Acquired Hearing Loss: Is Prevention or Reversal a Realistic Goal?

Colleen G. Le Prell

Noise exposure and aging are the most common causes of acquired hearing loss in humans. In addition, various workplace chemicals and prescription medications are toxic to the inner ear ("ototoxic") and result in hearing loss. Another possible auditory symptom produced by the same sources is tinnitus, a perception of ringing (or other) sounds "in the ears" (Spankovich et al., 2021).

Acquired hearing loss develops when sensory cells inside the inner ear are damaged. Resulting hearing loss is labeled based on the cause of the damage, including "noise-induced hearing loss" (NIHL), "drug-induced hearing loss" (DIHL), and "age-related hearing loss" (ARHL). In addition, hearing loss can develop suddenly with no known cause, in which case it is termed "idiopathic sudden sensorineural hearing loss" (ISSNHL). Some 30 to 60% cases of ISSNHL show spontaneous recovery, with the rest resulting in permanent acquired hearing loss (Montgomery et al., 2016).

In contrast to hearing loss that occurs with sensory cell loss, damage to the auditory nerve (AN) might make it harder to understand speech sounds or cause tinnitus (Kujawa and Liberman, 2015). Because these symptoms are not a hearing loss that can be measured using the traditional clinical "audiogram" test measure, these hearing deficits have been labeled "hidden hearing loss," even though they are not hidden to the patient (Schaette and McAlpine, 2011; Kujawa and Liberman, 2015).

Acquired hearing loss is a major public health issue affecting millions of people in the United States and globally. The past 20 years have included significant efforts to identify what biological events inside the inner ear occur during traumatic events such as noise exposure or ototoxic drug treatment. By identifying specific biological events that lead to the death of sensory cells in the inner ear, it has become possible to select experimental agents that might interrupt these events. Several experimental compounds that showed promise in successfully reducing NIHL, DIHL, or ARHL in preclinical (animal) models have been or will soon be tested in humans as possible inner ear medicines (Le Prell, 2021). Investigational medicines are tested in humans in clinical trials to determine safety, side effects, and effectiveness (Lynch et al., 2016).

Drugs that prevent acquired hearing loss could potentially prevent hearing loss that would normally develop in the absence of such drugs. However, these drugs would not benefit patients who have already developed hearing loss. For those patients, biological therapies that turn on cell development processes and drive development of new sensory cells are needed (i.e., medicines that enable missing sensory cells to be "regenerated"). Dramatic advances in regeneration therapies have been made, and the recovery of function may one day be feasible for those patients who already have acquired hearing loss.

This article first reviews how hearing is measured and the prevalence of acquired hearing loss based on epidemiological data. This is followed by a discussion of exciting advances in the development of investigational medicines for the inner ear. If successful within the regulatory testing and approval process, new inner ear therapies that prevent hearing loss or restore hearing function may one day be available to patients. Although much of this article focuses on threshold sensitivity, the audiometric gold standard (Ruben, 2021), it must be noted that speech communication is important to patients and tinnitus can be debilitating.

Normal Human Hearing

In the absence of ARHL, NIHL, DIHL, or other causes of hearing loss, the human auditory system is sensitive to frequencies from 20 Hz to 20 kHz, with the best sensitivity to sounds in the middle of this range, from

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approximately 250 Hz to 8 kHz. Sounds below 250 Hz or above 8 kHz must be presented at a higher decibel (dB) sound pressure level (SPL) to be heard. Perceptually, lower frequency sounds have lower pitches, like the rumble of thunder; higher frequency sounds have higher pitches, like a bird chirping. Patients with hearing loss are not equally affected across all sound frequencies, and ARHL, NIHL, and DIHL each have a characteristic pattern, with differences in the most affected sound frequencies. Clinical tests are used to document frequency-specific hearing loss.

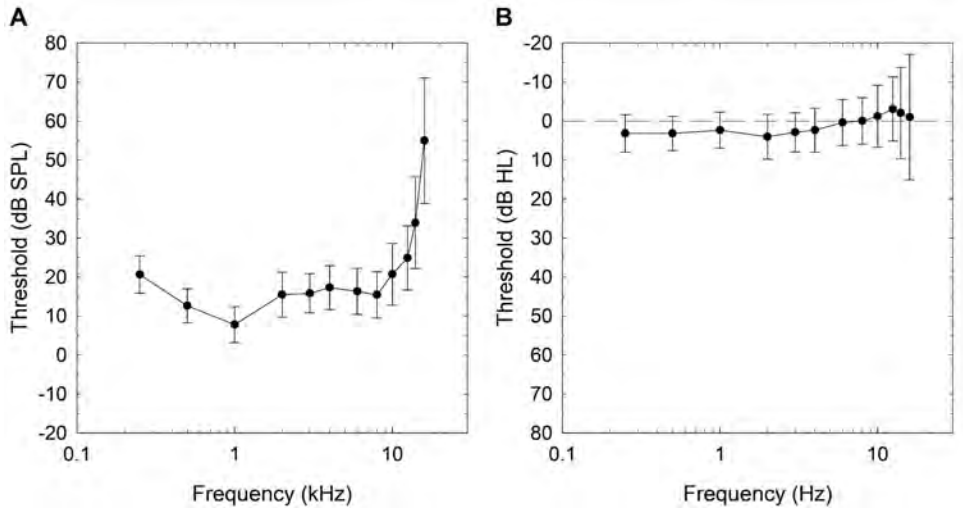
During clinical testing, an audiologist measures the lowest sound level that the patient reliably detects at different frequencies, with 0.25 to 8 kHz being the conventional test range. The lowest levels detected are the patient's "threshold" at each frequency, and these thresholds are plotted as the audiogram. The audiogram thus provides visual illustration of the quietest sound that can be reliably detected at each frequency.

The audiogram for a young adult with normal hearing is roughly "U-shaped," with the best sensitivity (lowest detection thresholds) within the conventional test range (0.25-8 kHz) and higher thresholds outside this range. The average threshold sensitivity for 66 normal-hearing young adult volunteers (27 male, 39 female, ages 18-29 years) tested by Spankovich et al. (2014) are shown in **Figure 1A**. Although frequencies below 250 Hz were not tested, the increased energy necessary for sound detection above 8 kHz is clear.

Clinical audiograms are not plotted as absolute sensory thresholds in decibel SPLs as in **Figure 1A**. Instead, they are shown as the difference between the patient's decibel SPL threshold and the reference equivalent threshold (RET) SPL as specified by the American National Standards Institute (2018). The decibel SPL threshold considered "normal" in the RET SPL is set as 0 dB hearing level (HL). Thus, a patient whose hearing matches the reference population has a 0 dB HL threshold at each frequency. Rather than the U-shaped audiogram, the young adult patient with normal hearing will have a flat audiogram.

To illustrate this, the thresholds plotted in **Figure 1A** are replotted in **Figure 1B** after conversion to decibel HLs. The average thresholds for the normal-hearing young adults are within 5 dB of the reference level at all tested frequencies. If a patient's hearing were poorer than the reference level, then their dB HL threshold would reflect the amount by which their hearing differs from the norm. Clinically, hearing loss is typically identified as "mild," beginning around 20-25 dB HL, and moderate, beginning

Figure 1. *Threshold sensitivity for 66 normal-hearing volunteers (27 male, 39 female, 18-29 years of age) tested by Spankovich et al. (2014). When plotted in decibel (dB) sound pressure level (SPL), the audiogram shows a roughly U-shaped form (**A**). When converted to dB hearing level (HL), the audiogram is flat (**B**).Values are means ± SD.*



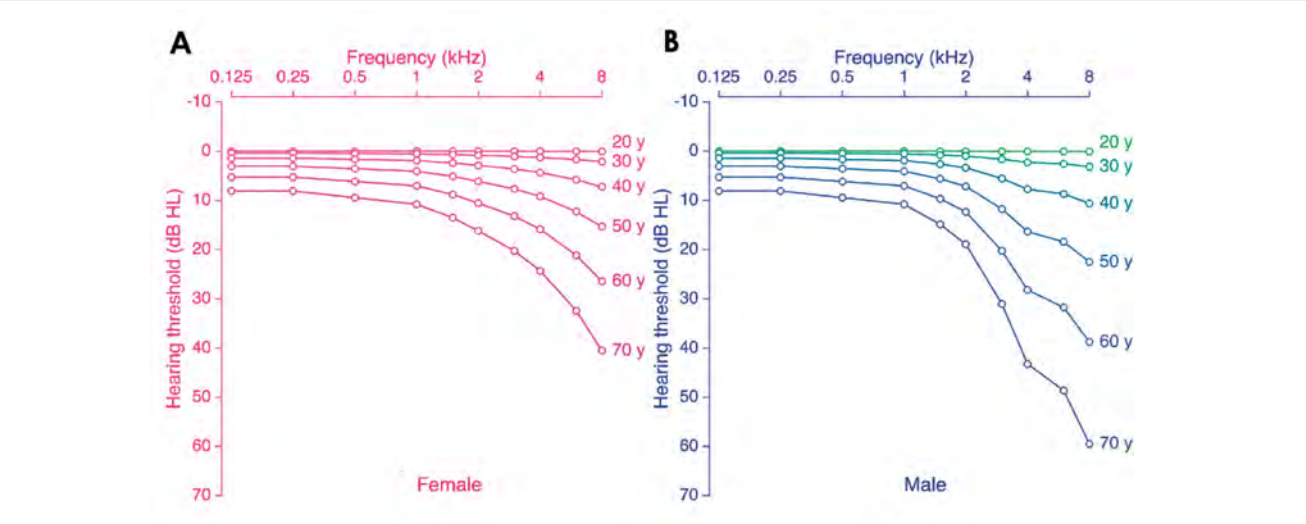


Figure 2. *Median age-related hearing loss (ARHL) for females (**A**) and males (**B**). ARHL is plotted as decibel HL where 0 dB HL is the reference level for normal-hearing young adults and ARHL is per the International Organization for Standardization (2017). Hearing loss increases from 20 to 70 years of age, with the higher frequencies affected first. Adapted from Wang and Puel (2020), licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0; creativecommons.org/licenses/by/4.0) license. Copyright 2020, Jing Wang and Jean-Luc Puel. Licensee MDPI, Basel, Switzerland.*

around 40-45 dB HL. Patients can have negative decibel HL thresholds, indicating that hearing is better than the reference level.

Age-Related Hearing Loss

Beginning at around 20 years of age, hearing slowly declines, with higher frequencies affected first and deficits progressing into the range of frequencies considered important for hearing speech (approximately 250 Hz to 4 kHz) as aging continues (see **Figure 2**). ARHL thus presents as a sloping hearing loss, with a greater hearing loss at higher frequencies than at lower frequencies; ARHL is pervasive in the US population. Based on nationally representative epidemiological data, about 50% of 50- to 59-year-old adults have high-frequency hearing loss (greater than a 25 dB HL average pure-tone threshold at 3, 4, and 6 kHz), increasing to about 75% of those age 60-69 (Agrawal et al., 2008).

At frequencies important for speech understanding, about 30% of 50- to 59-year-old adults have hearing loss (greater than a 25 dB HL average pure-tone threshold at 0.5, 1, 2, and 4 kHz), increasing to about 50% of those age 60-69 (Agrawal et al., 2008). This means that more than half of American adults over age 60 have hearing loss that can interfere with the detection of speech sounds.

The problem of untreated hearing loss is increasingly recognized as a major public health issue, with only about 20% of US adults with clinically significant hearing loss using hearing aids (Mamo et al., 2016). The high prevalence of hearing loss in combination with the low use of hearing aids suggests an urgent need for additional interventions, making medicines that would prevent ARHL of high interest (Wang and Puel, 2020).

Noise-Induced Hearing Loss

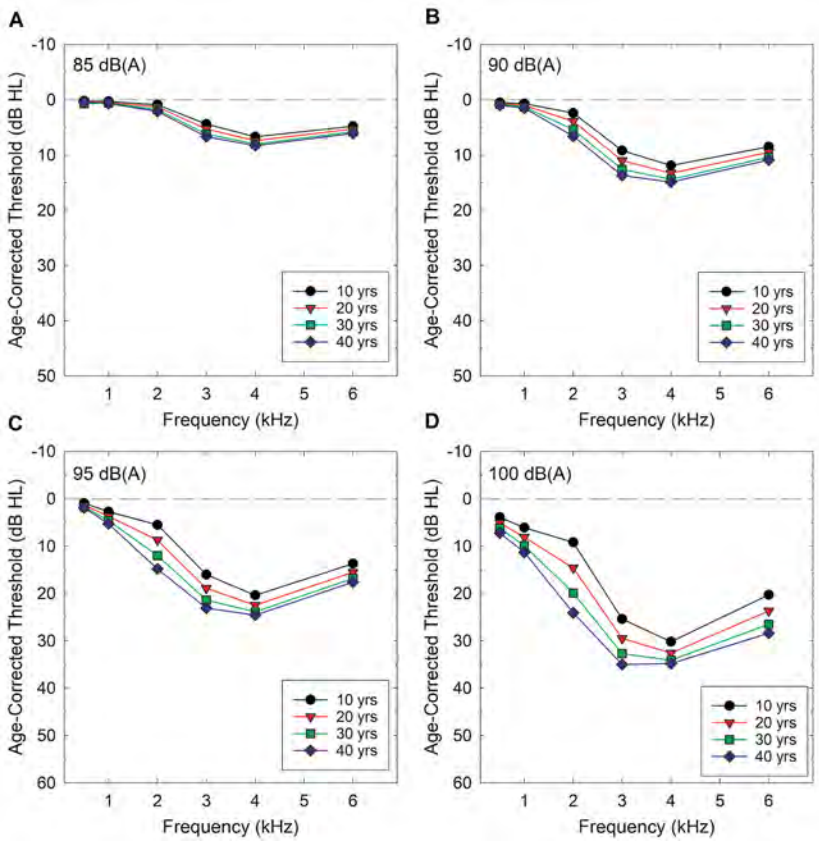
A working career can be some 40 years or so, and NIHL thus increases in parallel with ARHL developing across that same time span. NIHL occurs with any exposure long enough, loud enough, or repeated often enough to result in injury to the sensitive cochlear microstructures. NIHL typically presents as a "notched" audiometric configuration; a pattern of hearing loss in which thresholds at 3, 4, or 6 kHz are poorer than thresholds at lower frequencies (0.5 and 1 kHz) and 8 kHz. Words with energy in the affected frequency range, including for example words with the consonants "s," "f," and "th," may be affected first, with additional speech sounds becoming more difficult to detect or identify as NIHL progresses. Some 17% of the US adult workforce is exposed to hazardous workplace noise (Tak et al., 2009), and nearly 25% of US adults have a "notched" audiometric configuration

(Carroll et al., 2017). Thus, NIHL affects speech communication for millions of US adults.

Figure 3 illustrates "expected" noise-induced changes in hearing after subtracting expected ARHL for workers who are exposed to different amounts of noise for 8 hours per day. A-weighted decibels are decibel SPLs that have been "adjusted" as the US Occupational Safety and Health Administration (OSHA; 1983) requires for the measurement of workplace noise. Expected NIHL is illustrated for 8-hour exposures to 85 (**Figure 3A**), 90 (**Figure 3B**), 95 (**Figure 3C**), and 100 (**Figure 3D**) dB(A) exposures for durations of 10-40 years. Below 85 dB(A), occupational noise exposure is not regulated. Workers exposed to 85 dB(A) noise for 8 hours per day must be enrolled in a hearing conservation program and provided with hearing protection device (HPD) options, including earplugs or earmuffs. If workers are exposed to more than 90 dB(A) noise for 8 hours per day, they are required to use provided HPDs.

The data plotted in **Figure 3** come from tables provided by OSHA (1981) and include data collected before HPD use was regulated by OSHA. From the data in **Figure 3**, it is evident that significant occupational NIHL occurs within the first 10 years of exposure, with deepening and widening of the noise notch into additional frequency regions as exposure continues over the course of the 40-year working career. These patterns highlight the urgent need for interventions that effectively prevent NIHL. Although HPDs are highly effective when used consistently and correctly, NIHL associated with occupational exposure remains stubbornly persistent across industries (Themann and Masterson, 2019).

Figure 3. *Median noise-induced hearing loss (NIHL) after subtracting "expected" effects of age from the US Occupational Safety and Health Administration (1981) data tables for 85 (**A**), 90 (**B**), 95 (**C**), and 100 (**D**) decibel sound pressure levels (SPL), adjusting for A-weighted sound level as required by the Occupational Safety and Health Administration (1983). Adapted from Le Prell et al. (2022), with permission of Acoustical Society of America. Copyright 2022, Acoustical Society of America.*



Although **Figure 3** illustrates one set of expectations for age-corrected NIHL in workers, it must be noted that there is tremendous individual variation in the onset and progression of both ARHL and NIHL. This makes the precise division of hearing loss into ARHL and NIHL components difficult at the individual patient level. Multiple age-correction approaches are available (for a review, see Le Prell et al., 2022). The OSHA Technical Manual (OTM), which provides guidance on OSHA safety regulations, was completely revised and updated in 2021 (OSHA, 2021). One major change is that the updated OTM now refers to the age-correction factors of Flamme et al. (2020). Based on recent epidemiological data, these new tables allocate significantly less hearing loss to aging and thus more of the worker-observed hearing loss is attributed to noise.

Mechanisms of Pathology

Efforts to characterize the underlying pathology for NIHL, DIHL, and ARHL reveal that sensory cells and other important inner ear structures are damaged by noise, ototoxic drugs, and age-related breakdown, with pathology similar for all three types of loss. From a practical perspective, hearing loss identified as "ARHL" is not purely age related but rather reflects the accumulated loss of cells to both age-related breakdown and diverse microinjuries occurring across the life span. It is perhaps because of the overlapping patterns and mechanisms of cell death that experimental medicines have often shown a significant overlap in preventing NIHL and DIHL, albeit with more mixed findings for ARHL prevention.

Patterns of Cell Death and Cell Regeneration

One cell type long known to be highly vulnerable to noise, ototoxic drugs, and aging is the outer hair cell (OHC) of the cochlea (inner ear). If the OHCs are damaged, then NIHL, DIHL, or ARHL will develop; in other words, the normal audiogram shown in **Figure 1B** will change, shifting to look more like those shown in **Figure 2** in the case of ARHL or as a sum of the losses shown in **Figures 2** and **3** for a worker who is both noise exposed and aging. Readers are reminded that the hearing loss shown in **Figure 3** has been adjusted by values akin to those shown in **Figure 2** to illustrate NIHL after accounting for the expected ARHL.

Much of the above discussion has focused on the audiogram and detection thresholds. Patients are often concerned about sound identification in addition to sound detection. In other words, they can hear that speech is present, but they cannot sufficiently resolve the sound to understand the words. Subtle OHC damage is associated with deficits on hearing-in-noise tests (Parker, 2020).

Damage to other cells also compromises hearing in noise. Specifically, damage to inner hair cells (IHCs), a second type of sensory cell, or the AN fibers that carry sound information from the IHCs to the brain has recently been found to compromise the word understanding pathway (Grant et al., 2022). The IHCs and their connections with the AN are highly vulnerable to noise, drug, and aging injury (Liberman and Kujawa, 2017). Increased understanding of the importance of the IHC/AN pathway in speech understanding has created new inner ear drug targets in addition to those for the OHCs.

The past 15-20 years brought remarkable progress, with multiple new and fundamental insights into NIHL, DIHL, ARHL and the entire series of physiological events leading to cell death in the inner ear (Dinh et al., 2015). In parallel to improved understanding of cell death events, basic understanding of the molecular development of the inner ear has dramatically increased. The ability to deliver gene therapy or small molecule therapies that "reinitiate" developmental sequences that drive new cell division and development of those cells into new inner ear sensory cells has opened new doors to novel treatment approaches (Lewis, 2021).

Experimental Medicines for Hearing Loss Prevention

A wealth of basic scientific data show protection against NIHL, DIHL, and, to a lesser extent, ARHL, primarily within preclinical (animal) models. The data provide evidence of benefit for a variety of investigational medicines acting on different biochemical processes associated with sensory cell death. Data have been generated in diverse rodent models (rat, mouse, guinea pig, chinchilla) and in protocols that produce varied degrees of cochlear injury. Although the heterogeneity of experimental models precludes comparison of the relative benefits of different investigational medicines, the high rate at which positive results are reported highlights the promise that one or more investigational inner ear medicine will one day prove effective for human use. It is against this backdrop that one Special Issue was published in 2019 and a second

Special Issue will be published in 2023 in *The Journal of the Acoustical Society of America* (*JASA*).

The first *JASA* Special Issue, "Noise-Induced Hearing Loss: Translating Risk from Animal Models to Real-World Environments" (see bit.ly/3peiAXm; see introduction by Le Prell et al., 2019), addressed three specific themes: populations at risk for NIHL, models used in the preclinical testing of investigational inner ear medicines, and factors that influence individual risk for NIHL. Three human populations at significant risk for NIHL include workers exposed to occupational noise, military personnel, and musicians and other performing artists. Novel drugs are of particular interest for each of these populations, either because HPDs have not been broadly effective in protecting hearing for all who are required to use them (workers, soldiers) or because HPDs can prevent the user from hearing sounds that they need to hear to be effective in their jobs (soldiers, musicians, workers).

Clinical Assessment of Experimental Medicines

The second *JASA* Special Issue, "Noise-Induced Hearing Disorders: Clinical and Investigational Tools," provides comprehensive information about the measurement of noise-induced hearing deficits in clinical care and clinical trial settings. Although the audiogram in **Figure 1** is the clinical gold standard, diagnostic tests that identify the presence of specific noise-induced cochlear pathology provide additional tools for characterizing cochlear injury induced by noise, drugs, aging, or other injury process.

The second Special Issue explicitly addresses issues related to the selection of outcome measures and study end points in clinical trials investigating the prevention of hearing loss or restoration of auditory function. The audiogram is by far the most common outcome measure. A study end point is the specific analyzed parameter used to determine if the investigational treatment was effective. With the audiogram as an outcome measure, an audiometric end point could be a statistically significant reduction in the rate at which threshold shifts of 15 dB or greater are observed. If clinical trial participants receiving experimental medicine develop a hearing loss of 15 dB or greater significantly less often than the participants receiving an inert control (placebo), the audiometric end point would be accomplished.

Members of the public can learn about investigational medicines for the inner ear or experimental drugs being evaluated for other health conditions through ClinicalTrials.gov. Clinical trials under oversight of the US Food and Drug Administration (FDA) and clinical trials funded by the US National Institutes of Health (NIH) must be listed on this website. Clinical trials can also be voluntarily posted by study sponsors.

Role of the United States Food and Drug Administration

The FDA has a vast role in ensuring the safety, efficacy, and security of human and veterinary drugs, including biological products. The FDA prospectively reviews study outcome measures and end points when the clinical trial is submitted for review through the Investigational New Drug (IND) application process. It falls to the FDA to approve study end points that are ultimately used to determine if a drug is effective. Therefore, they must decide how much hearing loss is to be prevented for an investigational medicine to be deemed effective in preventing hearing loss. Similarly, they must determine how much hearing is to be recovered for a biological therapy to be deemed effective in restoring hearing.

Although the FDA would ideally have consistent standards for study end points, it must be recognized that expected hearing deficits vary widely from one clinical population to another. End points that are appropriate for one population may not be useful for a different population with a different pattern of hearing loss or a different time line for progression of hearing loss. It must also be remembered that not all clinical trials are under the oversight of the FDA. For those clinical trials that do fall under FDA oversight, the overarching goal is that study end points represent clinically meaningful benefits. The remainder of this article discusses outcome measures and study end points of interest for investigational inner ear medicine trials.

The Audiogram

The audiogram is by far the most common outcome measure for clinical trials evaluating prevention of NIHL, DIHL, or other forms of acquired hearing loss. Although the audiogram is almost universally used, audiometric end points differ significantly (Le Prell, 2021, 2022). As in studies using animal models, this makes it difficult to compare results across clinical trials completed to date.

Word Identification

Although the audiogram is the most common outcome measure (Le Prell, 2021, 2022), word identification in quiet and in noise are the most important functional measures for patients. Speech understanding is a key need, and about 10% of patients seek help for hearing-in-noise difficulties in the absence of any sound detection deficits (Parthasarathy et al., 2020).

The importance of speech communication to patients cannot be overstated. Communication difficulties and their impact on the quality of life were a key topic of discussion at the externally led patient-focused drug development (PFDD) meeting for people and families living with sensorineural hearing loss (Kelley et al., 2021). A PFDD is a structured meeting during which patients are invited to help the FDA and other stakeholders understand symptoms that matter most to patients, the impact of symptoms on daily life, and patient perspectives on therapies. The PFDD report for the meeting on sensorineural loss not only noted patient dissatisfaction with current hearing rehabilitation options but also the significant patient interest in and hope for regenerative therapies.

Difficulty identifying words delivered in quiet or against noise backgrounds is not captured by the audiogram. The term hidden hearing loss has therefore been used to describe difficulties understanding speech in noise (Kujawa and Liberman, 2015). Speech-in-noise measures have not routinely been included in clinical trials evaluating inner ear medicines to date (Le Prell, 2021, 2022), but their importance within the context of clinical trials is increasingly identified as important (Foster et al., 2022).

High-Frequency Hearing

Hearing at frequencies above 8 kHz has been described as important for music perception by musicians and other performing artists (Wartinger et al., 2019). Routine monitoring of hearing at frequencies above 8 kHz is therefore recommended for this population in the Santucci et al. (2020) guidance document. In the general population, measures of hearing at frequencies above 8 kHz will provide information about the function of the sensory cells in the inner ear regions that code those high frequencies, but whether damage to these regions will impact speech communication remains unclear (for a review, see Lough and Plack, 2022).

As discussed in the ***Role of the United States Food and Drug Administration***, the FDA is particularly concerned with clinically meaningful end points. Whether hearing preservation at frequencies above 8 kHz is clinically meaningful for some or all patients is thus an important question. This is a particularly important issue for DIHL and ARHL trials. Both DIHL and ARHL begin at frequencies above 8 kHz and progress to lower frequencies associated with speech communication over extended time periods. Protection of hearing above 8 kHz would be promising but does not necessarily assure that hearing at frequencies associated with speech communication will ultimately be protected.

Measures of Outer Hair Cell Function in Prevention and Regeneration Studies

Many regenerative therapies have the goal of OHC regeneration, although neural regeneration is also a goal (Lewis, 2021). The integrity of the OHC population can be evaluated by measuring distortion product otoacoustic emission (DPOAE) responses. DPOAEs provide a remarkably sensitive test of inner ear sensory cells using a miniature microphone inserted into the ear canal to measure nonlinear sound distortion elements (Lonsbury-Martin et al., 2017). DPOAE responses are only within the normal range if the OHC population is intact. Decreased DPOAE amplitude is observed if the OHCs are damaged or missing.

DPOAEs have been included in a few clinical trials evaluating investigational inner ear medicines, but, like high-frequency hearing, the clinical significance of DPOAE measures is uncertain. DPOAE amplitude will decrease with subtle OHC loss that is not yet sufficient to compromise threshold sensitivity as measured using the audiogram. This raises the possibility that DPOAEs could be considered a surrogate end point (i.e., a substitute measure that is expected to predict clinical benefit). On the other hand, DPOAE deficits are correlated with hearing-in-noise deficits (Parker, 2020), and the addition of hearing-in-noise measures might reduce the need for DPOAE surrogate measures of benefit.

To be clear, prevention of cell death is a positive finding. The crux of the issue with the use of DPOAEs in clinical trials is the extent to which the prevention of subtle injuries not yet noticeable to the patient/participant are clinically meaningful.

Measures of Inner Hair Cell/Auditory Nerve Pathway Regeneration

Seminal data from rodent models (Liberman and Kujawa, 2017) drove global interest in damage to the IHC/AN pathway and possible functional changes in humans with this pathology (Bramhall et al., 2019). A major challenge for human research is that there are no tests that specifically document the integrity of the IHC/AN pathway, although there are tests that measure the strength of electrical activity generated by the AN when it discharges in response to sound. Several datasets suggest that word understanding in quiet (Grant et al., 2022) and in noise (Grant et al., 2020; Mepani et al., 2020) is compromised when the IHC/AN pathway is inferred to be damaged based on decreased sound-evoked electrical activity of the AN. New data continue to emerge regarding tests for the integrity of the IHC/AN pathway in humans and provide growing evidence for age-related and, to a lesser extent, noise-induced pathology of the IHC/AN system in humans (Bharadwaj et al., 2022). Bramhall (2021) provides a careful discussion of the challenges of this type of work given that both OHC loss and the IHC/AN pathway pathology have the potential to impact neural measures and functional test results.

Summary and Conclusions

The topics reviewed here highlight the significant public health issue posed by acquired hearing loss, therapeutic insights gained through basic mechanistic inquiry, and the possible promise of both protective and regenerative medicine approaches. Clinical trials continue to emerge but do not yet provide clear insights into which experimental agents will be successful for which indications. New strategies better addressing acquired hearing loss are needed, hopefully including future FDA approval of safe and effective inner ear medicines. With success in clinical testing and FDA approval, new medicines could decrease the incidence and prevalence of acquired hearing loss, and regenerative therapies could decrease the impact of existing hearing loss. Despite the remaining challenges, major progress has been made, and there is good reason to believe that one or more experimental medicines will ultimately become new therapeutic options.

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About the Author

Colleen G. Le Prell
colleen.leprell@utdallas.edu

The University of Texas at Dallas
1966 Inwood Road
Dallas, Texas 75235, USA

Colleen G. Le Prell is the Emilie and Phil Schepps Professor of Hearing Science; chair of the Department of Speech, Language, and Hearing; and program head for the PhD Program in Speech, Language, and Hearing Sciences at the University of Texas at Dallas. She has received research funding from government, industry, and philanthropic sources. Clinical, translational, and applied research in her laboratory advances the understanding and prevention of noise-induced hearing loss.