

Recent Advances in the Treatment of Sensorineural Deafness

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Abstract

In the developed world, there are currently more than 100 million people afflicted with hearing loss. In the United States and European Community alone, there are an estimated 21 million people with significant conductive hearing loss, whilst there are over 90 million suffering from moderate to severe sensorineural hearing loss. Of these, more than 65 million hearing-impaired persons are without treatment. This article presents a review of the latest technological advances and treatment options for the hearing-impaired, including external and middle ear devices, bone-anchored hearing aids, cochlear implants and hybrids, auditory brainstem implants. Finally, we take a glimpse into the future prospects of stem cell treatment and hair cell regeneration with gene delivery to the inner ear for the treatment of sensorineural hearing loss.

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Key words: Auditory brainstem implants, Cochlear implants, Hair cell, Hearing aids, Hearing loss, Inner, Sensorineural

Introduction

There have been significant advances in the understanding of middle ear mechanics and inner ear physiology in the past 2 decades. With increasing exchange and co-operation between clinicians, scientists and engineers, many new and exciting developments have emerged. Many are still in the research stage of development whilst others have reached material fruition and are being tested in clinical trials in Europe and the US.

In this paper, a brief review of the latest advances presently available for clinical use, as well as a brief glimpse into the latest basic science research involving inner ear hair cell regeneration and stem cell research, is provided. There are 6 subsections with the following headings: I) external ear implantable devices; II) middle ear implantable devices; III) bone-anchored hearing aids; IV) cochlear implants and hybrid devices; V) auditory brainstem implants; and VI) inner ear hair cell regeneration and stem cell research.

I. External Ear Implantable Hearing Assistive Devices

For patients presenting with “ski-slope hearing loss” i.e., high-frequency sensorineural hearing loss (HF SNHL) with normal hearing at the low- and mid-frequencies, it is

difficult to significantly improve hearing with conventional hearing aids because they do not provide sufficient selective amplification.¹ Although these patients feel handicapped by speech comprehension difficulties in background noise or when engaged in concurrent conversation with several persons, there are few, if any, solutions for their handicap. One new device developed to help such patients with high-frequency hearing loss is the RetroX Auditory Implant.

RetroX Auditory Implant for HF SNHL

The RetroX (Auric GmbH, Rheine, Germany) is a new semi-implantable hearing aid designed for high-frequency sensorineural hearing loss. Because the external auditory canal is not occluded, the RetroX provides selective amplification of high-frequency sounds. The RetroX device (Figs. 1, 2 and 3) consists of an electronic hearing aid unit sited in the post-aural sulcus connected to a titanium tube implanted under the auricle between the sulcus and the entrance of the external auditory canal. Implanting requires minor surgery under local anaesthesia. Sound is received through an omnidirectional microphone located at the upper pole of the unit. A dual-band numeric processor, type Digital Sound Processor (DSP), then processes the sound signal. The cut-off frequency is adjustable between 700 Hz

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and 2400 Hz. The RetroX amplifies a frequency band between 200 Hz and 5000 Hz and provides a 43-dB gain at 1600 Hz with a maximum output of 132 dB at 2000 Hz. The sound is transmitted through the titanium tube toward the external auditory canal by means of a class D receiver. Although of limited power, this receiver produces an amplification peak mainly at high frequencies. Figure 4 shows the fitting range for the RetroX based on pure-tone audiometric thresholds.

Advantages of the RetroX device:

1. The external auditory canal is not occluded, which conveys all the advantages of open ear mould hearing aids.
2. The aesthetic appearance appeals to patients because of its small size and postaural location. Although not fully concealed, it is discreet.
3. There is no contraindication to radiologic imaging or nuclear magnetic resonance because titanium does not have ferromagnetic properties.
4. The surgery for implantation of the titanium tube is minor when compared with that required for middle ear implants. It is surface surgery, comparable to ornamental piercing, without risk to the eardrum, middle ear, inner ear, or facial nerve.
5. Before implantation, a trial test with a RetroX simulator is possible. This is important as certain publications suggest that high-frequency amplification might result in decreased speech recognition for some users with severe high-frequency hearing loss exceeding 55 dB HL, especially at and above 4 kHz.^{2,3} This might be the result of cochlear dead regions or severe auditory distortions, caused by recruitment. Vickers et al⁴ tested 10 subjects with high-frequency hearing loss; for 3 subjects without a cochlear dead region, comprehension improved with high-frequency amplification; for 7 patients with a cochlear dead region, high-frequency amplification did not improve intelligibility and, sometimes, even reduced it.

Disadvantages of the RetroX:

1. As with any open ear mould hearing aid, there is a risk of acoustic feedback, which may limit amplification.
2. The RetroX requires daily conscientious maintenance (brushing) as well as prevention of water from entering the external auditory canal (shower, swimming pool). Noncompliance may result in pyogenic granuloma or local infection around the tube.
3. The high purchase price (approximately US\$3065) is a considerable expense. Because the battery life is limited to 5 days (similar to conventional in-the-ear hearing aids), the battery budget must also be considered.
4. Cleaning the ear with a cotton bud or wearing anti-noise

protective ear plugs at work can be awkward because the titanium tube opens at the entrance of the external auditory canal.

Preliminary results: In a recent European study by Garin et al,⁵ all implanted patients were satisfied or even extremely satisfied with the hearing improvement provided by the RetroX device. They used the implant daily, from morning to evening. There was a statistically significant improvement of pure-tone thresholds at 1 kHz, 2 kHz, and 4 kHz. In quiet, their speech reception threshold improved by 9 dB. Speech audiometry in noise showed that intelligibility improved by 26% for a signal-to-noise ratio of -5 dB, by 18% for a signal-to-noise ratio of 0 dB, and by 13% for a signal-to-noise ratio of +5 dB.⁵

II. Middle Ear Implantable Hearing Assistive Devices

A) Vibrant Soundbridge (Med-El Symphonix)

The Vibrant Soundbridge (VSB) was the first FDA-approved implantable middle ear hearing device to treat sensorineural hearing loss. As a middle ear implant, it leaves the ear canal completely open. The VSB features a 94% improvement in patient satisfaction,⁶ with almost a thousand patients implanted worldwide. The VSB consists of 2 components (Figs. 5 and 6), one internally implanted and the other externally worn, working together to enhance normal middle ear hearing function. The external component is the digital Audio Processor, which is programmed by an audiologist to fit the user's specific hearing loss. The implanted receiver contains the Floating Mass Transducer™ (FMT). The Audio Processor picks up sound from the environment and transmits that sound across the skin to the implanted receiver. The implanted receiver converts the signal and transmits it to the FMT. The FMT is a tiny transducer attached to the long process of the incus that directly vibrates the ossicles by mimicking the natural motion of the ossicular chain, sending an enhanced signal to the cochlea.

Preliminary results: Clinical trials of the VSB conducted in the United States and Europe⁷⁻¹⁰ have reported the following:

1. Based on subjective responses, when comparing the VSB to their own hearing aids, a majority (86%) of patients reported significantly improved sound clarity and overall sound quality. 92% of patients completed the test requirements for the study endpoint.
2. The VSB significantly improved patients' perceived benefit in many listening situations, such as: familiar talkers, ease of communication, reverberation, reduced cues, background noise, aversiveness of sound, and distortion of sound.
3. The VSB significantly reduced acoustic feedback when compared to the patients' own hearing aids.

4. Patients reported that the VSB provided better overall fit and comfort compared to their own hearing aids, and reduced maintenance issues due to cerumen and moisture accumulation.
5. For most patients, the VSB did not significantly affect residual hearing; however, a small percentage (4%) of patients experienced a decrease in residual hearing.
6. The VSB provided equal or increased functional gain when compared to the patients' own hearing aid.

The US clinical trial of the VSB was initiated in February 1996 and conducted in 10 centres.⁶ The clinical trial used a single-subject, repeated measures study design with the patient's personal hearing aid acting as the control. Study enrollment was for 53 individuals with a moderate to severe sensorineural, bilateral hearing impairment. All patients were current or previous hearing aid users. The Phase III effectiveness data was based on $n = 53$. Performance measures used in the trial included standard audiometric tests and patient self-assessments. The Profile of Hearing Aid Performance (PHAP) measured patient's performance in 7 types of environments preoperatively with their hearing aid and postoperatively with the VSB, the Hearing Device Satisfaction Scale (HDSS) measured patient satisfaction in 17 categories preoperatively with their hearing aid and then postoperatively with their VSB, and the Soundbridge Hearing Aid Comparison Questionnaire (SHACQ) documented patient preference between the VSB and hearing aids in various listening situations.

Key results: The clinical data indicated the following:

1. Residual hearing was not significantly changed in 96% of patients, supporting the safety of the device (Fig. 7).
2. Improved sound quality and clarity with the VSB was reported on the HDSS (Fig. 8):
 - 88% of patients improved their satisfaction rating of quality of their own voice when using the VSB compared to their hearing aid.
 - 86% of patients reported satisfaction with the clarity of tone and sound with the VSB, compared to 31% with their hearing aid.
 - 94% of patients improved their satisfaction rating of overall sound quality when using the VSB compared to their hearing aid.
3. Patients reported that the VSB provided better overall fit and comfort compared to their own hearing aid on the HDSS.
4. The VSB provided equal or increased functional gain when compared to the patient's own hearing aid (Fig. 9).
5. The VSB significantly improved patients' perceived benefit in various listening situations, such as: familiar talkers, ease of communication, reverberation, reduced

cues, background noise, aversiveness of sound, and distortion of sound as measured by the PHAP (Fig. 10).

Adverse events: The VSB FMT is surgically implanted in the middle ear and has similar risks to other otologic procedures such as numbness, swelling, or discomfort around the ear, the possibility of facial palsy, disturbance of balance or taste. In order to evaluate the long-term effects of the implanted part of the device, audiological data from 39 patients implanted over several implant sites across France were collected and analysed retrospectively.¹¹ The mean follow-up time was 16 months; 25 patients had a follow-up period of over 1 year. Surgery was uneventful in all cases. The present study of the 39 implanted patients with a mid- to long-term follow-up found a statistically significant modification of hearing thresholds (pre- versus postoperative) for frequencies of 0.5 kHz and 4 kHz. However, the shift of threshold was rather limited (2.79 dB and 3.34 dB respectively), and this variation was not statistically different from the evolution of the opposite non-operated ear.

B) Soundtec® Direct System

The Direct System hearing aid is another FDA-approved semi-implantable device. The device consists of a small magnet that is secured onto the incudo-stapedial joint. This can be done as a day case procedure under local anaesthesia. The person wears what looks like a conventional hearing aid. The ossicles are vibrated electromagnetically. Feedback (squeal) is eliminated and distortion is reduced compared to digital hearing aids. Patients report improved sound quality and reduced occlusion effect. The major disadvantage is that the person still has to wear a hearing aid-type device in the ear. The Direct System consists of 2 components, a tiny rare-earth magnet and a sound processor. In the implant procedure, a tympanomeatal flap is raised, giving access to the middle ear. The micro-magnet, which has been hermetically laser-sealed in a titanium canister, is then placed on the incudo-stapedial joint and the eardrum flap is closed.

The procedure takes less than 30 minutes, and can be performed in a procedure room or outpatient clinic under local anaesthetic. The device cost is about the same as top-quality digital hearing aids currently on the market.

Preliminary results: There are several recent reports for the Direct System.¹²⁻¹⁵ In a recent FDA Phase II clinical trial of 103 patients at 10 sites across the US, individuals with bilateral moderate to moderately severe sensorineural hearing impairment who had worn optimally fit hearing aids for at least 45 days were implanted with the SoundTec Direct system.¹² Therapeutic intervention included the implantation of a 27-mg neodymium iron boron magnet encased in a laser-welded titanium canister onto the incudo-

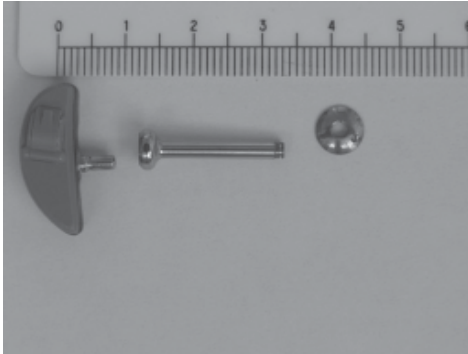


Fig. 1.



Fig. 2.



Fig. 3.

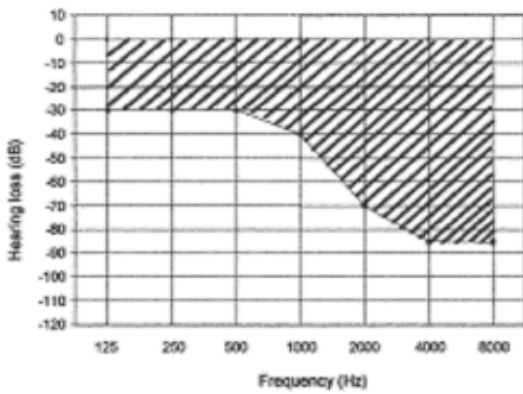


Fig. 4.

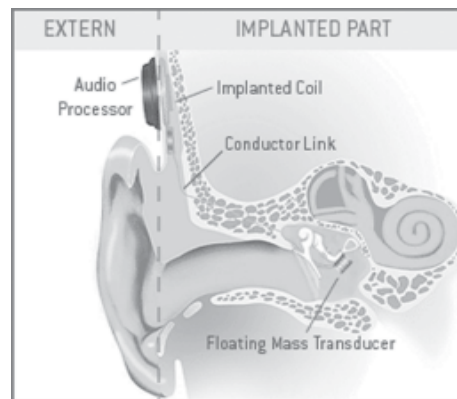


Fig. 5.

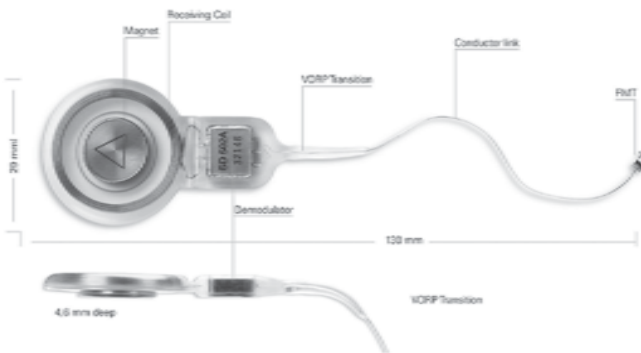


Fig. 6.

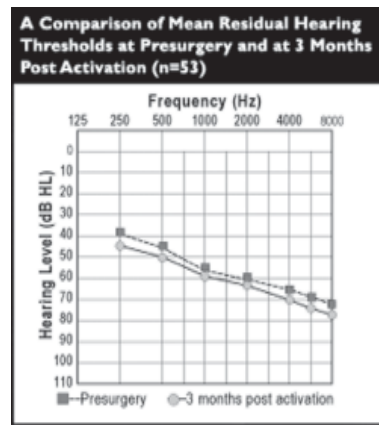


Fig. 7.

Fig. 1. The two parts of the RetroX: the implanted titanium tube and the hearing aid unit (photo courtesy of Dr Pierre Garin, Cliniques Universitaires U.C.L., Belgium).

Fig. 2. The titanium tube is implanted under the auricle. It opens into the postaural sulcus and into the external auditory canal (photo courtesy of Dr Pierre Garin, Cliniques Universitaires U.C.L., Belgium).

Fig. 3. The patient connects and disconnects the hearing aid unit to and from the posterior end of the tube (photo courtesy of Dr Pierre Garin, Cliniques Universitaires U.C.L., Belgium).

Fig. 4. Audiogram showing the fitting range for the RetroX.

Fig. 5. The Vibrant Soundbridge: components and implantation (reproduced with permission from Vibrant Med-El, Austria).

Fig. 6. Vibrant Soundbridge: receiver and Floating Mass Transducer (FMT) (reproduced with permission from Vibrant Med-El, Austria).

Fig. 7. Vibrant Soundbridge: Pre- and postoperative hearing thresholds (reproduced with permission from Vibrant Med-El, Austria).

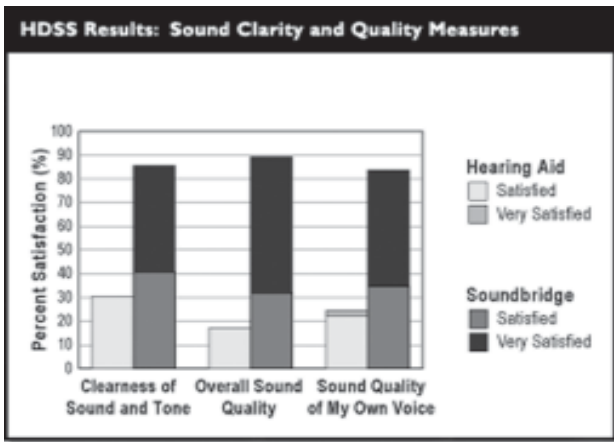


Fig. 8. Vibrant Soundbridge HDSS results (reproduced with permission from Vibrant Med-El, Austria).

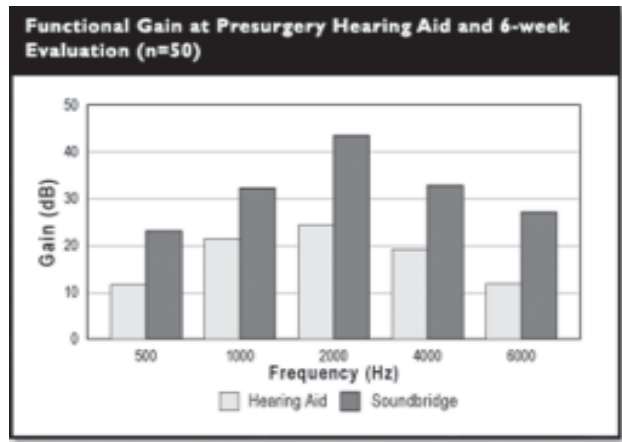


Fig. 9. Vibrant Soundbridge: functional gain results (reproduced with permission from Vibrant Med-El, Austria).

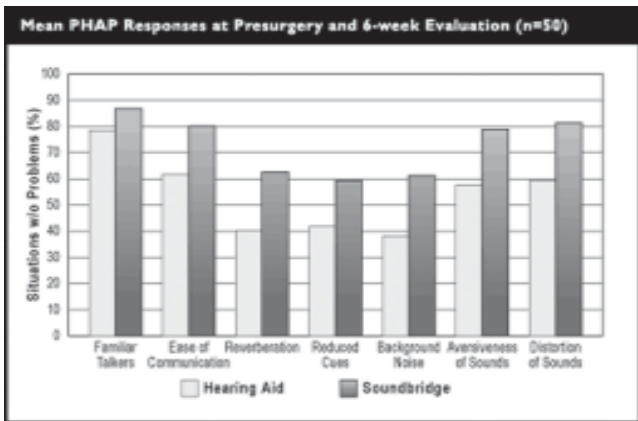


Fig. 10. Vibrant Soundbridge: PHAP results (reproduced with permission from Vibrant Med-El, Austria).

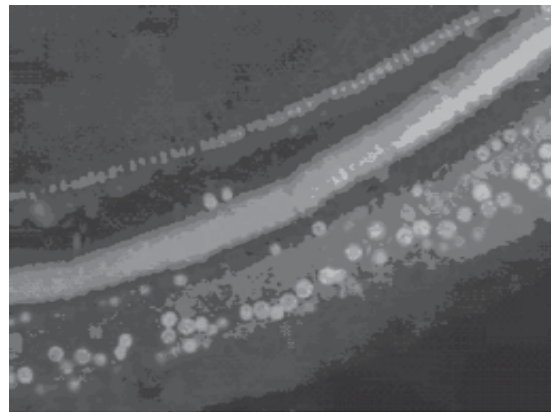


Fig. 11. Inner ear hair cell regeneration with Math1 gene therapy. Math1 expression (grey circles) in cells in and around the sensory epithelium of the inner ear from a guinea pig after gene therapy (photo courtesy of Dr Yehoash Raphael, University of Michigan Medical School, USA).

stapedial joint, followed, after a 10-week healing period, by fitting with a deep ear mould coil assembly and activation of the sound processor. Functional gain, speech recognition in quiet and noise, articulation index scores, perceived aided benefit, sound quality judgments, satisfaction, and presence of feedback and occlusion with the Direct System were compared with those of the patients’ optimally fit hearing aids. The results with the use of the Direct System compared with an optimally fit hearing aid provided an average 7.9-dB increase in functional gain in the speech frequencies (500 Hz to 4000 Hz) and a 9.6-dB gain in the higher frequencies (2, 3 and 4 kHz). There was a statistically significant average increase of 5.3% in speech discrimination. The mean speech perception in noise test score was improved, but the improvement was not statistically significant. Subjective tests using abbreviated profile of hearing aid benefit and the Hough Ear Institute Profile demonstrated scores statistically improved over the hearing aid condition. These subjective tests measured areas such as the presence of occlusion and feedback,

speech quality judgments, device preference, and perceived aided benefit. These results suggest that the Direct System provided significant reduction in feedback and occlusive effect as well as a statistically significant improvement in all the following categories: functional gain, articulation index scores, speech discrimination in quiet, perceived aided benefit, patient satisfaction and device preference over the patient’s optimally fit hearing aid. There are no longer-term data available for this device as yet to evaluate if there is any long-term change in audiometric thresholds.

III. Bone-anchored Hearing Aids

After more than 20 years of clinical use, the bone-anchored hearing aid (BAHA) (Entific Medical Systems, Sweden) is a well-established device in the fields of otology and audiology, with over 7000 implanted patients worldwide.¹⁶⁻¹⁸ An excellent review of the current status of BAHAs in adults and children is available¹⁹ and is

recommended for a comprehensive overview of the topic. With experience, the surgical procedure has been simplified over the years, and a one-stage procedure is now recommended for adults, and the time from implantation to fitting of the BAHA has fallen from 4 months to 6 weeks. The BAHA is presently FDA-approved for adults and children above the age of 6 years. In adults, the most common indication remains chronic otitis media. In Europe, BAHAs are frequently used in children as young as 18 months. The most common indication in children is bilateral ear malformations.

Single-sided Deafness

When faced with unilateral total deafness, the options of rehabilitation have remained disappointing. Recently, using the application of BAHA with transcranial bone conduction, patients regained “pseudo-stereophony” and reported a definite improvement in daily situations e.g., group conversation and sound localisation. There have been encouraging results reported by several European groups^{20,21} and the BAHA received FDA clearance for the treatment of single-sided deafness (SSD) in 2002. To evaluate the benefit of a BAHA contralateral routing of sound (CROS) in 20 patients with unilateral inner ear deafness, 21 patients were recruited.²¹ Fifteen had undergone acoustic neuroma surgery and 6 had unilateral profound hearing loss due to other causes. Only patients with thresholds of less than 25 dB HL (500 Hz to 2000 Hz) and an air-bone gap of less than 10 dB in the better ear were included. Evaluation involved audiometric measurements before intervention, when fitted with a conventional CROS, and after implementation and quantification of the patients’ subjective benefit with a hearing aid-specific instrument: the Abbreviated Profile of Hearing Aid Benefit (APHAB). Lateralisation scores were not significantly different from chance (50%) in any of the 3 conditions. Measurements of speech perception in noise showed an increase in the signal to noise ratio (S/N ratio) with the conventional CROS ($P = 0.001$) and with the BAHA CROS compared to the unaided condition, when speech was presented at the front with noise on the poor hearing side. On the other hand, a lower S/N ratio was seen with the BAHA CROS ($P = 0.003$) compared to the unaided situation, when noise was presented at the front with speech on the poor hearing side. The patient outcome measure (APHAB) showed improvement, particularly with the BAHA CROS. The poor sound localisation results illustrate the inability of patients with unilateral inner ear deafness to localise sounds. The speech-in-noise measurements reflect the benefit of a BAHA CROS in lifting the head shadow while avoiding some of the disadvantages of a conventional CROS. The benefit of the BAHA CROS was most clearly reflected in the patients’ opinions measured with the APHAB.

IV. Cochlear Implants and Hybrid Devices

With advances in speech processing strategies and coding technology, multi-channel cochlear implants (CIs) have proven to be effective instruments in rehabilitating adults and children with severe to profound sensorineural hearing loss. There are 3 major manufacturers of CIs, namely Cochlear Corporation (Australia), Advanced Bionics Corporation (USA) and Med-El (Austria). Patient performance with CIs has steadily improved over the years. The open set sentence score has increased from 12% in 1981 to 90% in 2001, and it is expected that newer speech processing (ADRO and Whisper) technologies will improve performance beyond 90% in the near future. Let us now explore 2 more recent developments: bilateral cochlear implantation and the CI hybrid device.

Bilateral Cochlear Implantation

There are increasing data that show the benefits of bilateral cochlear implantation in speech understanding, in both quiet and noise.²²⁻²⁵ The average score across subjects for sentence understanding was 31.1 percentage points higher with both CIs compared with the CI ipsilateral to the noise. The average score for recognition of monosyllabic words was 18.7 percentage points higher with both CIs than with one CI. These differences in average scores were significant at the 5% level.²² Another study showed a 4-dB gain in signal-to-noise ratios at the speech reception threshold. In addition, the gain in signal-to-noise ratios was stable for as long as 4.4 years.²³ These improvements were also seen in Chinese-speaking patients, where those with bilateral CIs were better than unilateral CIs at discriminating Cantonese lexical tones.²⁴

Another study compared the auditory behaviour of bilaterally implanted children while using both CIs, to their auditory behaviour when they were using one CI.²⁶ The parents scaled their judgements using a method of extended category scaling similar to that applied in the loudness scaling with the Würzburg hearing field. Each of the 5 verbal categories was subdivided into 10 numerical subdivisions, so that the parents were able to express judgements lying between the different categories. Eight out of 11 items showed that hearing with bilateral CIs was significantly better than with one CI ($P < 0.003$). The 2 items for which there was no significant difference between the 2 conditions were those related to the interest in auditory rehabilitation and to aversion to noise.²⁶

Cochlear Implants Emerging Technology: Cochlear Corporation

The Cochlear Nucleus 3 System has a titanium casing cushioned in silastic elastomer, and uses a self-curling perimodiolar array, which matches the shape of the cochlea. The array is held straight during insertion with a stylet.

Once in place, the array hugs the interior wall, where the auditory nerve fibres are located. In contrast, a straight array sits near the lateral (outside) wall, which is farther from the hearing nerve fibres. The atraumatic design of the electrode array aims to minimise damage to residual hearing. The Nucleus 3 System includes Neural Response Telemetry (NRT), which can determine how the nerve is responding to the implant. This is especially helpful for children or for patients who have been deaf for a long time. With the magnet removed, the system is MRI-compatible up to 1.5T Tesla. The Nucleus 3 supports a wide range of custom speech coding strategies, including the Advanced Combination Encoders (ACE) strategy.

Another new development is the Nucleus 24 Contour Advance, a contour electrode with a soft tip. This array will produce minimal cochlear trauma because minimum force is applied to the outer cochlear wall. It also ensures consistent array placement close to the modiolus. Cochlear is working on a totally implantable device (TIKI) but there are several challenges including how to perform upgrades, how to charge the batteries, battery replacement, and where to place the microphone. Another exciting project is a drug delivery system that will allow us to send drugs through the electrode array directly to the cochlea. A possible application is to stimulate auditory nerve fibres to grow towards the CI electrodes, creating a neuron-electrode interface, a situation that would almost certainly improve overall performance.

Cochlear Nucleus Hybrid Cochlear Implant

The rationale for the hybrid system is that many implant candidates have quite good low-frequency hearing but very poor high-frequency hearing. The hybrid works on the concept of combining electrical stimulation for high-frequency sound with acoustic hearing for low-frequency information in the same ear. Because the hair cells that respond to high frequencies are near the base of the cochlea, it is possible to insert a short array to stimulate the high frequencies, while leaving the low-frequency hair cells (located towards the apex of the cochlea) undamaged. There are currently about 15 patients using this hybrid system, which includes an implant with only 6 channels. A single-subject clinical trial design was recently reported.²⁷ A unique six-channel CI was designed for this clinical trial. The intracochlear electrodes were either 6 mm or 10 mm in length, based on a Nucleus CI-24 multichannel implant. Monosyllabic word understanding and consonant identification in a recorded sound-only condition were used to assess changes in speech perception. The follow-up period was greater than 12 months. Acoustic hearing was preserved in all 9 subjects. Preoperative monosyllabic word and sentence scores were unchanged in all subjects following implantation. A 30% to 40% improvement in consonant recognition occurred with the 10-mm electrode.

The 10-mm electrode subjects were able to understand 83% to 90% of the monosyllabic words using the implant plus binaural hearing aids. Scores were more than doubled when compared to preoperative scores achieved with hearing aids only. These results suggest that the human ear has the capability to integrate both acoustic and high-frequency electrically processed speech information. Placement of a short 10-mm electrode does not appear to damage residual low-frequency inner ear hair cell function, interfere with the micro-mechanics of normal cochlear vibration or decrease residual speech perception. The improvement in speech recognition was primarily due to the increased perception of higher-frequency consonantal speech cues. Such a device can provide a substantial benefit in terms of speech understanding to those with severe high-frequency hearing loss, while maintaining the benefits of residual lower-frequency acoustic hearing.

V. Auditory Brainstem Implants

The Auditory Brainstem Implant (ABI) provides direct stimulation of the dorsal cochlear nucleus in the brainstem, and is intended primarily for people with neurofibromatosis Type 2 (NF2). NF2 patients often develop bilateral acoustic neuromas (in addition to other tumours in the brain and spinal cord) and in the course of surgical treatment lose both auditory nerves, which eliminates the use of a CI for auditory rehabilitation. So the ABI device is implanted directly into the auditory brainstem at the same time as the tumour removal, into the fourth ventricle. Appropriate placement of the ABI is dependent on electrical auditory brainstem response testing performed intraoperatively. Performance with the ABI is not as good as with a CI, but it does help with speech and lip-reading.^{28,29} Early results are promising and include some open-set speech ability by some ABI implantees. Currently, Cochlear and Med-El offer ABI devices and more research is being conducted to improve performance, for example, the development of a penetrating electrode into the brainstem to improve tonotopic frequency representation in the cochlear nucleus.

VI. Inner Ear Hair Cell Regeneration and Related Stem Cell Research

The auditory sensory epithelium is a mosaic composed of sensory (hair) cells and several types of non-sensory (supporting) cells. All these cells are highly differentiated in their structure and function. Mosaic epithelia (and other complex tissues) are generally formed by the differentiation of distinct and specialised cell types from common progenitors. Most types of epithelial tissues maintain a population of undifferentiated (basal) cells, which facilitate turnover (renewal) and repair, but this is not the case for the organ of Corti in the cochlea.³⁰⁻³² Therefore, when cochlear hair cells are lost, they cannot be

replaced. Inner ear hair cell regeneration and related stem cell research offer what is probably the best hope for hearing restoration in the next few decades of scientific research.

Gene Therapy Triggers Growth of New Auditory Hair Cells in Mammals

Healthy hair cells are vital to the ability to hear, but ageing, infection, certain medications and exposure to loud noise can damage or destroy hair cells, causing sensorineural hearing loss. Since the discovery in the late 1980s that birds can regenerate damaged hair cells spontaneously, scientists have been trying to find a way to induce the replacement of lost hair cells in mammals. Recently, the University of Michigan successfully used gene therapy to grow new auditory hair cells in adult guinea pigs.^{30,31} This could potentially lead to new treatments for human deafness and age-related hearing loss. This breakthrough was achieved by inserting a gene called *Math1* into cells lining the inner ear. Non-sensory epithelial cells in adult guinea pig cochlea could generate new sensory hair cells following the expression of *Math1*. Significantly, some of these hair cells could attract the growth of new fibres from auditory neurons. After embryonic development, hair cell production ceases. Unlike other epithelial cells in the skin or gut, epithelia in the inner ear contain no stem cells, so there is no source for renewal. This is the main reason why hair cell loss is permanent. When *Math1* is overexpressed in the non-sensory cells of the mature cochlea, it causes them to transdifferentiate into hair cells (Fig. 11). Future research will focus on whether the regenerated guinea pig hair cells are functional and if they are able to transmit sound signals to auditory neurons.

Pluripotent Stem Cells from the Adult Mouse Inner Ear

In mammals, the permanency of acquired hearing loss is mostly due to the incapacity of the cochlea to replace lost mechanoreceptor cells, or hair cells. In contrast, damaged vestibular organs can generate new hair cells, albeit in limited numbers. Li et al³³ recently showed that the adult utricular sensory epithelium contains cells that display the characteristic features of stem cells. These inner ear stem cells have the capacity for self-renewal, and form spheres that express marker genes of the developing inner ear and the nervous system. Inner ear stem cells are pluripotent and can give rise to a variety of cell types in vitro and in vivo, including cells representative of ectodermal, endodermal and mesodermal lineages. These stem cells are capable of differentiating into hair cell-like cells and may lead to a new strategy for the replacement of lost inner-ear sensory cells.

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