been shown to induce a robust growth of neurites in cultured SGN (Staecker et al. 1995; Green et al. 2008 for reviews). Several NTFs have been shown to induce regrowth of afferent and efferent peripheral processes into the cochlea after hair cell loss in vivo when provided either intrascalar by mini-osmotic pumps (Altschuler et al. 1999; Miller et al. 2007; Glueckert et al. 2008) or more recently after gene transfer (Shibata et al. 2010).

In preclinical implant studies, treatment with these factors has been shown to enhance electrical responsiveness, increasing both threshold sensitivity and dynamic range of electrical auditory brain stem responses (ABR) (Miller et al. 2002; Yamagata et al. 2004; Maruyama et al. 2007, 2008). In these studies, it is not clear to what extent this enhanced responsiveness reflects maintenance of SGN and to what extent it reflects regrowth of peripheral afferent processes; it is likely that both factors contribute. Electrical stimulation may also induce regrowth of peripheral processes (Altschuler et al. 1999), and NTF-induced regrowth has been shown to be further enhanced by antioxidants (Maruyama et al. 2007, 2008). Immediately after implantation, it may be appropriate to infuse NTFs to initiate a burst of neurite regrowth, followed (or accompanied by) electrical stimulation with particular parameters for the first weeks, followed then by different parameters of electrical stimulation for maintenance of the connection and signal processing. Antioxidants may be used over a period before and after implantation to enhance regrowth, as well as protect from the trauma of implantation (Abi-Hachem et al. 2010), with little risk.

3.2 Restoration

3.2.1 Regeneration

The exciting discovery of hair cell regeneration after sensory cell death in the chick (e.g., Corwin and Cotanche 1988; Ryals and Rubel 1988) provided the great promise that key factors driving regeneration in birds could be introduced in mammals, including humans. Although this task has not yet been fully accomplished, great progress has been made. These efforts have spawned a set of strategies to identify and analyze the inducing factors, and the first steps toward creating new hair cells in the damaged mammalian ear have been taken. In species that naturally regenerate sensory cells when damaged, the source appears to be the supporting cells, and the mechanism often involves a dedifferentiation, reentry to cell cycling, and division, with one daughter cell becoming a hair cell and the second maturing to a replacement supporting cell, thus maintaining the mosaic of the sensory epithelium critical to mechanoelectric transduction (Kwan et al. 2009; Cotanche and Kaiser 2010 for recent reviews). If the factors that induce, modulate, and guide regeneration in the chick can be induced in mammals, perhaps a comparable regeneration can occur.

Important guidance has also come from an increased understanding of the transcription factors, their downstream pathways, and the molecular mechanisms that control the normal development of the mammalian cochlea and guide an eventual

hair cell versus supporting cell fate decision. Atoh1 is a key transcription factor in the hair cell fate choice (Maricich et al. 2009), and forced upregulation of Atoh1 by gene transfer can induce supporting cells into a hair cell phenotype in the mature cochlea in the profoundly deafened guinea pig with nerve fiber innervation and, remarkably, the return of hearing (Izumikawa et al. 2005). These findings provide a key validation of our understanding of many of the mechanisms involved in hair cell development and repair. However, translation to human application will be technically difficult when involving gene therapy (see Sect. 3.4.1 for further discussion), and a gene product (protein) approach affecting other key events in the differentiation process is also discussed later (Sect. 3.4.2).

3.2.2 Replacement: Cellular

An alternative to gene therapy for replacement of lost sensory cells or auditory nerve is use of exogenous cell implants. This approach has been applied to the neurodegenerative disorder Parkinson's disease, with initial promising results (see Winkler et al. 2005 for a review). Although technical hurdles need to be resolved before cell therapy becomes a realistic clinical tool for the treatment of Parkinson's disease, the promise of this strategy is clear. Importantly, the same approach could be applied to the dysfunctional inner ear. One could implant exogenous hair cells or auditory neurons or implant progenitor cells that are induced to become sensory cells or neurons. However, because the cochlea has an extremely complex three-dimensional structure, every cellular element needs to be precisely placed and oriented to achieve proper function. It is therefore difficult to imagine externally applied cells reaching the appropriate location and assuming the necessary functional connections to adequately replace missing hair cells and provide a functional replacement. The more common approach to restoring sensory cells in the inner ear has, therefore, focused on repair (as previously described) rather than replacement. Because the structural organization of the spiral ganglion is much less restrictive, it is conceivable to imagine a cell therapy approach focusing on the SGN being successful (see Li et al. 2004; Ulfendahl et al. 2007; Altschuler et al. 2008; for reviews).

Several cell types have been tested for the purpose of implantation into the inner ear for nerve or hair cell replacement. These range from the most immature embryonic stem cells to well-differentiated neural tissue (Ulfendahl et al. 2007; Altschuler et al. 2008; Edge and Chen 2008; for reviews). Stem cells are characterized by their capacity for self-renewal and give rise to many different cell types. Embryonic stem cells have been a major focus of research as transplantation candidates because they are both proliferative and capable of generating all tissues of the mammalian body. The cells replicate indefinitely in vitro, which makes it possible to culture them on a large scale and could create a nearly unlimited source of transplantable cells for auditory nerve replacement. Adult stem cells are found also in several tissues of the adult organism, where they normally produce new differentiated cells necessary for restoring degenerated cells.

The challenge in the use of undifferentiated stem cells, whether embryonic or adult, is to induce them to the appropriate phenotype. This could be done before placement in

the target site or after placement. The cochlear fluids can provide an avenue for infusion of agents to influence phenotype when stem cells are placed into scala tympani. Embryonic stem cells naturally differentiate into neurons and glia; however, the percentage reaching neuronal phenotype is small when no further treatment is applied. Gene transfer of the neuronal transcription factor Neurogenin2 (Ngn2) improved the percentage reaching a neuronal phenotype (Hu et al. 2005b). Mouse embryonic stem cells engineering for inducible expression of neuronal transcription factor Neurogenin1 (Ngn1) allowed for more natural transient expression. Twenty-four hours of induced Ngn1 expression was followed by infusion of GDNF and BDNF, which are the NTFs naturally received by SGN during development. This induced the majority of the implanted stem cells into a glutamatergic neuronal phenotype both in vitro and in vivo after placement into guinea pig scala tympani (Reyes et al. 2008).

An alternative to undifferentiated stem cells is to use progenitor cells; these are more specialized cells that will develop into mature, differentiated cells of a specific type that could reduce the risk of uncontrolled proliferation after transplantation. Such cells have been found in both auditory and vestibular components of the developing inner ear (Li et al. 2003a,b; Martinez-Monedero et al. 2008; Oshima et al. 2010). However, the number of progenitor cells rapidly declines after birth and only relatively small numbers remain in the sensory epithelium of the mature mammalian cochlea (Lopez et al. 2004). Interestingly, progenitor cells have been isolated from adult human modiolus removed during surgeries (Rask-Andersen et al. 2005); these progenitor cells formed neurospheres in vitro, and could be valuable for human application. Unfortunately, as in the animal studies, the populations of stem or progenitor cells in adult tissues are relatively small and do not proliferate as readily as embryonic stem cells, and thus may not be able to give rise to enough cells for cell replacement therapies.

An ideal situation would be to use tissue from the receiving subject itself, so-called autografting. An autologous graft essentially eliminates the host reaction. Naito et al. (2004) applied an autologous graft to the inner ear with promising results. The recent technique for reprogramming somatic cells into induced pluripotent stem (iPS) cells (Takahashi and Yamanaka 2006) is exciting. This method would allow iPS cells, derived from the recipient, to be transplanted back to the same individual after necessary modifications and without the risk of rejection. Nishimura et al. (2009) have recently applied the technique to the inner ear, although they did not transplant the cells back to the same individual.

If the challenge of generating replacement cells with appropriate sensory hair cell phenotype is met, there are still three remaining challenges: survival, integration into an appropriate location/niche, and finally, forming central nervous system (CNS) connections and achieving function. Survival of new neural connections may require the same or similar neurotrophic or maintenance factors as required by endogenous auditory nerve SGN (Ulfendahl 2007; Altschuler et al. 2008). Indeed, excellent in vivo survival of mouse embryonic stem cells implanted into guinea pig cochlea was found when exogenous NTFs were provided into scala tympani (Altschuler et al. 2008; Reyes et al. 2008). Cell survival was also greatly enhanced with a cografting approach in which, in addition to the embryonic stem cells, embryonic neural tissue was implanted (Hu et al. 2004b, 2005a). Because electrical activity has been shown to enhance SGN survival after deafness in vivo (Miller et al. 2003a) or

in vitro (Hansen et al. 2001, 2003; Green et al. 2008), it may also be that stem cells that reach a neuronal phenotype will have improved survival if they become activated by either cochlear electrical stimulation with a cochlear prosthesis or if they connect to remaining IHCs.

Although there is a challenge for integration into appropriate location and niche, the scala tympani provides access to the entire perilymphatic fluid compartment, and implanted donor cells may be able to travel to functionally relevant locations throughout the cochlea. Although the perilymphatic compartment is anatomically separated from the spiral ganglion, the barriers are literally "full of holes." Indeed, the separating bone structures contain microscopic fenestrae, canaliculae perforantes (Küçük et al. 1991), which provide a path for the implanted cells to reach the spiral ganglion region. An alternative, and possibly less damaging route, would be to access the perilymphatic compartment via the lateral semicircular canal of the vestibular part of the inner ear, as has been demonstrated by Iguchi et al. (2004).

For cells to replace or supplement SGN they must also bridge the connection between the ganglion region and the cochlear nucleus in the brain stem. Recent experiments have shown that embryonic stem cells or dorsal root ganglion cells transplanted to the transected auditory nerve migrated along the nerve fibers in the internal auditory meatus and, in some cases, even reached close to the cochlear nucleus in the brain stem (Hu et al. 2004a). Interestingly, embryonic brain tissue transplanted to the acutely transected ventral cochlear tract resulted not only in regeneration but also functional recovery (Ito et al. 2001). However, there are many chemical factors that produce a barrier between peripheral and central nervous system and could impede the ability of central processes of replacement neurons to make a connection in the cochlear nucleus. The central connection would also need to connect to cochlear nucleus neurons in a tonotopic manner.

It has been hypothesized that if the SGN population were to be supplemented with exogenous cells, the efficiency of the cochlear prosthesis would improve. Hu et al. (2009) reported on experiments in which embryonic dorsal root ganglion cells were implanted into the inner ears of deafened animals fitted with a scala tympani electrode for monitoring hearing function using electrically evoked ABR. NGF was infused to provide trophic support for the implanted cells. Indeed, extensive neurite projections were observed to extend from the implanted cells, through the thin bony modiolus, to the host spiral ganglion. However, no significant difference was seen in the electrical thresholds or input/output functions. The negative results could be due to the low survival rate of the implanted cells, or lack of functional contacts between the implanted cells and the host nervous system.

3.3 Replacement

3.3.1 Prostheses

Although cochlear prostheses represent one of the major treatment success stories, restoring hearing to thousands of the profoundly deaf, there are still major advances

remaining in the future. The patient population continues to increase as benefits are being shown from placing prostheses into patient ears with remaining hearing, and then providing a hybrid of acoustic and electrical stimulation to those patients. In patients with significant residual hearing, but low scores in speech discrimination tasks, implants can be of remarkable benefit, yielding improved abilities to understand speech (Lenarz 2009). These patients typically will demonstrate little or no hearing at 1 kHz and above; but will have significant remaining low-frequency hearing, showing losses in the 30–40 dB range below 1 kHz. To provide electrical hearing and preserve residual acoustic hearing, implants have been modified from long, scalar filling, and modiolar hugging; to short, thin, free-floating, with the recent addition of amplified acoustic stimulation of the low frequencies, in a "hybrid" device (Woodson et al. 2010 for recent review). Enhanced performance is seen in these ears with electrical stimulation, presumably because of a more physiologic auditory nerve, reflecting functioning hair cells throughout a major apical portion of the cochlea, which is further enhanced by the acoustic stimulation, the latter contributing significantly to sound localization and discrimination of speech in noisy backgrounds. There may also be a contribution from electromotile responses of surviving hair cells (e.g., Grosh et al. 2004).

One major area of challenge for current cochlear prostheses is to improve speech discrimination in noise. Many patients demonstrate remarkable speech discrimination in quiet but their scores rapidly deteriorate in noise (Munson and Nelson 2005; for general discussion of challenges resolving speech in noise, e.g., Shrivastav and Still, Chap. 7). Another long-standing challenge is to allow improved appreciation of music (Gfeller et al. 2008). There is increasing bilateral implantation of prostheses, providing a potential for improved sound localization. Increasingly, the benefits observed have offset the earlier reservations about bilateral implantation. In the past, unilateral implants were encouraged with the hope of reserving one ear for potential later technical improvements in the implant. However, the ease of replacement surgery in the vast majority of cases where required has reduced concerns related to bilateral implantation.

One solution to provide better speech discrimination in noise and allow appreciation of music and language nuances depending on tonal modulations would be an improved channel separation, allowing an increased number of stimulation sites on the prosthesis and dividing the signal into more channels. Directed regrowth of peripheral processes toward stimulation sites or using stem cells to provide a closer target for stimulation are also potential solutions. Another approach is to place prostheses directly in the auditory nerve (Middlebrooks and Snyder 2007), providing more intimate contact of electrode to neural element, or to place prostheses in central auditory system sites such as the cochlear nucleus (Colletti and Shannon 2005; Schwartz et al. 2008) or inferior colliculus (Lim et al. 2008, 2009). Implantation into the central auditory system further increases the implant patient candidate pool, as it allows prostheses for those with unimplantable cochleae or lost auditory nerve populations. The remarkable plasticity of the central auditory system (e.g., Kaltenbach, Chap. 8) suggests the potential for successful "remapping" of these tonotopically organized nuclei with the advent of electrical stimulation via a central auditory system implant.

With electrical stimulation benefits in part dependent on hair cell survival and acoustic hearing completely dependent on hair cell survival, primary concerns have focused on reducing the trauma of cochlear implantation (hence smaller implants, with much smaller fenestrae) and eliminating any negative long-term effects of the implant or stimulation. The same strategies used for protection and repair from NIHL and ototoxicity could also be used to reduce loss of residual hearing from cochlear implantation trauma. This could include use of NTFs, immunosuppressants, cell death pathway inhibitors (Bcl-2 genes, JNK inhibitors) (Van de Water et al. 2010), antioxidants (Abi-Hachem et al. 2010), and agents that may enhance cochlear blood flow. Acute delivery into the cochlea at the time of surgery in forms that allow delayed release over time may be possible, however, risk factors should be taken into consideration (Garnham et al. 2005). The antioxidants, with and without vasodilators, that are being evaluated in multiple human trials for prevention of NIHL could also be considered for trials to improve postimplant hearing preservation and have the advantage of oral delivery, low cost, and minimal or no systemic side effects when used at recommended intake levels.

These considerations lead to a final area in the future frontiers of cochlear prostheses: the use of drug delivery systems coupled with cochlear prostheses. The use of drug interventions coupled with implants to preserve residual hearing is based on the same strategies discussed to preserve and regrow the auditory nerve. Future implant frontiers will include the integration of drug delivery with implants with the ability to deliver locally and safely NTFs, proteins, and other agents, in some cases with biopolymer–nanoparticle encapsulation of drugs, in systems that will allow burst, delayed, and sustained release. In the future, biopolymer and nanoparticle systems will be used to deliver genetically designed cells fixed to implants that can release growth factors and serve as targets for nerve growth, or extend neurites that will grow into the auditory nerve and enhance connectivity to the CNS.

3.4 Methods

3.4.1 Gene Therapy

Gene therapy technology has improved in recent years, making it a promising technique for treating inner ear disorders; the inner ear holds several unique advantages as a model for gene therapy. First, the cochlea is anatomically well suited for in vivo gene therapy both accessible and with a fluid compartment (Salt and Plontke 2009 for review). The relative isolation of the cochlear compartments minimizes unwanted effects of the introduced gene into other tissues. The inner ear is fluid filled, allowing all functionally important cells to be accessed by a transfection reagent. The concentration and dosage of complexes introduced to the cochlea can easily be modulated with a single injection or longer infusion via an osmotic pump. Cochlear endolymph and perilymph volumes have been characterized in guinea pigs, rats, mice, and also humans (e.g., Thorne et al. 1999), so adverse effects of high volume

and pressure can be avoided. In addition, a variety of precise physiological measures, such as otoacoustic emissions, compound action potentials, evoked potentials, and ABR, have been developed to monitor the function of specific cells, which makes reliable assessment of efficacy and safety of gene therapy practical. Finally, many genes have been recently cloned in the mouse and human cochlea. More than 100 different genes have been identified that affect inner ear development or function, as well as many loci known to be involved in deafness (see also Gong and Lomax, Chap. 9). A transgenic technique has been demonstrated in shaker-2 mice to correct deafness (Probst et al. 1998).

Gene therapy with NTFs has been the most frequent application of gene therapy in inner ear animal research. For example, inoculation of an adenoviral vector encoding human GDNF gene (Ad.GDNF) into guinea pig cochleae via the round window membrane 4 days before injection of the ototoxic aminoglycoside antibiotic kanamycin (KM) and the loop diuretic ethacrynic acid (EA) provided better hearing and less hair cell damage compared with controls (Ad.lacZ vector) (Yagi et al. 1999). Coinoculation of two vectors, one encoding human TGF-beta1 gene and the other encoding human GDNF gene, into guinea pig cochleae 4 days prior to injection of the same ototoxic agent combination (KM and EA) provided better hearing and less hair cell loss compared to inoculation of only Ad.GDNF (Kawamoto et al. 2003). Endogenous antioxidant systems can be upregulated in the same way as endogenous NTF systems, with similarly protective benefits. Adenoviral vectors for overexpression of catalase and Mn superoxide dismutase (SOD2) protected hair cells and hearing thresholds from a combination of KM and EA when given 5 days before ototoxic insult. After inoculation, there was a significant increase in catalase and a moderate elevation in SOD2 levels in tissues of the cochlea inoculated with the respective vectors (Kawamoto et al. 2004). Gene therapy to prevent NIHL has been more challenging, perhaps because of the more complex mechanisms of cell death being initiated (e.g., Henderson et al. 2006; Hu, Chap. 5, for reviews). While exogenous GDNF administered intracochlearly can protect the inner ear from NIHL (Shoji et al. 2000a, b), Kawamoto et al. (2001) reported no difference in the protection afforded by Ad.GDNF versus control Ad. lacZ vectors.

As described previously, Atoh1 overexpression after gene transfer can promote hair cell regeneration from supporting cells after hair cell destruction (Izumikawa et al. 2005). Other more preliminary data suggest overexpression of Atoh1 may also promote recovery of the stereocilia of the cochlear hair cells after noise (Yang et al., Association for Research in Otolaryngology Meeting, 2010). The hair bundle is susceptible to acoustic trauma and ototoxic drugs, and mammalian cochlear hair cells lose the capability to regenerate the stereocilia spontaneously once lost. Atoh1 inoculated within the first week after noise exposure, however, induced stereociliary regeneration and the newly regenerated stereocilia were functional, as ABR and CM measured 1 and 2 months after Atoh1 inoculation showed significant hearing threshold improvement. These findings imply that Atoh1-based gene therapy has the potential to restore hearing after noise exposure (Izumikawa et al. 2005; Husseman and Raphael 2009).

3.4.2 Protein Transduction Therapy

The objective of gene therapy is gene delivery followed by expression of gene products that either possess a therapeutic biological activity or induce an altered cellular phenotype. Gene therapy approaches to a number of genetic disorders require long-term and appropriately regulated expression of the transgene. The short-term requirement for the presence of the therapeutic gene product raises the possibility of achieving the same objective by direct delivery of the gene product itself, rather than the gene. Recent developments in protein transduction (delivery of protein into cells) suggest this is now a realistic approach (see Tilstra et al. 2007).

Protein transduction domains (PTDs), or cell-penetrating peptides, are small peptides that are able to carry much larger molecules such as oligonucleotides, peptides, full-length proteins, 40 nm iron nanoparticles, bacteriophages, and even 200-nm liposomes across cellular membranes. They have proven useful in delivering biologically active cargoes in vivo and, remarkably, have the ability to transduce nearly all tissues, including the brain, following intraperitoneal administration of fusion proteins. At least three classes of PTDs have been described, including positively charged transduction domains (cationic), protein leader sequence–derived domains (hydrophobic), and peptides identified by phage display that are able to transduce cells in a cell-type-specific manner (tissue-specific). The positively charged cationic PTDs are the most efficient and the best characterized. These cell penetrating peptides (CPPs) include a TAT (transactivator of transcription) derived from human immunodefiency virus type 1 (HIV-1) that contains numerous cationic amino acids, where positive charges interact with the negatively charged cell membrane to facilitate permeability (Patsch and Edenhofer 2007 for review).

As described previously, a significant role of Bcl-2 genes has been implicated in NIHL as well as recovery from other auditory trauma. FNK, which has been constructed from Bcl-xL by site-directed mutagenesis based on the high-resolution crystal structure of the rat Bcl-xL, has three amino acid substitutions, Tyr-22 to Phe (F), Gln-26 to Asn (N), and Arg-165 to Lys (K), in which three hydrogen bonds stabilizing the central $\alpha 5$–$\alpha 6$ helices (the putative pore-forming domain) are abolished (Asoh et al. 2002). Compared with Bcl-xL, FNK protected cultured cells more potently from cell death induced by oxidative stress (hydrogen peroxide and paraquat), a calcium ionophore, growth factor withdraw (serum and IL-3), anti-Fas, cell cycle inhibitors (TN-16, camptothecin, hydroxyurea, and trichostatin A), a protein kinase inhibitor (staurosporine, STS), and heat treatment (Asoh et al. 2000). When FNK was fused with Tat-PTD of the HIV/Tat protein and added into culture media of human neuroblastoma cells and rat neocortical neurons, it rapidly transduced into cells and localized to mitochondria within 1 h and protected against staurosporine-induced apoptosis and glutamate-induced excitotoxicity (Asoh et al. 2002). When injected intraperitoneally, TAT-FNK gained access into mouse brain neurons and prevented delayed neuronal death in the gerbil hippocampus caused by transient global ischemia (Asoh et al. 2002). Similarly, TAT-FNK was diffusely distributed in the cochlea after an intraperitoneal administration to guinea pigs; the distribution was most prominent in the hair cells and supporting cells, followed by the SGN and

peaked 3 h after the injection (Kashio et al. 2007). Further, the TAT-FNK protein intraperitoneally injected for 8 h (3 h pre-insult, 5 h post-insult) significantly attenuated ABR threshold shifts and the extent of HC death induced by a combination of EA and KM, and it significantly reduced the amount of cleaved poly-(ADP-ribose) polymerase-positive HCs compared with that in the vehicle-administered controls (Kashio et al. 2007). When TAT-FNK was topically applied on the round window membrane of guinea pigs, this protein penetrated through the membrane, distributed diffusely throughout the cochlea with the greatest expression 6 h after application and continuing up to 24 h, and significantly reduced hair cell death and caspase-9 expression induced by a combination of KM and EA (Kashio et al., ARO meeting, 2010).

Recently, to increase the biological activity of transduced protein in cells, novel carriers that transduce the target protein in its active native structural form have been designed. For example, when a PEP-1 peptide carrier, which consists of three domains – a hydrophobic tryptophan-rich motif, a spacer, and a hydrophilic lysine-rich domain – was mixed with the target protein (e.g., GFP, β-gal) and then overlaid on cultured cells, the nondenatured target protein was transduced (Morris et al. 2001). PEP-1 peptide carriers fused with SOD1 have been shown to protect cells from paraquat-induced oxidative stress in vitro and dopaminergic neuronal cell death in vivo in paraquat-induced Parkinson disease mouse models (Choi et al. 2006). Considering the rapid progress in protein transduction technology, delivery of the therapeutic gene products (e.g., anti-apoptotic agents, antioxidants, and NTFs) to the inner ear for the optimal short period seems to be promising and needs to be studied more intensively with the goal of human application.

4 Summary and Conclusions

As detailed in this chapter, and other chapters in this volume, there have been many remarkable advances in our understanding of the mechanisms associated with NIHL that have illuminated paths toward its prevention and treatment. More basic research is still needed to choose the best paths and navigate their initial hurdles, to provide guidance on which of the many approaches discussed will be the most effective, and which combinations of therapies acting by different mechanisms can provide greatest benefit. Clearly the "dirty work" of translational research is now demanded. There is sufficient knowledge of mechanisms and there are interventions with sufficient safety to begin studies in humans. There is a need for the difficult-to-fund parametric dose–response measurements of efficacy and safety, in animals and then in people; and a need to move to clinical trials. The field is much further along in some paths than others. Cochlear prostheses are, of course, already a success story, with wide application and they continue to be refined and improved. Antioxidant clinical trials are already testing for protection from noise or ototoxins. Other approaches such as stem cell therapy or induced hair cell regeneration have shown great promise on the benchtop but have yet to move from it. The fact that such a large number of approaches are being considered for prevention and treatment

provides both a large opportunity and challenge for the future. They must all be tested, compared, and contrasted under the different conditions of noise and the different resulting pathologies. All the tools and knowledge are available to begin and complete that task. The promise is great; once the initial translational efforts bear fruit, there will be safe and effective measures that reduce the prevalence of deafness and tinnitus resulting from noise and other stressors. In addition, with the demonstration that NIHL can be medically treated, a paradigm change in perspective will lead to prevention and treatment of many other causes of hearing impairment.

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KeyWords
◎難聴
◎補聴器
◎人工内耳

補聴器

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Headline

1. 難聴は聴覚経路のいずれかに障害をきたし，言語音・環境音の聴取が困難となった状態をいうが，障害部位と程度，発症の時期により多様な臨床像を呈する．
2. 補聴器は適切な聴覚検査による診断のうえで，個々の生活環境に合わせた頻回の調整と聴覚リハビリテーションを併せて行うことが望ましい．
3. 人工内耳は補聴器が有効でないような重度聴覚障害児・者を対象とした埋込み型の機器である．聴取能の改善の程度は個人差が大きく，術後のリハビリテーションと機器調整は必須である．

難聴とは末梢から中枢にいたる聴覚経路のいずれかに障害をきたし，言語音・環境音の聴取が困難となった状態をいう．「難聴」という言葉を知らない者はいないが，その病態や難聴者の日常生活上の問題について社会的な理解は十分とはいえない．本稿では補聴器に代表される聴覚補償・代償機器についてその概要を述べる．

難聴とは

難聴は障害された聴覚経路の部位により，伝音難聴（外耳から中耳まで）と感音難聴（内耳とより中枢）と大きく二つに分類される．図1に標準純音聴力検査における代表的な伝音難聴と感音難聴の聴力図を示す．縦軸が音圧，横軸が周波数を表し，図の下に行くにつれて音は大きくなり，右へいくほど音色は高くなる．図2に一般的な音がこの聴力図のどこに対応しているかを示す．アルファベットで示しているのは音声の分布である．母音は低音域にあり子音は高音域に分布しているのがわかる．ヒトの可聴範囲は約20 Hz～20 kHzであるが，聴力図では言語音の聴取に重要な125 Hz～8 kHzを示している．難聴には，それぞれの音の高さが一様にきこえにくくなる場合の他，音の高さによりきこえ方が異なる場合がある．

図3に伝音難聴と感音難聴のきこえの違いをイメージ化して示す．伝音難聴は耳を手で塞いで音が小さくきこえる状態に近いため，声を大きくする等の増幅により聴取の改善が見込める．しかし感音難聴の場合は音が小さいだけでなく歪んできこえるため，単純な音の増幅だけでは明瞭に聴取することは困難となる．ラジオのチューニングがずれた状態でボリュームを上げてもききとれないのと同様である．

以上のように難聴は，程度と種類，また発症の時期により多様な臨床像を呈し，日常コミュニケーションに支障をきたすこととなる．言語習得前の発症である場合は専門的な療育が必須であり，高齢の場合には加齢に伴う中枢機能の影響も考慮する必要がある．

補聴器の概要

補聴器（hearing aid;HA）は音振動を増幅さ

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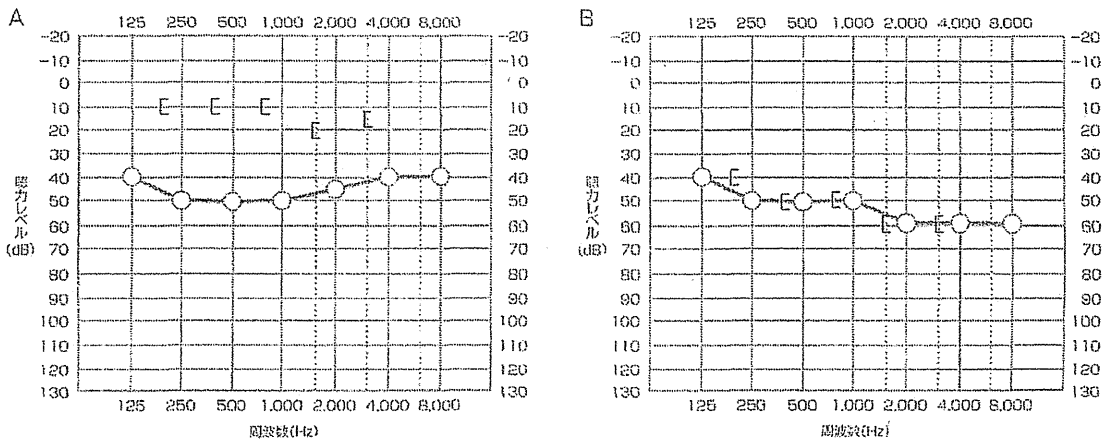

図1　代表的な伝音難聴（A）と感音難聴（B）の聴力図（いずれも右耳のみ）
[様の記号は骨導聴力閾値，○は気導聴力閾値を示す

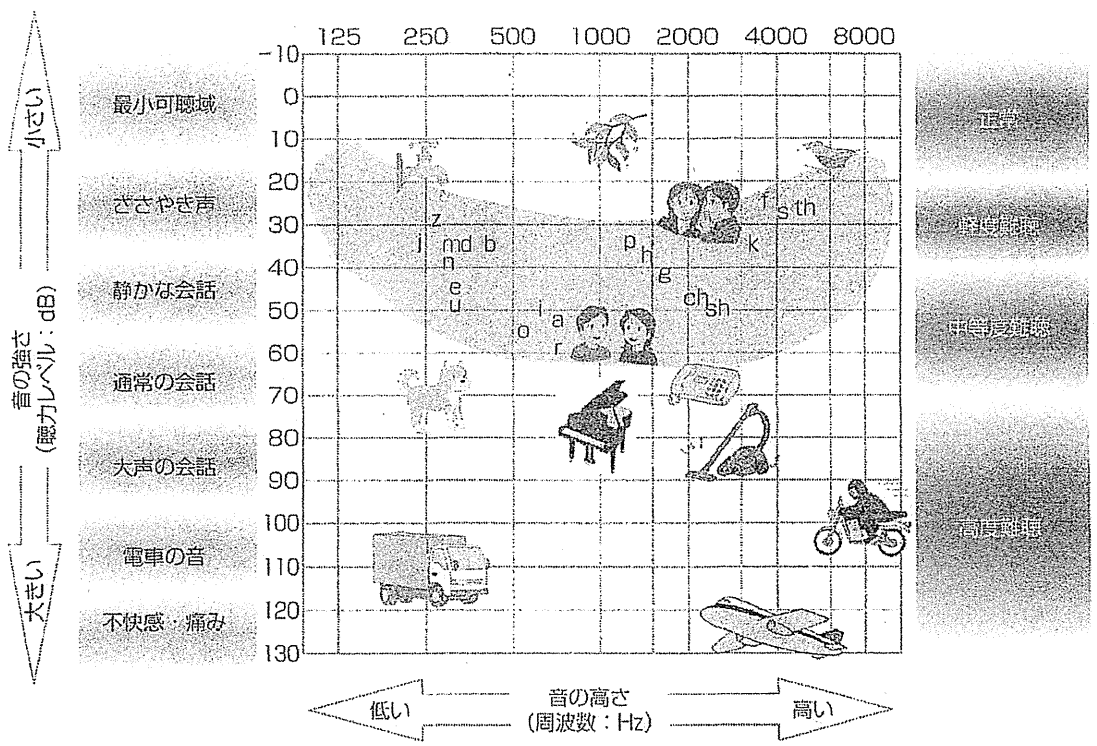

図2　聴力図　（文献1）より引用・改変）

せる機器であり，管理医療機器（クラス2）に分類される．おもにマイクロホンとアンプ，スピーカからなり，その歴史はオーディオ機器の進歩と同一である．当初は電気的増幅を使用しないラッパ様のものであったが，1900年頃の電気HAの登場以後，真空管，トランジスタ，集積回路と小型・軽量化した．近年ではデジタルHAの出現により，パーソナルコンピュータを用いて簡易に多様な調整が可能となった．

表1に代表的なHAの種類と特徴を示した．価格は数万円から数十万円以上と幅が広い