mediated by glycine.

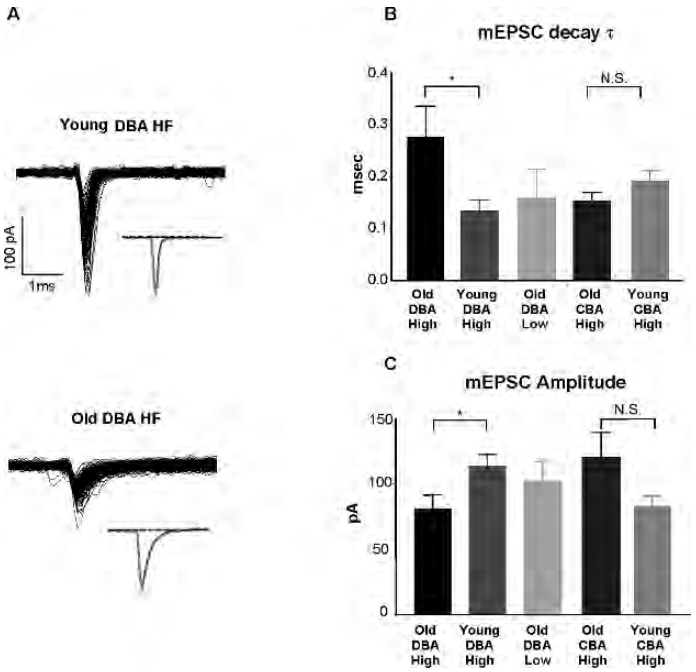

FIGURE 6.7. Spontaneous mEPSCs had slower decay time constant in hearing-impaired DBA bushy cells. (**A**) sample mEPSCs recorded from two bushy cells in HF regions from a young and an old DBA mouse. All detected mEPSCs were aligned to their onset. Insets: normalized average of the mEPSCs superimposed with the first-order exponential decay *(dark trace).* (**B**) decay time constants for young and old bushy cells in HF regions of DBA mice were significantly different. Decay time constants for all cells from normal hearing regions of the AVCN were comparable between old DBA and young CBA HF as well as old CBA HF cells. (**C**) spontaneous mEPSC amplitude was significantly different between hearing-impaired old DBA mice and young DBA mice. There were no statistical differences between the normal hearing low-frequency old DBA and the high-frequency young DBA cells, nor between the old CBA HF and the young CBA HF cells. HF = high frequency. (From Wang and Manis [2005], Fig. 6. Reprinted with permission.)

6.2 Inferior Colliculus

6.2.1 Structural and Neurochemical Alterations in Inferior Colliculus

Anatomical and neurochemical changes with age that have functional implications also occur at the level of the auditory midbrain, the inferior colliculus. Again utilizing the B6 and CBA strains, Willott et al. (1991) discovered that a major reorganization of the tonotopic map occurs in the IC of aging B6 mice. Regions expected to contain neurons tuned to high frequencies instead showed preferences for low frequencies, suggesting "rewiring" of these neurons to receive inputs from neurons in low frequency regions, where outputs from the

cochlear apex were still available. The IC in CBA mice showed no evidence of such dramatic age-related plasticity of neuronal responses.

In a series of biochemical and neuroanatomical investigations, Caspary et al. (1990) investigated age-related changes in the IC inhibitory system using the Fischer rat. The primary inhibitory neurotransmitter here that shapes complex sound responses in the ACNS is GABA. Using an antibody for GABA, it was found that the number of immunolabeled neurons in the ventrolateral central nucleus of the IC (high-frequency region) decreased with age. Basal levels and potassium ion-evoked effluxes of GABA from preparations of the central nucleus of the IC also diminished with age. By contrast, release of glutamate and aspartate (the main excitatory neurotransmitters in the IC), acetylcholine (another inhibitory transmitter), and the amino acid tyrosine, were stable with age.

Milbrandt et al. (1994) uncovered an age-related deficit in $GABA_B$ receptor binding using quantitative receptor binding assays. In this case, reductions were noted in the central nucleus, dorsal cortex and external nucleus, whereas nearby cerebellar tissue showed no such age-related changes and the rat IC volume was age stable. Perhaps as a compensation mechanism, $GABA_A$ receptors in the IC showed an upregulation with age (Milbrandt et al. 1996).

Utilizing quantitative immunogold electron microscopy procedures similar to their cochlear nucleus synaptic structure studies, Helfert's group explored the synaptic age-related changes in the IC (Helfert et al. 1999). Unlike the cochlear nucleus, the number of synaptic specializations for both excitatory and inhibitory terminals in the rat IC declined with age. These decreases were correlated with declines in dendritic size, and with synaptic density remaining relatively stable on the larger, surviving proximal dendrites. In a related investigation, Milbrandt et al. (1997) examined $GABA_A$ receptor subunit composition in the IC. Evidence was found for compensatory changes that enhanced responses to GABA in the subunits, despite an age-related decline in the number of synapses. In particular, the γ_1 protein subunit increased with age, while the α_1 declined (Caspary et al. 1999). Also noted was an age-linked upregulation of a GABA-mediated chloride influx that is likely a result of the age-related receptor subunit composition change. These enhancements may help compensate for the $GABA_B$ age deficits. A summary of IC changes in the GABA inhibitory system is given in Caspary et al. (1995) and Frisina (2001). It is still not clear how generalizable these findings in the rat are to other mammals, and it is enlightening to note that there are no age-related changes in GABA at the level of the cochlear nucleus (Banay-Schwartz et al. 1889; Raza et al. 1994).

6.2.2 Physiological Alterations in Inferior Colliculus

As discussed in the preceding text, starting in middle age humans typically experience deficits in auditory temporal processing that are manifested in declines in speech understanding. Auditory midbrain neurons of unanesthetized CBA mice show gap encoding properties very similar to auditory gap coding as measured behaviorally using inhibition of acoustic startle paradigms (Walton et al. 1997).

This gap coding at the level of the IC appears to decline with age. Specifically, the number of neurons having short gap thresholds is reduced. In addition, there is a strong tendency for IC single neurons and near-field evoked potentials to have longer gap recovery functions in the old CBAs, especially at moderate sound levels (Allen et al 2003). Tract-tracing studies utilizing horseradish peroxidase (HRP), demonstrated a significant age-related decline in contralateral inputs from all three divisions of the cochlear nucleus to the IC region shown to have the age-related neural temporal processing deficit (Frisina and Walton 2001).

The brain is highly plastic, in that intercellular connections are readily modified by life experiences. Although central plasticity is not generally associated with the birth of new cells, the capacity for forming and eliminating synapses presumably enhances the brain's adaptability, even into advanced age. Higher sensory centers do not become isolated and inactive following peripheral pathology, but instead undergo a shift in the balance of excitatory and inhibitory inputs to become retuned. This retuning leads to the overrepresentation of frequencies with a cochlear "drive" that remains somewhat intact, does not confer any clear advantage, and may induce tinnitus. Nevertheless, it is possible that some accompanying features of this plasticity assist the brain in reducing the impact of cochlear degeneration and the resulting loss of information.

7. Perceptual Effects of Peripheral Auditory Pathology

Age-related changes in the peripheral and ACNS take different forms and exert different effects on auditory perception. In animals as in humans, it is therefore important to distinguish between *direct* effects of aging on the auditory periphery and ACNS respectively, and the effects of peripheral pathology alone on the function of the ACNS. The latter is considered first. The most dramatic coding effects of peripheral pathology are expected to be elevated thresholds, reduced dynamic range (through loss of nonlinear compression) and reduced frequency resolution. Both sensory and strial ARHL would be expected to exert all three effects, through their impact on OHC-mediated active processes. Elevated thresholds will, of course, impair detection. In addition, broadening of tuning and reduced dynamic range will distort the representation of the stimulus spectrum. Sound localization may also be impaired (McFadden and Willott 1994). Neural ARHL presents a different set of predictions. Since the organ of Corti may not be directly affected, threshold sensitivity, dynamic range, and frequency tuning of individual surviving afferent neurons may be normal (depending on whether the IHC/afferent synapse is functioning normally). Central auditory activity associated with detection tasks may be little altered. However, peripheral neural redundancy (many neurons having a broad range of sensitivities and dynamic ranges innervating any given hair cell) may be important for preservation of the stimulus spectrum. Neural ARHL would reduce this useful redundancy, altering representation of the stimulus spectrum, and probably, detection of signals in noise.

8. Perceptual Effects of Central Auditory Pathology

8.1 Temporal Processing and Speech Reception

As introduced in Section 4.2, examination of human subjects with good auditory sensitivity (suggesting a relatively healthy cochlea) is a principal method for teasing out peripheral vs. central etiologies. Using gap detection methodologies, Gordon-Salant and Fitzgibbons (1993) and Schneider et al. (1994) found that aged subjects with reasonably good peripheral sensitivity nevertheless exhibited temporal processing problems. These problems became worse as the temporal processing task became more complex. Subsequent work by Frisina and co-workers implicated temporal processing deficits in speech-in-noise perceptual problems that can start in middle age (Frisina and Frisina 1997; Snell et al. 2002). Using a speech-in-noise perception task, they demonstrated that aged subjects required a higher signal-to-noise ratio for suprathreshold speech perception. When subject groups with different degrees of peripheral hearing loss were compared in terms of temporal processing or speech perception in background noise, it became clear that peripheral loss exacerbated the perceptual deficits in a manner correlated with the degree of hearing loss. In cases where the high frequency portion of the hearing loss exceeded 50–60 dB, the peripheral loss dominated the perceptual temporal- or speech-processing deficit.

8.2 Changes in Auditory Efferent Feedback

Using distortion product otoacoustic emissions (DPOAEs), Frisina and colleagues have shown that efferent feedback from the brain stem to the cochlea declines with age, starting in middle age (Kim et al. 2002). DPOAEs are sounds measured in the ear canal that reflect mechanical activity of outer hair cells. Because normal hearing sensitivity depends on nonlinear mechanical amplification by the OHCs, delivery of a two-tone stimulus (containing frequencies f_1 and f_2, with $f_2 > f_1$) to the normal cochlea will lead to the generation of a recordable complex tone. For diagnostic purposes, it is standard to isolate the cubic distortion product, $2f_1 - f_2$. Frisina's group measured the DPOAE amplitudes in quiet and in the presence of moderate intensity wideband noise presented to the contralateral ear. In healthy cochleae, such contralateral stimuli suppress the level of the recorded DPOAE through a process involving medial olivocochlear (MOC) efferent control of OHC responses. Comparison of DPOAE amplitudes with and without contralateral stimulation thus permits assessment of the strength of MOC feedback. A significant difference in the strength of the MOC effect was noted between young adults and middle-aged subjects at all frequencies tested. Lesser declines were observed between the middle-aged and old subjects.

It is useful, on discovering a clinical decline in humans, to assess whether the same phenomenon exists in animal models. Frisina's group performed parallel experiments assessing MOC function in CBA mice (Jacobson et al. 2003). The

mice showed a time course for age-linked MOC deterioration analogous to that in humans. Middle-aged animals showed a significant decline relative to the young adults, and further deficits in the efferent system were evident in old mice. As has been observed for humans (Varghese et al. 2005), wideband noise is more effective as a suppressing stimulus than narrowband signals such as pure tones.

8.3 Right Ear Advantage

Frisina's group also examined the effects of age on the peripheral "right ear advantage" (Tadros et al. 2005a). In most young adult listeners, the right ear shows a lower audiometric threshold and higher amplitude DPOAEs. Tadros et al. compared these measures in "golden ear" old subjects (audiograms in the normal range) to those in subjects with typical, sloping high-frequency hearing loss characteristic of presbycusis. The golden ear subjects tended to have lower thresholds and higher otoacoustic emission amplitudes in the right ear, whereas this situation was reversed in the presbycusis subject group (Fig. 6.8). These findings suggest that the peripheral right ear advantage is not lost with age per se, but rather is lost as a part of presbycusis hearing loss.

Jerger and colleagues conducted an elegant series of dichotic listening experiments to shed light on hemispheric changes in central auditory processing with age. Young adult observers with normal hearing typically perceive auditory information more accurately when presented to the right ear (Jerger and Martin 2004). The opposite is true for nonlinguistic materials. Jerger and Jordan (1992) and Jerger et al. (1994) provided convincing evidence that asymmetric cortical processing of speech materials increases with age, i.e., there is an increased right ear advantage in subjects with presbycusis. This robust finding was apparent for

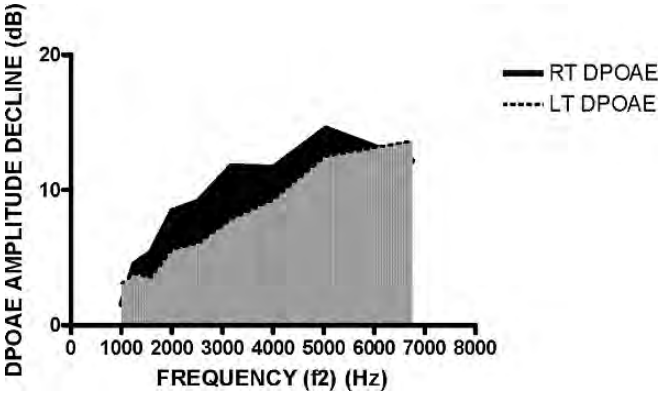

FIGURE 6.8. A significant difference in DPOAE amplitude decline, i.e., the normal hearing group relative to the presbycusis group. The right ear DPOAE decrement is more than the left ear decline especially in the f_2 = 2–5 kHz region. (From Tadros et al. [2005a], Fig. 3, with permission.)

measures of correct responses using speech material, as well as for reaction-time measurements of auditory performance (Jerger et al. 1995).

9. Cellular Aging Mechanisms in ARHL

Interfacing with the environment exposes all sensory epithelia to injury risk, because sensory stimuli contain energy that cannot all be usefully transduced. Just as excessive light injures the retina, excessive sound injures the organ of Corti. Unlike the retina, the organ of Corti is subject to both biochemical and mechanical injury in the course of its normal function. A lifetime of operating as an intermediary between the acoustic world and the brain inevitably yields injury that cannot be distinguished from ostensibly "pure" aging processes, so that aging-as-injury is a theme of this chapter.

Aging research in humans and animals has sought "longevity genes" and longevity-promoting environments and practices (Karasik et al. 2005; Sinclair 2005; Geesaman 2006; Harper et al. 2006). Alleles and environments that promote healthy aging and longevity—or the opposite—will probably often impact the apparent rate of ARHL. As in all tissues, however, the uniqueness of the cochlea arises from the activity of a unique set of genes. Some mutations in genes that govern hearing-specific structures and processes may therefore emerge as candidate "ARHL genes," actually meaning that certain alleles at particular loci can promote ARHL Most likely, all pro-ARHL alleles will be subject to strong environmental influences, as well as modulation by several other loci. Although no clear candidates have yet been identified in humans (Ates et al. 2005; Carlsson et al. 2005; Unal et al. 2005), possible ARHL-promoting genes and gene functions have been identified in mice. The following sections attempt to place ARHL into a wider context of cellular aging and the prevailing theories in this area.

9.1 Theories of Cellular Aging

Models of cellular aging can generally be placed into two categories: (1) Aging as a regulated "program" and (2) aging as dysregulation. The first category supposes that aging evolved as an adaptive process, and has largely fallen out of favor. It is far more likely that longevity is simply not selected *for* after peak reproductive age. Nevertheless, one type of "built-in" limitation, a limit on the total number of cell divisions in mitotically active cell populations, may yet be adaptive. Each time chromosomes are duplicated as part of mitosis, end segments called *telomeres* are shortened (von Zglinicki and Martin-Ruiz 2005). At some point, the telomeres become too short for duplication to occur. This mechanism of aging appears most relevant to tissues that emphasize cell replacement over repair, and may have evolved to help protect against cancer. While it may have some applicability to cochlear aging, its meaning for actual age-related *hearing loss* is less clear, as is considered further.

The notion of aging as dysregulation and loss of homeostasis forms the basis of several aging hypotheses having relevance to ARHL. Cellular changes with aging typically include crippling modifications to DNA, important housekeeping proteins, and membrane lipids (e.g., Fenech 1998; Squier and Bigelow 2000; Leutner et al. 2001). Why should this occur given that cells have a host of DNA repair enzymes, and are constantly making or importing new proteins and lipids? The most significant and debilitating changes may permanently alter the DNA "blueprints" themselves. Proteins made from corrupted genes may have reduced function and be subject to improper folding and aggregation (Squier 2001). Proteins whose job it is to promote proper folding (chaperones) and to degrade damaged proteins (proteasomes) are also subject to modification, so that nonfunctional proteins may accumulate.

9.2 Progressive Cell Injury by Oxidative Stress

If much of aging can be equated with injury, the question arises regarding the kinds of injury to which the cells are subject. Most likely is oxidative stress (see also Wangemann, Chapter 3). The evolution of aerobic (oxygen-based) metabolism made it possible for cells to increase their energy output, and their range of activities. Oxygen is useful precisely because of its ability to break down carbon–carbon and carbon–hydrogen chemical bonds, the types of bonds that form biomolecules. This ability, however, might also present a problem. Cells use oxygen to synthesize metabolic intermediates and to fuel energy production, but must avoid being oxidized themselves. Inevitably, some oxidative attack on cellular DNA, proteins, and lipids does occur and is exacerbated by nearly any type of environmental stress. The observation that most injury to cells appears to be oxidative led to the Free Radical Theory of Aging, first proposed by Harman (1956), which asserts that aging is basically progressive oxidation. Aerobic cells have evolved to fend off oxidative attack in several ways. First, key reactions involving oxygen are quarantined to the mitochondrion. Inevitably, however, reactive oxygen-containing molecules (also known as reactive oxygen species or ROS) "escape" the intended reactions and boundaries. Cells then reduce oxidative injury by antioxidants, which either catalyze reactions that remove ROS or attenuate the activity of ROS. The Free Radical Theory has found much support, and currently provides the major framework for aging research (Fenech 1998; Squier and Bigelow 2000; Leutner et al. 2001; Barda 2002; Sinclair 2005; Hulbert et al. 2006). Oxidative modifications to cell constituents have detectable biochemical "signatures" for localization and semiquantitation, and studies have shown age-related increases in such changes in a host of tissues. Consequently, dietary antioxidants both decrease age-related infirmity and increase lifespan in animals. Moreover, treatments that increase lifespan, such as caloric restriction, also bolster antioxidant defenses and reduce oxidative tissue injury.

Experiments in humans and animals support the contention that the Free Radical Theory is applicable to ARHL. Cochlear injury caused by noise, ototoxins, and ischemia involves oxidative stress (see Henderson, Hu, and Bielefeld, Chapter 7 and Rybak, Talaska, and Schacht, Chapter 8 on noise-induced and drug-induced hearing loss, respectively). Oxidative modification to DNA, proteins, and lipids of cochlear sensory cells is increased during aging (Jiang et al. 2006). The inactivation of genes encoding antioxidant enzymes SOD1 and glutathione peroxidase (GPx1) exacerbates apparent age-related cochlear pathology such as loss of hair cells and neurons, as well as thinning of stria vascularis (Ohlemiller et al. 1999, 2000; McFadden et al. 1999, 2001; Keithley et al. 2005). Interestingly, deficiency of SOD1 and GPx1 does not appear to shorten lifespan. Impairment of these critical and widely expressed antioxidant enzymes might be expected to promote broad pro-aging effects, and to decrease longevity. The narrower effects that are observed may testify to the special susceptibility of sensory epithelia to oxidative injury. Consistent with an involvement of oxidative stress in these pathologies, applications of antioxidants such as glutathione, D-methionine, and *N*-acetylcysteine reduce noise and ototoxic injury (reviews: Forge and Schacht 2000; Le Prell et al. 2006), and dietary application of vitamin E, vitamin C, or L-carnitine slow the progression of cochlear degeneration and hearing loss (Seidman 2000; Derin et al. 2004; Takumida and Anniko 2005; Le and Keithley 2006).

9.3 Mitochondrial Viability as a Key Factor in Aging

Mitochondria are both key targets of age-associated oxidative injury, and key mediators of aging effects on cells (Sastre et al. 2000; Kujothet al. 2005). Uniquely among intracellular organelles, mitochondria house their own DNA. This DNA codes for many essential components of energy production, but not for protective or repair components as nuclear DNA does. Damage to mitochondrial DNA also means that new mitochondria will carry the same errors, as new mitochondria come from replication of the old. Finally, as stated earlier, reactions carried out in mitochondria create most of the cell's ROS, and ROS production may be exacerbated in compromised mitochondria. All of these factors may combine to promote the accumulation of DNA errors within individual mitochondria, so that overall energy production is reduced, and the function of the entire cell is impaired. A related view of aging, known as the Mitochondrial Clock Theory (see Seidman 2000), is perhaps a corollary to the Free Radical Theory. Accumulation of mitochondrial DNA mutations with age has been observed in essentially all tissues including the cochlea (Bai et al. 1997; Seidman et al. 2002; Pickles 2004;) and can be reduced both by antioxidants and by caloric restriction (Seidman 2000). Medical conditions that impact cochlear blood flow and possibly ARHL (see later), also promote mitochondrial DNA mutations (Dai et al. 2004).

9.4 Calcium Dysregulation

Calcium is a critical regulator of cellular events (see Wangemann, Chapter 3). Its levels normally remain very low in cytoplasm and in extracellular fluids, so that minute changes can modulate specialized functions such as transduction in stereocilia and neurotransmitter release (e.g., Chan and Hudspeth 2005; Keen and Hudspeth 2006), as well as fundamental functions such as growth, division, and death (Lu and Means 1993; Krebs 1998). Major cytoplasmic proteins that buffer calcium or bind calcium for signaling include calmodulin, calbindin, parvalbumin, and calretinin (Lu and Means 1993; Schwaller et al. 2002). Because of the prominence of Ca^{2+} in many vital processes, it is not surprising that dysregulation of calcium may contribute to cellular aging (Squier and Bigelow 2000; Crompton 2004; Toescu 2005). Disruption of calcium homeostasis is part of the mechanism of excitotoxicity, and may be among the causes of neural ARHL (Lang et al. 2006a). In addition, the *Cdh23* gene locus modifies other loci related to calcium, such as the one encoding plasma membrane Ca^{2+}-ATPase 2 (*Pmca2*) (Davis et al. 2003). Thus, the sensory ARHL-like pathology associated with the $Cdh23^{ahl}$allele may in part reflect calcium dysregulation.

Age-related changes in ACNS function also involve changes in calcium regulation. Zettel et al. (1997) examined changes in intracellular calcium binding proteins in the region of the IC shown by Walton's group to undergo age-related decline in temporal processing. In both CBA and B6 strains, calbindin levels declined with age. However, calretinin exhibited upregulation with age in CBA mice. To test whether this upregulation was strain-dependent or activity-dependent, Zettel et al. (2001) deafened young adult CBA mice by cochlear ablation and examined changes in calretinin immunochemistry in the IC with aging. Control CBAs showed upregulation of calretinin with aging, but the deafened CBAs did not, supporting the idea that maintenance of neuronal activity in IC (through preservation of cochlear function) is important for calretinin regulation. Subsequent work in B6 mice by the same group (O'Neill et al. 1997) also revealed an age-related decline in calbindin-labeled neurons in the medial nucleus of the trapezoid body.

Canlon and colleagues (Idrizbegovic et al. 2001a,b) examined age-related changes in calcium-binding proteins in the cochlear nucleus of CBA mice. The percentage of neurons in the DCN staining for calbindin, calretinin, and parvalbumin was *upregulated* with age for ages up to 29 months. The age-related upregulation of calretinin and parvalbumin was correlated with the degree of peripheral hearing loss, as measured by inner and outer hair cell loss and spiral ganglion cell loss, suggesting peripherally induced central effects. Quantitative stereology using optical fractionation to obtain total neuron counts in PVCN and DCN revealed that the total number of PVCN neurons remained constant with age, whereas DCN cell numbers declined. Only parvalbumin showed an age-related upregulation in the PVCN.

Subsequent investigations by the same group contrasted the changes in the CBA cochlear nucleus with those in B6. Like CBA mice, B6 showed age-related *upregulation* of calbindin and parvalbumin in the DCN and PVCN for ages

up to 30 months (Idrizbegovic et al. 2003). Also as in CBA, calbindin and parvalbumin were correlated with peripheral hair cell and neurons loss in DCN and PVCN. The upregulation was accompanied by age-related declines in the absolute number of neurons in the DCN and PVCN (Idrizbegovic et al. 2004).

9.5 Limitations on Cell Repair and Replacement

Tissues that have sustained some degree of injury might compensate for cell loss by replacement of constituent cells by mitosis. Only a few cell types are normally replaced in the auditory system of adult mammals. Neurons are not replaced, nor are cochlear hair cells, nor most cells of the organ of Corti. This limitation places a premium on protective and repair capabilities. Clumping of hair cell stereocilia and deformation of the cuticular plate can be seen in aged humans (Scholtz et al. 2001), suggesting that normal bundle renewal is impaired in old hair cells, yet these nonfunctional hair cells may survive for some time. Supporting cells with pyknotic nuclei and dark cytoplasm are frequently observed in the organ of Corti of old mice (Ohlemiller and Gagnon 2004b). It is not clear whether cells showing these signs die and are replaced, or whether supporting cell pathology can also promote hair cell loss.

Within the cochlea, cell replacement appears limited to fibrocytes of the lateral wall and intermediate cells and marginal cells of the stria vascularis (Conlee et al. 1994; Yamashita et al. 1999; Dunaway et al. 2003; Hirose et al. 2005). Still these decrease in number with age (Wright and Schuknecht 1972; Ichimiya et al. 2000; Ohlemiller 2006), perhaps as a result of limits on proliferative capacity such as telomere status. Some new fibrocytes in ligament may derive from bone marrow (Lang et al. 2006b), so that it is not clear why there is net loss of fibrocytes with age. Both strial cells and fibrocytes in spiral ligament and limbus serve a distributed function, and are initially present in excess, as indicated by the fact that substantial numbers of these can be lost without any effect on hearing. While limits on strial cell replacement may play a role in strial ARHL (Ohlemiller 2006), it is at present not clear that ligament pathology is a significant factor in ARHL.

10. Risk Factors Affecting ARHL

The prevalence of clinically defined ARHL in the very old, while high, is not 100%. Although it appears in all societies, it occurs more frequently in industrial cultures than in nonindustrial cultures (Rosen et al. 1962). Such evidence argues that much of ARHL is influenced by the interplay between pro-ARHL alleles (or pro-aging alleles) and environment. No behavior, event, or environment carries a fixed degree of ARHL risk. Rather, the risk will depend on unknown alleles carried by the individual. Until such alleles are identified, the best strategy is to minimize environmental risks, which take many forms.

10.1 Noise and Ototoxins

Environmental risk factors for apparent ARHL include acute or chronic exposure to noise, ototoxic medications, industrial solvents, or combinations of these (Gilad and Glorig 1979b; Rosenhall et al. 1993; Rosenhall and Pedersen 1995; Toppila et al. 2001; Fransen et al. 2003; Fechter 2004). Assaults by these agents appear to promote largely oxidative injury that primarily injures hair cells (see Henderson, Hu, and Bielefeld, Chapter 7; Rybak, Talaska, and Schacht, Chapter 8). Note that the intention here is not to equate cochlear noise and ototoxic injury with ARHL, or to suggest that the cellular pattern of injury is exactly the same in all three cases although there are intriguing similarities. Both noise and ototoxin exposure can, for example, cause permanent strial injury (e.g., Ulehlova, 1983; Garetz and Schacht 1996; Hirose and Liberman 2003). They mostly do not, however, cause permanent EP reduction, and thus would not be expected to draw a diagnosis of strial ARHL. There is likewise no compelling evidence that ototoxins promote primary neural loss sufficient to bring a diagnosis of neural ARHL. By contrast, early noise exposure may yield neural ARHL (Kujawa and Liberman 2006). However, because the principal targets of noise and ototoxins will be hair cells, the diagnosis can often be confused with sensory ARHL.

10.2 Lifestyle and Risk of Vascular Pathology

Proper function of the cochlea, particularly the lateral wall, is energy intensive, and likely to be vulnerable to any restriction of blood flow. Accordingly, the role of vascular insufficiency has long been a prominent topic in ARHL research (reviews: Gilad and Glorig 1979b; Nakashima et al. 2003). Obesity and conditions to which it may lead (hyperlipidemia, hypercholesterolemia, hypertension, hyperhomocysteinemia, hyperlipoproteinemia, and cardiovascular disease) have all been implicated in ARHL (Rosen et al. 1970; Spencer 1973; Drettner et al. 1975; Tachibana et al. 1984; Axellson and Lindgren 1985; Pillsbury 1986; Saito et al. 1986; Sikora et al. 1986; Suzuki et al. 2000; Satar et al. 2001; Fransen et al. 2003). Poor health habits with regard to exercise, smoking, and diet may also be risk factors for ARHL insofar as they impact vascular health, tissue oxygenation, and diabetes risk (see later) (Rosenhall et al. 1993; Cruickshanks et al. 1998; Torre et al. 2005; Uchida et al. 2005), although probably only as part of a spectrum of conditions of aging. While it has been suggested that the most immediate cochlear target of vascular pathology is likely to be the stria, limited observations of affected human and animal cochleae suggest broad tissue degeneration, and no special relationship to strial ARHL.

10.3 Early Exposure to Stress

Environment extends to the prenatal environment. It has been hypothesized that prenatal stress can “program” individuals to pathology that resembles accelerated

aging, or to possible risk factors for age-related pathology such as hypertension and cardiovascular disease (Barrenas et al. 2003). Suggested mechanisms involve "redeployment" of resources by the fetus to favor some tissues and organs, leaving others with fewer stem cells or poorly vascularized, and permanent alterations in endocrine function (Barker 1998). One result of such events may be sensorineural hearing loss associated with shortened stature in adulthood (Barrenäs et al. 2005). A potentially related finding is that exposure of prenatal rats to glucocorticoid stress hormones increases susceptibility in the young adult to NIHL possibly due to an overall increased vulnerability to oxidative stress (Canlon et al. 2003).

10.4 Mineralocorticoid Levels

Aging is often accompanied by medical comorbidities such as decreases in hormonal levels. A decline in levels of aldosterone, a mineralocorticoid produced by the adrenal cortex, may affect ionic balance, partly by its actions on Na^+, K^+-ATPase and the K^+, Na^+, Cl^- cotransporter. Because these enzymes are highly expressed in the cochlear lateral wall and are critical to ion regulation in the cochlea, aldosterone may participate in the regulation of the EP. Alternatively, it may operate at a systemic level by averting hypertension or reducing inflammation. Blood aldosterone titer probably reflects both genetic and environmental influences. Frisina's group examined the relation between aldosterone levels and age-related hearing loss in aged human subjects who had good hearing and showed good health overall (Tadros et al. 2005b). Based on standard audiometric criteria, the subjects were classified into three groups: golden ear (audiometric thresholds in the normal range), mild/moderate hearing loss, and severe loss. Serum aldosterone levels were significantly different between the groups, with the golden ears showing the highest aldosterone, the mild/moderate group next, and the subjects with severe hearing loss the least amount of aldosterone (Fig. 6.9). Interestingly, all aldosterone levels were within normal clinical limits. Regression analyses showed significant correlations between aldosterone levels, pure tone thresholds, and hearing-in-noise test (HINT) scores. These results suggest that aldosterone may be protective against presbycusis, as has been found for autoimmune hearing loss (Trune et al. 2006). At present there is no direct evidence to indicate which cochlear structures are preserved or affected.

10.5 Diabetes Mellitus

Non-insulin-dependent (type 2, adult onset) diabetes mellitus often appears as a condition of aging, frequently as a complication of obesity. In middle age, diabetes also produces multisystemic pathology that mimics aspects of aging (Geesaman 2006). Chronically elevated plasma glucose promotes malconformation and aggregation of proteins in all tissues, yet with particularly deleterious

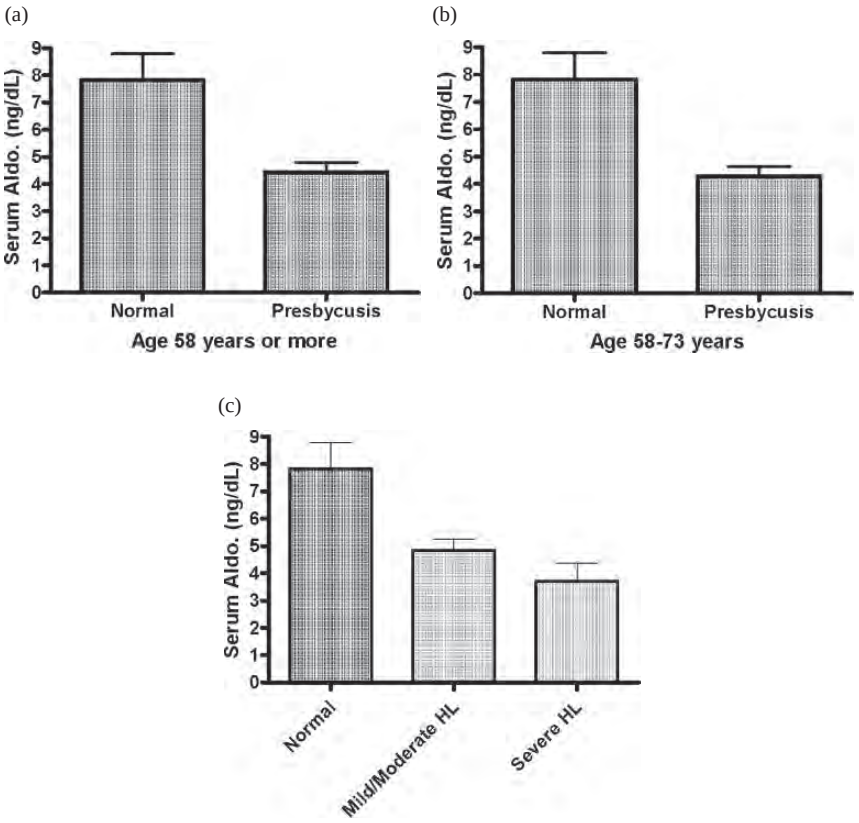

FIGURE 6.9. (**A**) A significant difference in serum aldosterone concentration was found between normal hearing and presbycusic groups, with a higher concentration in the normal hearing group. (**B**) A significant difference in serum aldosterone concentrations was found for the 58- to 73-year-old groups of normal hearing subjects and presbycusic subjects, with higher concentrations in the normal hearing group. This analysis eliminated the age factor. (**C**) A significant difference in serum aldosterone concentrations was found between normal hearing and both mild/moderate and severe presbycusic groups.(From Tadros et al. [2005b], Fig. 1. Reprinted with permission.)

consequences for the microvasculature. The most wide-ranging pathologies of diabetes therefore appear mediated by microangiopathy. Both type 1 (juvenile) and type 2 diabetes promote hearing loss and cochlear pathology in humans (Wackym and Linthicum 1986; Fukushima et al. 2005) and animals (Rust et al. 1992; Raynor et al. 1995; Ishikawa et al. 1995). Type 2 diabetes has been proposed as a cause of ARHL, but the evidence for this is mixed (Malpas et al. 1989; Ma et al. 1998; Ologe et al. 2005; Vaughan et al. 2005). To clarify whether presbycusis is accelerated in aged type 2 diabetics, a group of type 2 diabetics older than the age of 60 years were compared with a group of age- and sex-matched controls (Frisina et al. 2006). Both groups were otherwise

healthy and had no history of major health or hearing problems. Audiometric thresholds, otoacoustic emission levels, and speech thresholds revealed deficits in the diabetic group, with the right ear showing a more severe loss relative to the left (Fig. 6.10). Tests involving the ACNS, such as suprathreshold gap detection and HINT scores, also exposed relative deficits in the diabetic group. These findings support a causal link between type 2 diabetes and both peripheral and central aspects of ARHL.

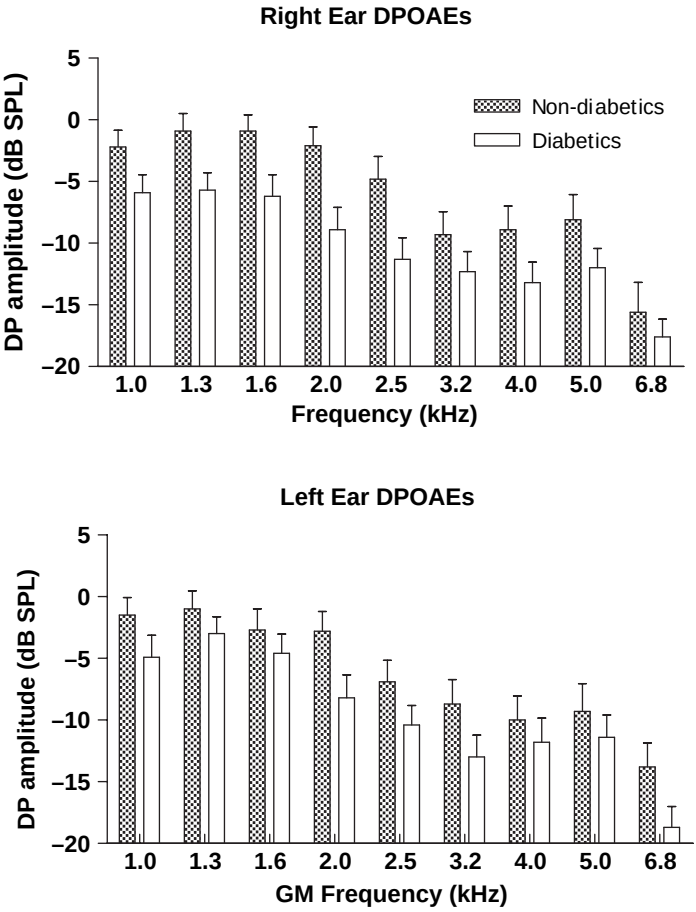

FIGURE 6.10. At all frequencies, DPOAEs were smaller for diabetics relative to non-diabetics. Like the threshold measures presented in the previous figures, the right ear was more affected than the left. ANOVA showed significant main effects of subject group (Right: $p < 0.0001$, $F = 31.1$, df= 1; Left: $p < 0.0001$, $F = 15.2$, df = 1). Interactions and subject group Bonferroni post-hoc analyses were not significant, except for the right ear at 2 kHz: $p < 0.05$, t = 2.82, df = 1. GM = geometric mean of f_1 and f_2. Error bars are SEM. (From Frisina et al. [2006], Fig. 3. Reprinted with permission.)

10.6 Caloric Restriction

By far the single best supported anti-aging regimen is caloric restriction (CR), chronic reduction of normal caloric intake by 10% to 20% (review: Sinclair 2005). In species ranging from flies and worms to humans, CR extends lifespan and reduces age-related pathology. Studies seeking the mechanism(s) by which CR delivers its impressive benefits have yielded many suspects, including slowing of metabolism, enhanced immune responses, decreased ROS production, enhanced ROS defenses, increased overall stress resistance, decreased circulating insulin levels, increased respiration (with decreased glycolysis), and reduced circulating thyroid hormones. Of more than 350 genes whose activity is significantly altered by CR in mice, at least 29 were also upregulated in the long-lived Snell dwarf mouse strain (Miller et al. 2002). However, there is little clear overlap among these 29 genes and genes shown to be upregulated in long-lived humans (Karasik et al. 2005). Moreover, different long-lived mouse strains show different subsets of the characteristics mentioned above (Harper et al. 2005). The most common gene profiles and characteristics shared by calorically restricted and long-lived organisms have led to the "Hormesis" hypothesis (Sinclair 2005), which proposes that enhanced stress resistance is the key to healthy aging. This key to longevity complements the Free Radical Theory of aging. Caloric restriction can slow the progression of ARHL in mice (Sweet et al. 1988; Park et al. 1990; Someya et al. 2006), presumably as part of an overall slowing of the aging process. The principles underlying CR are therefore clearly relevant to ARHL.

11. Prevention and Treatment of ARHL

11.1 Altering Behavior

As outlined in the preceding text, there are several behavioral/environmental factors whose association with added ARHL risk is plausible. Excessive noise, ototoxins, and smoking are clearly to be avoided. Conversely, behaviors that preserve overall health against aging (appropriate diet and exercise) very likely serve to preserve hearing as well.

11.2 Pharmacologic Approaches

Calcium channel blockers may be protective against ARHL (Mills et al. 1999), and dietary antioxidants have proven partially effective against age-related cochlear changes (Seidman 2000; Derin et al. 2004 ; Takumida and Anniko 2005; Le and Keithley 2006). A possible limitation to the ultimate efficacy of antioxidant therapy is that redox homeostasis comprises a complex web of checks and balances (see Wangemann, Chapter 3). When present at low concentrations, ROS perform important signaling functions. Exogenous agents, be they pro- or antioxidant, may disrupt this balance (Ohlemiller 2003).

Several drugs reproduce some of the positive effects of caloric restriction, including 2-deoxyglucose, metformin (and its analog phenformin, both used to treat diabetes), and resveratrol (Sinclair 2005). The first two compounds present their own health risks, and are not advocated as an anti-aging therapy. Resveratrol increases levels of SIRT1, a key longevity-promoting protein in mammals. It is one of the classes of sirtuin-activating compounds (STACS), which show tremendous promise in alleviating age-related pathology.

Another approach to protection is external stress applied in a controlled and noninjurious manner. This phenomenon, known as "preconditioning," has been demonstrated in brain, heart, and retina (Dirnagl et al. 2003; Ran et al. 2005; Whitlock et al. 2005). The types of stresses that may be protective include mild ischemia, hypoxia, and heat shock. Protection against cochlear noise injury has been linked to preconditioning by noise exposure, restraint (Wang and Liberman 2002), heat shock (Yoshida et al. 1999), and hypoxia (Gagnon et al. 2006). Protection by prior noise exposure includes both "noise conditioning" in which the initial exposure is noninjurious by itself (Niu and Canlon 2002), as well as "toughening," in which there is some permanent injury from the initial exposure (Hamernik et al. 2003). Protection against some ARHL as caused by the *Cdh23*^{ahl} allele in mice is also provided by "acoustic augmentation," wherein mice are raised in moderate background noise (Willott and Turner 1999). These protective regimens may be impractical to apply clinically, but the innate processes they engage may be amenable to pharmacologic manipulation. Mediators of preconditioning in brain and retina include transcription factors such as hypoxia-inducible factor 1α (HIF-1α), heat shock factor 1 (HSF-1), and NF-κB. Their gene targets may include vascular endothelial growth factor and erythropoietin, which may promote vascular remodeling and exert trophic effects (Prass et al. 2003; Brimes and Cerami 2005). HIF-1α can be upregulated pharmacologically, and erythropoietin has been applied with therapeutic effects (Brimes and Cerami 2005). The effects of protective manipulations may also be genetically modulated, as shown for hypoxic preconditioning against NIHL in mice (Gagnon et al. 2006). People who show weak preconditioning effects often may also adapt poorly to environments that pose chronic stress to the cochlea, and have higher risk for NIHL and apparent ARHL.

11.3 Restoration of Lost Hearing

The best strategy against ARHL is clearly to prevent it. Until that is possible, restoration of hearing will remain the principal intervention, and this currently means hearing aids and cochlear implants. Digital hearing aids are far advanced over their predecessors and present a wide range of user options, tailored to specific acoustic environments. Cochlear implants are increasingly recommended to older adults, and appear to promote the survival of afferent neurons after loss of their hair cell targets.

True restoration of lost cells, however, poses a tremendous challenge. Loss of any cell population in the cochlea may trigger irreversible changes in other cell

types. For example, sensory ARHL may begin with hair cell loss, but ultimately may be associated with replacement of the entire organ of Corti with a single undifferentiated cell layer. Currently most strategies for restoration are aimed at specific cell types, typically hair cells and neurons (see Raphael and Heller, Chapter 11). There are, however, many cell types in the organ of Corti and lateral wall whose functions and interdependence for survival are incompletely understood, and in some forms of ARHL the primary defect may lie in these cells. Successful gene therapies may require reprogramming of many types of the cells that make up the cochlear environment.

12. Questions for Future Research

Given the recent advances in areas of neuroregeneration and stem cell therapy, the future lies in biomedical interventions against ARHL. Generally, it would be very beneficial to start coordinating aging research across modalities, to focus in on a dietary regimen, including supplements as appropriate, to optimize sensory functioning in the elderly. However, interventions to the benefit of hearing must be scrutinized for their effect on vision, balance, touch, or taste. Agents to counteract the effects of the declining GABA (inferior colliculus) and glycine (cochlear nucleus) inhibitory systems in the auditory brain stem might embody such an example, where the generality of this phenomenon needs to be verified for the other senses.

Capitalizing on the presence of stem cells that are present in the inner ear and brain will require the development of gene therapy and/or pharmacological triggers to stimulate the differentiation into specialized cells of the cochlea or ACNS. The repair process may be more preventative or aimed at slowing down age-related changes. In contrast, restoration and regeneration are more important for full-fledged presbycusis, both peripheral, high-frequency hearing loss and central-understanding speech-in-background noise at suprathreshold, conversational levels.

Acknowledgments. R.D.F. was supported by NIH grants NIA P01 AG09524 from the National Institute on Aging, NIDCD P30 DC05409 from the National Institute on Deafness & Communication Disorders, and the Int. Ctr. Hearing Speech Res., Rochester NY. K.K.O. was supported by WU Medical School Dept. Otolaryngology, NIH P30 DC004665, and R01 DC08321. Thanks to P.M. Gagnon for assistance with figures.

References

Allen PD, Burkard RF, Ison JR, Walton JP (2003) Impaired gap encoding in aged mouse inferior colliculus at moderate but not high stimulus levels. Hear Res 186:17–29.

Ates NA, Unal M, Tamer L, Derici E, Karakas S, Ercan B, Camdevirin H (2005) Glutathione *S*-transferase gene polymorphisms in presbycusis. Otol Neurotol 26: 392–397.

Axellson A, Lindgren F (1985) Is there a relationship between hypercholesterolemia and noise-induced hearing loss? Acta Otolaryngol 100:379–386.

Bai U, Seidman MD, Hinojosa R, Quirk WS (1997) Mitochondrial DNA deletions associated with aging and possibly presbycusis: A human archival temporal bone study. Am J Otol 18:449–453.

Banay-Schwartz, M, Lajtha A, Palkovits M.(1889) Changes with aging in the levels of amino acids in rat CNS structural elements II. Taurine and small neutral amino acids. Neurochem Res 14:563–570.

Bao J, Lei D, Du Y, Ohlemiller KK, Beaudet AL, Role LW (2005) Requirement of nicotinic acetylcholine receptor subunit β*2* in the maintenance of spiral ganglion neurons during aging. J Neurosci 25:3041–3045.

Barda G (2002) Rate of generation of oxidative stress–related damage and animal longevity. Free Radic Biol Med 33:1167–1172.

Barker DJP (1998) In utero programming of chronic disease. Clin Sci 95:115–128.

Barrenäs M-L, Bratthall A, Dahlgren J (2003) The thrifty phenotype hypothesis and hearing problems. Br Med J 327:1199–1200.

Barrenäs M-L, Bratthall A, Dahlgren J (2005) The association between short stature and sensorineural hearing loss. Hear Res 205:123–130.

Bohne BA, Gruner MM, Harding GW (1990) Morphological correlates of aging in the chinchilla cochlea. Hear Res 48:79–91.

Borg E (1983) Delayed effects of noise on the ear. Hear Res 9:247–254.

Bredberg G (1968) Cellular pattern and nerve supply of the human organ of Corti. Acta Otolaryngol (Suppl)236:1–135.

Brimes M, Cerami A (2005) Emerging biological roles for erythropoietin in the nervous system. Nat Neurosci 6:484–494.

Briner W, Willott JF (1989) Ultrastructural features of neurons in the CB57BL/6J mouse anteroventral cochlear nucleus: young mice versus old mice with chronic presbycusis. Neurobiol Aging 10:295–303.

Brody H (1955) Organization of the cerebral cortex: III. A study of aging in the human cerebral cortex. J Comp Neurol 102:511–556.

Cable J, Jackson IJ, Steel KP (1993) Light (B^{lt}), a mutation that causes melanocyte death, affects stria vascularis function, in the mouse inner ear. Pigment Cell Res 6:215–225.

Canlon B, Erichsen S, Nemlander E,Chen M, Hossain A, Celsi G, Ceccatelli S (2003) Alterations in intrauterine environment by glucocorticoids modifies the developmental program of the auditory system. Eur J Neurosci 17:2035–2041.

Carlsson P-I,VanLaer L, Borg E, Bondeson M-L, Thys M, Fransen E, Van Camp G (2005) The influence of genetic variation in oxidative stress genes on human noise susceptibility. Hear Res 202:87–96.

Caspary DM, Raza A, Armour BAL, Pippin J, Arneric SP (1990) Immunocytochemical and neurochemical evidence for age-related loss of GABA in the inferior colliculus: implications for neural presbycusis. J Neurosci 10:2363–2372.

Caspary DM, Milbrandt, JC, Helfert RH (1995) Central auditory aging: GABA changes in the inferior colliculus. Exp Gerontol 30:349–360.

Caspary DM, Holder TM, Hughes LF, Milbrandt JC, McKernan RM, Naritoku DK (1999) Age-related changes in GABA a receptor subunit composition and function in rat auditory system. Neuroscience 93:307–312.

Caspary DM, Schatteman TA, Hughes, LF (2005) Age–related changes in the inhibitory response properties of dorsal cochlear nucleus output neurons: role of inhibitory inputs. J Neurosci 47:10952–10959.

Chan DK, Hudspeth AJ (2005) Ca^{2+} current-driven nonlinear amplification by the mammalian cochlea in vitro. Nat Neurosci 8:149–155.

Chen MA, Webster P, Yang Y, Linthicum FH (2006) Presbycusic neuritic degeneration within the osseous spiral lamina. Otol Neurotol 27:316–322.

Chisolm TH, Willott JF, Lister JJ (2003) The aging auditory system: anatomic and physiologic changes and implications for rehabilitation. Int J Audiol 42:2S3–2S10.

Conlee JW, Gerrity LC, Bennett ML (1994) Ongoing proliferation of melanocytes in the stria vascularis of adult guinea pigs. Hear Res 79:115–122.

Covell WP, Rogers JB (1957) Pathologic changes in the inner ear of senile guinea pigs. Laryngoscope 67:118–129.

Crompton M (2004) Mitochondria and aging: a role for the permeability transition? Aging Cell 3:3–6.

Cruickshanks KJ, Klein R, Klein BEK, T.L. W, Nondahl DM, Tweed TS (1998) Cigarette smoking and hearing loss. JAMA 279:1715–1719.

Dai P, Yang W, Jiang S, Gu R, Yuan H, Han D, Guo W, Cao J (2004) Correlation of blood supply with mitochondrial DNA common deletion in presbycusis. Acta Otolaryngol 124:130–136.

Davis RR, Newlander JK, Ling X–B, Cortopassi GA, Kreig EF, Erway LC (2001) Genetic basis for susceptibility to noise–induced hearing loss in mice. Hear Res 155:82–90.

Davis RR, Kozel P, Erway LC (2003) Genetic influences in individual susceptibility to noise: a review. Noise Health 5:19–28.

Delprat B, Ruel J, Guitton MJ, Hamard G, Lenoir M, Pujol R, Puel JL, Brabet P, Hamel CPJA (2005) Deafness and cochlear fibrocyte alterations in mice deficient for the inner ear protein otospiralin. Mol Cell Biol 25:847–853.

Derin A, Agirdir B, Derin N, Dinc O, Guney K, Ozcaglar H, Kilincarslan S (2004) The effects of L–carnitine on presbycusis in the rat model. Clin Otolaryngol 29:238–241.

Di Girolamo S, Quaranta N, Picciotti P, Torsello A, Wolf F (2001) Age-related histopathological changes of the stria vascularis: an experimental model. Audiology 40:322–326.

Dirnagl U, Simon RP, Hallenbeck JM (2003) Ischemic tolerance and endogenous neuroprotection. Trends Neurosci 26:248–254.

Drettner B, Hedstrand H, Klockhoff I, Svedberg A (1975) Cardiovascular risk factors and hearing loss. Acta Otolaryngol 79:366–371.

Dunaway G, Mhaskar Y, Armour G, Whitworth C, Rybak LP (2003) Migration of cochlear lateral wall cells. Hear Res 177:1–11.

Erway Lc, Willott JF, Archer JR, Harrison DE (1993) Genetics of age–related hearing loss in mice: I. Inbred and F1 hybrid strains. Hear Res 65:125–132.

Erway LC, Shiau Y–W, Davis RR, Kreig EF (1996) Genetics of age-related hearing loss in mice. III. Susceptibility of inbred and F1 hybrid strains to noise-induced hearing loss. Hear Res 93:181–187.

Fechter LD (2004) Promotion of noise–induced hearing loss by chemical contaminants. J Toxicol Appl Environ Health A 67:727–740.

Felder E, Schrott-Fischer A (1995) Quantitative evaluation of myelinated nerve fibers in cochlea of humans with age-related high-tone hearing loss. Hear Res 91:19–32.

Felder E, Kanonier G, Scholtz A, Rask-Andersen H, Schrott-Fischer A (1997) Quantitative evaluation of cochlear neurons and computer-aided three-dimensional reconstruction

of spiral ganglion cells in humans with a peripheral loss of nerve fibers. Hear Res 105:183–190.
Felix H, Pollak A, Gleeson MJ, Johnsson L–G (2002) Degeneration pattern of human first-order cochlear neurons. Adv Otorhinolaryngol 59:116–123.
Fenech M (1998) Chromosomal damage rate, aging, and diet. Ann NY Acad Sci 854: 23–26.
Ferraro JA, Minckler J (1977) The human lateral lemniscus and its nuclei. Brain Lang 4:156–164.
Fitzgibbons PJ, Gordon-Salant S (1996) Auditory temporal processing in elderly listeners. J Am Acad Audiol 7:183–189.
Forge A, Schacht J (2000) Aminoglycoside antibiotics. Audiol Neuro-Otol 5:3–22.
Fransen E, Lemkens N, Van Laer L, Van Camp G (2003) Age-related hearing impairment (ARHI): environmental risk factors and genetic prospects. Exp Gerontol 38:353–359.
Frisina RD (2001) Possible neurochemical and neuroanatomical bases of age-related hearing loss—presbycusis. Semin Hear 22:213–225.
Frisina DR, Frisina RD (1997) Speech recognition in noise and presbycusis: relations to possible neural mechanisms. Hear Res 106:95–104.
Frisina RD, Walton JP (2001) Aging of the mouse central auditory system. In: Willott JP (ed) From Behavior to Molecular Biology. New York: CRC Press, pp. 339–379.
Frisina RD, Walton JP (2006) Age-related structural and functional changes in the cochlear nucleus. Hear Res. 217:216–233.
Frisina DR, Frisina RD, Snell KB, Burkard R, Walton JP, Ison JR (2001) Auditory temporal processing during aging. In: Hof PR, Mobbs CV (eds) Functional Neurobiology of Aging. San Diego: Academic Press, pp. 565–579.
Frisina ST, Mapes F, Kim S-H, Frisina DR, Frisina RD (2006) Characterization of hearing loss in aged type II diabetics. Hear Res 211:103–113.
Fukushima H, Cureoglu S, Schachern PA, Kusunoki T, Oktay MF, Fukushima N, Paparella MM, Harada T (2005) Cochlear changes in patients with type I diabetes mellitus. Otolaryngol Head Neck Surg 133:100–106.
Gagnon PM, Simmons DD, Bao J, Lei D, Ortmann A, J., Ohlemiller KK (2007) Temporal and genetic influences on protection against noise-induced hearing loss by hypoxic preconditioning in mice. Hear Res 226: 79–91.
Garetz SL, Schacht J (1996) Ototoxicity: of mice and men. In: Van De Water TR, Popper AN, Fay RR (eds) Clinical Aspects of HearingNew York: Springer-Verlag, pp. 116–154.
Gates GA, Mills JH (2005) Presbycusis. Lancet 366:1111–1120.
Gates GA, Couropmitree NN, Myers RH (1999) Genetic associations in age–related hearing thresholds. Arch Otolaryngol Head Neck Surg 125:654–659.
Geesaman BJ (2006) Genetics of aging: implications for drug discovery and development. Am J Clin Nutr 83:466S–469S.
Gilad O, Glorig A (1979a) Presbycusis: The aging inner ear. Part I. J Am Audit Soc 4:195–206.
Gilad O, Glorig A (1979b) Presbycusis: The aging ear. Part II. J Am Audit Soc 4:207–217.
Glorig A, Wheeler D, Quiggle R, Grings W, Summerfeld A (1957) 1954 Wisconsin state fair hearing survey—statistical treatment of clinical and audiometric data. Am Acad Ophthalmol Otolaryngol (Monograph).
Gordon-Salant S, Fitzgibbons PJ (1993) Temporal factors and speech recognition performance in young and elderly listeners. J Speech Hear Res 36:1272–1285.

Gratton MA, Schulte BA (1995) Alterations in microvasculature are associated with atrophy of the stria vascularis in quiet-aged gerbils. Hear Res 82:44–52.

Gratton MA, Schmiedt RA, Schulte BA (1996) Age-related decreases in endocochlear potential are associated with vascular abnormalities in the stria vascularis. Hear Res 102:181–190.

Gratton MA, Smyth BJ, Lam CF, Boettcher FA, Schmiedt RA (1997) Decline in the endocochlear potential corresponds to decreased Na,K-ATPase activity in the lateral wall of quiet-aged gerbils. Hear Res 108:9–16.

Hamernik RP, Patterson JH, Turrentine GA, Ahroon WA (1989) The quantitative relation between sensory cell loss and hearing thresholds. Hear Res 38:199–212.

Hamernik RP, Qiu W, Davis B (2003) Cochlear toughening, protection, and potentiation of noise–induced hearing loss by non-Gaussian noise. J Acoust Soc Am 113:969–976.

Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11:98–300.

Harper JM, Wolf N, Galecki AT, Pinkosky SL, Miller RA (2003) Hormone levels and cataract scores as sex-specific, mid-life predictors of longevity in genetically heterogeneous mice. Mech Ageing Dev 124:801–810.

Harper JM, Galecki AT, Burke DT, Miller RA (2004) Body weight, hormones and T cell subsets as predictors of life span in genetically heterogeneous mice. Mech Ageing Dev 125:381–390.

Harper JM, Durkee SJ, Smith-Wheelock M, Miller RA (2005) Hyperglycemia, impaired glucose tolerance and elevated glycated hemoglobin in a long-lived mouse stock. Exp Gerontol 40:303–314.

Harper JM, Salmon AB, Chang Y, Bonkowski M, Bartke A, Miller RA (2006) Stress resistance and aging: influence of genes and nutrition. Mech Ageing Dev 127:687–694.

Hawkins JE, Johnsson L-G, Preston RE (1972) Cochlear microvasculature in normal and damaged ears. Laryngoscope 82:1091–1104.

Helfert RD, Sommer TJ, Meeks J, Hofstetter P, Hughes L F (1999) Age-related synaptic changes in the central nucleus of the inferior colliculus of the Fischer-344 rat. J Comp Neurol 406:285–298.

Helfert RD, Krenning J, Wilson TS, Hughes LF (2003) Age-related synaptic changes in the anteroventral cochlear nucleus of Fischer-344 rats. Hear Res 183:18–28.

Henry KR, Chole RA (1980) Genotypic differences in behavioral, physiological and anatomical expressions of age-related hearing loss in the laboratory mouse. Audiology 19:369–383.

Hequembourg S, Liberman MC (2001) Spiral ligament pathology: a major aspect of age-related cochlear degeneration in C57BL/6 mice. J Assoc Res Otolaryngol 2:118–129.

Hirose K, Liberman MC (2003) Lateral wall histopathology and endocochlear potential in the noise-damaged mouse cochlea. J Assoc Res Otolaryngol 4:339–352.

Hirose K, Discolo CM, Keasler JR, Ransohoff R (2005) Mononuclear phagocytes migrate into the murine cochlea after acoustic trauma. J Comp Neurol 489:180–194.

Hulbert AJ, Faulks SC, Harper JM, Miller RA, Buffenstein R (2006) Extended longevity of wild-derived mice is associated with peroxidation-resistant membranes. Mech Ageing Dev 127:653–657.

Ichimiya I, Suzuki M, Goro M (2000) Age-related changes in the murine cochlear lateral wall. Hear Res 139:116–122.

Idrizbegovic E. Canlon B. Bross LS. Willott JF. Bogdanovic N (2001a) The total number of neurons and calcium binding protein positive neurons during aging in the cochlear nucleus of CBA/CaJ mice: a quantitative study. Hear Res 158:102–115.

Idrizbegovic E, Viberg A, Bogdanovic N, Canlon B (2001b) Peripheral cell loss related to calcium binding protein immunocytochemistry in the dorsal cochlear nucleus in CBA/CaJ mice during aging. Audiol Neuro-Otol 6:132–139.

Idrizbegovic E, Bogdanovic N, Viberg A, Canlon B (2003) Auditory peripheral influences on calcium binding protein immunoreactivity in the cochlear nucleus during aging in the C57BL/6J mouse. Hear Res 179:33–42.

Idrizbegovic E. Bogdanovic N. Willott JF. Canlon B (2004) Age-related increases in calcium-binding protein immunoreactivity in the cochlear nucleus of hearing impaired C57BL/6J mice. Neurobiol Aging 25:1085–1093.

Ishikawa T, Naito Y, Taniguchi K (1995) Hearing impairment in WBN/Kob rats with spontaneous diabetes mellitus. Diabetologia 38:649–655

Jacobson M, KimS-H, Romney J, Zhu XX, Frisina RD (2003) Contralateral suppression of distortion-product otoacoustic emissions declines with age: a comparison of findings in CBA mice with human listeners. Laryngoscope 113:1707–1713.

Jerger J, Jordan C (1992) Age-related asymmetry on a cued-listening task. Ear Hear 13:272–277.

Jerger J, Martin J (2004) Hemispheric asymmetry of the right ear advantage in dichotic listening. Hear Res 198:125–136.

Jerger J, Chmiel R, Stach B, Spretnjak M (1993) Gender affects audiometric shape in presbycusis. J Am Acad Audiol 4:42–49.

Jerger J, Chmiel R, Allen J, Wilson A (1994) Effects of age and gender on dichotic sentence identification. Ear Hear 15:274–286.

Jerger J, Alford B, Lew H, Rivera V, Chmiel R (1995) Dichotic listening, event-related potentials, and interhemispheric transfer in the elderly. Ear Hear 16:482–498.

Jiang H, Talaska AE, Schacht J, Sha S-H (2006) Oxidative imbalance in the aging inner ear. Neurobiol Aging 28: 1605–1612.

Johnson KR, Zheng QY, Erway LC (2000) A major gene affecting age-related hearing loss is common to at least 10 inbred strains of mice. Genomics 70:171–180.

Johnson KR, Zheng QY, Noben-Trauth K (2006) Strain background effects and genetic modifiers of hearing in mice. Brain Res 1091:79–88.

Johnsson L-G, Hawkins JE (1972) Strial atrophy in clinical and experimental deafness. Laryngoscope 82:1105–1125.

Karasik D, Demissie S, Cupples AL, Kiel DP (2005) Disentangling the genetic determinants of human aging: biological age as an alternative to the use of survival measures. J Gerontol Biol Sci 60A:574–587.

Keen EC, Hudspeth AJ (2006) Transfer characteristics of the hair cell's afferent synapse. Proc Natl Acad Sci USA 103:5537–5542.

Keithley, EM, Croskrey KL (1990) Spiral ganglion cell endings in the cochlear nucleus of young and old rats. Hear Res 49:169–177.

Keithley EM, Feldman ML (1979) Spiral ganglion cell counts in an age-graded series of rat cochleas. J Comp Neurol 188:429–444.

Keithley EM, Canto C, Zheng QY, Fischel-Ghodsian N, Johnson KR (2004) Age-related hearing loss and the ahl locus in mice. Hear Res 188:21–28.

Keithley EM, Canto C, Zheng QY, Wang X, Fischel-Ghodsian N, Johnson KR (2005) Cu/Zn superoxide dismutase and age-related hearing loss. Hear Res 209:76–85.

Kim S-H, Frisina DR, Frisina RD (2002) Effects of age on contralateral suppression of distortion-product otoacoustic emissions in human listeners with normal hearing. Audiol Neuro-Otol 7:348–357.

Konigsmark BW, Murphy EA (1970) Neuronal populations in the human brain. Nature 228:1335–1336.

Konigsmark BW, Murphy EA (1972) Volume of the ventral cochlear nucleus in man: Its relationship to neuronal population and age. J Neuropathol Exp Neurol 31:304–316.

Krebs J (1998) The role of calcium in apoptosis. Biometals 11:375–382.

Krenning J, Hughes L, Caspary D, Helfert, RH (1998) Age–related glycine receptor subunit changes in the cochlear nucleus of Fischer-344 rats. Laryngoscope 108:26–31.

Kujawa SG, Liberman MC (2006) Acceleration of age–related hearing loss by early noise: Evidence of a misspent youth. J Neurosci 26:2115–2123.

Kujoth GC, Hiona A, Pugh TD, Someya S, Panzer K, Wohlgemuth SE, Hofer T, Seo AY, Sullivan R, Jobling WA, Morrow JD, Van Remmen H, Sedivy JM, Yamasoba T, Tanokura M, Weindruch R, Leeuwenburgh C, Prolla TA (2005) Mitochondrial DNA mutations, oxidative stress, and apoptosisin mammalian aging. Science 309:481–484.

Lambert PR, Schwartz IR (1982) A longitudinal study of changes in the cochlear nucleus in the CBA mouse. Otolaryngol Head Neck Surg 90:787–794.

Lang H, Schulte BA, Schmiedt RA (2002) Endocochlear potentials and compound action potential recovery: functions in the C57BL/6J mouse. Hear Res 172:118–126.

Lang H, Schulte BA, Schmiedt RA (2003) Effects of chronic furosemide treatment and age on cell division in the adult gerbil inner ear. J Assoc Res Otolaryngol 4:164–175.

Lang H, Schulte BA, Zhou D, Smythe NM, Spicer SS, Schmiedt RA (2006a) Nuclear factor κB deficiency is associated with auditory nerve degeneration and increased noise-induced hearing loss. J Neurosci 26:3541–3550.

Lang H, Ebihara Y, Schmiedt RA, Minamiguchi H, Zhou D, Smythe N, M., Liu L, Ogawa M, Schulte BA (2006b) Contribution of bone marrow hematopoietic stem cells to adult mouse inner ear: mesenchymal cells and fibrocytes. J Comp Neurol 496: 187–201.

Le T, Keithley EM (2006) Effects of antioxidants on the aging inner ear. Hear Res 226: 194–202.

Le Prell CG, Yamashita D, Minami SB, Yamasoba T, Miller JM (2006) Mechanisms of noise-induced hearing loss indicate multiple methods of prevention. Hear Res 226: 22–43.

Leutner S, Eckert A, Muller WE (2001) ROS generation, lipid peroxidation and antioxidant enzyme activities in the aging brain. J Neural Transm 108:955–967.

Lu KP, Means AR (1993) Regulation of the cell cycle by calcium and calmodulin. Endocr Rev 14:40–58.

Ma F, Gomez-Martin O, Lee DJ, Balkany T (1998) Diabetes and hearing impairment in Mexican American adults: A population-based study. J Laryngol Otol 112:835–839.

Malpas S, Blake P, Bishop R, Robinson B, Johnson R (1989) Does autonomic neuropathy in diabetes cause hearing deficits? N Zeal Med J 102:434–435.

Martin JS, Jerger JF (2005) Some effects of aging on central auditory processing. J Rehab Res Dev 42:25–44.

McBride DJ, Williams S (2001) Audiometric notch as a sign of noise-induced hearing loss. Occup Environ Med 58:46–51.

McFadden SL, Willott JF (1994) Responses of inferior colliculus neurons in C57BL/6J mice with and without sensorineural hearing loss: effects of changing the azimuthal location of an unmasked pure-tone stimulus. Hear Res 78:115–131.

McFadden SL, Ding D, Reaume AG, Flood DG, Salvi RJ (1999) Age-related cochlear hair cell loss is enhanced in mice lacking copper/zinc superoxide dismutase. Neurobiol Aging 20:1–8.

McFadden SL, Ding D-L, Ohlemiller KK, Salvi RJ (2001) The role of superoxide dismutase in age-related and noise-induced hearing loss: clues from Sod1 knockout mice. In: Willott JF (ed) From Behavior to Molecular Biology. New York: CRC Press, pp. 489–504.

McGeer EGG, McGeer PL (1975) Age changes in the human for some enzymes associated with metabolism of catecholamines, GABA and acetylcholine. In: Ordy JM, Brizzee KR (eds) Neurobiology of Aging. New York: Plenum Press, pp. 287–305.

Mikaelian DO, Warfield D, Norris O (1974) Genetic progressive hearing loss in the C57b16 mouse. Acta Otolaryngol 77:327–334.

Milbrandt JC, Albin RL, Caspary DM (1994) Age-related decrease in GABAb receptor binding in the Fischer 344 rat inferior colliculus. Neurobiol Aging 15:699–703.

Milbrandt JC, Caspary DM (1995) Age-related reduction of [3H]strychnine binding sites in the cochlear nucleus of the Fischer 344 rat. Neuroscience 67(3): 713–719.

Milbrandt JC, Albin RL, Turgeon SM, Caspary DM (1996) $GABA_A$ receptor binding in the aging rat inferior colliculus. Neuroscience 73:449–458.

Milbrandt JC, Hunter C, Caspary DM (1997) Alterations of $GABA_A$ receptor subunit mRNA levels in the aging Fischer rat inferior colliculus. J Comp Neurol 379:455–465.

Miller RA, Chang Y, Galecki AT, Al-Regaiey K, Kopchick JJ, Bartke A (2002) Gene expression patterns in calorically restricted mice: partial overlap with long-lived mutant mice. Mol Endocrinol 16:2657–2666.

Mills JH, Matthews LJ, Lee FS, Dubno JR, Schulte BA, Weber PC (1999) Gender-specific effects of drugs on hearing levels of older persons. Ann NY Acad Sci 884:381–388.

Minowa O, Ikeda K, Sugitani Y, Oshima T, Nakai S, Katori Y, Suzuki M, Furukawa M, Kawase T, Zheng Y, Ogura M, Asada Y, Watanabe K, Yamanaka H, Gotoh S, Nishi-Takeshima M, Sugimoto T, Kikuchi T, Takasaka T, Noda T (1999) Altered cochlear fibrocytes in a mouse model of DFN3 nonsyndromic deafness. Science 285:1408–1411.

Nakashima T, Naganawa S, Sone M, Tominaga M, Hayashi H, Yamamoto H, Liu X, Nuttall AL (2003) Disorders of cochlear blood flow. Brain Res Rev 43:17–28.

Niu X, Canlon B (2002) Protective mechanisms of sound conditioning. Adv Otorhinolaryngol 59:96–105.

Nixon JC, Glorig A (1962) Changes in air and bone conduction threshoulds as a function of age. J Laryngol 76:288–298.

Ohlemiller KK (2002) Reduction in sharpness of frequency tuning but not endocochlear potential in aging and noise-exposed BALB/cJ mice. J Assoc Res Otolaryngol 3: 444–456.

Ohlemiller KK (2003) Oxidative cochlear injury and the limitations of antioxidant therapy. Semin Hear 24:123–133.

Ohlemiller KK (2006) Contributions of mouse models to understanding of age- and noise-related hearing loss. Brain Res 1091:89–102.

Ohlemiller KK, Gagnon PM (2004a) Apical-to-basal gradients in age-related cochlear degeneration and their relationship to 'primary' loss of cochlear neurons. J Comp Neurol 479:103–116.

Ohlemiller KK, Gagnon PM (2004b) Cellular correlates of progressive hearing loss in 129S6/SvEv mice. J Comp Neurol 469:377–390.

Ohlemiller KK, McFadden SL, Ding D-L, Reaume AG, Hoffman EK, Scott RW, Wright JS, Putcha GV, Salvi RJ (1999) Targeted deletion of the cytosolic Cu/Zn-superoxide dismutase gene (SOD1) increases susceptibility to noise-induced hearing loss. Audiol Neuro-Otol 4:237–246.

Ohlemiller KK, McFadden SL, Ding D-L, Lear PM, Ho Y-S (2000) Targeted mutation of the gene for cellular glutathione peroxidase (Gpx1) increases noise-induced hearing loss in mice. J Assoc Res Otolaryngol 1:243–254.

Ohlemiller KK, Lett JM, Gagnon PM (2006) Cellular correlates of age-related endocochlear potential reduction in a mouse model. Hear Res 220:10–26.

Ologe FE, Okoro EO, Oyejola BA (2005) Hearing function in Nigerian children with a family history of type II diabetes. Int J Pediatr Otorhinolaryngol 69:387–391.

O'Neill WE, Zettel ML, Whittemore KR, Frisina RD (1997). Calbindin D-28k immunoreactivity in the medial nucleus of the trapezoid body declines with age in C57BL/6, but not CBA/CaJ, mice. Hear Res 112:158–166.

Otte J, Schuknecht HF, Kerr AG (1978) Ganglion cell populations in normal and pathological human cochleae: Implications for cochlear implantation. Laryngoscope 38:1231–1246.

Park JC, Cook KC, Verde EA (1990) Dietary restriction slows the abnormally rapid loss of spiral ganglion neurons in C57BL/6 mice. Hearing Res 48:275–280.

Pauler M, Schuknecht HF, Thornton AR (1986) Correlative studies of cochlear neuronal loss with speech discrimination and pure-tone thresholds. Arch Otolaryngol 243: 200–206.

Pauler M, Schuknecht HF, White JA (1988) Atrophy of the stria vascularis as a cause of sensorineural hearing loss. Laryngoscope 98:754–759.

Pekkonen E (2000) Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. Audiol Neuro-Otol 5:216–224.

Pichora-Fuller MK (2003) Processing speed and timing in aging adults: psychoacoustics, speech perception, and comprehension. Int J Audiol (Suppl 1)42:S59–67.

Pickles JO (2004) Mutation in mitochondrial DNA as a cause of presbyacusis. Audiol Neuro-Otol 9:23–33.

Pillsbury HC (1986) Hypertension, hyperlipoproteinemia, chronic noise exposure: Is there synergism in cochlear pathology? Laryngoscope 96:1112–1138.

Polich J, Howard L, Starr A (1985) Effects of age on the P300 component of the event–related potential from auditory stimuli: peak definition, variation, and measurement. J Gerontol 40:721–726.

Prass K, Scharff A, Ruscher K, Lowl D, Muselmann C, Victorov I, Kapinya K, Dirnagl U, Meisel A (2003) Hypoxia-induced stroke tolerance in the mouse in mediated by erythropoietin. Stroke 34:1981–1986.

Pujol R, Rebillard G, Puel J-L, Lenoir M, Eybalin M, Recasens M (1991) Glutamate neurotoxicity in the cochlea: a possible consequence of ischaemic or anoxic conditions occurring in ageing. Acta Otolaryngol (Stockh) 476:32–36.

Pujol R, Puel J-L, D'Aldin CG, Eybalin M (1993) Pathophysiology of the glutamate synapses of the cochlea. Acta Otolaryngol 113:330–334.

Ran R, Xu H, Lu A, Bernaudin M, Sharp FR (2005) Hypoxic preconditioning in the brain. Dev Neurosci 27:87–92.

Raynor EM, Carrasco VN, Prazma J, Pillsbury HC (1995) An assessment of cochlear hair-cell loss in insulin-dependent diabetes mellitus diabetic and noise-exposed rats. Arch Otolaryngol Head Neck Surg 121:452–456.

Raza A, Milbrandt JC, Arneric SP, Caspary DM (1994) Age-related changes in brainstem auditory neurotransmitters: measures of GABA and acetylcholine functions. Hear Res 77:221–230.

Rosen S, Olin P, Rosen HV (1970) Dietary prevention of hearing loss. Acta Otolaryngol 70:242–247.

Rosen S, Bergman M, Plester D, El Mofti A, Satti M (1962) Presbycusis study of a relatively noise-free population in the Sudan. Ann Otol Rhinol Laryngol 71:727–742.

Rosenhall U, Pedersen KE (1995) Presbycusis and occupational hearing loss. Occup Med 10:593–607.

Rosenhall U, Sixt E, Sundh V, Svanborg A (1993) Correlations between presbycusis and extrinsic noxious factors. Audiology 32:234–243.

Ruckenstein MJ, Milburn M, Hu L (1999a) Strial dysfunction in the MRL-Fas^{lpr} mouse. Otolaryngol Head Neck Surg 121:452–456.

Ruckenstein MJ, Keithley EM, Bennett T, Powell HC, Baird S, Harris JP (1999b) Ultrastructural pathology in the stria vascularis of the MRL-Fas^{lpr} mouse. Hear Res 131:22–28.

Rust KR, Prazma J, Triana RJ, Michaelis OEt, Pillsbury HC (1992) Inner ear damage secondary to diabetes mellitus. II. Changes in aging SHR/N-cp rats. Arch Otolaryngol Head Neck Surg 118:397–400.

Saito T, Sato K, Saito H (1986) An experimental study of auditory dysfunction associated with hyperlipoproteinemia. Archives of Otorhinolaryngol 243:242–245.

Saitoh Y, Hosokawa M, Shimada A, Watanabe Y, Yasuda N, Murakami Y, Takeda T (1995) Age-related cochlear degeneration in senescence-accelerated mouse. Neurobiol Aging 16:129–136.

Salvi RJ, Lockwood AH, Frisina RD, Coad ML, Wack DS, Frisina DR (2002) PET imaging of the normal human auditory system: responses to speech in quiet and in background noise. Hear Res 170:96–106.

Sastre J, Pallardo FV, De La Asuncion JG, Vina J (2000) Mitochondria, oxidative stress and aging. Free Radic Res 32:189–198.

Satar B, Ozkaptan Y, Surucu HS, Ozturk H (2001) Ultrastructural effects of hypercholesterolemia on the cochlea. Otol Neurotol 22:786–789.

Schacht J, Hawkins JE (2005) Sketches of otohistory. Part 9: Presby[a]cusis. Audiol Neuro–Otol 10:243–247.

Schmiedt RA, Lang H, Okamura H, Schulte BA (2002) Effects of furosemide applied chronically to the round window: A model of metabolic presbycusis. J Neuroscience 22:9643–9650.

Schneider BA, Pichora-Fuller MK, Kowalchuk D, Lamb M (1994) Gap detection and the precedence effect in young and old adults. J Acoust Soc Am 95:980–991.

Scholtz AW, Kammen-Jolly K, Felder E, Hussl B, Rask-Andersen H, Schrott-Fischer A (2001) Selective aspects of human pathology in high-tone hearing loss of the aging inner ear. Hear Res 157:77–86.

Schuknecht HF (1953) Lesions of the organ of Corti. Trans Am Acad Ophthalmol Otolaryngol 57:366–383.

Schuknecht HF (1964) Further observations on the pathology of presbycusis. Arch Otolaryngol 80:369–382.

Schuknecht HF (1993) Pathology of the Ear, 2nd ed. Philadelphia: Lea and Febiger.

Schuknecht HF, Gacek MR (1993) Cochlear pathology in presbycusis. Ann Otol Rhinol Laryngol 102:1–16.

Schuknecht HF, Watanuki K, Takahashi T, Belal AA, Kimura RS, Jones DD (1974) Atrophy of the stria vascularis, a common cause for hearing loss. Laryngoscope 84:1777–1821.

Schulte BA, Schmiedt RA (1992) Lateral wall Na,K-ATPase and endocochlear potentials decline with age in quiet-reared gerbils. Hear Res 61:35–46.

Schwaller B, Meyer M, Schiffmann S (2002) 'New' functions for 'old' proteins: the role of the calcium-binding proteins calbindin D-28K, calretinin and parvalbumin, in cerebellar physiology. Studies with knockout mice. Cerebellum 1:241–258.

Seidman MD (2000) Effects of dietary restriction and antioxidants on presbyacusis. Laryngoscope 110:727–738.

Seidman MD, Ahmad N, Bai U (2002) Molecular mechanisms of age-related hearing loss. Ageing Res Rev 1:331–343.

Seldon HL, Clark GM (1991) Human cochlear nucleus: comparison of Nissl-stained neurons from deaf and hearing patients. Brain Res 551:185–194.

Shimada A, Ebisu M, Morita T, Takeuchi T, Umemura T (1998) Age-related changes in the cochlea and cochlear nuclei of dogs. J Vet Med Sci 60:41–48.

Siemens J, Lillo C, Dumont RA, Reynolds A, Williams DS, Gillespie PG, Muller U (2004) Cadherin 23 is a component of the tip link in hair-cell stereocilia. Nature 428:950–955.

Sikora MA, Morizono T, Ward WD, Paparella MM, Leslie K (1986) Diet-induced hyperlipidemia and auditory dysfunction. Acta Otolaryngol 102:372–381.

Sinclair DA (2005) Toward a unified theory of caloric restriction and longevity regulation. Mech Ageing Dev 126:987–1002.

Snell KB, Frisina DR (2000). Relations among age-related differences in gap detection and speech perception. J. Acoust Soc Am 107: 1615–1626.

Snell KB, Mapes FM, Hickman ED, Frisina DR (2002). Word recognition in competing babble and the effects of age, temporal processing, and absolute sensitivity. J Acoust Soc Am 112: 720–727.

Someya S, Yamasoba T, Weindruch R, Prolla TA, Tanokura M (2007) Caloric restriction suppresses apoptotic cell death in the mammalian cochlea and leads to prevention of presbycusis. Neurobiol Aging 28(10): 1613–1622.

Spencer JT (1973) Hyperlipoproteinemia in the etiology of inner ear disease. Laryngoscope 83:639–678.

Spicer SS, Schulte BA (2002) Spiral ligament pathology in quiet-aged gerbils. Hear Res 172:172–185.

Spicer SS, Schulte BA (2005) Pathologic changes of presbycusis begin in secondary processes and spread to primary processes of strial marginal cells. Hear Res 2005: 225–240.

Squier TC (2001) Oxidative stress and protein aggregation during biological aging. Exp Gerontol 36:1539–1550.

Squier TC, Bigelow DJ (2000) Protein oxidation and age-dependent alterations in calcium homeostasis. Front Biosci 5:d504–526.

Stamataki S, Francis HW, Lehar M, May BJ, Ryugo DK (2006) Synaptic alterations at inner hair cells precede spiral ganglion cell loss in aging C57BL/6J mice. Hear Res 221: 104–118.

Starr A, Picton TW, Kim R (2001) Pathophysiology of auditory neuropathy. In: Sininger Y, Starr A (eds) Auditory Neuropathy: A New Perspective on Hearing Disorders San Diego: Singular, pp. 67–81.

Suzuka Y, Schuknecht HF (1988) Retrograde cochlear neuronal degeneration in human subjects. Acta Otolaryngol Suppl 450:2–20.

Suzuki K, Kaneko M, Murai K (2000) Influence of serum lipids on auditory function. Laryngoscope 110:1736–1738.

Swartz KP, Walton JP, Crummer GC, Hantz EC, Frisina RD (1992) P3 event-related potentials and performance of healthy old and Alzheimer's dementia subjects for music perception tasks. Psychomusicol 11: 96–118.

Swartz KP, Walton JP, Hantz EC, Goldhammer E, Crummer GC, Frisina RD (1994) P3 event-related potentials and performance of young and old subjects for music perception tasks. Int J Neurosci 78:223–239.

Sweet RJ, Price JM, Henry KR (1988) Dietary restriction and presbyacusis: periods of restriction and auditory threshold losses in the CBA/J mouse. Audiology 27:305–312.

Tachibana M, Yamamichi I, Nakae S, Hirasugi Y, Machino M, Mizukoshi O (1984) The site of involvement of hypertension within the cochlea. Acta Otolaryngol 97:257–265.

Tadros SF, Frisina ST, Mapes F, Kim S-H, Frisina DR, Frisina RD (2005a) Loss of peripheral right ear advantage in age-related hearing loss. Audiol Neuro-Otol, 10:44–52.

Tadros SF, Frisina ST, Mapes F, Frisina DR, Frisina RD (2005b) Higher serum aldosterone correlates with lower hearing thresholds: a possible protective hormone against presbycusis. Hear Res 209:10–18.

Takumida M, Anniko A (2005) Radical scavengers: a remedy for presbycusis. A pilot study. Acta Otolaryngol 125:129–1293.

Tarnowski BI, Schmiedt RA, Hellstrom LI, Lee FS, Adams JC (1991) Age-related changes in cochleae of Mongolian gerbils. Hear Res 54:123–134.

Toescu EC (2005) Normal brain ageing: models and mechanisms. Philos Trans R Soc Lond B 360:2347–2354.

Toppila E, Pyykko I, Starck J (2001) Age and noise-related hearing loss. Scand Audiol 30:236–244.

Torre P, Cruickshanks KJ, Klein BEK, Nondahl DM (2005) The association between cardiovascular disease and cochlear function in older adults. J Speech Lang Hear Res 48:473–481.

Trune DR, Kempton JB (2002) Female MRL.MpJ-Fas^{lpr} autoimmune mice have greater hearing loss than males. Hear Res 167:170–174.

Trune DR, Kempton JB, Gross ND (2006) Mineralocorticoid receptor mediates glucocorticoid treatment effects in the autoimmune mouse ear. Hear Res 212:22–32.

Uchida Y, Nakashima T, Ando F, Niino N, Shimokada H (2005) Is there a relevant effect of noise and smoking on hearing? A population-based aging study. Int J Audiol 44:86–91.

Ulehlova L (1983) Stria vascularis in acoustic trauma. Arch Otorhinolaryngol 237: 133–138.

Unal M, Tamer L, Dogruer ZN, Yildirim H, Vayisoglu Y, Camdevirin H (2005) *N*-acetyltransferase 2 gene polymorphism and presbycusis. Laryngoscope 115:2238–2241.

Varghese GI, Zhu XX, Frisina, RD (2005) Age-related declines in contralateral suppression of distortion product otoacoustic emissions utilizing pure tones in CBA/CaJ mice. Hear Res 209:60–67.

Vaughan N, James K, McDermott D, Griest S, Fausti S (2005) A 5-year prospective study of diabetics and hearing loss in a veteran population. Otol Neurotol 27:37–43.

von Zglinicki T, Martin-Ruiz CM (2005) Telomeres as biomarkers for aging and age–related disease. Curr Mol Med 5:197–203.

Wackym PA, Linthicum FH (1986) Diabetes mellitus and hearing loss: clinical and histopathologic relationships. Am J Otol 7:176–182.

Walton JP, Frisina RD, Ison JE, O'Neill WE (1997) Neural correlates of behavioral gap detection in the inferior colliculus of the young CBA mouse. J Comp Physiol A 181:161–176.

Wang Y, Liberman MC (2002) Restraint stress and protection from acoustic injury in mice. Hear Res 165:96–102.

Wang Y, Manis P B (2005) Synaptic transmission at the cochlear nucleus end bulb synapse during age-related hearing loss in mice. J Neurophysiol 94: 1814–1824.
Wangemann P (2002) K^+ recycling and the endocochlear potential. Hear Res 165:1–9.
Whitlock NA, Agarwal N, Ma JX, Crosson CE (2005) Hsp27 upregulation by HIF-1 signaling offers protection against retinal ischemia in rats. Inv Ophthalmol Visual Sci 46:1092–1098.
Willott JF (1991). Aging and the Auditory System: Anatomy, Physiology, and Psychophysics Sam Diego: Singular.
Willott JF, Bross LS (1990) Morphology of the octopus cell area of the cochlear nucleus in young and aging C57BL/6J and CBA/J mice. J Comp Neurol 300:61–81.
Willott JF, Bross LS (1996) Morphological changes in the anteroventral cochlear nucleus that accompany sensorineural hearing loss in DBA/2J and C57BL/6J mice. Dev Brain Res 91:218–226.
Willott JF, Turner JG (1999) Prolonged exposure to an augmented acoustic environment ameliorates age-related auditory changes in C57BL/6J and DBA/2J mice. Hear Res 135:78–88.
Willott JF, Jackson LM, Hunter KP (1987) Morphometric study of the anteroventral cochlear nucleus of two mouse models of presbycusis. J Comp Neurol 260:472–480.
Willott JF, Parham K, Paris Hunter K (1991) Comparison of the auditory sensitivity of neurons in the cochlear nucleus and inferior colliculus of young and aging C57BL/6J and CBA/J mice. Hear Res 53: 78–94.
Willott JF, Bross LS, McFadden SL (1992) Morphology of the dorsal cochlear nucleus in C57BL/6J and CBA/J mice across the life span. J Comp Neurol 321:666–678.
Willott JF, Milbrandt JC, Seegers Bross L, Caspary DM (1997) Glycine immunoreactivity and receptor binding in the cochlear nucleus of C57BL/6J and CBA/CaJ mice: effects of cochlear impairment and aging. J Comp Neurol 385:405–414.
Willott JF, Turner JG, Carlson S, Ding D, Bross LS, Falls WA (1998) The BALB/c mouse as an animal model for progressive sensorineural hearing loss. Hear Res 115:162–174.
Wright CG, Schuknecht HF (1972) Atrophy of the spiral ligament. Arch Otolaryngol 96:16–21.
Wu W-J, Sha S, McLaren JD, Kawamoto K, Raphael Y, Schacht J (2001) Aminoglycoside ototoxicity in adult CBA, C57BL, and BALB mice and the Sprague-Dawley rat. Hear Res 158:165–178.
Xiu A–P, Kikuchi T, Minowa O, Katori Y, Oshima T, Noda T, Ikeda K (2002) Late-onset hearing loss in a mouse model of DFN3 non-syndromic deafness: morphologic and immunohistochemical analyses. Hear Res 166:150–158.
Yamashita H, Shimogori H, Sugahara K, Takahashi M (1999) Cell proliferation in spiral ligament of mouse cochlea damaged by dihydrostreptomycin sulfate. Acta Otolaryngol 119:322–325.
Yoshida N, Kristiansen A, Liberman MC (1999) Heat stress and protection from permanent acoustic injury in mice. J Neurosci 19:10116–10124.
Zettel ML, Frisina RD, Haider SEA, O'Neill WE (1997) Age-related changes in calbindin D–28K and calretinin immunoreactivity in the inferior colliculus of CBA/CaJ and C57B1/6 mice. J Comp Neurol 386:92–110.
Zettel ML, O'Neill WE, Trang TT, Frisina RD (2001) Early bilateral deafening prevents calretinin up-regulation in the dorsal cortex of the inferior colliculus of aged CBA/CaJ mice. Hear Res 158:131–138
Zimmermann CE, Burgess BJ, Nadol JB (1995) Patterns of degeneration in the human cochlear nerve. Hear Res 90:192–201.