Otoacoustic Emissions: Can Laboratory Research Improve Their Clinical Utility?

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Are research-based otoacoustic emissions clinically useful?

From the Research Bench

The existence of otoacoustic emissions (OAEs), the sounds generated in the cochlea of the inner ear and measured with an acoustic probe fitted snugly in the outer ear canal, has been known for almost 40 years. The schematic drawing in **Figure 1** illustrates the fit of the acoustic probe in the outer ear canal.

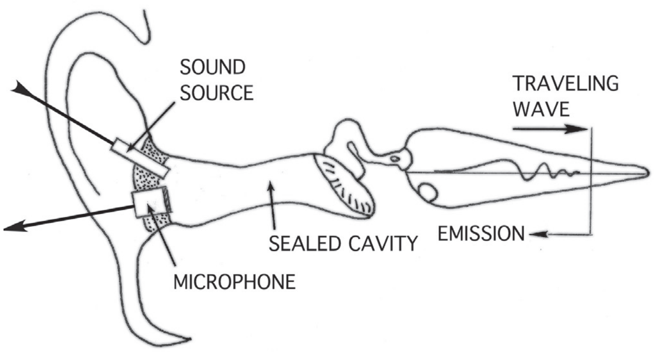

Figure 1. *Schematic of emissions measurement system. Both the miniature sound source and microphone transducer are sealed into the outer ear canal using a soft disposable foam ear tip incorporating two sound ports for stimulus delivery and microphone pickup of emitted sounds. The acoustic stimulus sets up a traveling wave in the cochlea of the inner ear (**right**), which is measured in the cochlea as an otoacoustic emission. The middle ear lies between the outer ear (**left**) and cochlea.*

The original descriptions of OAEs in humans (Kemp, 1978) described emitted responses that exist either without external stimulation (naturally occurring in the absence of acoustic stimulation) as spontaneous OAEs (SOAEs) or as evoked OAEs that are elicited using various types of acoustic stimuli. For example, short-lasting moderate sounds like clicks and tone pips elicit transient-evoked OAEs (TEOAEs), whereas much longer continuous low-level pure tones evoke stimulus-frequency OAEs (SFOAEs). When two longer pure-tone bursts that are related in frequency (f_1 lower frequency and f_2 higher frequency) are presented simultaneously, they produce distortion-product OAEs (DPOAEs). Initially, the main appeal of these cochlear-based responses primarily concerned basic-research issues related to the peripheral auditory nervous system.

Consequently, the existence of OAEs brought about significant modifications to the prevailing mathematical models of inner ear function that needed to acknowledge the reality of such active intracochlear processing. Accordingly, as a research tool, it was well appreciated that OAEs provided a noninvasive window on the preneural mechanical activities of the cochlea that as a group is known as the cochlear amplifier. Moreover, during the initial years after their discovery, some efforts were made to relate OAEs to parallel neural and psychoacoustical phenomena. Thus, emitted responses were described in several experimental species commonly used at that time as research models of hearing impairments such as noise-induced hearing loss and drug-induced ototoxicity in common laboratory animals including Old World monkeys, gerbils, guinea pigs, chinchillas, and rabbits.

As discussed in greater detail below, within a decade or so after their original discovery, both hearing scientists and audiology-trained practitioners recognized the remarkable potential utility of evoked OAEs as a test of the status of cochlear function based on their objective, efficient, quantitative, and, particularly, noninvasive properties. The purpose of this review is to summarize the current status of OAEs with respect to both the research and clinical fields and to deduce from these analyses what the future holds for the application of emission measures in these specialized arenas.

Significant Theoretical Issues

The presence of cochlear emissions was hypothesized in the late 1940s based on mathematical models of cochlear nonlinearity (Gold, 1948). However, OAEs could not be measured until the late 1970s when technology enabled the development of the extremely sensitive low-noise microphones needed to record these responses. Exactly how OAEs arise and how they are propagated in and out of the cochlea, through the middle ear, and to the acoustic probe consisting of a sound emitter and pickup sensor seated in the outer ear canal is still being debated (e.g., He and Ren, 2013). Both experimental findings and related theoretical notions suggest that there are two fundamental mechanisms of OAE generation as proposed by Shera and Guinan (1999). In the nomenclature established by Shera and Guinan (1999), SOAEs, TEOAEs, and SFOAEs are considered to arise mostly from coherent linear reflections produced by impedance discontinuities such as differences in the strengths of outer hair cell (OHC) micromechanical forces or possibly structural microirregularities such as out-of-place OHCs or disarranged hair bundles (i.e., stereocilia) that are distributed along the cochlear partition (e.g., Lonsbury-Martin et al., 1988), whereas DPOAEs result from nonlinear distortion processes secondary to but inherent to normal cochlear function (for examples of the four OAE types, see Whitehead et al., 1994). Thus, the prevailing view is that the sources of OAE generation are reflection- (SOAEs, TEOAEs, and SFOAEs) or a combination of reflection and distortion- (DPOAEs) generating processes.

A current understanding about the microprocesses that underlie the generation of OAEs is that the electromotility of the OHC receptors is due to receptor potential-initiated movements of prestin "motor" molecules that are embedded in the lateral membrane of the OHCs (see the discussion about electromotility and its discovery in Brownell, 2017). Indeed, further reasoning presumes that OAEs are in some way generated as a by-product of a combination of these electromotile-based vibrations of the OHCs, such as shortening/lengthening, along with the stimulation-induced nonlinear openings and closings of the ion-based transduction channels at the tips of OHC stereocilia. As noted above, the existence of OAEs provides solid evidence that the cochlea is an active participant in the processing of acoustic signals in that the miniscule movements of the subcomponents of the OHCs act to enhance the sensitivity and frequency tuning of the vibrations of the cochlear partition.

In the current theories of cochlear function, the OHCs act as a "cochlear amplifier" in the form of a biological micromechanical feedback system that enhances and sharpens the peak of the broader Békésy traveling wave (TW; von Békésy, 1960). With OHC damage, the sensitivity and sharp tuning of basilar membrane (BM) vibrations are greatly reduced, and the passive mechanical analysis and poor tuning of the Békésy TW predominate. It is well established that when the OHCs are damaged or eliminated through degeneration processes, the sharp tuning and sensitivity of the cochlea are greatly compromised and OAEs are reduced or absent.

In the case of reflection emissions, the peak of the TW likely plays an important role as a source of reflection and filtering for TEOAEs, SFOAEs, and SOAEs. Hence, OHC damage greatly affects these types of OAEs. In contrast, DPOAEs appear to be generated mainly in the nonlinear "distortion" aspects of the OHC transduction process that probably involves the stereocilia of the OHCs. This explains why DPOAEs evoked by high-level primaries persist after the administration of certain ototoxins (drugs that damage the sensory cells of the ear) such as various diuretics. In this instance, the BM vibrations are absent due to the reduction in the driving voltage across the OHC to stimulate the hair bundle nonlinearities. However, for high-level stimuli, this lack of gain is overcome and DPOAEs can again be observed at such suprathreshold levels of stimulation.

Middle Ear Influences on Measures of Otoacoustic Emissions

Before proceeding with a review of the status of OAEs in today's audiology clinic, it is important to address how the middle ear transmission pathway affects the measured features of emissions. Because both the stimulus and the OAEs pass through the middle ear, they are modified in cases of

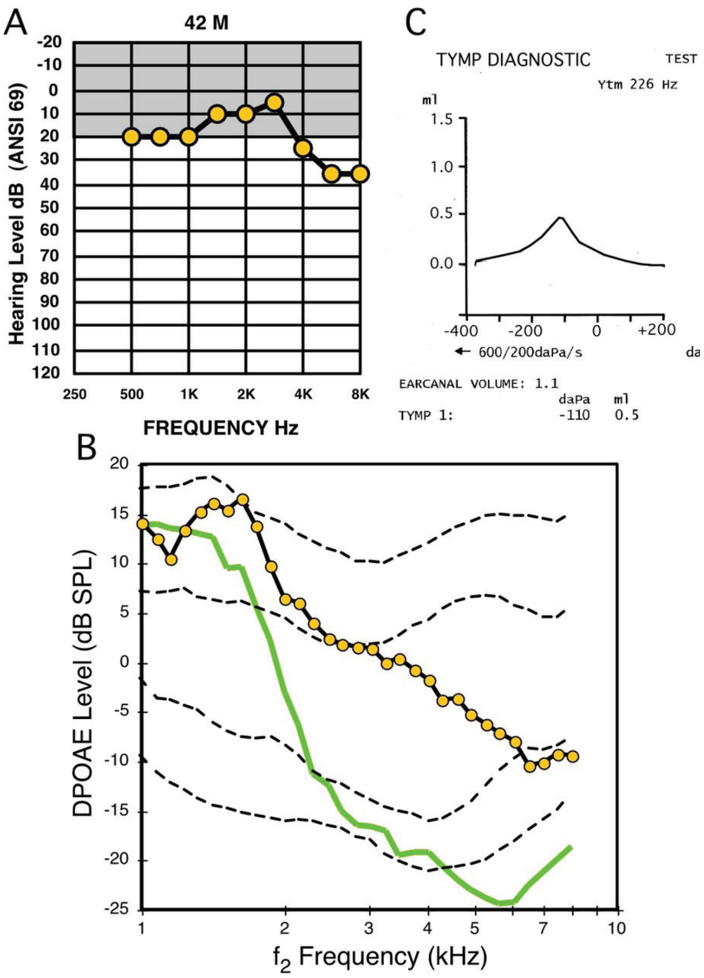

__Figure 2.__ Influence of negative middle ear pressure on evoked otoacoustic emissions (OAEs) measured in a 42-year-old male patient complaining of a hearing impairment. __A:__ Conventional audiogram showing reasonably normal-hearing thresholds in response to pure tones for the left ear, especially for frequencies <4 kHz (__yellow circles__). __Gray area__, extent of normal-hearing limits for adults. ANSI 69, calibration standards established for testing hearing level in decibels by the American National Standards Institute in 1969 for clinical audiometers. __B:__ Distortion-product OAE (DPOAE) levels as a function of f_2 frequencies (DP-gram) ranging from 1 to 8 kHz at 6 frequency points per octave elicited by moderate f_1 and f_2 primary tones (__yellow circles__). Note the increased levels of the measurement system's noise floor (__green curve__) for f_2 frequencies <2 kHz that interfere with measuring low-frequency DPOAEs. Also present are reduced DPOAE levels for frequencies >3 kHz that likely reflect aging factors. The variability in emission levels (±1 standard deviation) in normal-hearing ears is represented by the __top 2 dashed lines__. A similar variability of the related noise floor is indicated by the __bottom__ 2 __dashed lines__. These variabilities are also indicated for the DP-gram plot in __Figure 3B__. SPL, sound pressure level. __C:__ A diagnostic tympanogram (TYPM) indicating the presence of a negative pressure of about −110 decapascal (daPa) for the left ear.

impaired sound conduction. The adverse effects of middle ear dysfunction on the level and frequency attributes of OAEs has been demonstrated in patient groups with various disorders of the conduction apparatus such as perforations or anomalies of the tympanic membrane, ossicular chain dislocations, and middle ear diseases such as chronic otitis media (Owens et al., 1992). Middle ear disease in the form of negative intratympanic pressure significantly reduces the levels of both TEOAEs and DPOAEs, particularly for the low- to midfrequencies. It is clear from **Figure 2B** that elevated noise floors (**green curve**) for frequencies <2 kHz interfere with measuring the lower frequency DPOAEs in ears with negative middle ear pressure as indicated in **Figure 2C**. Although in this case involving a 42-year-old male the audiometric hearing thresholds in **Figure 2A** were normal over the 1.5- to 3.5-kHz range, the related plot in **Figure 2B** showing DPOAEs as a function of the f_2 test stimuli (DP-gram) were approaching the frequency-distribution area representing abnormally low-level emissions as indicated by the −1 SD boundary.

From studies of the adverse influence of middle ear anomalies on OAE measures, it is well established that if emissions are to be used in clinical settings to assess cochlear status, normal middle ear function is essential. Thus, to distinguish between the effects of middle ear pathology and cochlear abnormalities on emitted responses, it is necessary to evaluate middle ear function at the time of OAE testing (Kemp et al., 1986).

To the Clinic

As the initial basic studies on emitted responses were ongoing, the significant benefits of OAEs as a clinical test began to be appreciated. It became clear that OAEs offer the practitioner several beneficial features as objective measures of the ear's ability to process acoustic stimuli. Over the past 35 years or so, a great number of studies have demonstrated that evoked OAEs are useful in contributing to the differential diagnosis of a sensorineural hearing loss; screening of cochlear function in infants and other difficult-to-test patients; monitoring OHC healthiness in patients exposed to either ototoxic drugs or excessive sounds or suffering from certain progressive hearing ailments; evaluating the status of the descending cochlear efferent system; and identifying functional or feigned hearing loss.

An example of this latter application is illustrated in **Figure 3** for a 42-year-old male factory worker who operated a wood lathe for about 20 years. This individual claimed that he had poor low-frequency hearing along with no hearing above

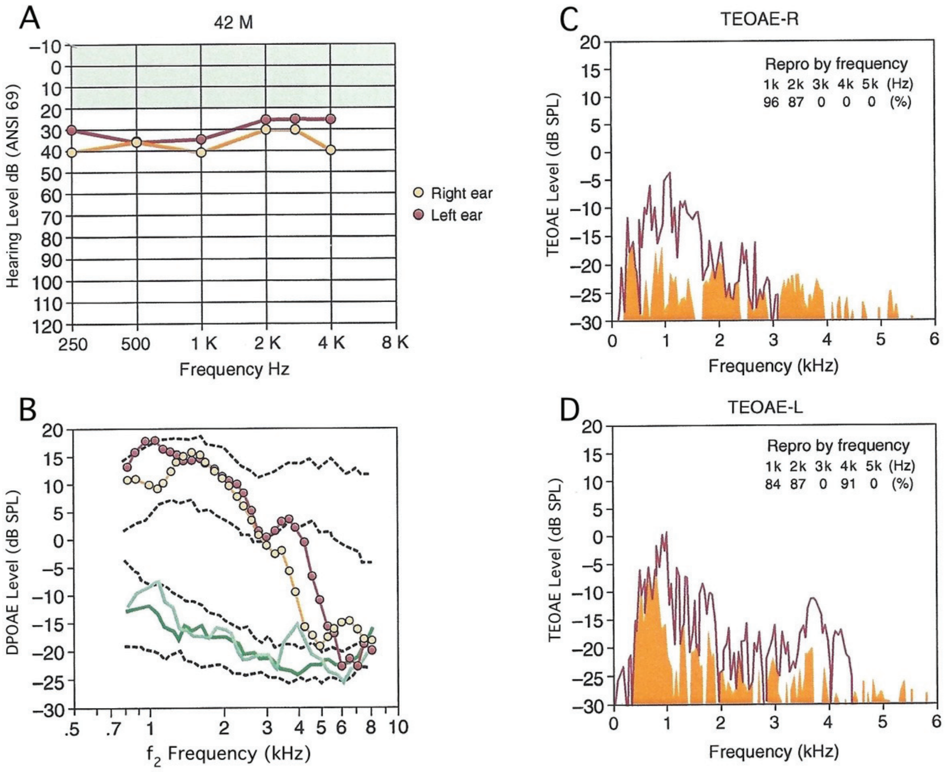

Figure 3. *A possible case of functional hearing loss in a 42-year-old male factory worker who operated a wood lathe.* ***A:*** *The audiogram shows a relatively flat bilateral hearing loss up to ~4 kHz. For frequencies >4 kHz, the patient claimed that test tones were inaudible.* ***B:*** *DP-gram shows normal-appearing DPOAEs up to ~3-4 kHz where reductions in DPOAE levels are then evident; this occurs initially for the right ear (**yellow circles**), which was more exposed to the lathe noises.* ***C and D:*** *Transient-evoked OAE (TEOAE) spectral plots for the right (**C**) and left (**D**) ears from about 200 Hz to 5 kHz also show poorer click-evoked TEOAEs for the right ear (TEOAE-**R**).* ***White areas****, emission levels;* ***orange areas****, noise-floor levels. "Repro by frequency", test-retest correlations for two series of click presentations.*

about 4 kHz due to an occupational noise exposure. Together, the normal levels of DPOAEs for frequencies below ~3-4 kHz and an asymmetric pattern of reduced DPOAEs suggest that both an exposure to excessive noise and aging contributed to the decreased levels of DPOAE activity for f_2 frequencies above 4-5 kHz. Interestingly, rather than resolving the legitimacy of the apparent functional hearing loss illustrated in **Figure 3A**, the poorer DP-gram and TEOAE emissions observed for the right ear, which was closest to the lathe, support the diagnosis of a noise-induced hearing loss rather than a feigned hearing loss.

Early on, then, the three major applications of OAE testing in clinical settings became apparent, including the differential diagnosis of hearing loss, hearing screening in difficult-to-test patients such as newborns and infants, and the serial monitoring of hearing impairment under progressive conditions. The rationale for using OAEs in each of these major practical uses is based on one significant beneficial feature of emitted responses that consists of their specificity for testing the functional status of OHCs, which represent not only the majority of the sensory receptors for hearing but also are the most sensitive receptors to the external agents that adversely affect hearing.

This attribute, in particular, makes OAEs an ideal clinical measure for determining objectively the sensory component of a sensorineural hearing loss. In addition, other features of OAEs make it a clinically useful measure of the biological activity that initiates hearing. That is, among its advantageous characteristics as a clinical test is its representation of an objective response that is noninvasively and simply measured from the outer ear canal. Thus, emitted responses can be rapidly obtained, which makes them an ideal screening test, especially for identifying hearing impairment in newborns. Finally, because OAEs are stable and reliably measured over lengthy time intervals, they make excellent monitors for detecting progressive pathological changes in cochlear function, which is particularly true with regular exposure to either ototoxic drugs or extreme industrial noise levels.

Of the two general classes of reflection- and distortion/reflection-generated OAEs, the TEOAEs and DPOAEs, respectively, have been the most clinically useful tests of cochlear function. The SOAEs have not been as clinically useful as the evoked OAEs for several reasons. First, as assessed by commonly available commercial equipment, the prevalence of SOAEs is only observed in about 50% of normal-hearing individuals (Moulin et al., 1993). And, second, the individually based uniqueness of both the frequencies and levels of SOAEs make it difficult to develop this type of naturally emitted response into a standardized clinical test based on what is considered to be "normal."

Until recently, SFOAEs have typically been measured only by research-based phase-tracking devices because it is complicated to extract them from the ear canal sound at a time when the eliciting low-level stimulus is present at the identical frequency. However, using sophisticated technology (e.g., inverse fast Fourier transforms) along with specialized stimulation protocols (e.g., swept tones), SFOAEs are becoming more straightforward to measure and interpret given the simplicity of their generation (e.g., Kalluri and Abdala, 2015). Even though SFOAEs are considered to be the steady-state version of TEOAEs, there is great promise in the ultimate clinical usefulness of SFOAEs.

In contrast, within a decade after the discovery of TEOAEs, reasonably affordable and simply operated commercial equipment based on averaging procedures used for evoking conventional auditory brainstem responses (ABRs) was available. Because the TEOAE is measured after the transient-eliciting stimulus occurs, ears from different individuals produce a response that exhibits unique spectral patterns (see **Figure 3C,D**). This idiosyncratic property makes it difficult to develop a set of standardized metrics that describe the average TEOAE for normal-hearing individuals. Due to this difficulty in determining "normal" TEOAEs in terms of frequencies and level values, they are most often described as being either present or absent. Thus, one of the most popular uses of TEOAEs clinically is as a test for screening auditory function, particularly in newborns.

DPOAEs commonly measured at the $2f_1–f_2$ frequency (an arithmetic formula in which the DPOAE frequency is equal to two times the value of the lower frequency f_1 primary tone minus the value of the higher frequency f_2) and elicited by presenting simultaneously two long-lasting pure-tone bursts at the lower (f_1) and higher (f_2) frequencies are likely produced by the nonlinear aspects of the OHC transduction process in which new frequencies are generated that are not present in the input signal. The frequencies and levels of the tone bursts or primary tones are important in that the largest DPOAEs are elicited by f_1 and f_2 primaries that are within about one-half octave of each other (e.g., the optimal frequency ratio used for humans is $f_2/f_1 = 1.22$) and with levels (L_1 and L_2) that are offset. For example, typical clinical protocols measure the $2f_1–f_2$ DPOAE, which is the largest DPOAE in human ears, in response to primary-tone levels of $L_1 = 65$ and $L_2 = 55$ dB sound pressure level (SPL; Stover et al., 1996).

DPOAE levels in the form of the DP-gram are measured, as a rule, from about 800 Hz to 8 kHz at 6-10 frequency points/octave. The test frequency is usually represented by the f_2 frequency, which is assumed to correspond to the frequency region on the BM at which the TWs of the primary f_1 and f_2 tones maximally overlap. This assumption is based on a combination of theoretical considerations, experimental studies, and observations of the generation of DPOAEs in pathological ears. Although typically measured to 8 kHz to match the upper limit of the conventional audiogram, the high-frequency limit for measuring DPOAEs can be extended to 20 kHz (Dreisbach and Siegel, 2001). Given that high-frequency hearing for test stimuli > 4 kHz is most vulnerable to cochlear pathologies such as pharmaceutical-induced ototoxicity, it is notable that well-developed monitoring programs have incorporated test frequencies up to at least 10 kHz (e.g., Konrad-Martin et al., 2014).

Hearing Screening

As noted above, one of the most widely used applications of evoked OAEs is in newborn hearing screening. Because early identification and habilitation (treatment) are directly linked to the successful development of the language and speech skills of a hearing-impaired child, a reliable method for identifying newborn hearing loss is essential.

Traditionally, the ABR has been used to screen infants identified as being "at risk" for hearing loss. However, such high-risk registers identify, at most, only one-half of the children eventually proven to have significant sensorineural hearing loss (Mauk et al., 1991). During the 1990s, the notion of using TEOAEs to test all newborns was proposed in the form of developing "universal newborn hearing screening" programs. In this manner, a rapid pass/fail decision could be achieved that would reveal whether a given threshold of hearing was less than or greater than ~30 dB hearing loss (Brass and Kemp, 1994). Indeed, currently, TEOAEs are being used in many national (e.g., Prieve and Stevens, 2000) and international (Grandori and Lutman, 1996) settings as indicators of hearing difficulties in newborns.

Overall, TEOAEs have been used much more extensively than DPOAEs in newborn hearing screening. However, with the introduction of specially designed DPOAE instrumentation, they have become an acceptable estimator of newborn hearing capability (Gorga et al., 2000). Most certainly, the Rhode Island Hearing Assessment Project (Vohr and Maxon, 1996) has been a model program in the application of OAEs to the early hearing detection and intervention (EHDI) approaches developed in the United States. However, screening protocols that optimally combine TEOAEs or DPOAEs and automated ABR (AABR) testing in a two-stage protocol (e.g., TEOAE or DPOAE testing followed by AABR testing of initial failures) are still being evaluated for their optimal effectiveness (Akinpelu et al., 2014). Furthermore, results showing that 23% of those identified with permanent hearing loss at approximately 9 months of age passed the AABR but failed the OAE test at birth (Johnson et al., 2005) illustrate the need for continued surveillance of hearing status during childhood. Thus, although substantial progress has been made, many gaps remain with current EHDI programs (White, 2003) and with universal newborn hearing screening in general (Wada et al., 2004).

Although the objective and rapid-test administration properties of evoked OAEs make them an ideal procedure for hearing screening in large numbers of military personnel or industrial workers who are exposed to high levels of environmental sound, their application to these necessary monitoring programs has not been widely instituted (e.g., Seixas et al., 2005). There are only a few isolated reports in the literature on using OAE screening to identify hearing problems in military personnel, musicians, or school children. Furthermore, to our knowledge, there is no published work on the worthwhile application of using OAEs to generally screen for hearing impairment in the elderly.

Evaluating Efferent System Function

OAEs have become a convenient tool for examining the influence of the descending efferent auditory nervous system on OHC activity. This system arises from various structures in the central auditory system to provide feedback to the ear through synapses on the OHCs (Guinan, 2006). Thus, the OHCs receive descending input directly from auditory brainstem structures. Using moderate broadband noise applied to the ear opposite (contralateral) to the test ear, Collet and colleagues (1990) took advantage of this anatomical arrangement to noninvasively assess the status of efferent system function. The underlying assumption of comparing OAE levels in the presence and absence of the contralateral noise stimulation is that the emitted responses provide the most direct means of observing a major efferent effect on OHC activity that consists of a reduction in the levels of both TEOAEs and DPOAEs of ~0.5-1 dB in the overall emission level.

In recent years, modified stimulus protocols (e.g., extending primary-tone on-times from <100 ms to ~1 s) have been used to test the adaptation properties of DPOAEs, in particular by using both monaurally (Kim et al., 2001) and binaurally (Meinke et al., 2005) applied stimuli. Primary tones applied ipsilateral to the test ear have the advantage of activating a larger portion of the descending cochlear efferent innervation to OHCs than does the contralateral-noise approach. Moreover, clearly, the binaural administration of primary tones provides an opportunity to evaluate the functional status of the entire efferent system innervating the OHCs of a given test ear.

Certainly, work aimed at uncovering the clinical usefulness of evoked OAEs as part of a test battery for examining auditory efferent system function is only in its beginning stages. Based on the interesting findings to date in select patient populations, the reduction in the normal contralateral noise-induced decrement in DPOAE levels in, for example, aging ears in the presence of normal emissions (Kim et al., 2002) suggests that it is likely that efferent testing using evoked OAEs will eventually become an important part of the assessment of more centrally based hearing impairments, such as central auditory-processing disorders. Moreover, based on the notion that an important functional role of the cochlear efferent system is to protect the ear from noise-induced hearing loss, there is a current interest in relating the robustness of indigenous efferent activity to the ear's susceptibility to sound overexposure (e.g., Luebke et al., 2014).

Summary: The Future of Clinical OAEs

Clearly, applications of OAEs in the hearing sciences and clinical audiology are varied. Without a doubt, OAEs are useful in the research laboratory for evaluating and/or monitoring the status of cochlear function in experimental animal models. Moreover, clinically, they contribute to determining the differential diagnosis of cochlear versus more centrally based or retrocochlear disorders. Furthermore, their practical features make them helpful in the hearing screening of newborns worldwide. Additionally, they have proven useful in monitoring the progressive effects of agents such as ototoxins and loud sounds on cochlear function. In fact, there is accumulating evidence that it is possible to detect such adverse effects of drugs or noise or a developing familial hearing disorder on OHC function using OAEs before a related hearing loss can be detected by pure-tone audiometry. And OAEs are providing a noninvasive means for assessing the integrity of the cochlear efferent neural pathway. In general, OAEs supply unique information about cochlear function in the presence of hearing problems, and this capability makes them ideal response measures in both the basic- and clinical-hearing sciences.

Most certainly, the dedicated and steady accumulation of a scientific knowledge base about the processes that generate OAEs has laid the basis for developing successful clinical applications using this unique response measure of cochlear function. Remarkably, the practical uses of OAEs began to be apparent in less than a decade after their initial discovery. Consequently, the discovery of OAEs is a good example of combining both scientific and clinical research to steadily advance the study of both normal hearing and hearing impairment. The discovery of OAEs certainly measures up to the ideal of being significant for both laboratory-based research in the hearing sciences and translational audiological applications in the clinic.

Even with the somewhat satisfactory success of evoked OAE assays, particularly with respect to newborn hearing screening, emissions testing in general has been underutilized in clinical practice as a noninvasive check of cochlear dysfunction. However, with the growth of the field's knowledge base concerning emission-generating sources along with the development of more precise measurement systems, OAEs have the potential of becoming more efficient tests of such cochlear properties as nonlinearities, frequency tuning, inner and middle ear transmission, and medial efferent system regulation. Thus, given the complexity of cochlear-generating mechanisms, unmixing the linear reflection and nonlinear distortion origins of DPOAEs, for example, may result in unique sensitivities to cochlear pathology (e.g., Abdala and Dhar, 2012). Furthermore, other approaches suggest that DPOAE components can come, in certain circumstances, from distant basal cochlear regions that are sometimes 1-1.5 octaves from the BM place tuned to the f_2 test stimuli (Martin et al., 2010). Such added contributions from greater frequency regions than anticipated may be better understood using such novel methods as measuring DPOAEs intracochlearly using a noninvasive assay (Martin et al., 2016).

Moreover, further development of in the ear canal calibration systems (as shown in **Figure 1**) using compensatory methods will better limit intersubject variability by controlling for the individual acoustics of different ear canals. And the use of swept-tone rather than discrete-tone presentations promises to result in test times that are clinically acceptable (e.g., Abdala et al., 2015). Together, these contemporary views of OAEs promise to eventually result in more efficient and accurate assessments of hearing thresholds that pinpoint the site of lesion within the impaired cochlea. It is exciting to anticipate what is ahead for the clinical applications of OAEs.

Acknowledgments

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Biosketches

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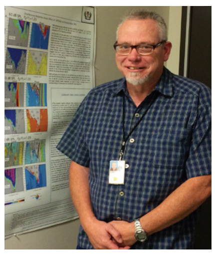

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