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Otoacoustic emissions and cochlear function

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Otoacoustic emissions are sounds produced by the inner ear. In humans, and other mammal species, all normal ears produce otoacoustic emissions in response to sound stimuli. Within the inner ear, a mechanism called the cochlear amplifier utilizes metabolic energy to enhance the sound-induced vibration of the basilar membrane. The enhanced basilar-membrane vibration forms the basis of normal hearing sensitivity. The operation of the cochlear amplifier is impaired by a variety of traumas, resulting in reduced basilar-membrane vibration and, thus, hearing loss. Impaired operation of the cochlear amplifier is associated with reduced or abolished otoacoustic emissions. Otoacoustic emissions and the action of the cochlear amplifier are both characterized by sharp frequency tuning and a high degree of nonlinearity. Thus, otoacoustic-emission generation is intimately related to the normal function of the cochlea, and appears to reflect the action of the cochlear amplifier. Otoacoustic emissions are in widespread use for the assessment of cochlear function in basic-science studies, and in clinical applications. Nevertheless, the cochlear processes underlying the enhancement of basilar-membrane motion and the generation of otoacoustic emissions are not well understood.

Keywords: Otoacoustic emission, Distortion, Nonlinearity, Cochlea, Outer hair cell

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1. INTRODUCTION

Otoacoustic emissions (OAEs) are low-level sounds produced by the inner ear. They are measured using a small probe, containing a sensitive microphone and one or two miniature loudspeakers, that is sealed into the ear canal. In humans, and a number of other mammal species, all normal ears produce otoacoustic emissions in response to sound stimuli.[1,2] Moreover, in humans and some other species, some ears continuously emit sounds.[2] The generation of OAEs appears to be intimately related to the normal function of the cochlea. Many traumas that impair inner-ear function, causing hearing loss, also reduce or abolish OAEs. Studies utilizing OAEs have provided considerable insight into both the normal function of the inner ear, and the dysfunctions of cochlear mechanisms underlying certain hearing losses. In addition, OAE-based tests show great potential for the clinical assessment of cochlear function and the detection of hearing loss.[1-3] For these reasons, OAEs are now in widespread use in basic-science and clinical applications.

This article provides an overview of the properties of OAEs measured in humans and common laboratory mammals, and outlines what is known of the nature of the processes underlying OAE generation, and the relationship of these processes to cochlear function and dysfunction.

2. MEASUREMENT OF OTOACOUSTIC EMISSIONS

The measurement of OAEs is described in detail in previous publications.[2-5] Figure 1 shows a schematic of a typical equipment set-up used for the measurement of OAEs. A probe containing a sensitive miniature microphone is sealed into the ear canal with a foam or rubber eartip. The microphone output is fed via a preamplifier and amplifier (microphone amplifier) and analog-to-digital (A/D) converter to a digital signal-processor mounted in a

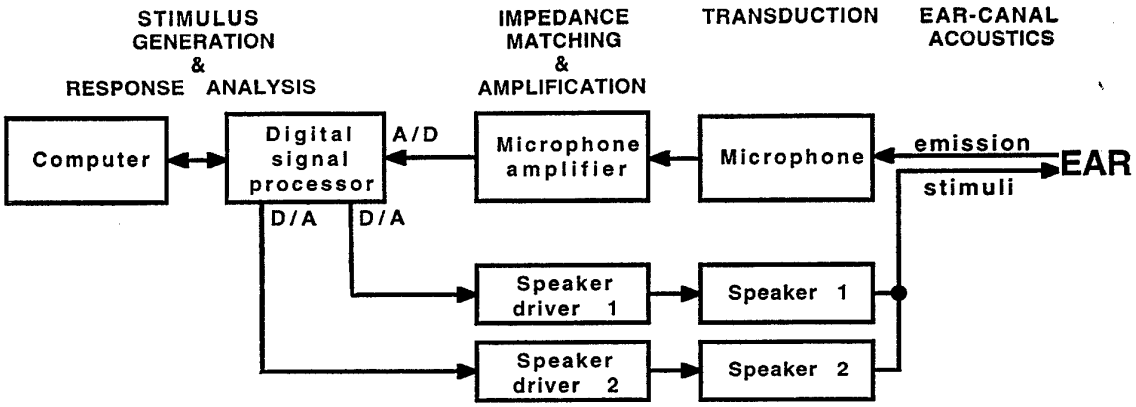

Fig. 1 Schematic of a typical equipment set-up for the measurement of OAEs. See text for explanation.

personal computer. To allow otoacoustic responses to be evoked by sound stimuli, one or two loudspeakers are either built into the probe, or deliver sound to the ear canal via tubes passing through the probe. Voltage commands for each loudspeaker are generated by the digital signal-processor and passed via separate digital-to-analog (D/A) circuits, amplifiers and impedance-matching devices (speaker drivers) to each loudspeaker. Devices designed for the measurement of OAEs are commercially available.

In the absence of deliberate sound stimulation, about 65% of human ears produce continuous, narrow-band acoustic signals, called spontaneous OAEs, at one or more frequencies.[2] Spontaneous OAEs are visible in spectra of samples of the microphone output as sharp peaks above the background noise. The spectra are typically computed by fast-Fourier transformation, and averaged. An example of spontaneous OAEs in a normal human ear is shown in Fig. 2A. Spontaneous OAEs are also present in several other species of mammal, but appear to be less prevalent in these species than in humans.[2,6]

Sound-evoked OAEs are low-level sounds consisting of energy at the frequency or frequencies present in the acoustic stimulus, and also at harmonic and intermodulation-distortion products of frequencies present in the stimulus.

The emission of energy at frequencies present in the stimulus is measured using either transient or steady-state stimuli.[2,7-9] When evoked by a transient, broad-band acoustic stimulus such as a click or tonepip, they are called transient-evoked OAEs (TEOAEs). When evoked by a single, continuous pure-tone stimulus, they are called stimulus-frequency OAEs (SFOAEs). To measure TEOAEs, the transient stimulus is presented over a single speaker, and the microphone output over a number of milliseconds after the stimulus is ensemble averaged. In humans, typically several hundred samples of a 20-ms period after the stimulus are averaged. A click-evoked OAE obtained in this manner from a normal human ear is shown in Fig. 2B. The TEOAE consists of a sound waveform occurring some milliseconds after the stimulus, and lasting for several milliseconds. Comparison of fast-Fourier transforms of the TEOAE (top right, upper) and stimulus (top right, lower) waveforms show that the TEOAE consists of energy at frequencies present in the broad-band stimulus, although the TEOAE amplitude varies irregularly with frequency despite the relatively flat stimulus spectrum.

A SFOAE is a continuous tonal emission at the same frequency as the stimulus tone. Because the SFOAE is present at the same time and at the same frequency as the much larger stimulus, SFOAEs are more difficult to measure than TEOAEs. SFOAEs are typically measured indirectly by their physical interference with the stimulus tone in the sealed ear canal.[7-9]

The components of evoked OAEs that occur at harmonic and intermodulation-distortion products of frequencies present in the stimulus are called distortion-product OAEs (DPOAEs). DPOAEs are typically evoked by two simultaneously presented, continuous pure tones, called primary tones. Each primary tone is presented via a separated speaker in order to avoid the generation of artifactual distortion products that can occur when a single

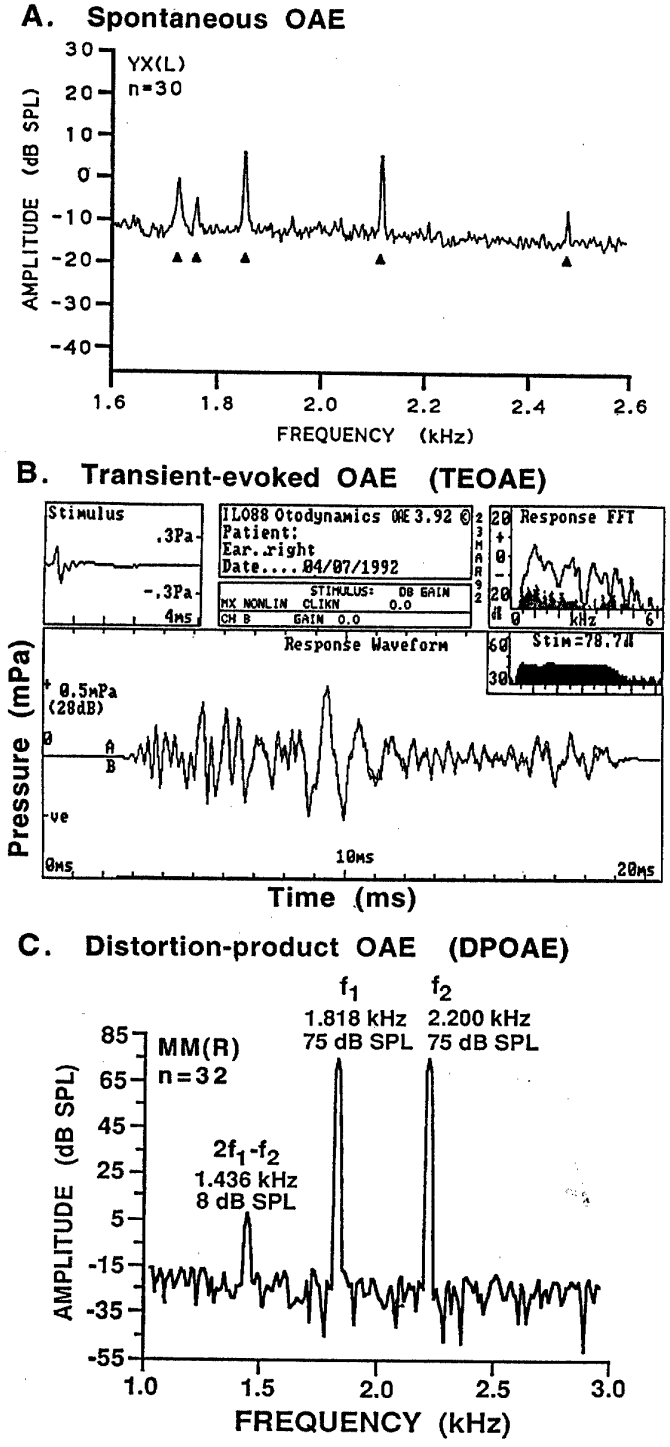

Fig. 2 Examples of OAEs from normal human ears. A: Spontaneous otoacoustic emissions measured in the absence of deliberate sound stimulation. Trace shows the average of 30 spectra of 400-ms samples of the microphone output. Five spontaneous OAEs are visible as peaks above the noise floor (marked with arrowheads). B: Transient-evoked otoacoustic emission in response to a 79-dB_{peak} SPL click presented at 0 ms. Two independently averaged responses (A and B) are over-plotted to show the extremely high repeatability of the emission waveform.[4] Because the speaker and middle-ear undergo passive ringing for a few milliseconds after the click stimulus, and it is important that this ringing not be mistaken for a genuine TEOAE response, the initial 2.5 ms of the waveform has been blanked to remove the stimulus and passive ringing. The click-stimulus waveform is shown on the same time scale, but a much compressed pressure scale, in the upper left panel. The frequency spectrum of the TEOAE response, estimated as the cross-power of the two waveforms, is indicated by the unshaded region in the upper right panel ('Response FFT'). The spectrum of the background noise, estimated as the difference power of the two waveforms, is indicated by the stippled area in this panel. The response signal-to-noise ratio is 10~20 dB over most of the frequency range in which it is present. The shaded area in the panel below the 'Response FFT' panel shows the frequency spectrum of the stimulus click, for comparison. C: Distortion-product otoacoustic emission. Frequency spectrum of the sound field in the sealed ear canal of a normal human ear upon stimulation by two pure tones of frequencies f_1=1.818 and f_2=2.2 kHz, and levels of 75 dB SPL. The peak above the noise floor at 1.436 kHz is the $2f_1-f_2$ DPOAE. The spectrum was obtained from the ensemble average of 32 92-ms samples.

speaker is driven by two sinusoids. For a given pair of primary tones at frequencies f_1 and f_2, where $f_2>f_1$, DPOAEs appear as tonal signals at one or more frequencies including both even-order (*i.e.*, $n[f_2\pm f_1]$ and even harmonics, *e.g.*, f_2-f_1, $2f_1$) and odd-order (*i.e.*, $[n+1]f_1\pm nf_2$, $[n+1]f_2\pm nf_1$, and odd harmonics, *e.g.*, $2f_1-f_2$, $2f_2-f_1$, $3f_1-2f_2$, $3f_1$) distortion components. DPOAEs are typically measured by conventional averaging of samples of the microphone output (locked to a constant distortion-product phase, which is determined from the phases of f_1 and f_2), followed by fast-Fourier transformation. An example from a normal human ear is shown in Fig. 2C. In all mammals tested to date, the largest DPOAE component is the 'cubic difference tone', $2f_1-f_2$. In humans, $2f_2-f_1$ is also often conspicuous, but other DPOAE components are typically very small or absent. In cats, rabbits,

and several rodent species, DPOAEs are much larger than in humans.[2,10] In these species, more than 20 DPOAE components can be detected in response to certain primary-tone pairs.[11]

It is emphasized that the stimuli typical used to elicit the various evoked-OAE phenomena are arbitrary, in that they are selected for ease of OAE measurement. Thus, two tones presented in order to evoke DPOAEs at intermodulation-distortion frequencies will also produce SFOAEs at each of the stimulus frequencies. Similarly, a click-evoked TEOAE contains components at distortion-product frequencies generated by interactions among the various frequency components of the broad-band stimulus.

The measured amplitudes of OAEs are influenced by factors in the inner ear, middle ear, and ear canal that influence propagation of sound energy from the site of generation within the cochlea to the ear-canal microphone. In particular, although the transmission of sound from the cochlea to the ear canal has not been directly measured, it is clear that the normal middle ear substantially influences OAEs,[8,12-15] and many alterations of middle-ear status have been shown to have large effects on measured OAE amplitudes.[10] In addition, the presence and impedance of the measurement probe in the ear canal also influences measured OAE properties.[14,16]

3. BASIC PROPERTIES OF OTOACOUSTIC EMISSIONS

In general, OAEs appear to be produced across most, if not all, of the frequency range of hearing of each species. Thus, spontaneous and evoked OAEs occur at audio frequencies in humans and other mammals,[2,10] and have been measured above 60 kHz in some bat species.[17]

TEOAEs and SFOAEs represent outputs of a single mechanism in response to transient and steady-state stimuli, respectively.[7-9] Essentially all normal human ears exhibit TEOAEs and SFOAEs.[1,2] However, in any one ear there is variation of the amplitudes of TEOAEs and SFOAEs across frequency, with both OAE types robust at some frequencies and both small or undetectable at others. The pattern of amplitude variation across frequency varies greatly between individual ears. TEOAEs and SFOAEs appear not to have a real threshold, in that the lowest stimulus-level at which they can be detected depends upon background noise and instrumentation sensitivity. The growth of TEOAE and SFOAE amplitude is compressively nonlinear, *i.e.*, <1 dB per dB increase of stimulus level, over most of the stimulus-level range, although at very low stimulus levels, growth approaches linearity.[18] At moderate stimulus levels, their amplitudes saturate at levels rarely exceeding 20 dB SPL.[1,2,7,8,18] The compressive nonlinearity of TEOAEs and SFOAEs is, perhaps, their most characteristic feature.

Spontaneous OAEs are thought to be produced by the same underlying process as TEOAEs and SFOAEs, apparently as a result of feedback of the output of the emission generator into its input. At frequencies where this feedback is positive, if the loop gain is sufficient, self-sustaining oscillation will result which is observed in the ear canal as a spontaneous OAE.[8,18,19] Thus, spontaneous OAEs can be thought of as continuously self-evoking evoked OAEs. Consistent with this view, spontaneous OAEs are found in regions of strong TEOAE and SFOAE response, and rarely exceed 20 dB SPL.[2,8,9,18,19] Spontaneous OAEs are definitive evidence of a metabolic-energy utilizing, high-frequency vibratory mechanism within the inner ear.

Because $2f_1-f_2$ is the largest DPOAE, it has been the most studied. The amplitude of the $2f_1-f_2$ DPOAE depends systematically on frequency, stimulus level, frequency separation, and level difference of the primary tones.[2,10,20] If the primary tones are spaced too far apart in frequency, $2f_1-f_2$ DPOAEs cannot be detected, indicating that the DPOAE is generated after some filtering of the stimuli. For those primary-tone frequencies yielding the largest $2f_1-f_2$ DPOAEs, these emissions are robust at low stimulus levels. When both primary tones are increased in level, DPOAE amplitudes increase at a rate of about 1 dB/dB, on average, but growth tends to saturate above stimulus levels of $65\sim75$ dB SPL. The 1 dB/dB growth rate over a wide range of stimulus levels suggests that DPOAEs evoked by low- and moderate-level primary tones are not generated by a simple 'overloading' nonlinearity. At higher stimulus levels, there may be further growth at rates greater than 1 dB/dB.

DPOAEs are $20\sim35$ dB larger in cats, rabbits, and several rodent species than in humans and macaque monkeys.[2,10,20] In contrast, TEOAEs

and SFOAEs appear somewhat smaller in cats, rabbits and rodents than in humans and monkeys. The reason for these large species differences is unknown. Despite these differences of absolute amplitudes, however, the various otoacoustic emission phenomena are qualitatively very similar across species.[2,10]

4. THE LOCATION OF THE OTOACOUSTIC-EMISSION GENERATOR

Several manipulations and disease states known to selectively affect the cochlea,[1-3,8,21-28] *e.g.*, perfusion of toxins through the cochlear fluids,[21,26] reduce or abolish OAEs. Thus, OAEs must originate within the cochlea. Moreover, manipulations thought to selectively affect the organ of Corti, *e.g.*, electrical stimulation of the efferent innervation of outer hair cells,[22,23] influence OAEs, indicating that OAEs are generated within the organ of Corti.[2,10]

TEOAEs and SFOAEs occur in response to stimuli far below hearing threshold,[8-18] and TEOAEs demonstrate very little adaptation, and essentially perfect waveform inversion with stimulus polarity.[24] These findings are inconsistent with neural involvement in OAE generation. DPOAEs were not reduced by section of the auditory nerve,[25] or by application of drugs that abolished auditory-nerve activity.[21,26] These findings indicate that neither afferent or efferent auditory-nerve activity is necessary for the generation of OAEs. Thus, OAEs must be generated before the level of the afferent synapse.

Each point along the basilar membrane vibrates maximally in response to a specific stimulus frequency, called the characteristic frequency. The characteristic frequency decreases from the basal to the apical end of the basilar membrane. Several lines of evidence indicate that OAEs are generated primarily in the region of the basilar membrane with characteristic frequencies close to the stimulus frequency(s). First, fatiguing or damaging a localized region of the cochlea, *e.g.*, by exposure to an intense tone, selectively reduces those OAEs evoked by stimuli around the characteristic frequencies of the affected region of the cochlea.[2,10,24,27]

Second, OAEs can be suppressed, *i.e.*, reduced in amplitude, by sounds presented in addition to the evoking stimuli.[2,7,8,13,18,27,28] Plotting the level of a suppressor tone required to reduce OAE amplitude by a criterion amount yields an iso-suppression contour. These contours are sharply tuned, with suppressors close in frequency to the evoking stimuli most effective, and lower- and higher-frequency suppressors less effective, indicating that OAEs are generated primarily in a narrow region of the cochlea close to that encoding the stimulus frequencies. For TEOAEs, SFOAEs and spontaneous OAEs, these contours demonstrate similar shapes to frequency-tuning curves obtained from the activity of single auditory-nerve fibers, and psychophysically, indicating that these OAEs are generated at a late stage of cochlear filtering. For $2f_1-f_2$ DPOAEs, the tuning of suppression is typically somewhat broader, presumably reflecting the fact that DPOAEs reflect the interaction of two stimulus tones of separate frequencies.

Third, the latencies of TEOAEs, SFOAEs, and DPOAEs (*i.e.*, the time between stimulus onset and either onset or maximum amplitude of the response) increase as stimulus frequency decreases. In humans, latencies vary from <1 ms above 10 kHz to >12 ms below 1 kHz.[1,7,8,19,29-31] In rabbits and rodents, although the absolute latencies of OAEs are much smaller than in humans, a similar frequency-dependence of latency is seen. The latency of auditory-nerve responses progressively increases with apical location along the basilar membrane.[32] Thus, it is likely that the increasing latencies of lower-frequency OAEs reflect more apical locations of OAE generation.

5. THE PHYSIOLOGICAL VULNERABILITY OF OTOACOUSTIC-EMISSIONS

Otoacoustic emissions are characterized by their extreme dependence on metabolic energy. The effective energy supply to the organ of Corti is the endolymphatic potential. The endolymphatic potential can be rapidly and reversibly decreased by reducing the oxygen supply to the cochlea by induction of hypoxia or anoxia, or by acute administration of loop diuretics, *e.g.*, furosemide or ethacrynic acid. In experimental animals, these manipulations cause rapid, reversible reduction or abolition of TEOAEs, SFOAEs, and spontaneous OAEs,[2,6,10,33,34] and of DPOAEs evoked by low- and moderate-level stimuli (*i.e.*, below $55\sim70$ dB SPL).[2,10,21,35-37] However, DPOAEs evoked by higher-level stimuli are less affected by these manipulations, *i.e.*, the metabolic vulnerability of

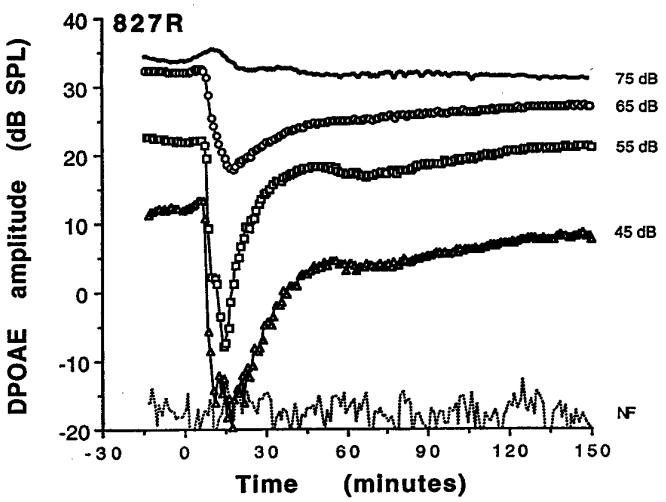

Fig. 3 The effects of the loop diuretic ethacrynic acid on $2f_1-f_2$ DPOAEs in a rabbit ear. Stimuli were $f_1=7.541$, $f_2=9.426$ kHz. The amplitude of the DPOAE at 5.656 kHz is plotted as a function of time for equilevel primary tones at 75 (bold line), 65 (circles), 55 (squares), and 45 (triangles) dB SPL. The noise floor (faint line) is also shown. Ethacrynic acid (40 mg/kg) was injected intravenously at 0 min.

DPOAEs is stimulus-level dependent. Figure 3 illustrates the stimulus-level dependence of the effects of ethacrynic-acid injection on DPOAE amplitudes in a rabbit. Other traumas, including perfusion of the cochlea with salicylate,[88] chronic administration of gentamicin,[89] and noise overexposure, also have level-dependent effects on DPOAEs in experimental animals.[2,10]

These findings suggest that DPOAEs evoked by stimuli below or above 55～70 dB SPL are generated by partially or completely separate mechanisms. Further evidence in support of this hypothesis comes from studies of the dependence of the amplitude and phase of $2f_1-f_2$ DPOAEs upon stimulus parameters in rabbit.[20,86] These studies indicate that the $2f_1-f_2$ DPOAE is the vector sum of two discrete components, which demonstrate differential variations with stimulus parameters. One component is highly vulnerable to trauma, and dominates the total ear-canal $2f_1-f_2$ signal at low- and moderate-stimulus levels (below 55～70 dB SPL). The other component is less vulnerable to trauma, and demonstrates steeper growth such that it dominates the total ear-canal $2f_1-f_2$ signal at higher stimulus levels. At stimulus levels around 55～70 dB SPL, the two components of the $2f_1-f_2$ DPOAE can be of similar amplitude. Variation of stimulus parameters allows the relative phase of the low- and high-level components to be systematically manipulated, so that the vectors of the two components add or cancel. Figure 4 shows DPOAE amplitude (top) and phase (bottom) as a function of stimulus level for two primary-tone pairs. For one primary-tone pair (left), the sharp minimum of DPOAE amplitude associated with a rapid jump of DPOAE phase indicates cancellation of the two components around 57 dB SPL, suggesting that the two components were equal in amplitude and approximately 180° out of phase at this stimulus level. For a different pair of primary-tone frequencies (right), the two components were in a different phase relation at the stimulus level at which they were equal in amplitude and, thus, did not cancel.

The different properties of the distinct low-level and high-level components of $2f_1-f_2$ DPOAEs observed in rabbits and rodents must reflect differences of underlying generation mechanisms. It is not known whether the generators of the low-level and high-level DPOAE components are completely separate, or whether they share common elements (*e.g.*, the nonlinearity producing distortion-products in each case may be the same, but with a metabolically-dependent enhancement of the distortion products at low but not high stimulus levels). It is not yet known whether humans possess distinct low-level and high-level DPOAE components similar to those described in rabbit and rodent ears. Whereas the vulnerability to trauma of DPOAEs in humans is greater at lower stimulus level, studies searching for evidence of two discrete components of DPOAEs are complicated by the inability to use many of the ototoxic manipulations employed in animal experiments, by the small amplitudes of DPOAEs in human ears, and by possible interactions of DPOAEs with SFOAEs and spontaneous OAEs in human ears.

It is noted in passing that the even-order f_2-f_1 DPOAE (the 'quadratic difference tone') demonstrates some quite distinct properties to the odd-order $2f_1-f_2$ DPOAE (the 'cubic difference tone'), suggesting that there may be differences in the mechanisms underlying the generation of even-order and odd-order DPOAEs.[35,40,41]

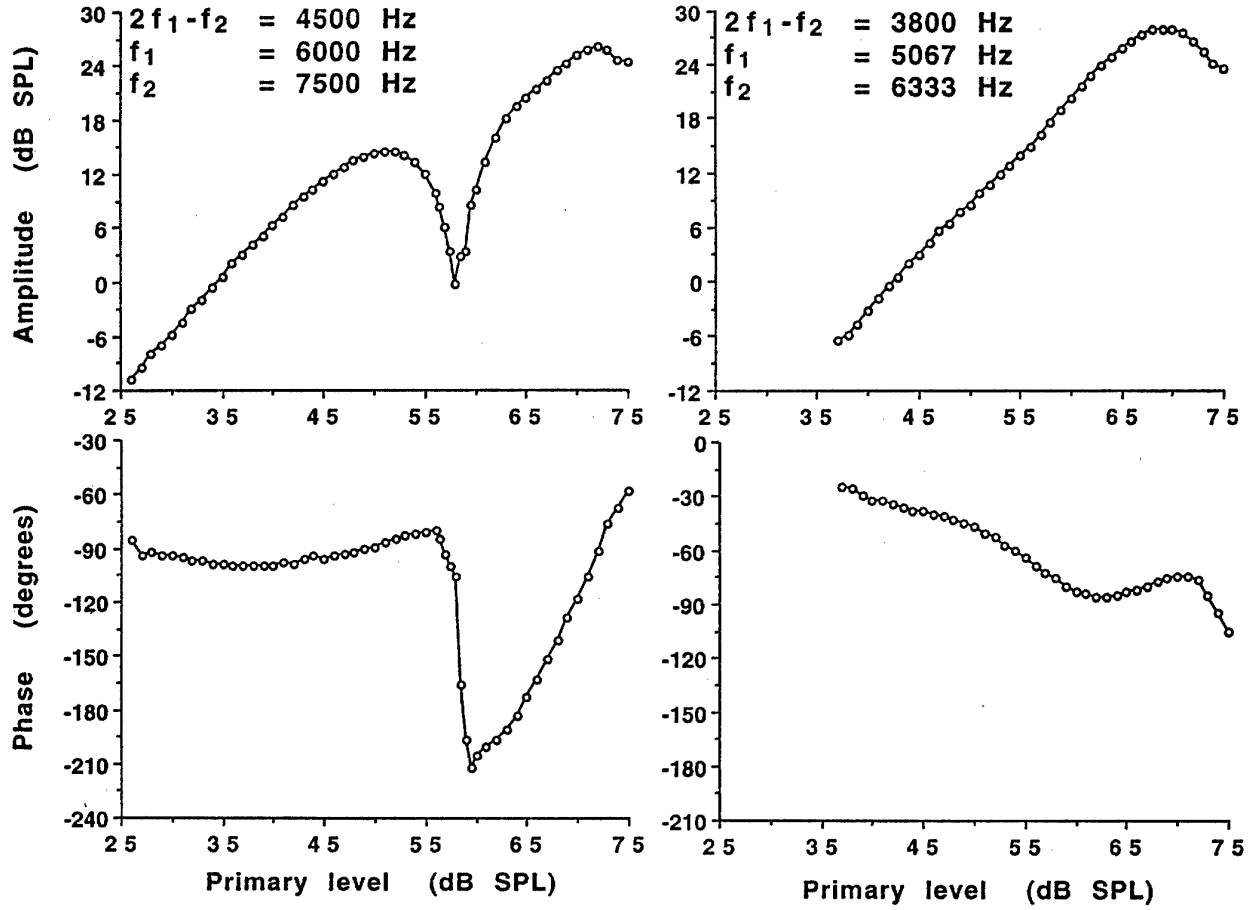

Fig. 4 Amplitude (top) and phase (bottom) of $2f_1-f_2$ DPOAEs in a rabbit ear plotted as a function of equilevel primary-tone intensity for two different primary-tone frequency pairs. The phase reference was arbitrary, and lag is negative. For the primary-tone pair at left, the sharp minimum of DPOAE amplitude associated with a rapid phase jump around 57 dB SPL indicates cancellation of two out-of-phase components of the $2f_1-f_2$ signal which were of approximately equal-amplitude at this stimulus level. For the primary-tone pair at right, no cancellation was observed.

6. SUMMARY: THE NATURE OF THE OTOACOUSTIC-EMISSION GENERATORS

At low and moderate stimulus levels, OAEs are characterized by: (1) a high degree of nonlinearity, reflected as compressive growth of TEOAEs and SFOAEs with saturation at moderate stimulus levels, suppression of OAEs, and pronounced distortion-product OAEs, (2) sharp frequency tuning, as revealed by suppression studies, and (3) extreme vulnerability to metabolic insult, and to other cochlear traumas.

The emission of stimulus-frequency energy is an inherently low-level phenomenon, since TEOAEs and SFOAEs saturate at moderate stimulus levels. The low-level $2f_1-f_2$ DPOAE component also saturates at moderate stimulus levels, and demonstrates qualitatively similar vulnerability to a variety of cochlear traumas as do TEOAEs and SFOAEs. Each of these evoked-emission phenomena are generated primarily in the region of maximum basilar-membrane response to the evoking stimuli, by a nonlinear process located pre-neurally in the organ of Corti, that requires metabolic energy, and can produce vibrations at audio and ultrasonic frequencies.

The high-level $2f_1-f_2$ DPOAE component also appears to be generated pre-neurally in the organ of Corti, but by a partially or completely different process to that which generates the low-level DPOAE component. What are the mechanisms responsible for the various OAE phenomena?

7. BASILAR-MEMBRANE VIBRATION AND THE 'COCHLEAR AMPLIFIER'

It has recently become possible to directly measure the vibration of the basilar membrane without greatly compromising cochlear function.[42,48] These measurements have shown that in healthy ears there are two distinct components of the vibration at any one place along the basilar-membrane. One component is relatively unaffected by physiological manipulations. This component is broadly tuned and quite linear, and appears to be the passive response of the basilar membrane to sound stimulation. In contrast, the other component is extremely vulnerable to metabolic insult, being reduced or abolished by manipulations that decrease the energy supply to the organ of Corti, such as anoxia or injection of loop diuretics.[42-44] This latter component is sharply tuned, in that the vibration of the basilar membrane at a particular place along its length is reduced by metabolic insult only within a relatively narrow range of frequencies around the characteristic frequency. Outside the sharply-tuned region of enhancement, basilar-membrane vibration is relatively unaffected by various cochlear traumas, and appears similar in healthy and dead ears. The vulnerable, sharply-tuned component of basilar-membrane vibration reflects the action of a mechanism in the organ of Corti that responds to sound by utilizing metabolic energy to increase the sound-induced vibration of the basilar-membrane.[42-46] This mechanism has been called the 'cochlear amplifier'.[47]

The action of the cochlear amplifier is associated with substantial nonlinearity. In response to stimulus frequencies around the characteristic frequency, within the metabolically-vulnerable region, the growth of basilar-membrane vibration with stimulus level is compressively nonlinear at low and moderate stimulus levels,[42-46] and stimulus-evoked basilar-membrane vibration can be suppressed by stimuli presented in addition to the evoking stimulus.[48,49] Outside the frequency region of enhancement, growth of basilar-membrane vibration is quite linear, and suppression is small or absent.[42-49] Distortion products are also present in basilar-membrane vibration.[48,50] At low and moderate stimulus levels, the distortion products appear to be generated in the region along the basilar membrane with characteristic frequencies around the primary-tone frequencies, *i.e.*, in the region where the cochlear amplifier acts to enhance the basilar-membrane vibration produced by the primary tones.[21,48]

The enhancement of basilar-membrane motion by the cochlear amplifier is greatest at low stimulus levels, and decreases with increasing stimulus level such that at high levels there is little or no enhancement.[42-47] Thus, the passive component appears to dominate basilar-membrane vibration in response to high sound levels, even in healthy ears in the frequency region in which vibration is greatly enhanced at low and moderate stimulus levels. Traumas that reduce or eliminate the region of enhancement of basilar-membrane motion also reduce or eliminate the compressively-nonlinear growth, and the suppression and distortion-products observed in basilar-membrane vibration at low and moderate stimulus levels.

The enhancement of basilar-membrane motion yields increased sensitivity, dynamic range and frequency selectivity of basilar-membrane vibration at low and moderate stimulus levels.[42-47] Basilar-membrane vibration results in stimulation of the inner hair cells, which are innervated by the large majority of afferent auditory-nerve fibers. The two components of basilar-membrane vibration are reflected in the responses of inner hair cells, and in the responses of auditory-nerve fibers, as the highly vulnerable, sharply-tuned 'tip' and less-vulnerable, broadly tuned 'tail' of frequency tuning curves. The compressively-nonlinear growth, and the suppression and distortion products, observed in basilar-membrane vibration are also reflected in inner hair cell and neural responses.

8. THE MECHANISM OF THE COCHLEAR AMPLIFIER

For a number of reasons, the cochlear amplifier is thought to be based in the outer hair cells. Outer hair cells have little afferent, but a large efferent, innervation, suggesting a motor rather than sensory role for these cells. Electrical stimulation of the efferent innervation of the outer hair cells appears to reduce the action of the cochlear amplifier.[45,46,51] In addition, traumas that appear to selectively damage outer hair cells also reduce the action of the cochlear amplifier.[44-46]

Isolated outer hair cells observed *in vitro* demonstrate electromotility, *i.e.*, cycle-by-cycle shape changes in response to acoustic-frequency electrical

stimulation.[52,53] The electromotile mechanism appears to consist of large numbers of an unidentified molecular entity, located within the basolateral membrane of the outer hair cell, that changes shape in response to alterations of voltage across this membrane.[46] *In vivo*, this membrane experiences cycle-by-cycle voltage changes, *i.e.*, the outer hair cell receptor potential, upon sound stimulation. Thus, it is thought that the primary role of outer hair cells is to generate mechanical force in response to their a.c. receptor potential in order to enhance the sound-evoked vibration of the basilar membrane. Although the details of this process are unknown, it is thought that the enhancement involves a feedback loop between outer hair cell electromotility and basilar-membrane vibration. The outer hair cells are ideally located within the organ of Corti to influence basilar-membrane vibration. Inner hair cells and other organ of Corti cell types do not demonstrate electromotility *in vitro*.

It is not known whether the sharp tuning of the enhancement of basilar-membrane vibration is inherent to the cochlear amplifier, or arises from interaction of the broadly-tuned passive motion of the basilar membrane with the cochlear amplifier.[45-48] It is also not known over what length of the basilar membrane the cochlear amplifier acts in order to enhance motion in response to a given stimulus frequency at its characteristic place, although recent evidence suggests that this action may occur primarily within a relatively narrow region (<2 mm) basal to and around the characteristic place.[54,55]

9. THE COCHLEAR AMPLIFIER AND OTOACOUSTIC EMISSIONS

The output of the cochlear amplifier is compressively nonlinear, demonstrates suppression, and includes stimulus-frequency and distortion-product frequency components. The action of the cochlear amplifier is sharply tuned, and extremely vulnerable to metabolic and other cochlear trauma. Thus, the action of the cochlear amplifier is primarily a low and moderate stimulus-level phenomenon, that has its influence primarily in the region of maximum basilar-membrane response to the evoking stimuli. The cochlear amplifier is a nonlinear process located pre-neurally in the organ of Corti, that requires metabolic energy, and can produce vibrations at audio and ultrasonic frequencies.

These properties are very similar to those described above for TEOAEs, SFOAEs and the low-level component of DPOAEs. Thus, it is thought that these OAE phenomena represent a leakage of energy from the action of the cochlear amplifier, *i.e.*, from outer hair cell electromotility. From this viewpoint, the physiological vulnerability, sharp tuning, and nonlinearity of OAEs reflect these properties of the cochlear amplifier. Indeed, these properties are remarkably similar when observed in basilar-membrane vibration and in OAEs.

The origin of TEOAEs, SFOAEs, and the low-level component of DPOAEs in outer hair cell electromotility is consistent with the observation that OAEs are reduced by several traumas that are thought to primarily affect outer hair cells, *e.g.*, certain noise overexposures, and aminoglycoside poisoning,[2,10,39] and that stimulation of the efferent innervation of outer hair cells alters OAEs.[22,23] In addition, it is parsimonious to assume that the unique mechanism within outer hair cells that produces electromotility at high frequencies *in vitro* also underlies the generation of sounds by the cochlea at these frequencies *in vivo*.

In contrast, the high-level DPOAE component present in rabbits and rodents appears not to reflect the action of the cochlear amplifier. It is less vulnerable to metabolic and other traumas than either the cochlear amplifier, or TEOAEs, SFOAEs and the low-level component of DPOAEs. In guinea pigs with gentamicin-induced cochlear damage, DPOAEs evoked by high-level stimuli were normal in regions where outer hair cells were severely damaged, and DPOAEs evoked by low-level stimuli were greatly reduced or absent.[39] These findings suggest that the high-level DPOAE component does not require outer hair cells. However, this component does show behaviors indicating that it has a physiological origin within the organ of Corti. Thus, it appears to require the integrity of some component(s) of the organ of Corti, it is influenced by fatigue,[36] and it appears more vulnerable to trauma than is the passive component of basilar-membrane motion. Thus, the mechanism responsible for generation of the high-level DPOAE component is unknown, and does not appear simply related either to the cochlear amplifier, or to the passive component of basilar-membrane vibration.[36]

Reduced action of the cochlear amplifier results in reduced basilar-membrane motion in response to

low-level stimuli and, thus, elevated hearing thresholds.[44-47] Because the cochlear amplifier, and outer hair cells, appear particularly vulnerable to a variety of traumas that affect the inner ear, much of the sensorineural hearing loss observed clinically is thought to result from reduced action of the cochlear amplifier, *i.e.*, from a reduction of outer hair cell electromotility. Dysfunction of the cochlear amplifier can result from damage to the outer hair cells themselves, or may be secondary to damage to other components of the inner ear on which normal function of the outer hair cells depends.[10,44,45]

Hearing losses caused by dysfunction of the cochlear amplifier are sensory losses. Other sensory losses may also occur, *e.g.*, by traumas that influence the inner hair cell mechanoelectric or synaptic transduction processes. Such traumas, and also dysfunctions of the auditory nerve or central auditory system, would presumably have little effect on OAEs, although they would result in hearing loss.[2,8,10] The clinical diagnostic application of OAEs is based upon the evidence indicating that OAEs reflect the action of the cochlear amplifier, *i.e.*, the presumed action of the outer hair cell system. To the extent that this is true, OAEs can provide information specifically about those hearing losses arising from dysfunction of the cochlear amplifier.

10. SOME UNCERTAINTIES

Although TEOAEs, SFOAEs, and the low-level component of DPOAEs appear to reflect the action of the cochlear amplifier, the precise relationship between these OAE phenomena and the enhancement of basilar-membrane motion is not clear. In normal human ears, in frequency regions where hearing threshold is normal, *i.e.*, where cochlear-amplifier function is presumably quite uniform across frequency, TEOAE and SFOAE amplitudes vary dramatically with frequency. Typically, in any one ear, these emissions are strong over broad regions, several hundred Hertz wide, and weak or undetectable between these regions, in a pattern that is unique to each ear[7,8,24] (within each region of strong response, hearing threshold and OAE amplitudes show a correlated fine-structure with frequency). Moreover, TEOAEs and SFOAEs are larger in humans and monkeys than in several non-primate mammal species, some of which have hearing sensitivity similar to or better than that of humans.[2,10] Thus, it appears that the function of the cochlear amplifier is necessary but not sufficient for the emission of stimulus-frequency energy, and that additional, unidentified factor(s) are required for the generation of TEOAEs and SFOAEs.

As discussed above, TEOAEs, SFOAEs, and spontaneous emissions appear to be manifestations of the same underlying mechanism, that gives rise to the emission of stimulus-frequency energy. This mechanism is nonlinear in that both TEOAEs and SFOAEs show compressive growth and suppression. It is parsimonious to assume that the nonlinearity responsible for these behaviors also produces the distortion products manifested as DPOAEs. Consistent with this assumption, DPOAEs evoked by low-level primaries show properties suggesting an origin in the same mechanism as TEOAEs and SFOAEs. Thus, these DPOAEs appear to be generated in the region of the basilar-membrane with characteristic frequencies around the primary-tone frequencies, and they show similar vulnerability to cochlear traumas that reduce the action of the cochlear amplifier.

However, the relationship of the low-level component of DPOAEs to the emission of stimulus-frequency energy is not unambiguous. Thus, studies in humans[56] and macaque monkeys[57] have shown that after administration of salicylate, TEOAEs, SFOAEs, and spontaneous OAEs can be substantially reduced with little or no effect on DPOAEs evoked by low and moderate level stimuli from the same frequency region of the same ear. Figure 5 illustrates the differential effect of salicylate on TEOAEs (Fig. 5A) and DPOAEs (Fig. 5B) in a macaque monkey.[57] If DPOAEs arise from the same process as TEOAEs and SFOAEs, it is difficult to explain how DPOAEs can be unaffected by factors that greatly reduce TEOAEs and SFOAEs. Moreover, whereas TEOAEs and SFOAEs are somewhat smaller in rabbits and rodents than in humans and monkeys, DPOAEs in rabbits and rodents are 20～30 dB larger than those in humans and monkeys.[2,10] These observations suggest some dissociation of the mechanisms responsible for the emission of distortion-product energy and stimulus-frequency energy. This, in turn, implies that DPOAEs have a somewhat different relationship to the action of the cochlear amplifier than do TEOAEs and SFOAEs. It is possible that the stimulus-frequency and distortion-product components of OAEs

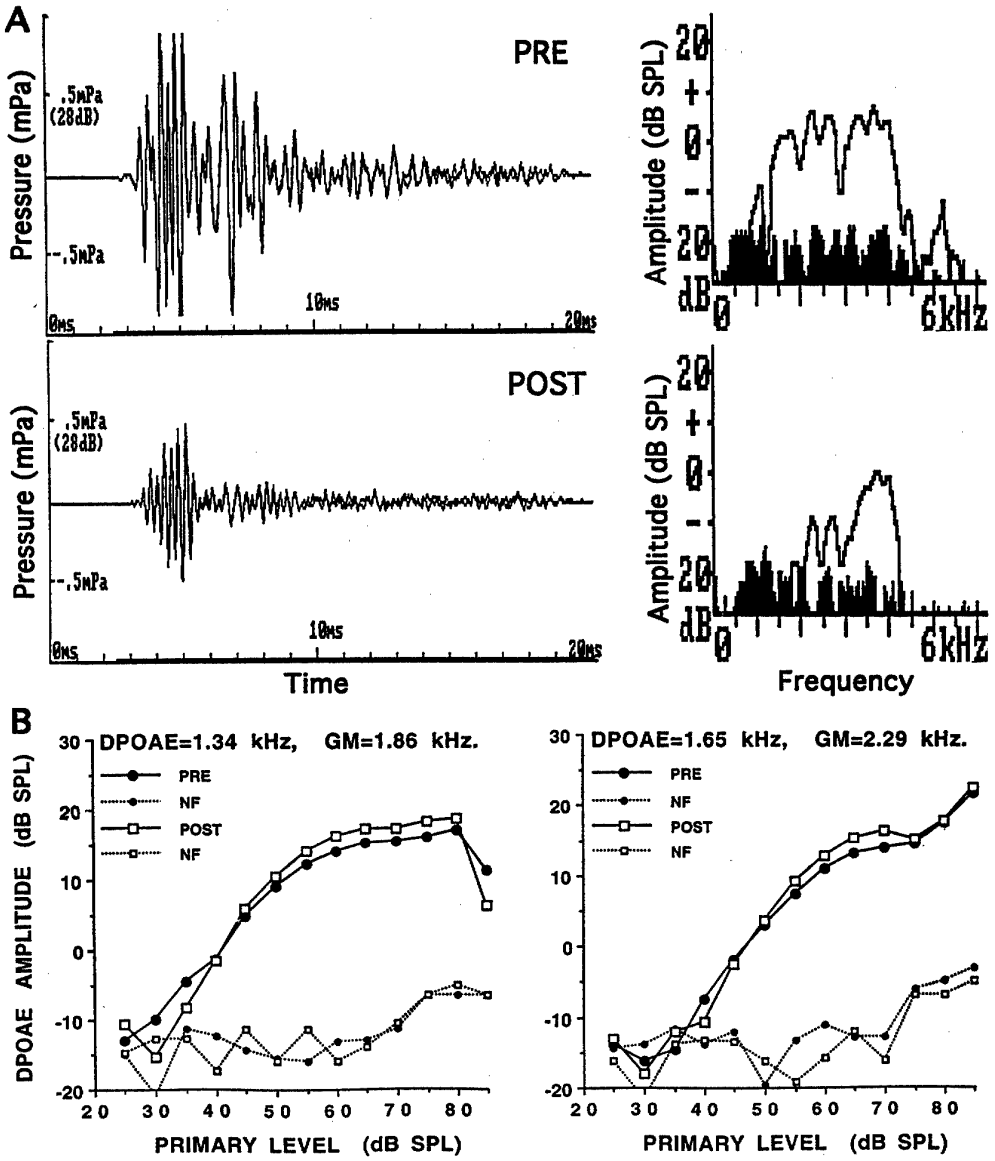

Fig. 5 A: Time waveforms (left), and associated frequency spectra (right), of click-evoked TEOAEs in a pigtail macaque ear before (PRE), and approximately six hours after (POST), a subcutaneous injection of sodium salicylate (100 mg/kg). The TEOAEs were substantially reduced, especially at low frequencies, post-salicylate. The TEOAEs were measured with equipment similar to that used for Fig. 2B. B: Growth functions of $2f_1-f_2$ DPOAEs obtained before (filled circles) and approximately six hours after (open squares) the salicylate injection, at frequencies within the region of maximum TEOAE reduction. The corresponding noise floors (NF) are also shown. Both the DPOAE frequency and the geometric mean (GM) of the stimulus-tone frequencies, *i.e.*, $(f_1 \times f_2)^{0.5}$, are given in each panel. Primary tones were equilevel. The DPOAEs were not reduced despite a greater than 20-dB reduction of TEOAE amplitudes at some of the frequencies of DPOAE measurement. The blood-plasma salicylate level obtained shortly after the post-injection OAE measurements was 22.1 mg%.

reflect somewhat different aspects of cochlear-amplifier function.

11. WHAT IS THE NONLINEAR ELEMENT IN COCHLEAR FUNCTION?

The nonlinearity(s) responsible for the nonlinear phenomena manifested in measurements of basilar-membrane vibration and in otoacoustic emissions must be located in the mechanical properties of the cochlear partition, or in the electrophysiological properties of outer hair cells. Whereas the precise relationship of distortion-product generation to

suppression and compressive growth with stimulus level is unknown, all three of these pheomena appear to be intimately associated with the action of the cochlear amplifier.[45,46,48-50] Specifically, the vulnerability to metabolic insult of these nonlinear phenomena suggests that normal function of the outer hair cells is required for their expression.

Several stages in the functioning of outer hair cells have been demonstrated to be nonlinear. The stiffness of outer hair cell stereocilia varies nonlinearly with stereocilia displacement, especially for small displacements from the resting position.[58] A similar displacement-dependent stereociliar stiffness is present in frog saccular hair cells, and this nonlinearity has been shown to give rise to quadratic and cubic distortion products in stereociliar motion.[59] In addition, the hair-cell mechanoelectric transduction process is nonlinear, *i.e.*, the current that enters the outer hair cell as a result of displacements of the stereocilia from their resting position is a nonlinear function of stereocilia displacement.[60,61] Moreover, the voltage change of outer hair cells in response to current injection is also nonlinear around their resting potential, in that depolarizing outer hair cells increases membrane conductance, presumably because of the effects of voltage- and ligand-gated ion channels in the basolateral membrane.[60] Thus, the receptor potential of outer hair cells will be a nonlinear function of the (already nonlinear) transduction current.[61]

The outer hair cell receptor potential is thought to be the effective stimulus for electromotility *in vivo*. Nonlinearities in the receptor potential will, therefore, be reflected in the cell's motile response.[62] Moreover, the voltage-to-movement function of the electromotile process is itself nonlinear, and this nonlinearity can produce both harmonics and d.c. components in outer hair cell electromotility in response to large sinusoidal voltage stimuli *in vitro*,[53,62] although it is probable that this nonlinearity does not contribute greatly to harmonic distortion in response to the small receptor potentials occurring at low and moderate sound levels *in vivo*. Recently, outer hair cell electromotility *in vitro* in response to two simultaneous pure-tone voltage stimuli was shown to contain prominent cubic and quadratic distortion-products,[68] although the nonlinearity underlying the generation of these distortion products was not identified.

Thus, there is a cascade of nonlinearities between outer hair cell stimulation and electromotility. Each nonlinearity has a different transfer function, and each of these transfer functions depends differentially upon stimulus frequency. It is thought that the action of the cochlear amplifier involves a feedback loop between basilar-membrane motion and outer hair cell electromotility. The combination of a cascade of nonlinearities within a feedback system is extremely complex. Moreover the structure of the organ of Corti within which outer hair cells act is also complex. It will be a considerable challenge to determine the precise nature of the nonlinear processes responsible for the generation of distortion products and the other nonlinear phenomena present in basilar-membrane motion and otoacoustic emissions.

12. CONCLUSIONS

The cochlear amplifier is a mechanism, apparently based in outer hair cells, that enhances the passive, sound-induced vibration of the basilar membrane in response to low- and moderate-level stimuli near the characteristic frequency of each place along the basilar membrane. The enhancement of basilar-membrane vibration is thought to involve the unique electromotile property of outer hair cells. The mechanism(s) that generate TEOAEs, SFOAEs, and the low-level component of DPOAEs, are closely related to the action of the cochlear amplifier. However, the generator of the high-level DPOAE component does not appear obviously related either to the cochlear amplifier, or to the passive vibration of the basilar membrane. The action of the cochlear amplifier is highly nonlinear, resulting in compressive growth, suppression, and distortion-products, both in basilar-membrane vibration and in OAEs.

Decreased action of the cochlear amplifier results in reduced basilar-membrane vibration and, thus, hearing loss. Because the cochlear amplifier, and outer hair cells, appear to be especially vulnerable to a number of cochlear traumas, it is thought that much, but not all, of the sensorineural hearing losses observed clinically involve reduced action of the cochlear amplifier. Because OAEs are decreased in association with reduced action of the cochlear amplifier, they can provide information about these sensory hearing losses. This relationship has made OAE testing valuable for the clinical assessment of cochlear condition and the detection of hearing loss,

as well as for the scientific study of inner-ear function.[1-3] However, despite the widespread use of OAEs in basic-science and clinical applications, the precise relationship of the various OAE phenomena to the action of the cochlear amplifier is unclear. Moreover, it is not known how the cochlear amplifier itself functions. Thus, both the mechanism of outer hair cell electromotility, and the manner in which this electromotility enhances basilar-membrane motion *in vivo*, are obscure.

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