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Reflections on the Last 25 Years of the American Otological Society and Thoughts on its Future

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Purpose: To review contributions of the American Otological Society (AOS) over the most recent quarter century (1993–2018) and to comment on possible future evolution of the field during the quarter century to come.
Methods: Retrospective review of selected topics from the AOS transactions, distinguished lectureships over the past 25 years, and selective reflection by the authors. Speculation on potential advances of the next quarter century derived from emerging topics in the current literature and foreseeable trends in science and technology are also proffered for consideration (and possible future ridicule).
Results: Integration of multiple disciplines including bioengineering, medical imaging, genetics, molecular biology, physics, and evidence based medicine have substantially benefitted the practice of otology over the past quarter century. The impact of the contributions of members of the AOS in these developments cannot be over estimated.
Conclusions: Further scientific advancement will certainly accelerate change in the practice of otologic surgery and medicine over the coming decade in ways that will be marvelous to behold. **Key Words:** Future—History of otology—Sesquicentennial.

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On the occasion the 150th anniversary of the American Otological Society (AOS), it is appropriate to reflect on the changes to the field of otology. This manuscript focuses on the most recent quarter of a century. Much has changed in the practice of otology since eight inaugural members gathered in the beautiful new Ocean House Hotel in Newport, Rhode Island on July 22, 1868 to establish the American Otological Society and, in fact, a great deal of that change has occurred in the past 25 years. Much of the progress in otology has been made possible by the application of basic science discovery to clinical medicine. Although by no means a comprehensive review, a few of the important advances in otology for the last quarter century from the authors' opinions are highlighted. The programs from the Annual AOS meetings were reviewed for trends and progress, with particular attention paid to lectures from the Guests of Honor and our Scientific Lectures at the annual meetings such as the Saumil Nalin Merchant Memorial Scientific Lecturers (Table 1).

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ADVANCES IN OTOLOGY OVER THE QUARTER CENTURY

First, a few cursory observations in reviewing the programs from the Annual Meeting of the AOS from 1993 to 2017 are preffered. Remarkably, the earlier programs from 1993 to 2004 have no financial disclosures in the program whatsoever. These have certainly proliferated in recent years. Financial disclosures first appeared in 2005. Soon they occupied more space in the program than the program itself along with ''Identification of Professional Practice Gaps,'' ''Goals & Objectives,'' ''Learning Objectives,'' ''Desired Results,'' and ''Full Disclosures'' from all authors on all presentations. The growing administrative burden of meeting the regulatory requirements is clearly evident and emblematic of many similar encumbrances on the time of the members of the AOS which detract from time spent in patient care, research, and teaching. It also burdens those who administer the AOS educational programs.

Certainly of much greater significance, through the past 25 years there is strong evidence of increasing intersections of clinical and basic science at the Annual AOS meeting (Table 1). Such collaborations have greatly accelerated the acquisition of key knowledge to push clinical treatments forward. The Guest of Honor in 1993, Cesar Fernandez, spoke on ''The Need for Research in

TABLE 1. *Twenty five years of special lectures at the American Society of Otological Society*

Year	Guest of Honor	Lecture Title	Scientific/Merchant Lecture	Lecture Title
1993	D. Thane R. Cody, M.D.	Remarks	None	
1994	Cesar Fernandez, M.D.	The need for research in Otology	None	
1995	Richard R. Gacek, M.D.	The periodicity of the professional career	None	
1996	James L. Sheehy, M.D.	Tinnitus: a few thoughts	None	
1997	Mansfield F. W. Smith, M.D.	The heritage and duty of the American Otological Society	None	
1998	Robert A. Jahrsdoerfer, M.D.	You've come a long way baby	None	
1999	Barbara A. Bohne, Ph.D.	Degeneration of the Cochlea after noise damage: primary versus seconday events	None	
2000	Dearld E. Brackmann, M.D.	Balancing the satisfaction of the practice of medicine with personal and family life	None	
2001	James B. Snow, Jr., M.D.	Progress in the prevention of otitis media through immunization	NONE	
2002	David J. Lim, M.D.		None	
2003	James F. Battey, Jr., M.D., Ph.D.	Remarks	None	
2004	Ugo Fisch, M.D.	Surgical management of temporal paragangliomas: a long-term review	None	
2005	George A. Gates, M.D.	Science in Otology: past, present and future	None	
2006	Richard A. Chole, M.D., Ph.D.	Bacterial biofilms: the source of tissue destruction in cholesteatomas?	Bradford J. May, Ph.D. Beverly Wright, Ph.D. Charles Limb, M.D.	Basic science seminar how we hear, how we listen
2007	Fred H. Linthicum, Jr., M.D.		Bob Shannon, Ph.D.	Speech understanding from implants: cochlear, brainstem and midbrain
2008	H. Richard Harnsberger, M.D.	Decision support in the 21st century	Richard D. Rabbitt, Ph.D.	Pathological semicircular canal afferent signals transmitted to the brain during benign positional vertigo and their biomechanical origins
2009	Robert J. Ruben, M.D.	The Promise of Otology	Alec N. Salt, Ph.D.	Opportunities and techniques for local drug delivery to the inner ear
			Scott Plotkin, M.D., Ph.D.	The new frontier: targeted therapies for NF2-related vestibular schwannomas
2010	Edwin W. Rubel, Ph.D.	Toward a new era of hearing Habilitation	Jay T. Rubinstein, M.D., Ph.D.	Characterization of the electrically-evoked compound action potential of the vestibular nerve
2011	Richard A. Miyamoto, M.D.	Cochlear implants: past, present and future?	Kirk Aleck, M.D.	Patterns of inheritance as illustrated by disorders of hearing
2012	Vincente Honrubia, M.D.	Vestibular testing, after 50 years still a challenge	Carol Bauer, M.D.	The neuroscience of tinnitus-implications for treatment
2013	Bruce J. Gantz, M.D.	Electric + acoustic speech processing: what have we learned about the auditory system	Neil Segil, Ph.D.	Can we restore lost hearing? Molecular control of cell fate and cell division in the development and regeneration of the inner ear
2014	David A. Moffat, Ph.D.	Ethical dilemmas in otology	Josef P. Rauschecker, Ph.D.	The gray area—tinnitus and the brain
2015	Joseph B. Nadol, Jr., M.D.	An imperative for otology	M. Charles Liberman, Ph.D.[a]	Hidden hearing loss: permanent cochlear nerve loss after temporary noise-induced threshold shift

TABLE 1 *(Continued)*

Year	Guest of Honor	Lecture Title	Scientific/Merchant Lecture	Lecture Title
2016	Blake Wilson, Ph.D.	The development of the modern cochlear implant and the first substantial restoration of a human sense using a medical intervention	Andy Groves, Ph.D.	30 years of hair cell regeneration: promising progress or pie in the sky?
2017	John W. House	Otosclerosis treatment: a journey through the last century and a half	A. James Hudspeth, Ph.D.	The active ear: how hair cells provide a biological hearing aid

[a]Saumil Nalin Merchant Memorial Lectureship began 2015.

Otology.'' Subsequent Guests of Honor noted for their contributions to basic science of otology included Barbara Bohne (1999), David Lim (2001), James Battey, Jr. (2002) and Edwin Rubel (2010).

The first basic science seminar was introduced in 2006 when a panel discussed ''How We Hear, How We Listen'' with Bradford May, Beverly Wright, and Charles Limb. In 2007, a ''Basic Science'' lecture was formally added to the AOS annual program, a trend that has continued to the present. The Basic Science Lecturer was renamed the Saumil Nalin Merchant Memorial Lecture in 2015 in honor of Dr. Merchant, a gifted clinician-scientist who made great contributions in many areas including temporal bone histopathology.

The AOS Research Grant Program to fund the mission of advancing the science and practice of otology underwent marked change in scope and magnitude. The AOS Council approved over $5.6 million in research grants to early stage clinicians and scientist for basic and clinical research. Initially funding was limited to the study of otosclerosis and Menière's disease, but this restriction was recently released and now research relevant to any aspects of the ear, hearing, and balance disorders are invited. AOS Research Fund awardees have been highly successful in recent years in obtaining substantial extramural peer-reviewed grants to advance their contributions to the field.

The following observations highlight a few of the specific areas where important progress has been made and is ongoing.

Genetics of Hearing Loss

As described by medical geneticist Kirk Aleck in the 2011 AOS Scientific lecture, ''Patterns of Inheritance as Illustrated by Disorders of Hearing,'' our understanding of the genetic basis of hearing loss has expanded geometrically over the last quarter century, perhaps realizing more progress than in any other area of otology. Approximately 80% of prelingual deafness is genetic, most often autosomal recessive and nonsyndromic (1). As of 2017, among patients with nonsyndromic genetic hearing loss 70 autosomal recessive, 25 dominant, and five X-linked genes have been identified (2). A series of mitochondrial mutations have also been associated with hearing loss. In recent times genetic studies, initially single gene testing, now increasingly supplanted by multi-gene panels, have become available. Widespread clinical use is hampered by lack of insurance funding. Connexin mutations, which impair a gap junction protein, are the most common among nonsyndromic hearing loss having been identified in 24% of patients with congenital hearing loss when screening 660 hearing impaired patients. Ushers and Waardenbergs were the most common causes of syndromic hearing loss. With the steadily lowering costs of DNA sequencing, routine screening for highly prevalent types of acquired hearing loss such as vulnerability to noise and aging related hearing loss may be developed. While the primary value of genetic studies at present is to establish prognosis and to advise concerning the risk to subsequent generations, gene therapy has commenced and will be refined in the coming years (3).

Imaging

Innovation in medical imaging has greatly clarified and illuminated the practice of otology. H. Richard Harnsberger highlighted these advances in a talk as the Guest of Honor at the annual meeting in 2008 entitled ''Decision Support in the 21st Century.'' Refinement of magnetic resonance imaging (MRI) and high-resolution computerized tomography (CT) have made precise anatomical diagnosis possible and opened the way for the detection of new disease processes. For example, air contrast CT was the most sensitive and specific method for detecting intracanalicular lesions before the introduction of gadolinium enhanced MR (Fig. 1). Air contrast CT, popularized in the early 1980s, provided excellent resolution and became the procedure of choice for imaging tumors of the internal auditory canal (4). Injection of intrathecal air was not without its attendant discomfort and risk including headache, back pain, nausea, and neck stiffness (5). With high-resolution MRI, far more vestibular schwannomas were detected than with CT. This likely led to an increase in the number of patients having tumors removed that previously went undiagnosed and untreated.

Another recent advance in MRI is the ability to image protein deposition in the cochlea which helps clarify the cause of hearing loss associated with vestibular schwannomas (VS). It has been known for some time that the

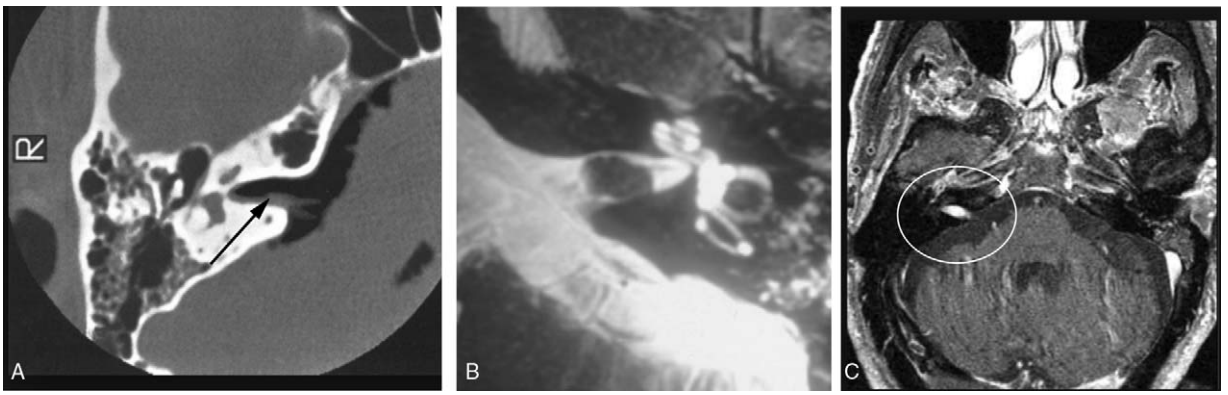

FIG. 1. *A*, Air-contrast CT demonstrating a small mass in the right internal auditory canal (IAC) (*black arrow*). *B*, T2-weighted magnetic resonance image of a small intracanalicular vestibular schwannoma in the left IAC. *C*, T1-weighted image with contrast with clear enhancement in the right IAC. CT indicates computerized tomography.

size of VS was not directly correlated with the hearing loss. Holliday et al. (6) confirmed this finding and observed that elevated intralabyrinthine protein demonstrated on MRI FLAIR (fluid-attenuated inversion recovery sequences) images were correlated decreased pure-tone audiometric averages (Fig. 2). Increased protein in the cochlea likely correlates with histopathologic findings which showed an acidophilic precipitate in the scala media of patients with VS (Fig. 3). Characterizing these proteins may help explain why some tumors cause hearing loss and others don't, regardless of size. To this end Dilwali et al. (7) have identified secreted proteins from VS, some which are otoprotective of hearing (FGF2) and some which are associated with poorer hearing (TNF-α). Their direct link to the scala media protein imaged, if any, is yet to be discovered.

Further refinement of MRI has led to diffusion tensor imaging, which can differentiate cranial nerves from the adjacent and compressing tumors (8) (Fig. 4). Looking forward, nuclear magnetic resonance (NMR) in combination with MRI may allow the detection of the chemical composition of tumors, thus reducing the need for surgical biopsy to make a certain pathologic diagnosis. Furthermore, precise knowledge of the molecular makeup of discrete tumors in the future may allow prediction of tumor growth and thus guide treatment timing and options.

More Selective Treatment of Cranial-base Tumors

In the past 25 years, there has been a shift in the treatment of vestibular schwannomas (VS). Combining stereotactic localization for radiation and better imaging techniques has allowed the inclusion of radiation or observation as treatment options. Clearly a higher percentage of patients with VS are being observed for tumor growth before intervention than two decades ago (9). Stereotactic radiation has increasingly been selected as a treatment option in the same period. Stereotactic radiation is more likely to be recommended to the elderly or medically infirm with documented tumor growth, but patients of all ages are considering the relative merits of each approach. Why are patients and practitioners selecting a conservative observational approach in recent years? MRI can accurately detect growth, therefore, observing for non-growth is the least aggressive initial treatment option. One argument for early intervention in smaller tumors has been pointed toward the possibility of hearing preservation. Success may be in part dependent upon a distinct cleavage plane between the VS and the cochlear nerve (Fig. 5), but some VS invade the cochlear

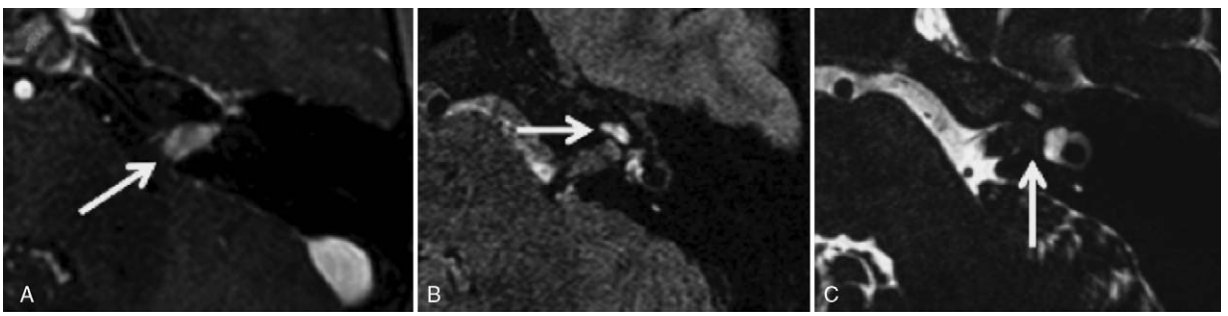

FIG. 2. *A*, MRI of an intracanalicular vestibular schwannoma on T1-weighted image with contrast. *B*, FLAIR sequence imaging showing bright signal in the cochlea likely representing protein deposition. *C*, T2-weighted image showing loss of CSF bright signal where tumor displaces it in the lateral internal auditory canal. From Holliday et al. (6). FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

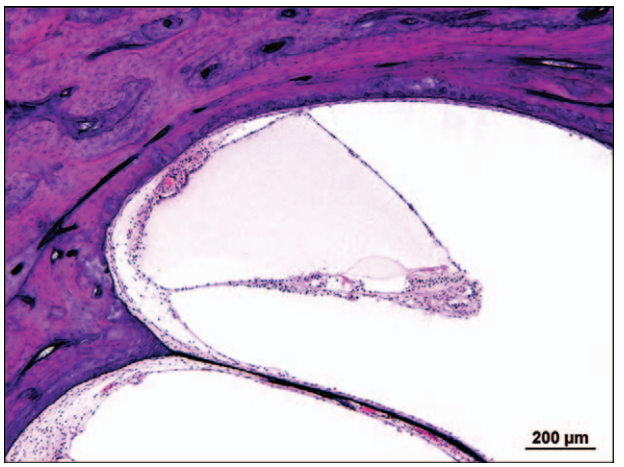

FIG. 3. Acidophilic protein filling the scala media of a patient with neurofibromatosis type 2. Photo courtesy of Dr. Alicia Quesnel.

nerve and have a poor cleavage plane as pointed out in 1984 by AOS member, Neely (10). Figure 6 shows gross infiltration of the 8th cranial nerve with no distinct cleavage plane in one tumor and a clearly defined separation in another. Hearing preservation operations have not been as successful as would be desired, leading patients to a more conservative initial approach in tumors where brainstem compression is not an immediate concern.

The first successful medical intervention for VS was presented by Plotkin et al. (11), the Basic Science Lecture in 2009. Surprisingly, he and his colleagues demonstrated improved sensorineural hearing in 50% of neurofibromatosis type 2 (NF2) patients treated with the vascular endothelial growth factor inhibitor bevacizumab (Fig. 7). Additionally, over 50% of NF2 associated VS showed a decline in tumor volume when so treated (Fig. 8). Clarification of the tumor biology leads patients ever closer to targeted drug options.

Another major shift has been in the treatment of glomus jugulare tumors. Twenty-five years ago the majority of patients were treated surgically, but now surgical resection is seldom employed, as stereotactic radiation has greatly decreased the number of tumors that require surgery. Cranial nerve sparing with radiation represents a significant advantage over surgical resection in many cases (13–15).

Menière's Syndrome

The treatment of Menière's syndrome has also shifted. When conservative measures such as diuretics and diet fail, otologists have largely adopted intratympanic treatment including intratympanic steroids or intratympanic aminoglycosides, at least as a second line therapy. The latter have been shown effective in limiting Tumarkin crisis and both have resulted in significant control of vertigo. Hearing preservation is still problematic however (16–19).

Inner ear imaging can now demonstrate endolymphatic hydrops (20). Dilute gadolinium in the middle ear via transtympanic injection has shown apparent hydrops on T2-FLAIR weighted images in the scala media. This may eventually play a role in more precise understanding of the underlying causes of Menière's syndrome, and may be useful for determining treatment options as we go forward, although the exact relationship of hydrops and the symptom complex is not completely understood yet. The genetics of familial Menière's disease is also not yet elucidated, but segregation in different populations and various potential genes have been implicated. When identified, it will hopefully help unlock the mystery of its pathogenesis.

The ability to measure vestibular function has evolved from the measurement of only one of the five sensory elements of the vestibular system, typically the horizontal semicircular canal with caloric stimulation, to the addition of measurements of the saccule and utricle with vestibular evoked myogenic potentials (VEMP) (21,22). The presence of cervical VEMP response in Menière's syndrome patients has been associated with Tumarkin crisis and may predict the onset of Menière's in the second ear (23).

In the 1980s and 1990s surgical procedures for the relief of vertigo were undertaken much more frequently than today. Procedures such as endolymphatic sac decompression or shunting and vestibular neurectomy were major topics during AOS meetings both in presentations and the subject of innumerable panel discussions.

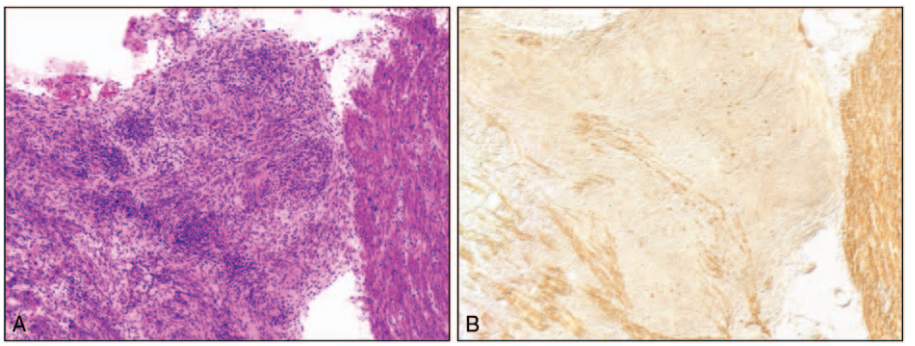

FIG. 4. Cleavage plane between vestibular schwannoma and cochlear nerve *A*, H&E Stain, *B*, anti-neurofilament stain. Image courtesy of Jennifer O'Malley.

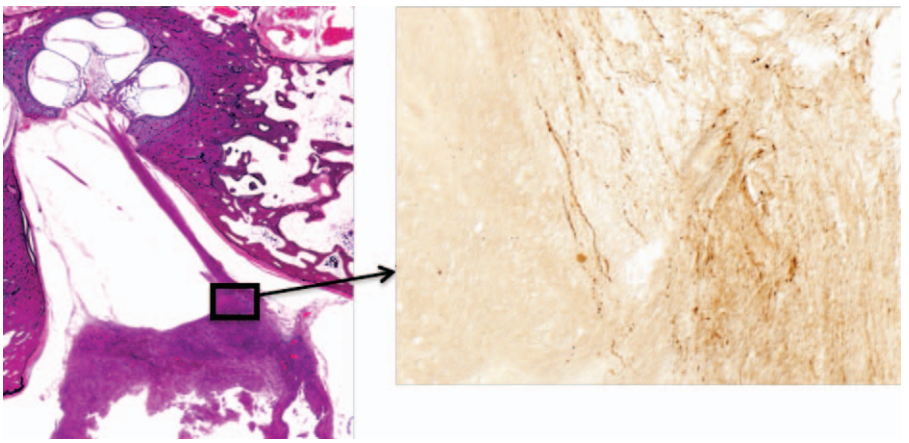

FIG. 5. Lack of distinct cleavage plane between vestibular schwannoma and cochlear nerve infiltration and distortion *A*, H&E stain, *B*, anti-neurofilament stain. Image courtesy of Jennifer O'Malley.

These have become much less fashionable today largely due to the rise of less invasive intratympanic drug therapies with corticosteroids and aminoglycosides.

Migraine Related Dizziness

The most common cause of episodic vertigo has been discovered to be migraine-related, another significant change in the past 25 years. Migraine related episodic vertigo is five times more common than vertigo associated with Menière's syndrome and affects children as well as adults (24–26). Separating migraine from other forms of episodic vertigo is not always readily accomplished by history or other laboratory measurements. Recently, however, Murdin and Schilder demonstrated that migraine sufferers have decreased thresholds for several test batteries measured on the platform chair, which provides motion in all rotational and translational axes (24). This objective data, the coming ''vestibulogram,'' further helps distinguish migrainous vertigo physiologically from Menière's disease. Not yet clinically available, this type of test holds promise for more discreet diagnosis in the near future (27). Recognition of the role of migraine in vertigo has led to more aggressive treatment options including adjustments in life style, diet, and prophylactic and acute pharmacologic controls measures.

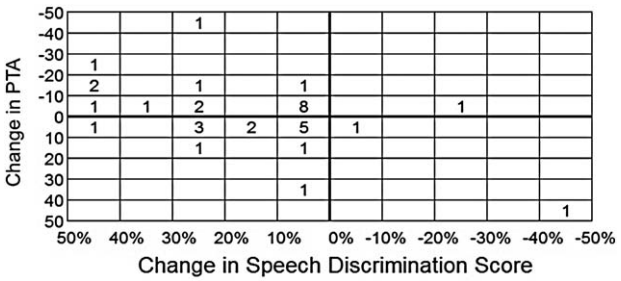

FIG. 6. Change in pure-tone average and speech discrimination of patients with NF2 treated with bevacizumab. Data extracted from Plotkin et al. (11).

Benign Paroxysmal Positional Vertigo

The management of benign paroxysmal positional vertigo (BPPV) was altered radically when Parnes and McClure (28) described the underlying pathophysiology in 1992 with the demonstration of free floating particulate matter within the membranous duct of the posterior semicircular canal (PSSC). Confirmation by scanning electron microscopy showed otoconia within the lumen of the endolymphatic compartment of the PSSC (29) (Fig. 9). The particle repositioning maneuver, initially described by Epley (31) in 1980, was not widely adopted until the underlying pathophysiology was clarified. This work fundamentally changed the way BPPV is treated today.

Dehiscent Superior Semicircular Canal

Minor et al. (32) published a landmark article in 1998 identifying the underlying the association of the dehiscent superior semicircular canal (DSSC) with the symptom complex marked by autophony, disequilibrium, aural fullness, Tullio phenomena, pulse-synchronous oscillopsia, hyperacusis, and low-frequency conductive hearing loss (Fig. 10). Previously, this symptom complex

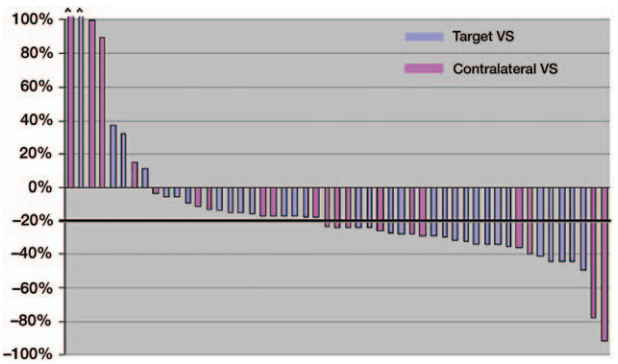

FIG. 7. Waterfall plot demonstrating the percent change in vestibular schwannoma tumor volumes following treatment with bevacizumab. Plotkin et al. (11).

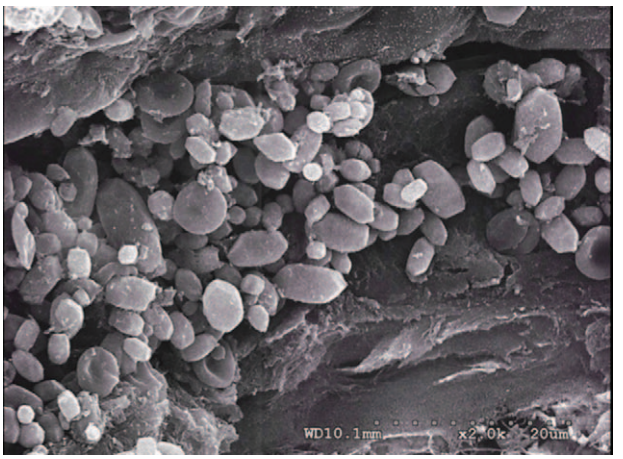

FIG. 8. Otoconia demonstrated in the posterior semicircular canal on scanning electron microscopy in a patient with intractable BPPV. Scale bar 2.5 μm. Images courtesy of Parnes and Chole (12). BPPV indicates benign paroxysmal positional vertigo.

was poorly understood. Symptoms are frequently improved with canal plugging or resurfacing techniques, but the underlying pathogenesis of the dehiscence is still unknown. Even with plugging techniques all symptoms are not yet completely resolved and BPPV may occur posttreatment, however, overall serious complications have been few with plugging techniques (33). Interestingly, recent data suggest that near-dehiscence of the superior semicircular canal is associated with symptoms similar to complete dehiscence and that plugging a nearly dehiscent canal also results in improved symptoms (34).

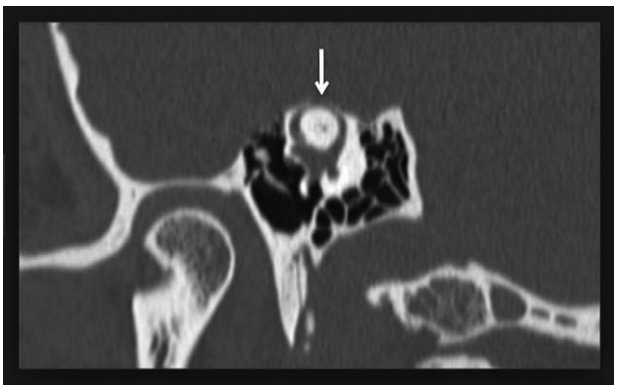

FIG. 10. Dehiscence (*arrow*) of the superior semicircular canal on CT as initially described by Minor et al. (32). CT indicates computerized tomography.

Cochlear Implants

Throughout the past 25 years, the program for the Annual AOS meeting has been filled with advances in cochlear implant technology and application. Most recently, Wilson (35), was the 2016 Guest of Honor at the 149th Annual AOS annual meeting and spoke on the topic ''The Development of the Modern Cochlear Implant and the First Substantial Restoration of a Human Sense Using a Medical Intervention.'' Cochlear implants are a product of the merger of bioengineering and clinical otology. Many key contributors have been leaders of the AOS over the years. Wilson proposed that of all positive changes to the field of otology over the past quarter century, the greatest accomplishment is the cochlear

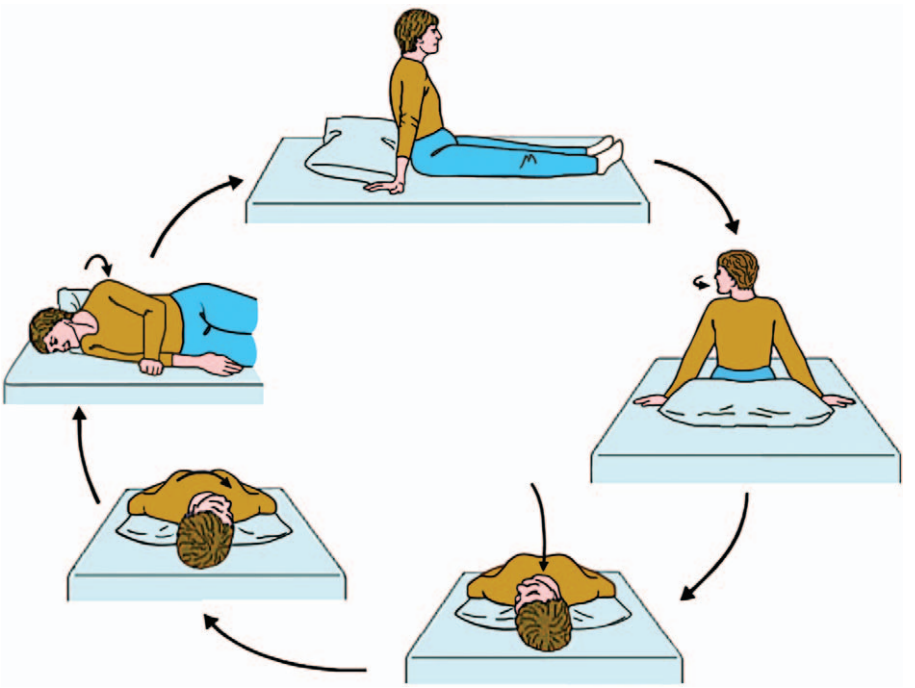

FIG. 9. Particle repositioning maneuver described by Epley in 1980. (Image Courtesy of Chicago Dizzy Clinic as shown in Welling and Barnes (30)).

implant. The ability of a profoundly deaf patient to gain open-set speech discrimination is a modern medical accomplishment unparalleled in bioengineering to date. The impact this has on deaf patients is transforming, especially for deaf children who had poor prospects of gaining communication skills which would allow interaction with the hearing world. There have been over 12,000 articles published on cochlear implants in the past 25 years. To date, approximately 220,000 patients worldwide have received cochlear implants.

Ongoing areas of CI study include modification and relaxation of eligibility requirements, hearing sparing electrodes to allow potential electric–acoustic hybrid stimulation and optimizing fitting paradigms. Bruce J. Gantz (AOS president 2010) was the guest of honor for the annual AOS meeting in 2013 where he summarized this ongoing work in a talk entitled ''Acoustic + Electric Speech Processing: What Have We Learned about the Auditory System.'' He noted that basic science questions are being answered through clinical applications, such as the gradual shift in frequency response to shorter hybrid implants (36,37).

Whether or not cochlear implants should be employed for single-sided deafness and tinnitus suppression is actively being studied in a number of institutions (38,39). The optimal timing of bilateral cochlear implantation as contrasted with a period of bimodal stimulation is an ongoing debate with solid data needed to further clarify these options (40).

Future understanding of auditory cortex plasticity may allow pharmacologic intervention to habilitate the congenitally deafened adult who did not receive early auditory stimulation (41,42). The ability to process sound signals into speech understanding may be followed by further voice development and integration into the hearing world.

The field of optogenetics allows for selective nerve stimulation with optical sources may further refine our ability to discretely stimulate the auditory and vestibular pathways in the future or even the auditory cortex directly (43,44).

Implantable Hearing Aids

Much excitement was generated around active implantable middle ear hearing aids in the past quarter century. Fully implantable and partially implantable devices have been studied. Patient's rationalizations for avoiding conventional hearing aids are well known including cosmesis, irritation of the ear canal, activity limitation, and poor sound quality, particularly in noise. On the other side of the ledger, challenges have been many including battery technology, implantable microphone fibrosis, unreimbursed cost in excess of conventional aids, long-term viability of the mechanical devices in the biologic environment leading to device failure and removal or replacement, decline in unaided hearing as a result of implantation, and MR incompatibility. Failure to clearly demonstrate objective improvement in performance when compared with appropriately fit conventional hearing aids on a variety of audiologic tests has perhaps been the major deterrent to wide-spread acceptance of these devices (45,46).

Osseointegrated Implantable Hearing Devices

Another area of marked progress has been in osseointegrated bone conduction hearing devices, particularly for applications in congenital aural atresias and patients with severe eczema of the external auditory canal. The patient with a chronically draining middle ear is also a candidate. Implantation procedures have been simplified, but irritation and granulation around transcutaneously implanted devices has not been completely overcome. Osseo-integrated devices for single-sided deafness, when compared with conventional CROS aids, have not been shown to be clearly superior (47).

Endoscopic Ear Surgery

Within a few decades following the introduction of the operating microscope in the 1920s, nearly all ear surgery involved microsurgery. While endoscopes have been used as adjuncts to the microscope in ear surgery for quite some time, in recent years fully endoscopic ear surgery is increasingly popular (48). Even the most delicate of ear surgery, stapedectomy, has been performed endoscopically in a few centers (49). Advantages are greater visualization and illumination of recesses such as the sinus tympani and the ability to peer into the epitympanum without removal of the scutum. Disadvantages which have deterred many otologists include the need for one handed surgery, a limitation likely to be overcome by future technological advances.

WHAT WAS IN VOGUE 25 YEARS AGO?

Perilymphatic Fistulae

A number of years ago a presentation was given in a national meeting on the topic of perilymphatic fistulae (PLF) in which a map of the prevalence of PLF in the United States was flashed briefly. The speaker stated that the prevalence of spontaneous PLF seemed to segregate much like religion in the country with strong geographic predilection. The speaker then quickly proceeded to the body of the presentation. A recent retrospective survey of over 1,000 patients evaluated for vertigo concluded that less than 1% of cases were attributed to PLF (50). It is the author's suspicion that the discovery of dehiscent superior semicircular canals resulted in fewer explorations of the middle ear for PLF. It is conceivable that patching the round and oval windows did help decrease the symptoms associated with the third window effect created by DSSC. Recent modeling indicates otherwise however (51). There appears to be a good deal of interest on the topic from Japan as a recent national study examined for the presence of an inner ear specific, Cochlin tomo-protein (CTP), in middle ear lavage from suspected PLF patients. Only 20% of patients with suspected PLF showed CTP, if there was no associated physical trauma, lesion of the middle ear, or recent stapes surgery. Patients with acute

trauma who waited longer than 30 days for middle ear exploration were significantly less likely to find positive CTP presence (52). The usefulness of CTP may help clarify the true incidence of PLF going forward.

Decompression of Vascular Loops for Disequilibrium

McCabe and Harker (53) proposed vascular loops as a cause of incapacitating disequilibrium in 1983 and decompression of the same was recommended for the control of disabling positional vertigo in 1984 by Jannetta (54). A prolonged I–III interval on ABR was proposed as a result of significant vascular compression of the cochlear nerve. Several case series presented good outcomes from various decompression techniques (55,56). Although this condition may still occur, in the author's experience, lack of symptoms in patients with vascular loops found contacting the 8th nerve complex on routine MRI are so prevalent, it has led to a substantial decline in decompressions for vascular loops. A detailed investigation of the relationship between cochleovestibular symptoms and the type of vascular compression showed no relationship. Sirikci et al. (57) concluded that diagnosis of vascular conflict should not be based on imaging findings alone.

SPECULATIONS ON FUTURE ADVANCES IN OTOLOGY OVER THE NEXT QUARTER CENTURY

Application of Molecular Biological Techniques

Looking forward to the next decades in our field brings a great deal of excitement and anticipation. This will occur in many ways, but most likely through continued merger of scientific disciplines. In the inaugural Saumil Nalin Merchant Memorial Lectureship, M. Charles Liberman delivered a talk which gave an example of the advances being seen today entitled ''Hidden Hearing Loss: Permanent Cochlear Nerve Loss after Temporary Noise-Induced Threshold Shift.'' Cochlear synaptopathy resulted from cochlear nerve degeneration after ''temporary'' noise induced hearing loss (58). This condition is characterized by pure-tone thresholds returned to normal, but synapses with the inner ear hair cells were lost at levels of acoustic trauma below those necessary to induce permanent hair cell damage and permanent sensorineural loss. Kujawa and Liberman (59) demonstrated further that Neurotrophin-3, when applied to animal models of cochlear synaptopathy demonstrate the regeneration of neurite outgrowth to reconnect with the inner hair cells with concomitant improved hearing thresholds.

The 2016 Merchant lecturer was Andy Groves who spoke on the topic of hair cell regeneration in his scholarly presentation ''30 Years of Hair Cell Regeneration: Promising Progress or Pie in the Sky?'' He related characterization of the changes in the transcriptome of neonatal mouse cochlear supporting hair cells between 1- and 6-day old mice (60). The importance of the Notch pathway inhibition was demonstrated corroborating the work of Edge and others in unlocking the insights in the mechanism of regeneration of mammalian hair cells (61).

Lustig led a panel of experts at the 2016 meeting on ''Hurdles to Human Gene Therapy.'' He previously showed restoration of hearing in the VGLUT3 knockout mouse using virally mediated gene therapy (62). Staecker, another distinguished panelist discussed how his team knocked down a significant hurdle by delivering atonal (CGF166) via an adenoviral vector to the live human inner ear with the intent of regeneration (63). This study is ongoing in phase I/II. An ophthalmologist on the panel, Pierce, described their work in vision restoration using adeno-associated viral (AAV2) mediated correction of an inherited retinal dystrophy in children which showed efficacy in both eyes out to 3-year follow up (64).

The high interest and importance of this areas of study was highlighted by the address of Neil Segil at the 146th annual meeting entitled ''Can We Restore Lost Hearing? Molecular Control of Cell Fate and Cell Division in the Development and Regeneration of the Inner Ear'' (65). Other important advances demonstrating restoration of hearing in young mouse models such as TMC1 and Usher Type 2c (66,67). Shibata et al. (68) demonstrated the feasibility of RNA-interference-mediated suppression delivered via a viral vector to slow progression of hearing loss in autosomal-dominant nonsyndromic hearing loss.

As gene editing becomes more widely applicable, specific defects may be selectively corrected in various mutation affecting hearing. Major challenges with translating gene therapy from bench to bedside are improving efficiency of targeted delivery without causing further trauma or off-target editing. Specialized viral vectors such as Ancestral 80 have beautiful distribution throughout the inner and outer hair cells from base to apex in the mouse model while minimizing immunogenicity (69).

Many congenital lesions causing pediatric hearing loss are present at birth with the absence of normal anatomic structure development. Very early intervention, even prenatal intrauterine intervention, may be necessary to allow critical structural development. Recent delivery to the amniotic fluid in utero of antisense oligonucleotides (ASO), with subsequent rescue of hearing and balance phenotypes in a mouse model of Ushers syndrome (type 1), was shown by the Brigande lab (70). The delivered ASO targeted a causal splice site mutation and showed it corrected gene expression in the therapeutically relevant inner ear target tissues. Recent major advances in ASO therapies include ''improved specificity, potency, stability, delivery, and biodistribution and toxic effects have been minimized'' according to the authors. This may bring a whole new realm of intervention.

As with ASOs, other gene editing systems are dramatically increasing genome engineering activities for research and eventually therapeutic purposes. Clustered regularly interspaced short palindromic repeats (CRISPR)-associated Cas9 endonucleases have made genome editing much more directed and efficient than older homologous recombination techniques, potentially revolutionizing gene editing. Improved specificity

limiting off-target activity is crucial but seems to be advancing (71–73). The application to otologic disease is eminent and very exciting.

Tissue Regeneration

Growth factor stimulated repair of tympanic membrane (TM) perforations has been successfully explored in animal models as early as the 1980s (74–76). Recent manufacturing of clinical grade growth factors led to successful human trials in Japan (77,78). Tissue engineering for TM repair is evolving quickly and will lead to a significant change in the way that perforated TMs are treated in the near future—opined that ''a regenerative method of tympanic membrane repair could be the greatest advance in otology since the cochlear implant'' (79). It could simplify the traditional myringoplasty and tympanoplasty by making it an office procedure.

Precision Diagnostics

It is most probable that future members of the AOS will not speak of ''sensorineural hearing loss'' as generality covering lesions from the cochlea to the cortex. More discrete diagnostic testing will become commonplace allowing discrete treatment paradigms. We will speak of inner or outer hair cell dysfunction, cochlear synaptopathy, cochlear nerve dyssynchrony, brainstem lesions of the dorsal cochlear nucleus afferents, or failure of efferent feedback. Importantly human temporal bone histologic findings will be necessary in deciphering the discrete underlying pathology necessary and cannot be neglected, as was so elegantly described by the Guest of Honor in 2016, Joseph Nadol (AOS president 2009). Diagnostic imaging will help us decipher delayed auditory cortex development and methods then devised to improve the natural language development of the deaf.

The need for similarly improved diagnostic testing of the vestibular system was highlighted by Vincente Honrubia in 2013, when as the Guest of Honor be presented his thesis on ''Vestibular Testing, after 50 Years Still a Challenge.'' We might predict that in the near future we will have access to a simplified clinical ''vestibulogram'' which will give discrete information from all 10 vestibular sensory end organs. The central nervous system advances will also be additive.

Vestibular Prosthesis

Another exciting development which follows from the highly successful cochlear implant is the development of the vestibular implant for patients impaired by severe bilateral vestibular dysfunction. Della Santina, Lewis, Rubinstein, and others have made important progress on the development of a device to will resupply vestibular afferent function to the profoundly vestibulopathic system (80–83). Further refinement of multichannel stimulating paradigms, reduction of post implantation variation, and channel interference will likely lead to a successful human vestibular prosthesis within the relatively near future. Given the aging of the population and the high cost of falls among the elderly, sensor based fall reduction technologies are likely to enter widespread use in the coming years (84).

Tinnitus Intervention

Several decades ago when a patient would ask ''what shall I do about the ringing in my ear, doctor? A well-respected otologist (Harold Schuknecht, AOS President 1977) would answer, ''what size shoe do you wear.'' When informed, he would instruct the patient to buy a pair two sizes smaller, and then their tinnitus would not bother them so much. He would promptly exit the room.

What strides have we made in understanding and treating tinnitus in the last quarter century? Other than being more capable of ruling out tumors of the cerebellopontine angle, vascular malformations, and intracranial hypertension, it could be argued that we have not made substantial progress in terms of treatments. Masking is not a new concept, but still useful. Tinnitus retraining has been shown to be more effective than standard supportive therapy in a recent blinded controlled study by Bauer et al. (85) when combined with hearing aids. Effective pharmacologic agents are yet to be proven.

Auditory neuroscience, however, has progressed substantially recently in understanding the pathophysiology of tinnitus. Carol Bauer's Basic Science Lecture in 2012 ''The Neuroscience of Tinnitus-Implications for Treatment'' was outstanding (86). Rauschecker et al. (87), the scientific lecturer in 2014, presented ''The Gray Area – Tinnitus and the Brain'' to bring us a look at the advances in understanding of tinnitus. Advancing neuroscience certainly gives hope that understanding the generators of abnormal spontaneous activity in the auditory pathways (dorsal cochlear and ventral cochlear nucleus, the inferior colliculus, and the auditory cortex) or a lack of suppression of spontaneous activity may lead to the eventual successful treatment of this symptom. Modulation of the auditory cortex which appears to be hyperactive in tinnitus, may be another treatment option. While auditory input is decreased from the damaged cochlea in the region of the auditory cortex due to hearing impairment, the output from the cortex remains intact to communicate with other parts of the brain. This persistent output which does not correlate with input may be interpreted as the presence of tinnitus. (See Roberts et al. (88) for an excellent review).

Keeping the hyper-excitable theories in mind, a top-down approach to cortical or deep brain stimulation for tinnitus suppression may provide new treatment options (89,90). Pharmacologic control becomes possible with better understanding of the neural modulation of these hyper-excitability-related signals (91).

Deep brain or cortical stimulation directly may also play a role. Early application in human tinnitus sufferers is equivocal (92,93). The usefulness of transcranial magnetic stimulation is also not clearly determined and may be further explored (94). Directed extracranial electrical suppression is being developed now and may become relevant.

Surely with excellent collaborative efforts, tinnitus treatments should advance significantly past the ''smaller shoe-size'' paradigm.

Eustachian Tuboplasty

Chronic Eustachian tube (ET) dysfunction has been treated with tympanostomy tubes for decades. The results from a recent multicenter controlled study evaluating balloon dilation of the ET for chronic ET dysfunction by Poe (95) may change the way we intervene in the future. The study compared tympanogram normalization in patients treated with topical steroids alone to patients with steroids and eustachian tuboplasty. The favorable results for the eustachian tuboplasty group caused the FDA to recommend early termination of the study and the procedure was FDA approved for adults. Pediatric studies will soon follow. Replacement of tympanostomy tubes with ET dilation would be a major paradigm shift. Long-term sustainability is yet unknowns. Likewise, the applicability to the pediatric population, and ultimately the cost/benefit ratio need to be clarified, but this could be a great paradigm shift in the field of a very common problem.

Hearing Aids

Disruptive innovation is upon us in the hearing aid versus personal sound amplification units (PSAPs) arena as comparative studies and devices appear in greater numbers. A recent report tested hearing in noise with nine PSAPs against a conventional hearing aid, at about 1/10th the cost. Of the nine, the best five were selected and three showed similar benefit to the more expensive traditional hearing aid. At least one device showed worse discrimination than no device at all (96). The audiologist's professional role in guiding patients through this maze of new devices will accelerate quickly from this point. As only 20% of patients with mild to moderate hearing loss currently use hearing devices, there should be an increased role for the audiology professional in counseling patients regarding hearing devices with a model where the professional counseling is unbundled from the sale of a hearing device. This will benefit both our colleagues in audiology and a growing number of patients.

There has long been an unjustified stigma associated with wearing a hearing aid. The widespread cultural bias that the wearer is older and less intellectually acute (i.e., ''deaf and dumb'') has in the past limited adoption of these devices among the hearing impaired. This is in marked contrast to eye glasses which culturally are accepted as stylish and a mark of intelligence. In the future, wearing of an ear device may be as universal as using a cell phone is today. Led by youth proud to adopt the latest devices, the current Bluetooth ear-piece revolution is a forerunner of what is likely to come. These devices will interface with computers and phones, be a conveyer of information and entertainment, and serve as a telemetry system for continuous biometric monitoring of health. Future digital ear devices may enhance signal to noise ratios in adverse listening situations, such as noisy restaurants, thereby improving the sense of hearing even among the normal hearing population. Connected with high-speed cloud based computers, they will translate across all languages in real time. Such highly capable devices can readily incorporate an ability to adjust their output to accommodate for hearing loss. Importantly, as hearing devices become widely used, consumer electronic devices cost will plummet from their unreasonably high cost of today just as technological capabilities soar. As this transition occurs, the stigma associated with hearing devices can be expected to fade and a much higher fraction of hearing loss patients will adopt their use (97).

Surgery Within the Living Cochlea

Early 21st Century surgeons can operate within the brain, heart, liver, kidney, and eye while sustaining or even improving the organ's native function. The ability to perform procedures within a functioning, but diseased cochlea remains impossible with today's technology. It is the only organ in the body which remains inaccessible to surgical intervention for functional gain of its ordinary physiological function. Because of the organ's extreme fragility, new methods need to be developed which enable intervention while preserving Organ of Corti homeostasis. Fundamental is atraumatic creation of a ''cochleaport'' which affords temporary access and can be effectively resealed to restore cochlear wall integrity. As the cochlea is both minute and mechanically delicate, internal procedures are beyond the ability of the unaided human hand. Robotic micromanipulators of the type used in basic research which step down larger hand motions into microscopic scale and extinguish tremor will be needed. Miniature, steerable endoscopes, and light sources will also be needed to assist therapies such as targeted placement of cells and drugs or, e.g., use of a laser to reduce endolymph production in hydrops.

Hearing Testing

In the 20th century, automation alleviated workers of repetitive mechanical tasks in factories. In the 21st century, any process which can be explained as an algorithm can potentially be automated, even complex and sophisticated tasks typically done by highly educated workers (98,99). The impact of advances in artificial intelligence and computer image analysis are just now being felt in medicine. It can be foreseen that advanced computer image analysis may 1 day greatly enhance the diagnostic ability of radiologists to interpret images (e.g., CT, MRI) and for pathologists to be supplanted in the microscopic diagnosis and molecular diagnosis of disease. In hearing health care it seems inevitable that artificial intelligence systems should be able to readily replace human audiologists for most routine hearing testing. With the reduced burden of diagnostic studies, audiologist will evolve to have a greater emphasis upon the rehabilitative aspects such as counseling and hearing device fitting. With regard to oto-surgical practice,

robotic and image guided surgery is likely to be an adjunct to surgical craft for the foreseeable future rather than a replacement. Office practice of otology, with its human interaction is likely to be less impacted by automation. It will be a long time before computers will be able to communicate empathy and show compassion (98,99).

Otologic Education

Finally, just a word about where otologic education may head in the near future. Immediate access to the world's body of published science makes our trainees today light years ahead of our where our senior membership was at the same level of training (at least in the present authors' case). Surgical training is moving to a virtual world with very realistic simulators that will shape the skills of our young surgeons before they engage in the surgical theater (100,101). This has been enabled by technological advances in immersive learning and is especially important due to the increasing difficulty of obtaining sufficient anatomical material for traditional temporal bone dissection courses. Automated testing for board certification of surgical skills may be administered virtually in the future. It may be anticipated that fellowship-trained neurotologists, who focus their clinical practice on diseases of the ear and lateral cranial base, will be increasingly called on to provide inner ear surgery and medicine including stapedectomies, cochlear implants, and gene infusions. The team approach to science and patient care is evolving which improves the results for all.

SUMMARY

Predicting the future is always fraught with danger, but it is not inconceivable that in the next decade the discipline of otology will see application of molecular and gene transfer techniques to significantly change the way we deal with various maladies including sensorineural hearing loss and tinnitus. Specific targets and ideal delivery mechanisms are the subjects of intense interest. The biotechnology industry's interest and investment is rising with the growing population of baby boomers world-wide who need hearing restoration, balance rehabilitations, and tinnitus suppression.

In the 1950s, it was said that otology was a declining as a field because most surgeries were done to drain infections and antibiotics were greatly reducing these. Stapedectomy was the major innovation of this time and it reinvigorated the field. Looking forward, a 0.5 to 1% deafness rate with this procedure should no longer be acceptable as it was in the era of analog hearing aids. Stapes footplate surgery is conducted right at the margin of what a human surgeon's hand-eye coordination can safely perform. Technical refinements such as use of highly precise robotic tools may reduce the incidence of sensory loss to that of refractive eye surgery or, with advances in hearing aid technology, indications for this procedure may decline. As biological therapies and technological advances provide safer alternatives to surgery, otologic surgeons may well become much more focused on the implantation of devices.

Advances in wearable digital technology will almost certainly lead to routine coupling of man and machine in the population at large with the ear likely to feature prominently in placement of biosensors as well as communication devices. As leading experts in this interface, future otologists may be occupied with designing and managing these connections and adopting their use to accommodate for hearing impairment.

The future contributions of the members of the AOS in team-science with our colleagues from many disciplines will surely see even more rapid advances for the welfare of our patients in the coming decades. The growth of international science opens new avenues of collaboration as does the rapid sharing of knowledge. A whole new story will surely be told when the bicentennial is celebrated in 2068. Perhaps the larger question then will be when scientific advances allow all to hear, will we have made any significant progress in the human ability to listen. Brian F. McCabe (AOS President, 1986) would often say ''the proof is in the pudding.'' The scientific future is indeed bright!

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