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Otoacoustic Emissions — Mechanisms and Applications

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Not every doctor can look into a mouse's ear without laughing.
E. B. White, *Stuart Little*

LEARNING OBJECTIVES

- Understand basic OAE types, how they are measured and applied, and the rationale for specific stimulus and recording parameters
- Understand OAE source types and how they have been distinguished experimentally
- Understand how different OAEs are generated, the kinds of information they carry, and how they are interpreted in the clinic
- Understand DPOAE fine structure and its modulation by efferent feedback as an example of OAE source-type mixing
- Understand how and why current research may affect the application and/or interpretation of OAEs in the future

Key Words. Auditory brainstem response (ABR), auditory neuropathy (AN), basilar membrane (BM), click-evoked OAE (CEOAE), contralateral acoustic stimulation (CAS), distortion, distortion product (DP), distortion-product "audiogram" (DP-gram), distortion-product OAE (DPOAE), fine structure, fast Fourier transform (FFT), input/output (I/O), inverse FFT (IFFT), magnitude and phase, medial olivocochlear (MOC), otoacoustic emissions (OAE), outer hair cell (OHC), polar plot, reflection, signal-to-noise ratio (SNR), spontaneous OAE (SOAE), stimulus-frequency OAE (SFOAE), transient-evoked OAE (TEOAE)

A CURIOUS CASE

Imagine for a moment that you are one of those doctors. A young mouse (P40) walks into your clinic and complains both of reduced sound tolerance and difficulty tuning double stops on his diminutive violin due to inaudible Tartini tones. Audiologic tests reveal that your muscular patient has:

- Normal pure-tone audiograms (both air-conducted and bone-conducted) and normal threshold auditory-brainstem responses (ABRs);

- Reduced loudness discomfort levels (LDLs);
- No distortion-product otoacoustic emissions (DPOAEs); and
- Unusually large click-evoked otoacoustic emissions (CEOAEs).

Although some details of the case imagined above have been fictionalized, the basic storyline has been shamelessly ripped from the headlines. In particular, a recent *Nature* article (Verpy et al., 2008) reports a mutant mouse with many of the same features, including near normal thresholds, reduced suppressive masking, and the absence of measurable DPOAEs. Although these findings clearly require independent corroboration, your case may not be entirely hypothetical after all.

Even if the published report and its conclusions prove erroneous, it is worth asking yourself, "How is it even *possible*?" On the face of it, many elements of the case seem contradictory. The reduced sound tolerance and lowered LDLs suggest some sort of hearing impairment. But hearing loss appears inconsistent with the normal audiograms and ABRs. Normal thresholds, in turn, appear inconsistent with the absence of DPOAEs, which suggests a problem with the outer hair cells (OHCs) and the cochlear amplifier. But a problem with the OHCs appears inconsistent with the unusually large CEOAEs, which seem to imply enhanced OHC function. So how is it all possible? Can you come up with a hypothesis to explain what might be going on?

While you chew on the mouse, this chapter reviews some of what we think we know about mechanisms of OAE generation and their clinical applications. Broadly speaking, the chapter has two parts. In part one, we provide a brief reminder of conventional OAE nomenclature, review the physical and physiological mechanisms believed responsible for generating OAEs, and highlight a few practical implications. In part two, we delve a little deeper into selected clinical applications of OAEs, sometimes returning to issues touched upon briefly in part one. Finally, newly armed with information about OAEs that may help us think more clearly about some of the paradoxes in the case, we return to your patient mouse.

WHIRLWIND TOUR OF OAE TYPES

We begin with a quick review of OAE types. Otoacoustic emissions are conventionally known by the stimuli used to evoke them (e.g., Probst et al., 1991). The most basic distinction is between *spontaneous* and *evoked* OAEs. As their name implies, spontaneous emissions occur "spontaneously," that is, in the absence of any purposeful stimulation. Evoked emissions arise in response to acoustic stimuli.

Figure 5–1A shows an example of human spontaneous otoacoustic emissions (SOAEs) recorded in the ear canal using a low-noise microphone. The spectrum of the pressure in the ear canal is shown versus frequency. The multiple narrow spikes indicate frequencies at which this ear is whistling while it works. There are several major subtypes of evoked otoacoustic emission. The first to be reported were transient- or click-evoked OAEs (TEOAEs or CEOAEs). One measures them by recording the response to a short, transient sound, such as an acoustic click. As illustrated in Figure 5–1B, the emission occurs as a small echo some milliseconds later. Components of the emission whose latency is sufficiently long can be separated from the often much larger stimulus by time windowing (e.g., by zeroing out the early portion of the response). Figure 5–1C shows another subtype of evoked otoacoustic emission: distortion-product OAEs (DPOAEs). DPOAEs are usually measured in response to two primary tones at frequencies f_1 and f_2 (with $f_1 < f_2$). Nonlinearities in the cochlea produce intermodulation distortion at combination-tone frequencies, most prominently at $2f_1–f_2$. These distortion components find their way to the ear canal via multiple pathways. Because they occur at frequencies different than the stimulus tones, the emissions are easily extracted from the measured pressure using Fourier analysis.

The third and final major subtype of evoked OAE is stimulus-frequency emissions (SFOAEs). Although SFOAEs are in some respects the simplest OAE to interpret—the stimulus is just a single pure tone, usually of low to moderate level—they are the hardest to measure because they occur at the same time and at the same frequency as the stimulus (see Figure 5–1D). Consequently, simple time window-

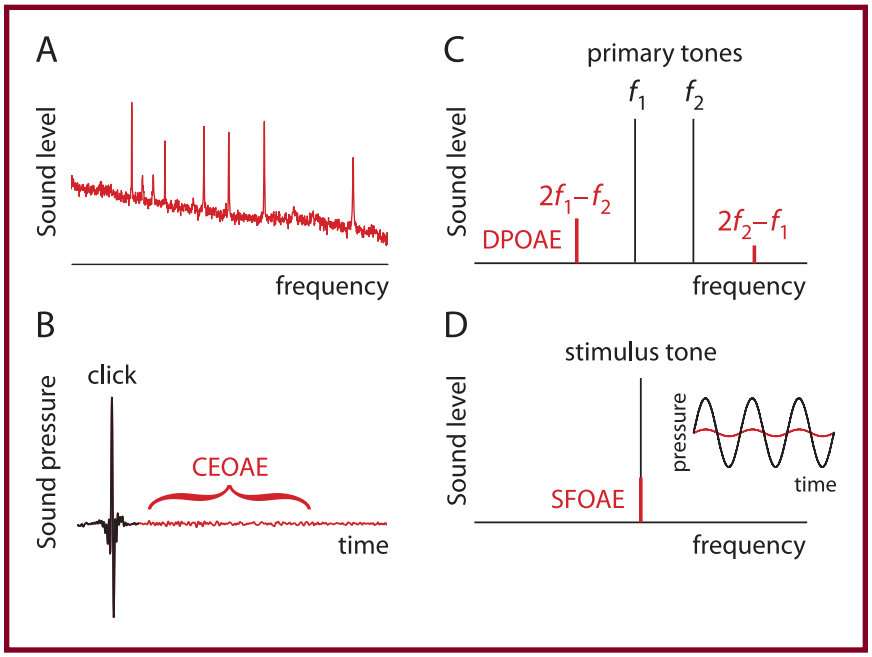

Figure 5–1. The four principal types of otoacoustic emissions. *Panel A:* Spontaneous OAEs (SOAEs) occur in the absence of purposeful stimulation. *Panel B:* Click-evoked OAEs (CEOAEs) can be separated from the click stimulus by time-windowing. *Panel C:* Distortion-product OAEs (DPOAEs) occur at combination-tone frequencies, such as $2f_1–f_2$. *Panel D:* Stimulus-frequency OAEs (SFOAEs) occur simultaneously with and at the same frequency as the tonal stimulus.

ing and/or Fourier analysis (the common methods used to measure CEOAEs and DPOAEs) do not work. Other, more roundabout methods have been developed; the most popular takes advantage of the fact that SFOAEs can be suppressed by other tones (e.g., Kemp & Chum, 1980).

ARE DIFFERENT OAES DIFFERENT?

This brief tour of the many OAE types naturally leads one to ask the question chosen for the title of this section: Are these different OAEs different? What do we mean by that? Each OAE type reviewed above is evoked by a different stimulus and is measured in a different way. As a result, each has been awarded a different name. In that sense they are clearly different. But are they really different? Are they, for example, generated in different ways? Do they tell us different things about the cochlea? To answer these questions we need to talk not about stimuli but about mechanisms.

Possible Sources of Reverse Waves

During normal hearing, vibration of the stapes sets the cochlear fluids into motion and generates a forward traveling wave, visible on the basilar membrane. OAEs involve energy flow in the reverse or backward direction. Theoretically, how might reverse waves get produced inside the cochlea?

Intrinsic Mechanical Irregularities

One simple way to generate reverse waves is by reflection. Consider, for example, the variation along the cochlea of the amplificatory forces produced by outer hair cells. In a textbook or review article, one

might see a schematic similar to Figure 5–2A. Perhaps the OHC forces are shown stronger near the base of the cochlea, where characteristic frequencies are higher, viscous forces are larger, and the need for amplification is greater. The important point here is not the overall shape of the curve, which remains uncertain in vivo, but that the curve is idealized as smooth. However, one thing we know for sure about the curve is that it cannot be smooth. Hair cells and other structures in the organ of Corti are subject to random developmental perturbations. As a consequence, different hair cells are different. In the real cochlea, as opposed to some idealized model or schematic, the curve must look more like the curve in Figure 5–2B. Superimposed on the overall trend are intrinsic cell-to-cell variations due to the discrete cellular architecture of the organ of Corti. When a traveling wave is launched along the duct, these micromechanical irregularities act to scatter or partially reflect the energy back toward the stapes (Talmadge et al., 1998; Zweig & Shera, 1995). This is one way that reverse waves can get produced.

Induced Sources

Not only do the forces produced by OHCs vary from cell to cell, they also depend on the amplitude of the stimulus wave. The curve in Figure 5–2C shows a schematic of how OHC forces depend on the displacement of the hair bundle. When the wave amplitude (and hence bundle displacement) is small, the forces grow in direct proportion to the wave and the system behaves linearly. But hair cells cannot produce unlimited force, so as the wave amplitude

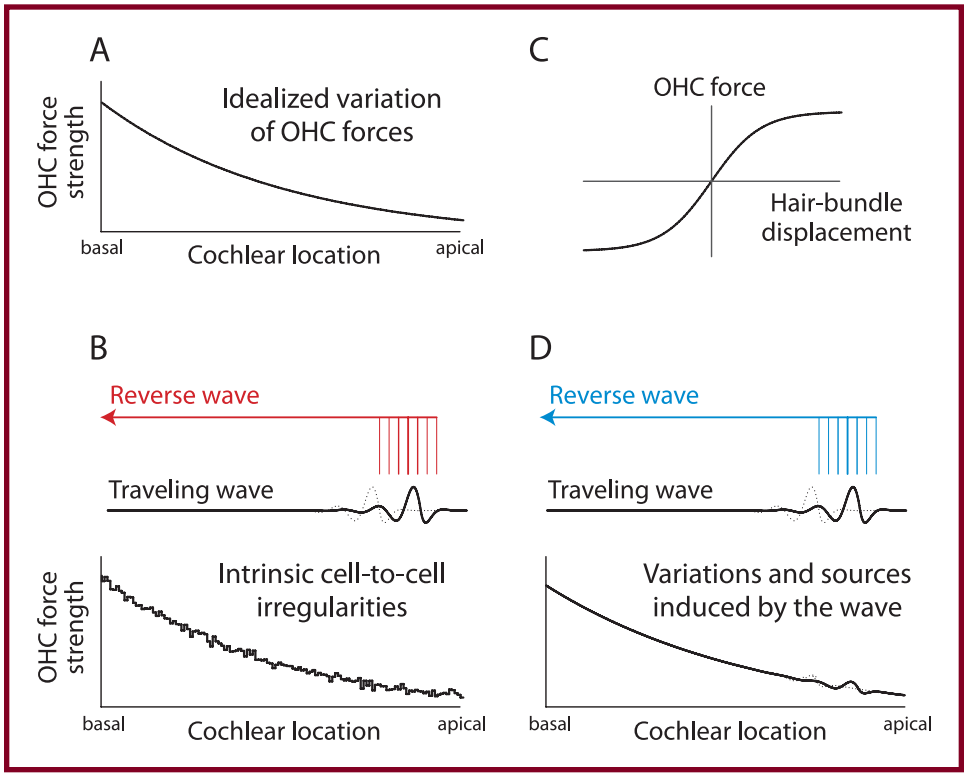

Figure 5–2. Hypothetical mechanisms for generating reverse waves. *Panel A:* Unrealistically smooth, textbook representation of the spatial variation of mechanical properties within the cochlea. *Panel B:* Intrinsic cell-to-cell irregularities act to scatter forward- traveling waves. *Panel C:* The forces produced by OHCs depend nonlinearly on the displacement of their hair bundles. As a result, OHC forces depend on local wave amplitude. *Panel D:* Nonlinearities in the mechanics act as sources of reverse waves.

grows, the forces eventually saturate. The result is a nonlinear curve with roughly sigmoidal (S-shaped) form. Because of this nonlinearity, the traveling wave itself can induce local distortions or sources of energy in the mechanics that also give rise to reverse waves, as illustrated quite schematically in Figure 5–2D. An important difference with the previous case is that sources shown here are *induced by the wave*. As a result, when the wave frequency changes and the wave envelope shifts along the cochlea, the induced distortions move along with it. (Intrinsic irregularities, of course, remain fixed in place.)

Thus, one might hypothesize at least two different types of OAEs, distinguished by the mechanisms that give rise to reverse waves. Those generated by scattering from intrinsic irregularities we will call "reflection-source OAEs"; they require cochlear irregularity but not nonlinearity. Those that arise from sources induced by the wave through mechanisms such as nonlinear distortion we will call "distortion-source OAEs"; they require nonlinearity but not irregularity.

Distinguishing Source Types Through OAE Phase

Can OAEs from different source types be distinguished experimentally? Although OAE mechanisms do not come color-coded in the ear canal, they can be distinguished by the frequency dependence of their *phase*. Because OAE magnitude is the only quantity now measured in most applications (many commercial OAE systems cannot even measure the phase!), OAE phase may seem obscure or unimportant. But as we will see, the truth is quite the contrary.

Magnitude and Phase

What exactly *is* emission phase? Figure 5–3A shows a sinusoidal waveform (pressure vs. time) as it might be recorded using a microphone in the ear canal. The magnitude of the waveform is just the height of the peaks, that is, the position of the peaks along the pressure axis. The phase is exactly analogous: The phase is just the position of a waveform peak along the time axis. In particular, to get the phase in radians one measures time backwards (by convention) to the nearest peak, multiplies by 2π, and divides by the interval T between peaks (or, equivalently, multiplies by the frequency). Thus, the waveform in the figure has a phase of approximately $2\pi \times (¼) = \pi/2$ radians. (Although we measured time back to the first peak we encountered, we could have used the second peak, the third peak, or indeed any other peak. Phases separated by an integer multiple of 2π are indistinguishable.)

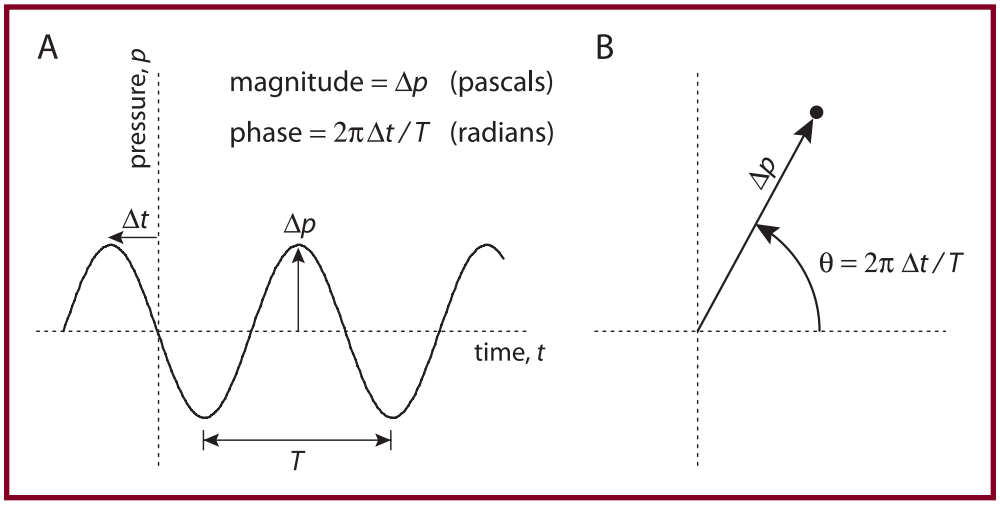

Figure 5–3. Magnitude and phase. *Panel A:* A waveform's magnitude and phase are proportional to the distance to the waveform peaks measured along the pressure and time axes, respectively. *Panel B:* Polar representation of magnitude and phase.

As we will see below, it is often convenient to show magnitude and phase together in the same plot using a so-called *polar plot*. A polar plot represents the value of the pressure at some frequency by a point in the plane (see Figure 5–3B). The point can be located by a vector from the origin. The pressure magnitude is just the length of the vector and the phase is the angle measured counterclockwise from the horizontal axis.

Predicted Phase Versus Frequency Curves

How does OAE phase enable us to distinguish generation mechanisms?

Intrinsic Mechanical Irregularities. First, we consider the case of intrinsic irregularities. The top panel of Figure 5–4A shows a schematic of the stapes and the basilar membrane going from base to apex. As we argued before, the BM presumably has many mechanical irregularities distributed along its length. When a traveling wave is launched along the cochlear duct, the irregularities act to partially reflect the forward traveling energy.

For simplicity, let us pretend that there is just a single point-like irregularity, indicated by the red asterisk. (The conclusion is the same if we consider multiple, distributed irregularities, but the argument

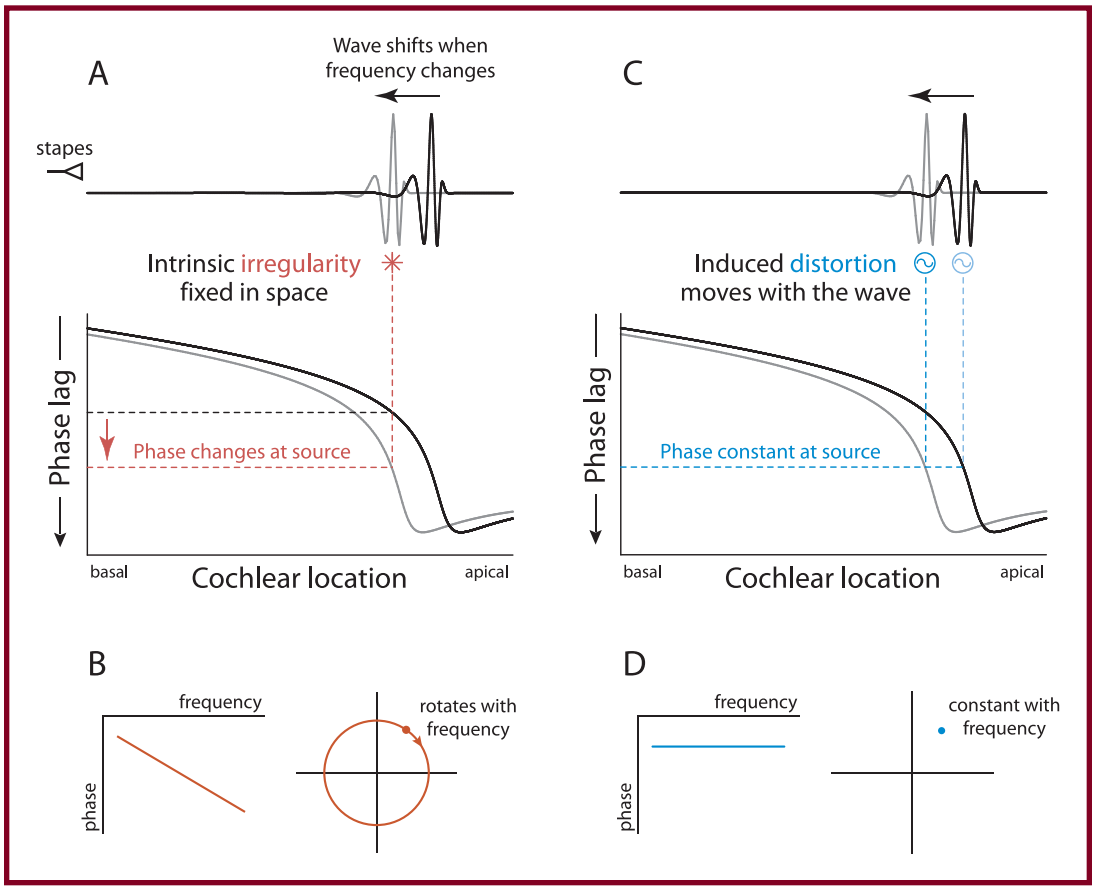

Figure 5–4. Predicted phase-versus-frequency functions depend on source type. *Panel A:* Because intrinsic irregularities are fixed in space, changing the stimulus frequency changes the phase of the forward-traveling wave at the source site. *Panel B:* Emissions generated by intrinsic irregularities are expected to have a steep phase gradient (rapidly rotating phase). *Panel C:* Because induced sources move with the wave, changing the stimulus frequency keeps the phase of the forward-traveling wave at the source site constant. *Panel D:* Emissions generated by induced sources are expected to have an almost constant phase.

is more tiresome.) We want to figure out the phase of the OAE that results from reflection by this irregularity. The phase of the reverse (reflected) wave will be determined by the phase of the forward (incident) wave at the site of reflection. To find that phase, we plot the phase of the forward wave as a function of cochlear location. As shown by the black curve in the bottom panel of Figure 5–4A, the phase varies with distance, slowly in the base of the cochlea and then more rapidly as the wavelength decreases near the characteristic place. To find the phase at the site of the irregularity, we drop a dashed line down to the black phase curve and read off the value (whatever it is) using the black horizontal dashed line.

Now consider what happens when we increase the stimulus frequency. When the frequency increases, the wave peak shifts closer to the stapes, as illustrated by the gray curve in the top panel. What is the phase of this new wave at the site of the reflecting irregularity? Again we drop a line down to the corresponding phase curve (gray) and read the value off the ordinate (red horizontal dashed line). Note that the phase of the incident wave at the irregularity is now different. As a result the phase of the OAE in the ear canal will also change. Thus, we expect the OAE phase versus frequency curve to look something like the schematic shown in the left panel of Figure 5–4B. The predicted OAE phase slopes downward, with the phase decreasing as the stimulus frequency increases. The right panel of Figure 5–4B shows the same prediction as a polar plot. As the frequency increases, the point representing the OAE pressure rotates clockwise around the origin (i.e., the point representing zero pressure) and traces out a roughly circular trajectory in the plane. (We have simplified the plot by keeping the OAE magnitude constant.)

Induced Sources. Let us now consider distortions or sources induced by the wave. For simplicity, we again consider just a single source, denoted in Figure 5–4C by the blue ~ symbol located near the peak of the wave. As before, the OAE phase depends on the phase of the forward wave at the source, which we find by dropping a line down to the corresponding phase curve and reading off the value. What happens when the frequency increases? The wave shifts to the left (gray curve), just as it always does. But this time, because the source is induced by the wave, the source location also shifts. Reading off the wave phase at the new source location, we find that because the source has moved with the wave, the phase at the source does not change. We therefore expect that the resulting OAE phase will be nearly independent of frequency, as shown schematically in the left panel of Figure 5–4D. In the corresponding polar plot (right panel), the OAE pressure does not rotate around the origin but remains at the same spot in the plane (again, assuming constant OAE magnitude).

Correspondence Between OAE Type and Source Mechanism

Is there any correspondence between the OAE types reviewed above and the two hypothesized mechanisms of generation? To answer this question we examine each of the various types in turn, beginning with the simplest emission to interpret and working towards the more complicated cases.

Stimulus-Frequency OAEs

Figure 5–5A shows a plot of human SFOAEs over a 6-kHz range. The SFOAE magnitude shows the pattern characteristic of SFOAEs: a slowly varying amplitude punctuated at irregular intervals by deep notches. Do SFOAEs arise by reflection, by distortion, or via some other mechanism altogether? One cannot tell by looking only at the emission magnitude — one needs to examine the phase. As shown in the bottom panel of Figure 5–5A, the phase varies quite rapidly with frequency, falling through more than 30 cycles over the two and a half octave range of the figure. (Thirty cycles represents more than 180 radians or almost 11000 degrees!) This rapid variation of phase is qualitatively consistent with the pattern expected from scattering by intrinsic irregularities (see Figure 5–4B). Stimulus- frequency emissions evidently belong in the reflection-source category.

Distortion-Product OAEs

What would one expect for DPOAEs? When waves at the primary frequencies f_1 and f_2 interact along the

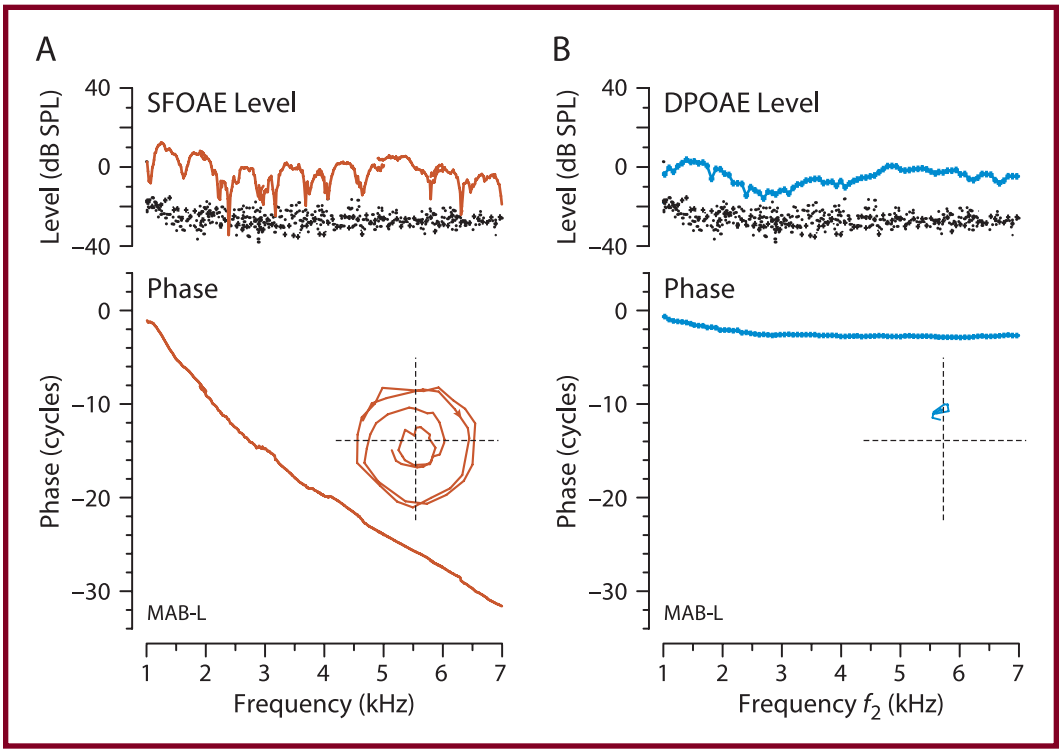

Figure 5–5. Different phase slopes imply different source types. *Panel A:* SFOAEs measured in a human subject have a rapidly rotating phase. Probe and suppressor levels were 40 and 55 dB SPL, respectively. *Panel B:* DPOAEs at $2f_1–f_2$ measured in the same year have a nearly constant phase. Primary levels L_1 and L_2 were 50 and 40 dB SPL, respectively; the primary frequency ratio was fixed at f_2/f_1 = 1.2. Insets in both panels show short segments of the data in polar form. Adapted with permission from Shera and Guinan (1999).

basilar membrane, nonlinearities in the mechanics, principally in the OHCs, produce forces at combination-tone frequencies, such as $2f_1–f_2$ (Figure 5–6). The strongest force sources are generally located near the peak of the f_2 wave. The outputs of all sources combine to produce reverse waves that propagate back to the stapes and ear canal. As the sources are induced by the interactions between the two waves, the sources will move with the waves as the primary frequencies are varied. Thus, as long as the primary frequency ratio f_2/f_1 is held fixed during the frequency sweep (so that the relative positions of the wave envelopes do not change) we would expect that DPOAE phase will be almost constant.

Almost constant DPOAE phase is exactly what one finds in the measurements. Figure 5–5B shows DPOAE level and phase versus frequency in the same subject whose SFOAEs are shown in panel A.

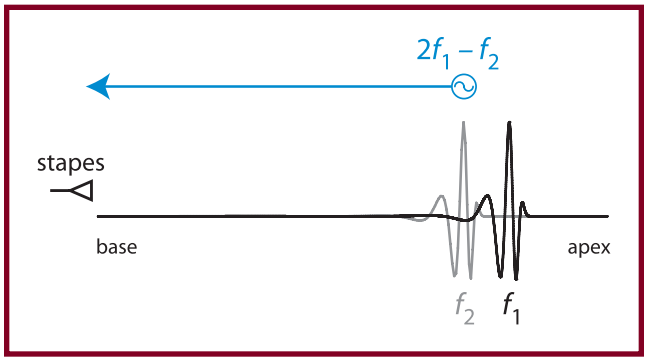

Figure 5–6. Intermodulation distortion near the peak of the f_2 response creates a reverse wave at frequency $2f_1–f_2$.

Although the DPOAEs and SFOAEs have generally similar mean amplitudes, their phase behavior is completely different. To emphasize this difference,

the insets in Figure 5–5 show a segment of the data in polar form. Whereas the SFOAEs rotate rapidly around the origin, the DPOAE vector remains almost constant. Thus, as their name suggests, DPOAEs measured at near-optimal frequency ratios appear consistent with an origin via wave-induced distortion sources.

Transient/Click-Evoked OAEs

What do we expect for transient or click-evoked emissions? Over the years, two very different models for the generation of click-evoked OAEs have been proposed. The first model predicts that CEOAEs are generated by reflection-source mechanisms; the second that they arise via distortion-source mechanisms. Although they come to opposite conclusions, both models make use of the mathematical fact that clicks can be decomposed into a sum of pure tones (Fourier analysis).

The first model is based on the analogy with SFOAEs sketched in Figure 5–7A. As demonstrated above, OAEs evoked by a single pure tone evidently arise by a reflection-like process involving intrinsic irregularities. Now because a click can be represented as a sum of pure tones, and because there are irregularities all along the cochlea just waiting to scatter whatever comes their way, this model supposes that each frequency component of the click scatters more or less independently. In this view, click-evoked OAEs are simply a sum of stimulus-frequency OAEs, all evoked nearly simultaneously.

The second model is based on the analogy with DPOAEs illustrated in Figure 5–7B. DPOAEs are generated when the different frequency components in a complex stimulus interact nonlinearly. Now because the click is a sum of pure tones, it contains many tonal components that can interact to produce distortion products. This model therefore supposes that click-evoked OAEs are the equivalent of wideband DPOAEs.

Which, if either model of CEOAE generation, is correct? Figure 5–8 provides the answer. The top two panels show CEOAE magnitudes (dark red curves) at two different levels, and the bottom panel shows the corresponding phases. The steep slope of the phase curves implies that CEOAEs originate via reflection-source mechanisms, as suggested by the analogy with SFOAEs. In fact, a comparison with SFOAE measurements in the same subject at the same effective stimulus levels (orange curves) demonstrates that CEOAEs and SFOAEs have almost identical spectral characteristics. The small differences that do exist are comparable to session-to-session measurement variability. Evidently, CEOAEs and SFOAEs are the same reflection-source emission measured in different ways (Kalluri & Shera, 2007b).

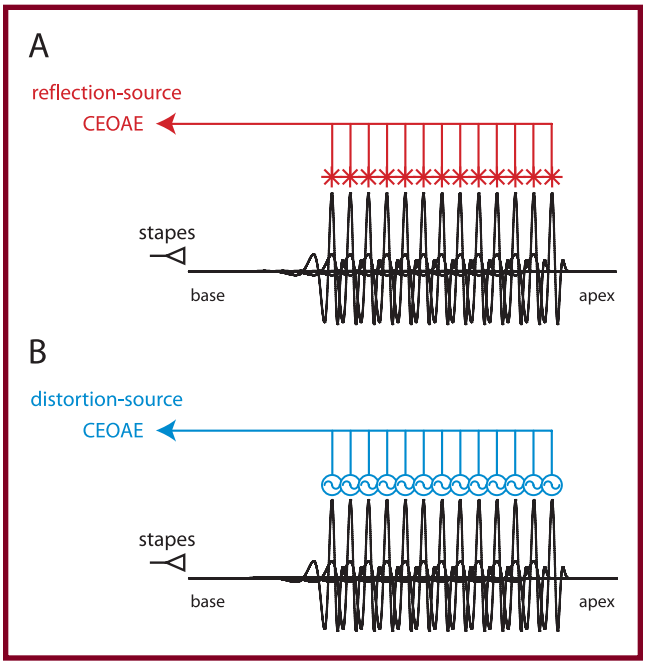

Figure 5–7. Proposed models for CEOAE generation. *Panel A:* CEOAEs arise as reflection-source OAEs by scattering from intrinsic irregularities located all along the partition. *Panel B:* CEOAEs arise as distortion-source OAEs through intermodulation distortion among the multiple frequency components of the click.

Spontaneous OAEs

Finally, we turn to spontaneous otoacoustic emissions. Where do they belong in the schema? Figuring out how to classify SOAEs is a little harder. SOAEs are fixed in frequency, so we cannot simply vary their frequency and look at their phase. Furthermore, emission phase is only defined with respect to the phase of the applied stimulus, and spontaneous emissions have no applied stimulus. So we appear

to have hit a roadblock. Unfortunately (for the story is a fascinating one), it would take us too far afield to show how the roadblock can be circumvented. It turns out, however, that there is strong evidence that many SOAEs, although perhaps not all, are just another type of SFOAE (Shera, 2003). In particular, SOAEs appear to be *continuously self-evoking SFOAEs*, just as Kemp first suggested (Kemp, 1979). As such, SOAEs arise predominantly via reflection-source mechanisms.

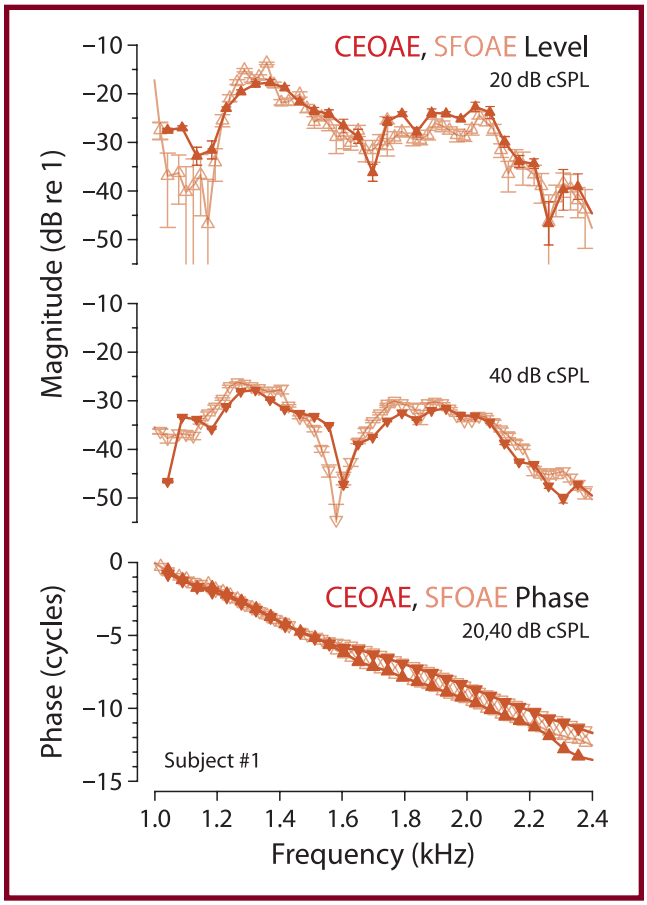

Figure 5–8. Click-evoked and stimulus-frequency OAEs at matched intensities. The magnitude and phase of CEOAE (*solid symbols*) and SFOAE (*open symbols*) transfer functions are shown versus frequency at two stimulus levels in a human subject. Emission magnitudes are shown relative to the stimulus spectrum. Stimulus levels are given in dB cSPL (bandwidth-compensated SPL; see Kalluri and Shera, 2007a), which reduces to dB SPL for pure tones. Adapted with permission from Kalluri and Shera (2007b).

Mixing Among Source Types

If you worry that the clean correspondence between emission type and source type outlined in the preceding section seems too tidy, you are right to be skeptical. After all, the cochlea contains both intrinsic irregularities *and* induced sources. So why should a given stimulus evoke emissions from just a single source type? Surely, OAEs must normally be mixtures of both. If so, our examination to date has only identified the *dominant* component produced by each stimulus.

The idea behind source-type mixing is nicely illustrated by DPOAEs. Figure 5–9A builds on Figure 5–6, which illustrates the generation of distortion products through an induced distortion source near the peak of the f_2 wave. In Figure 5–6, we pretended

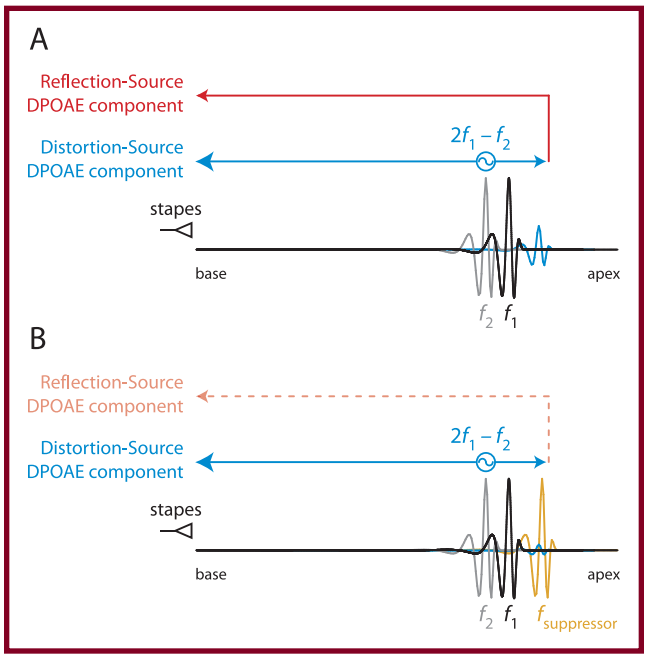

Figure 5–9. Mixing and unmixing of DPOAEs. *Panel A:* The distortion source at frequency $2f_1$–f_2 generates waves that propagate in both directions (see Figure 5–6). The forward wave is partially reflected nears its characteristic place, generating a reflection-source OAE. *Panel B:* The distortion- and reflection-source components of the total DPOAE can be separated (mostly) by using a suppressor tone near $2f_1$–f_2 to suppress the generation of reverse waves near the distortion-product place.

that such sources generate waves that propagate in only a single direction, back toward the stapes. In principle, however, distortion sources also generate forward waves that travel apically to their characteristic places. Like all forward waves, these waves would encounter intrinsic irregularities that act to scatter some of the energy back toward the stapes, producing reflection-source emissions. This reasoning predicts that measured DPOAEs receive contributions from both source types.

Unmixing DPOAEs

One can determine whether this hypothetical mixing process actually occurs by attempting to separate, or unmix, measured DPOAEs into their putative components. One way to unmix is to use a suppressor tone to reduce the amplification of the $2f_1–f_2$ wave near its characteristic place and thereby (nearly) eliminate the reflection source component from the emission (see Figure 5–9B). Measuring the DPOAE without the suppressor tone yields the total DPOAE (the sum of both components). Measuring again with the suppressor turned on yields an estimate of the distortion-source component by itself. By subtracting the two, one can then recover the reflection-source component.

When one applies this suppression-based unmixing method in human subjects one obtains DPOAE components that behave exactly as one would expect based on the hypothesized mixing (e.g., Kalluri & Shera, 2001). Figure 5–10 shows that the phase of the putative distortion-source component appears nearly constant while the phase of the putative reflection-source component varies rapidly, just as if the reflection-source component were an SFOAE. In fact, by measuring SFOAEs under comparable conditions in the same subject one can show that the reflection component really *is* an SFOAE: the two have almost identical magnitude and phase versus frequency functions (dotted lines in Figure 5–10).

Figure 5–11A shows that when the distortion- and reflection-source components sum in the ear canal they yield a total DPOAE whose magnitude and phase manifest a quasiperiodic variation known as DPOAE fine structure. (Note how remnants of this fine structure, presumably due to incomplete

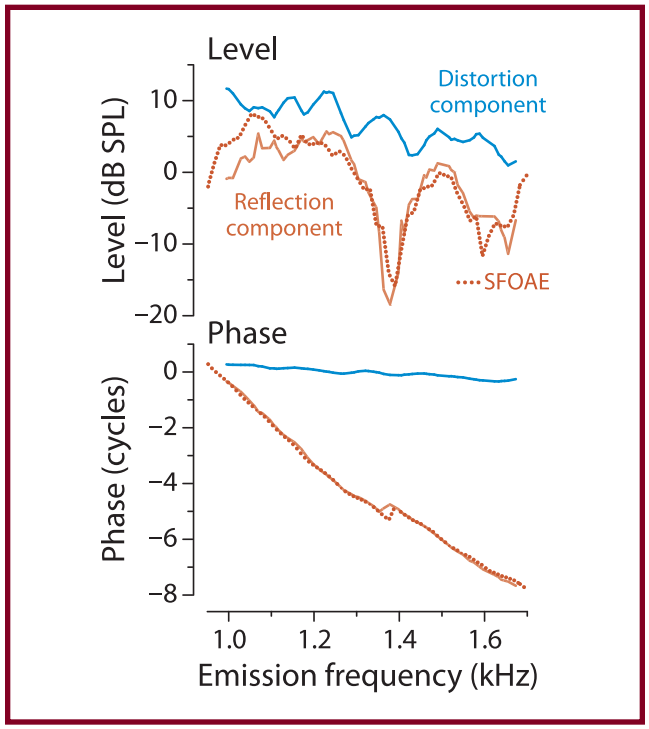

Figure 5–10. Unmixed DPOAE components. The figure shows the magnitude and phase of the distortion- (*blue*) and reflection-source (*solid red*) components obtained by unmixing the $2f_1–f_2$ DPOAE using a suppressor tone, as illustrated in Figure 5–9. The dashed red curve shows the SFOAEs measured under comparable conditions in the same subject. The DPOAE stimulus parameters were: f_2/f_1 = 1.2 and $\{L_1, L_2\}$ = {60, 45} dB SPL. The suppressor tone level was 50 dB SPL, at a frequency 44 Hz below the DP frequency. The SFOAEs were measured in the presence of an "f_1-primary mimicker" at 60 dB SPL using probe and suppressor levels of 40 and 55 dB SPL, respectively. Adapted with permission from Kalluri and Shera (2001).

unmixing, appear as peaks and valleys in the magnitude of the distortion-source component in Figure 5–10.) Why does the total DPOAE look like this? The idealized polar plot shown in Figure 5–11B provides the answer. At every frequency, vectors representing the distortion- and reflection-source components sum to yield the total DPOAE (black dot). Recall that whereas the distortion-source vector remains nearly constant with frequency (see Figures 5–4D and 5–5B), the trajectory of the reflection-source component rotates clockwise (see Figures 5–4B and

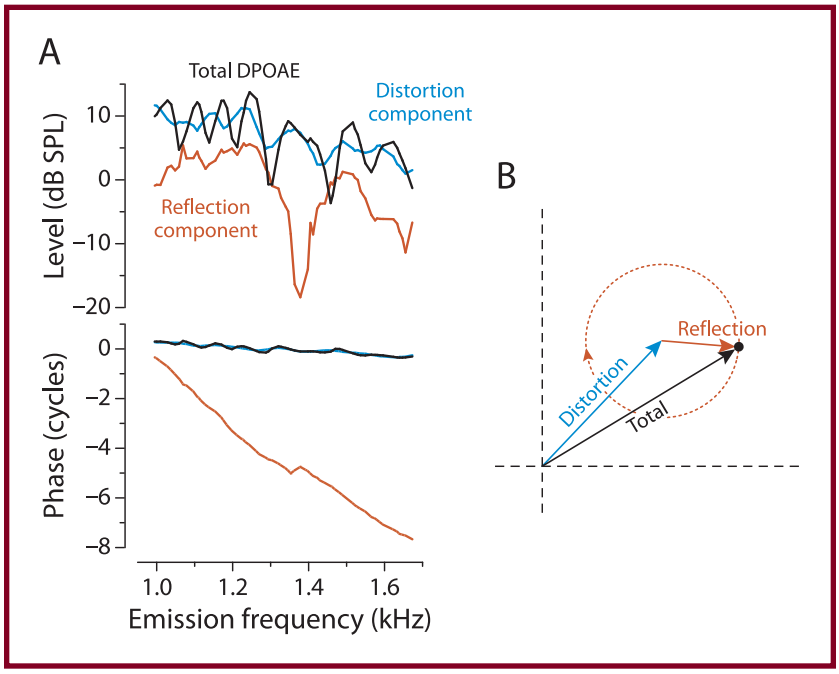

Figure 5–11. The total DPOAE and its components. *Panel A:* The black line shows the total measured DPOAE along with its distortion- and reflection-source components from Figure 5–10. *Panel B:* Polar plot showing how the distortion- and reflection-source components combine to produce oscillatory structure in the magnitude and phase of the total DPOAE.

5–5A). The dot representing the total DPOAE therefore moves along the dashed circle, cycling around the tip of the distortion-source vector. As a result, the length of the vector from the origin to the dot (i.e., the magnitude of the total DPOAE) varies up and down periodically. The angle of the total DPOAE vector also varies, producing a periodic oscillation in DPOAE phase.

Question 1

Are OAEs useful for assessing cochlear function at high frequencies?

Answer 1

Yes. Otoacoustic audiometry at frequencies out to 50 kHz and beyond is used routinely to assess hearing in laboratory animals such as mice. In humans, forward and reverse middle ear transmission may reduce OAE amplitudes at high frequencies (e.g., above 5 kHz), but many of the problems associated with measuring high-frequency OAEs in humans can be traced to the difficulty of obtaining reliable acoustic calibrations. Improving the accuracy of high-frequency calibrations in the ear canal may open up an important new window on the human cochlea.

SEVEN SHORT PRACTICAL IMPLICATIONS

Different OAEs Are Different

OAEs evidently come in two fundamentally different flavors: Those that arise as if by scattering from intrinsic micromechanical irregularities and those that arise from induced sources such as nonlinear distortion. As the cochlea contains both intrinsic irregularities and mechanical nonlinearity, most emissions are mixtures of reverse waves produced by both source types, as we have verified for DPOAEs. In any given OAE measurement the relative contributions made by the different source types depend on the stimulus parameters (e.g., intensity, frequency, and f_2/f_1 ratio) as well as on factors such as species, cochlear status, and so on.

Different OAEs Are the Same

Click-evoked emissions, stimulus-frequency emissions, spontaneous emissions, and the reflection-source component of DPOAEs, although known by different names and measured in different ways, all appear to be generated by similar underlying mechanisms. More generally, we have seen how the conventional emission nomenclature that describes the evoking stimulus maps onto the mechanism-based source classification. We emphasize, however, that the broad correspondence we have outlined identifies only the dominant emission produced by each stimulus. For interpreting OAEs, we would argue that knowing the source type (i.e., how the OAE is produced within the cochlea) is generally more relevant than knowing the stimulus type.

Different OAEs Depend on Different Cochlear Properties

Distortion-source OAEs appear to require mechanical nonlinearity (but not irregularity). As a result, distortion-source OAEs depend on the form and strength of cochlear nonlinearities. An example of a relevant nonlinearity is the nonlinear relation between the displacement of the hair bundle and the force produced by the OHCs. These forces result from voltage-induced conformational changes in motor proteins embedded in the lateral wall of the OHC soma. Schematized in Figure 5–12, the relation between bundle displacement and somatic force is nonlinear because at one extreme (the far left) most of the transduction channels in the bundle are closed. In this case, displacing the bundle farther in the negative (leftward) direction has little effect on the voltage across the cell membrane and the cell therefore produces little additional force. At the other extreme (the far right), most of the channels are open, and additional displacement in the positive direction has little effect. In the middle, the curve transitions smoothly between these two limits, its exact "shape" determined by details of cellular biophysics. For example, the so-called operating point of the nonlinear function defines where along the curve the cell operates when input dis-

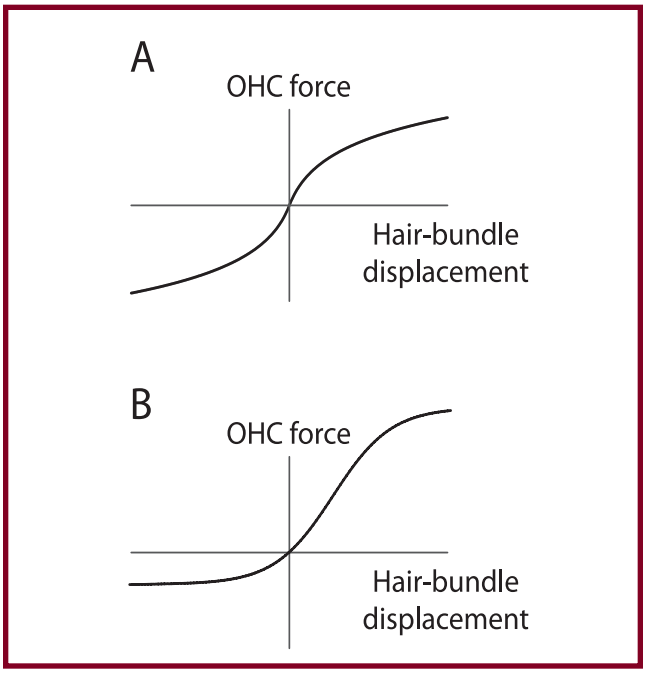

Figure 5–12. Hypothetical OHC transduction curves. *Panel A:* Slowly saturating and antisymmetric around the operating point. *Panel B:* Rapidly saturating and asymmetric around the operating point.

placements are small (i.e., where the curve crosses the vertical axis). The operating point is presumably controlled by homeostatic mechanisms in the cell, including the mechanisms of hair-bundle adaptation and the like. If these mechanisms are disturbed or begin to malfunction, then the operating point and perhaps even the basic form of the nonlinearity can change, thereby altering the amount of distortion generated within the cochlea. In this way, the generation of distortion-source OAEs depends on the detailed shape of the curve (e.g., Lukashkin et al., 2002; Weiss & Leong, 1985). For example, a change from the slowly saturating, antisymmetric form of the curve shown in Figure 5–12A to the more rapidly saturating asymmetric form shown in Figure 5–12B would generally produce substantial changes in the magnitude of DPOAE components.

Reflection-source OAEs, by contrast, require mechanical irregularity (but not nonlinearity), and they are therefore sensitive to the spatial distribution of intrinsic irregularities present in the cochlea. For example, models predict that an "ideal" cochlea free of micromechanical irregularity would generate negligible reflection-source OAEs, even when the OHCs were working normally. When irregularity is present, the models indicate that the largest contributions to the emission generally come from the region surrounding the peak of the traveling wave, where the effects of cochlear amplification are greatest (for pure tone stimulation at low and moderate stimulus levels). As a result, reflection-source OAEs should be especially sensitive to small changes in the gain of the cochlear amplifier.

Different OAEs Depend on Similar Cochlear Properties

Otoacoustic emissions from both source types depend on cochlear amplification, and thus on the functional status of the OHCs and their modulation by efferent feedback from the brain. In addition, of course, the measurement of both OAE types also relies on the integrity of forward and reverse transmission through the middle ear.

The fact that reflection-source OAEs depend on cochlear amplification but do not require nonlinearity highlights an important distinction often blurred in the literature: Amplification and nonlinearity are not equivalent. In principle, it is perfectly possible to have strong amplification without much (or any) nonlinearity and, vice versa, to have strong nonlinearity without amplification. Mechanical input-output functions measured on the basilar membrane provide a familiar example of the former (Figure 5–13). At low levels near threshold, where the amplifier gain is greatest, BM growth functions in normal ears have unity slope (just as they do in dead or passive preparations) and cochlear mechanics appear linear. In this regime, the cochlea manifests robust amplification but little if any nonlinearity. Thus, evidence for one of the two phenomena (amplification or nonlinearity) does not automatically constitute evidence for the other. And, likewise, the absence of one does not imply the absence of both.

Measurement Methods Matter

Discussions of OAE recording methods often focus on issues such as stimulus calibration, measurement system distortion, and artifacts. The common theme might be summarized with the useful warning: Just because you're measuring it doesn't make it real. Here we emphasize a different point associated with measurement system protocol: Just because you're *not* measuring it, doesn't mean it's not there.

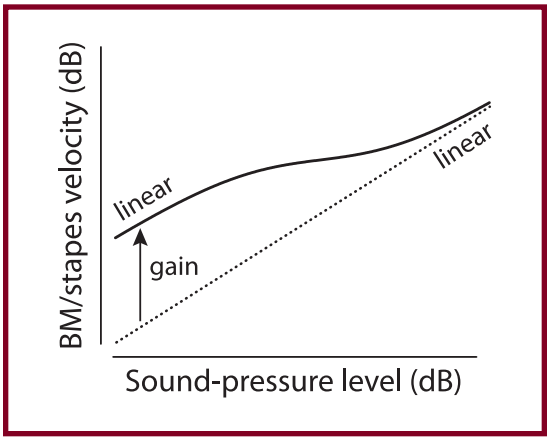

Figure 5–13. Schematic of a mechanical input-output function measured on the basilar membrane showing linear behavior in the region of maximal gain at low stimulus levels.

The measurement of click-evoked OAEs provides a useful example. There are two measurement protocols in common use, the linear protocol and the nonlinear protocol (Figure 5–14). In the linear protocol, the OAE is extracted (by time windowing) from a waveform obtained by averaging responses to identical clicks. This preserves linear components of the OAE but is susceptible to artifacts (e.g., contamination by the acoustic response of the middle ear). In the nonlinear protocol, the OAE is extracted by dividing the stimulus sequence into blocks of $N + 1$ clicks: N identical clicks of one polarity followed by a single click of N times the amplitude and opposite polarity (typically, $N = 3$). Averaged waveforms obtained using nonlinear protocols have the advantage that they are less sensitive to artifacts (e.g., middle-ear responses cancel out). But because the method blindly removes all linear component of the response, the procedure can also eliminate much if not all of the actual OAE from the recording. Thus, even though a robust OAE has been generated by the ear, it may not show up in the measurement.

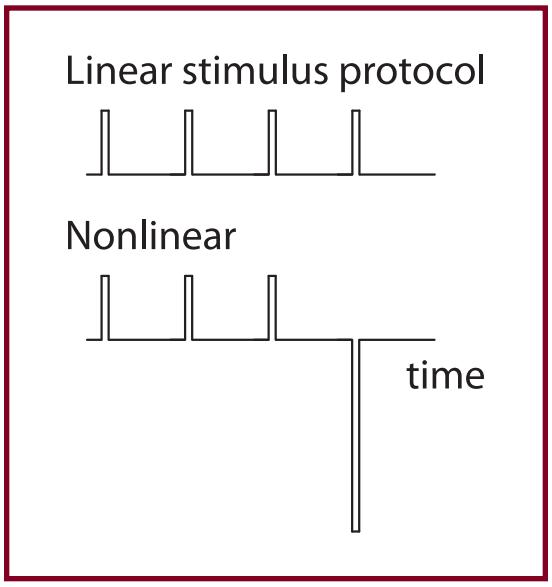

Figure 5–14. Stimulus trains for the linear and nonlinear CEOAE measurement protocols. The linear protocol (*top*) averages the responses to a series of identical clicks. The nonlinear protocol averages the responses to N clicks of one polarity and a single click of N times the amplitude and opposite polarity.

Mixing Can Muddle Matters

The complications that can arise due to uncontrolled mixing of source components are perhaps best illustrated with an example. Imagine that we want to use DPOAEs to determine the nature and strength of the efferent feedback to the cochlea elicited by contralateral acoustic stimulation. Suppose that we proceed naively by selecting DPOAE test frequencies without regard to DPOAE fine-structure patterns in our individual test subjects. In some subset of our subjects we therefore unwittingly make measurements near a local fine-structure maximum (e.g., at a frequency similar to that identified with the marker "P," for "peak," in Figure 5–15A). In this case, the polar plot representing the source components (recall Figure 5–11B) resembles the left-hand panel of Figure 5–15B: At frequencies near marker "P" the distortion- and reflection-source vectors point in nearly the same direction and therefore combine to produce a local maximum in the total measured DPOAE.

Assume now that efferent activation reduces the magnitude of the reflection-source component while leaving the distortion-source component unchanged. [Preferential reduction of the reflection-source component closely approximates what actually happens in the cochlea (Abdala et al. 2009); it is consistent with the idea that reflection-source OAEs are relatively more sensitive to changes in the gain of the cochlear amplifier.] If the reflection-source component decreases in magnitude, the circle around which the component source vector rotates contracts somewhat (right-hand panel of Figure 5–15B). Adding the two components to obtain the total DPOAE yields a vector shorter than that obtained during the baseline measurement without contralateral sound (left-hand panel). During efferent activation we therefore measure a decrease in the total DPOAE, and we conclude that MOC feedback decreases DPOAEs, a conclusion consistent with the notion that efferent feedback reduces the gain of the amplifier.

But suppose that rather than measuring at marker "P," near a fine-structure peak, we measure at marker "V," near a valley. Because fine-structure patterns vary idiosyncratically between individuals, this will happen by chance in some fraction of our subjects. Near a valley, the polar plot looks like that shown in the right-hand panel of Figure 5–15C.

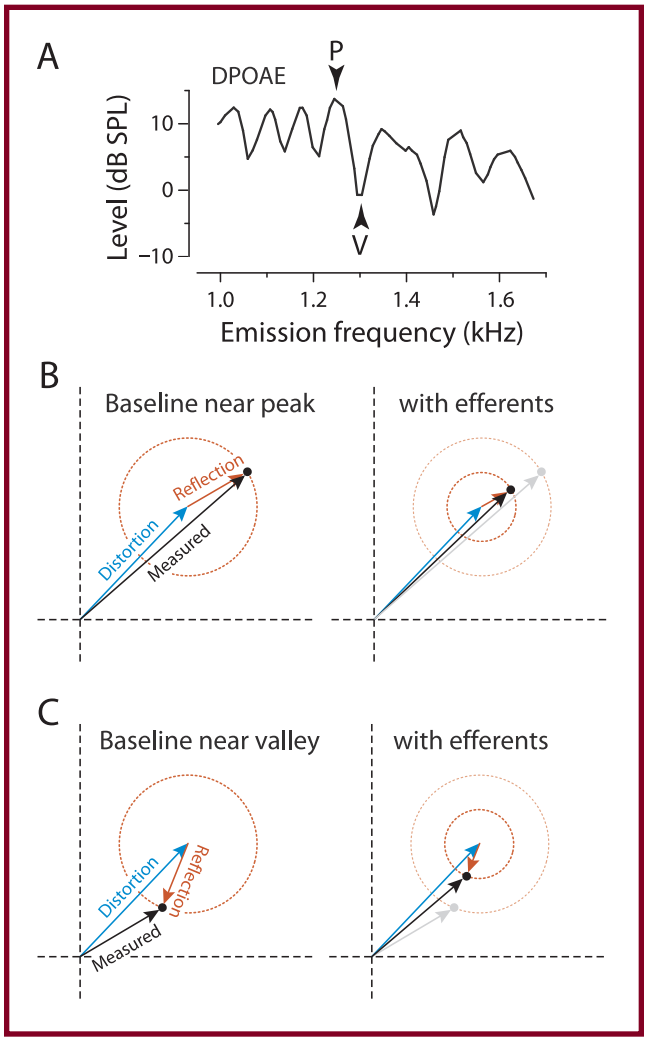

Figure 5–15. Source-type mixing complicates the measurement of efferent effects on OAEs. *Panel A:* The DPOAE measurements from Figure 5–11 showing fine structure peaks (e.g., "P") and valleys (e.g., "V"). *Panel B:* Polar plots show the effect of efferent stimulation on the measured DPOAE near a fine-structure peak ("P"), where the distortion- and reflection-source components sum in phase. *Panel C:* Polar plots show the effect of efferent stimulation on the measured DPOAE near a fine-structure valley ("V"), where the components sum out of phase.

The distortion- and reflection-source vectors now point in nearly opposite directions, the components partially cancel, and the total measured DPOAE is therefore at a minimum. When we activate the efferents with contralateral sound, the circle again contracts. But this time, decreasing the magnitude of the reflection-source component *reduces the cancellation* between the components and therefore increases the total DPOAE. In this case, we conclude that MOC feedback increases DPOAEs.

These two subject groups therefore yield opposite results. In other subjects, where we happen to measure at frequencies intermediate between peaks and valleys, we would find that efferent activation has a relatively small effect on DPOAEs. Note that we obtain these different results in different subjects (or, indeed, at different frequencies within a single subject) *even though the effect of efferents is exactly the same in all cases.* By not controlling for source-type mixing, we have, at the very least, substantially increased the variability of our data. Taking the data at face value, we might even be tempted to conclude that the MOC efferent effect was tripolar, sometimes decreasing the gain of the cochlear amplifier, sometimes increasing it, and sometimes leaving it nearly unchanged.

Emission Phase Can Be Helpful

We have seen how emission phase plays a central role in distinguishing mechanisms of OAE generation. In addition to this theoretical role, emission phase also has practical, day-to-day utility. To illustrate, note that most OAE studies look only at emission level. For example, a typical study looks for significant level differences between a "treatment" and a control group. In the hypothetical study illustrated in Figure 5–16A, the experimental manipulation (treatment) had no significant effect on OAE level. But treatments can also affect emission phase, as illustrated in the polar plot of Figure 5–16B. In fact, the two "clouds" representing the distribution of data points in this figure have been chosen so that they lie precisely on a circle centered at the origin. In other words, the *only* significant difference between the means of the two groups is in their phase: there is no difference in mean level.

This is not just a hypothetical example. Figure 5–16C shows real data from a study that examined the effects of posture on DPOAEs. The polar plot in panel C shows the DPOAEs in one subject measured both in a normal sitting position and then again when the subject was reclined at −45 degrees to the

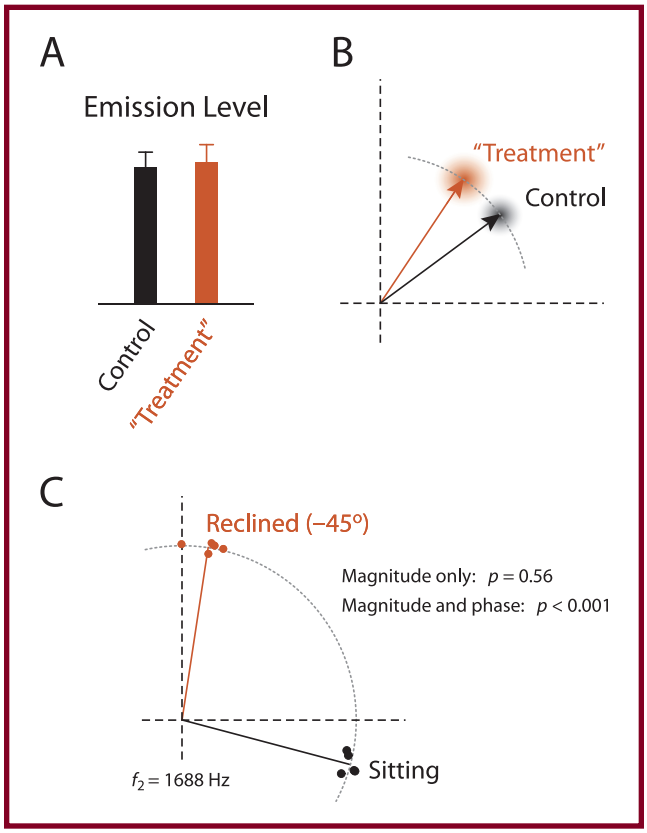

Figure 5–16. Value of considering phase in emission studies. *Panel A:* Many OAE studies look only at OAE levels, potentially missing effects of the applied treatment. *Panel B:* Polar plot showing that treatments can affect OAE phase, even in the absence of any effect on level. *Panel C:* Data from a study of posture on DPOAEs showing no appreciable effect on emission level but a very significant effect on OAE phase (Adegoke et al., 2008).

horizontal. As the circle joining the two groups of measurements makes clear, the DPOAE measurements differ primarily in their phase. Indeed, the mean emission levels are statistically indistinguishable (p = 0.56). However, when one considers differences in both magnitude *and* phase (or in phase alone), the effect of posture becomes extremely significant ($p < 0.001$).

In the general case, differences can occur in both magnitude and phase. Good practice would be to consider and measure both when designing and interpreting experiments. Analyzing possible changes along both coordinates can only increase the sensitivity of the measurements and improve the statistical significance of the results. In addition, it may reduce the number of measurements needed to properly evaluate the "treatment."

Question 2

Are OAEs ever audible outside of the ear?

Answer 2

Yes. Audible sounds made by the ear are occasionally reported, often in pets (presumably because they live in close contact with humans). Ruggero et al. (1984) document a nearly 60 dB SPL tone emitted by the ear of a dog. Contrary to what you might have read in the media, sounds coming from a dog's ear do not usually mean that Fido is an alien invader communicating with the mother ship by radio.

CURRENT CLINICAL APPLICATION OF OAES

Diagnostic Assessment of Hearing

OAEs are routinely applied in audiology clinics and hospitals throughout the United States and much of the world. They made their way into the service delivery system in the early 1990s before their diagnostic efficiency had been described and before the most appropriate parameters for testing had been established. Their rapid inclusion into the clinic repertoire was no doubt fueled by the unique, preneural information they provided without requiring patient response, sedation, or electrode application. OAEs were (and remain) particularly attractive to pediatric audiologists whose patients often cannot provide a reliable behavioral response to sound. As soon as a commercial OAE system was available for purchase (Otodynamics ILO88, 1988), its integration into the clinic commenced at a rapid pace. Once implemented in the audiology clinic, it became important for clinicians to understand that OAEs do not test

hearing. The value of OAEs as an audiologic test (regardless of their source or generation mechanism) lies in their *association* to hearing. This association has been empirically documented and found to be reliable; therefore, though not directly a test of hearing, OAEs can inform one *about* hearing. This correlation forms the basis for their inclusion into the hearing assessment battery.

CEOAEs

The first OAE to make its way into the audiologic repertoire was the transient- or click-evoked otoacoustic emission. This response was hailed as a rapid, overall, non-frequency-specific window into cochlear function from base to apex. When a broadband stimulus is presented, the cochlea provides a slightly delayed echo of this stimulus. As detailed in the first part of this chapter, models suggest that the CEOAE is a linear reflection produced by mechanical irregularities along the basilar membrane. When measured for clinical purposes, the response is analyzed and displayed in a number of ways so that that the audiologist can ascertain its presence/absence. The time-averaged waveform is sampled for approximately 20 ms poststimulus and stored in two different memory buffers, A and B, as shown in Figure 5–17 (superimposed blue and green traces). The superimposition of the two waveforms allows the tester to observe their similarity. A cross-correlation score provides a statistical measure of this similarity. A strong correlation, or high "reproducibility" score, is expected in a normal ear. It indicates that the recorded signal is not random but represents energy that is repeatable and consistently present at given time intervals following the presentation of a stimulus. The whole-wave reproducibility of the two waveforms displayed in Figure 5–17 is strong at 92%. Early studies of the CEOAE suggested that a reproducibility score of ≥50% indicates response presence (Kemp et al., 1986).

A Fourier analysis of the A and B traces is also conducted. The spectrum that is common to both traces provides a measure of CEOAE overall amplitude, whereas the noise floor is calculated as the difference between the A and B recording. To provide more frequency-specific information, CEOAE responses are band-filtered, typically in half-octave intervals. CEOAE amplitude and SNRs are calculated within these frequency bands, as shown in Figure 5–17 (bottom panel). By combining observations of reproducibility, overall response amplitude and narrowband analysis of SNR, the CEOAE is determined to be present or absent. A caution already noted in a previous section of this chapter involves the measurement of CEOAEs with nonlinear averaging. This measurement technique may weaken overall CEOAE response amplitude by eliminating linear elements that are important to the response.

CEOAE Parameters

The CEOAE is typically recorded with a broadband click, whose level is set by the tester. In most systems, once the probe tip is fit, an in-the-ear level measurement is recorded at the microphone. The clinician is then able to manipulate voltage to increase/decrease ear canal level as needed to achieve an acceptable value. One of two click levels is typically applied in the clinic: a lower level click in the range of 78 to 80 dB pSPL or a high-level click presented between 84 to 86 dB pSPL. Either level appears to identify hearing loss well if the loss is ≥30 dB HL; however, the lower level CEOAE test may be sensitive to even more mild hearing loss in the mid-frequency range (Harrison & Norton, 1999). Some researchers have recommended using a low-level click for neonatal hearing screening and including the high-level click condition only if the infant does not pass the initial screen (Norton et al., 2000). By using multiple stimulus levels, it may be possible to differentiate between individuals with slight or mild hearing loss and those with a greater degree of loss.

Efficacy of CEOAEs in Detecting Hearing Loss

CEOAEs are measurable in nearly 100% of normal-hearing individuals with normal middle ear function (Bonfils et al, 1988; Kemp, 1978; Kemp et al., 1986; Norton & Neely, 1987; Probst et al., 1986). They are most reliable when recorded in narrow frequency bands from 1000 to 3000 Hz (Franklin et al., 1992). Infants generally produce higher CEOAE levels than adults and response levels decrease with increasing age (Norton & Widen, 1990; Prieve, 1992). Initial work established that hearing loss decreases the

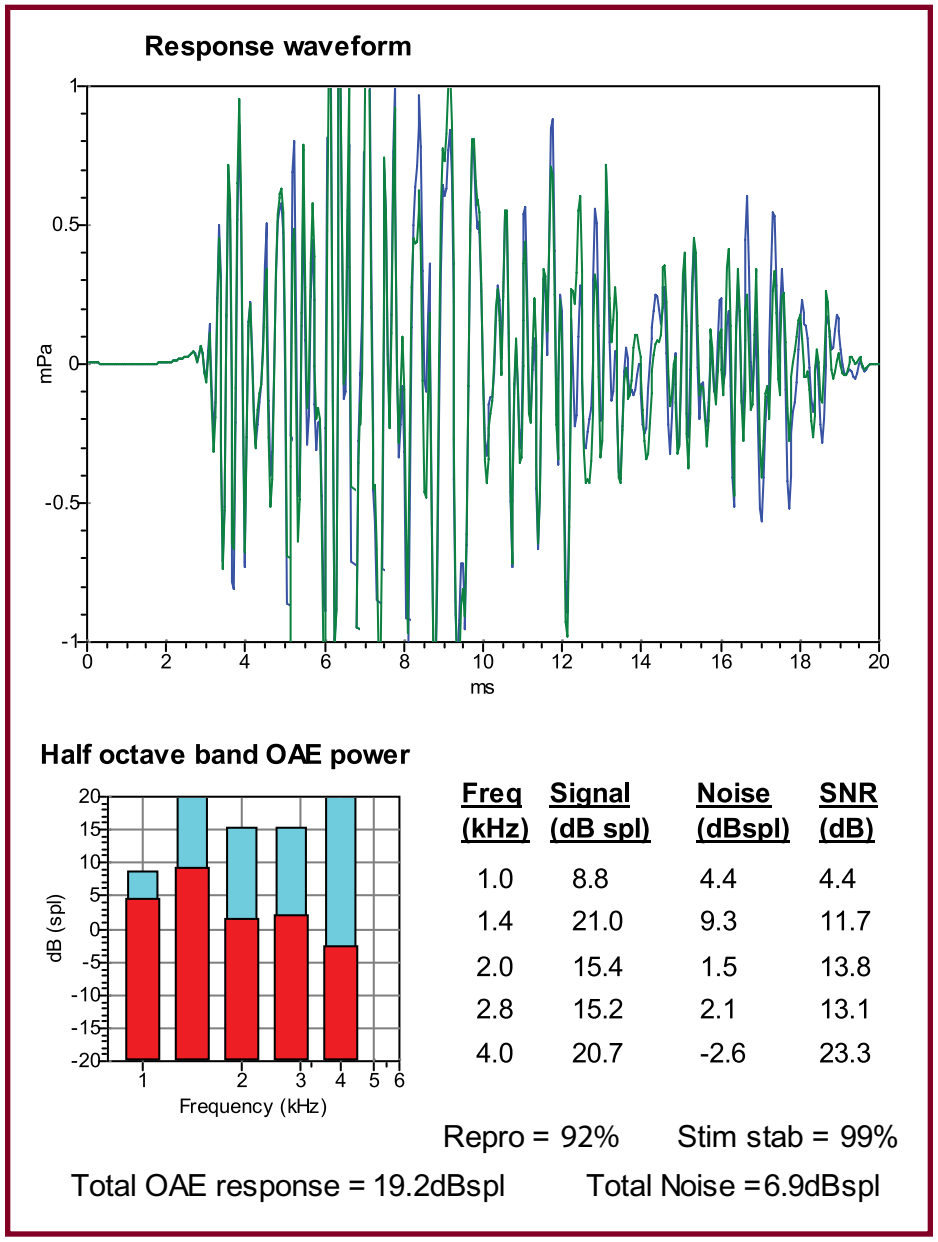

Figure 5–17. Normal CEOAE result recorded with the commercial Otodynamics ILO292 Echoport (v6) system. The large upper panel displays two superimposed, highly reproducible time-averaged waveforms (*blue, green*); the bottom panel shows narrow-band analysis of the CEOAE, including measures of SNR and amplitude in half-octave intervals. Red bars depict the noise floor and cyan bars show the CEOAE.

likelihood of recording CEOAEs (Bonfils et al., 1988; Kemp, 1978; Kemp et al, 1986). Kemp and colleagues, in one of the seminal CEOAE papers, suggested that the reproducibility of two nearly simultaneously collected time-averaged waveforms should be 50% or greater for the emission to be considered present. If reproducibility is <50%, the CEOAE is considered absent and hearing loss is likely (Kemp et al., 1986). These first studies showed a clear association between CEOAEs and hearing status.

Later studies assessed the efficacy of CEOAEs in detecting hearing loss. Gorga and colleagues (1993) initially reported that CEOAEs could detect hearing loss best in frequency bands centered at 1000 and 2000 Hz, with poor performance at 500 Hz and reduced accuracy at 4000 Hz. Measures of SNR and waveform reproducibility were better indicators than overall amplitude. In general, the better the hearing threshold, the larger the CEOAE amplitude (Collet et al., 1993; Probst & Harris, 1993). In the latter part of the decade, two large-scale studies quantified the performance of CEOAEs in groups of hearing-impaired individuals. The first study (Hussain et al., 1997) showed that CEOAE SNR optimally identified hearing loss in frequency bands centered at 2000 and 4000 Hz and showed the poorest performance at 1000 Hz. When multiple response variables were considered in combination, test performance was enhanced slightly, most notably in the low frequencies. The second investigation (Harrison & Norton, 1999) similarly reported that narrow-band filtered responses centered at 2000 and 4000 Hz detected hearing loss well, whereas responses from octave-wide frequency bands centered at either 500 or 1000 Hz did not enhance test accuracy.

These studies established that the CEOAE can be reliably recorded in normal-hearers and its accuracy in detecting hearing loss is optimal when considering narrowband responses in the mid-frequency range. The CEOAE is typically absent when hearing loss exceeds 30 to 40 dB HL.

DPOAEs

As reviewed earlier in this chapter, DPOAEs are evoked by presenting two simultaneous pure tones (f_1, f_2) to the ear ($f_2 > f_1$). Nonlinearity in OHC function produces intermodulation distortion at the region of greatest overlap between traveling waves evoked by the primary tones. Linear reflection is also produced around the peak of the apicalward traveling wave at the distortion product characteristic frequency. DPOAEs are present in most normal ears (Lonsbury-Martin et al., 1990). The most robust and reliably present DPOAE in mammals is the cubic distortion tone at $2f_1–f_2$. The initial advantage accorded DPOAEs (versus CEOAEs), was their perceived frequency-specific nature. Early work using ipsilateral suppression in laboratory animals established the generation site for the DPOAE to be around the primary tone frequencies (Abdala et al., 1996; Brown & Kemp, 1984; Kummer et al., 1995; Martin et al., 1987). Thus, in the clinic, DPOAEs are thought to evaluate the focal region around f_2 (higher frequency of the two primaries) even though the frequency of the distortion product itself is $2f_1–f_2$. These assumptions about a focal region of assessment should be re-examined because, as detailed in the first part of this chapter, the DPOAE receives contributions from both distortion generated between f_1 and f_2 and linear reflection produced at the DP characteristic frequency. Both emissions reverse propagate basally, combining in the ear canal to produce a "mixed-type" OAE that includes contributions from more than one cochlear site.

As implementation of DPOAEs in the audiology clinic advanced, the "DP-audiogram" (later shortened to "DP-gram") became the tool of choice for hearing assessment (Lonsbury-Martin et al., 1990). The DP-gram depicts DPOAE amplitude as a function of f_2 and usually includes a measure of the mean noise floor. The overall amplitude of the DPOAE and its relationship to the noise floor are considered in establishing the DPOAE as absent or present. Figure 5–18 shows a mean DP-gram including DPOAE level, noise floor, and a measure of response variability (standard deviation) from a group of 43 normal-hearing adults. The smaller adjacent graph shows an individual DP-gram from a normal-hearing adult.

A second DPOAE graph, the input/output (I/O) function, plots DPOAE amplitude versus primary tone level for a given f_2. The I/O function is not routinely applied in the clinic probably because it is time consuming and under most circumstances, is not more diagnostic than a DP-gram. It is more widely used for auditory research. Figure 5–19 shows a DPOAE I/O graph from one adult subject for an f_2 of 3000 Hz.

DPOAE Parameters

The clinical DP-gram is recorded by presenting pairs of primary tones across the frequency range of interest. Several stimulus parameters must be selected by

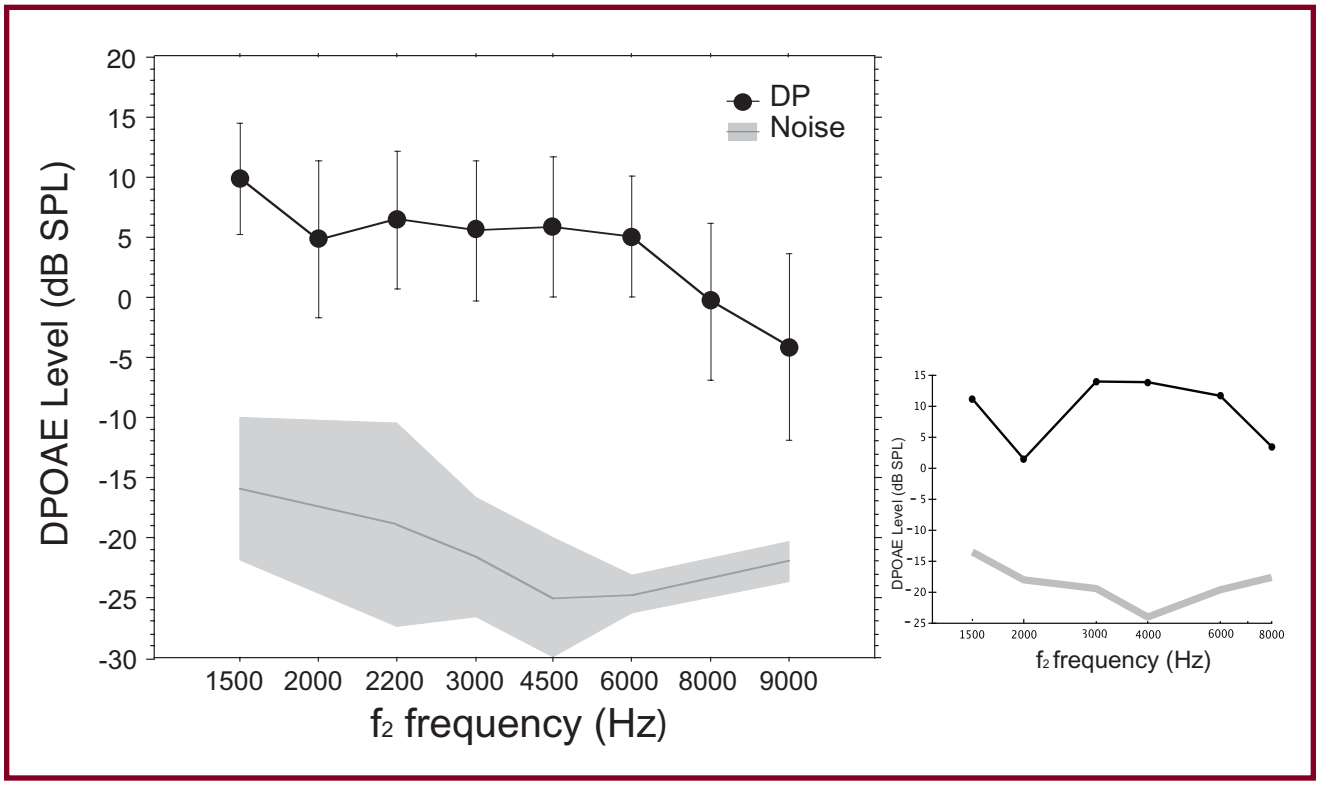

Figure 5–18. Normal DP-grams: Mean DPOAE level and noise floor (±1 SD) as a function of f_2 for 43 normal-hearing adults. Mean levels ranged from –5 to 10 dB SPL. The smaller adjacent graph shows an individual DP-gram from one adult.

the audiologist prior to DPOAE testing. The range of test frequencies and levels (i.e. low, moderate, high) must be set, as well as the level and frequency separation between primary tones.

The choice of stimulus parameters for DPOAE testing influences outcome. DPOAEs are most reliable and show optimal test performance for primary tone frequencies between 1500 and 6000 Hz and manifest reduced performance for lower or higher frequencies (Gorga et al., 1997). Thus, regardless of test frequencies included, this mid- to high-frequency range should be weighted heavily in assessment. The overall average f_2/f_1 ratio producing the most robust DPOAE is 1.2 for both adults and infants though it varies slightly with level and frequency (Abdala, 1996; Gaskill & Brown, 1990; Harris et al., 1989). Moderate-level primary tones (50 to 65 dB SPL) appear to achieve optimal DPOAE test performance for detection of hearing loss in most cases; lower stimulus levels do not augment diagnostic accuracy (Stover et al., 1996). The level difference between primary tones, (L_1, L_2) required to optimize both adult and infant response amplitude is between 10 to 15 dB, with the lower frequency of the two primaries, L_1, higher in level than L_2 (Abdala, 1996; Gaskill & Brown, 1990). More recent work has shown that the $L_1 > L_2$ rule is ideal for low-to-moderate primary tone levels but at higher levels, equilevel primary tones may work best (Boege & Jannsen, 2002; Kummer et al., 2000). In summary, to optimize hearing loss detection and to ensure a robust response, DPOAEs are ideally recorded from 1500 to 6000 Hz, f_2 should be presented at a frequency 1.2 times higher than f_1 and primary tone levels should be moderate, ~65 (L_1) and 55 dB SPL (L_2). It is important that these parameters not be applied rigidly as individual clinical cases might warrant alternative testing strategies.

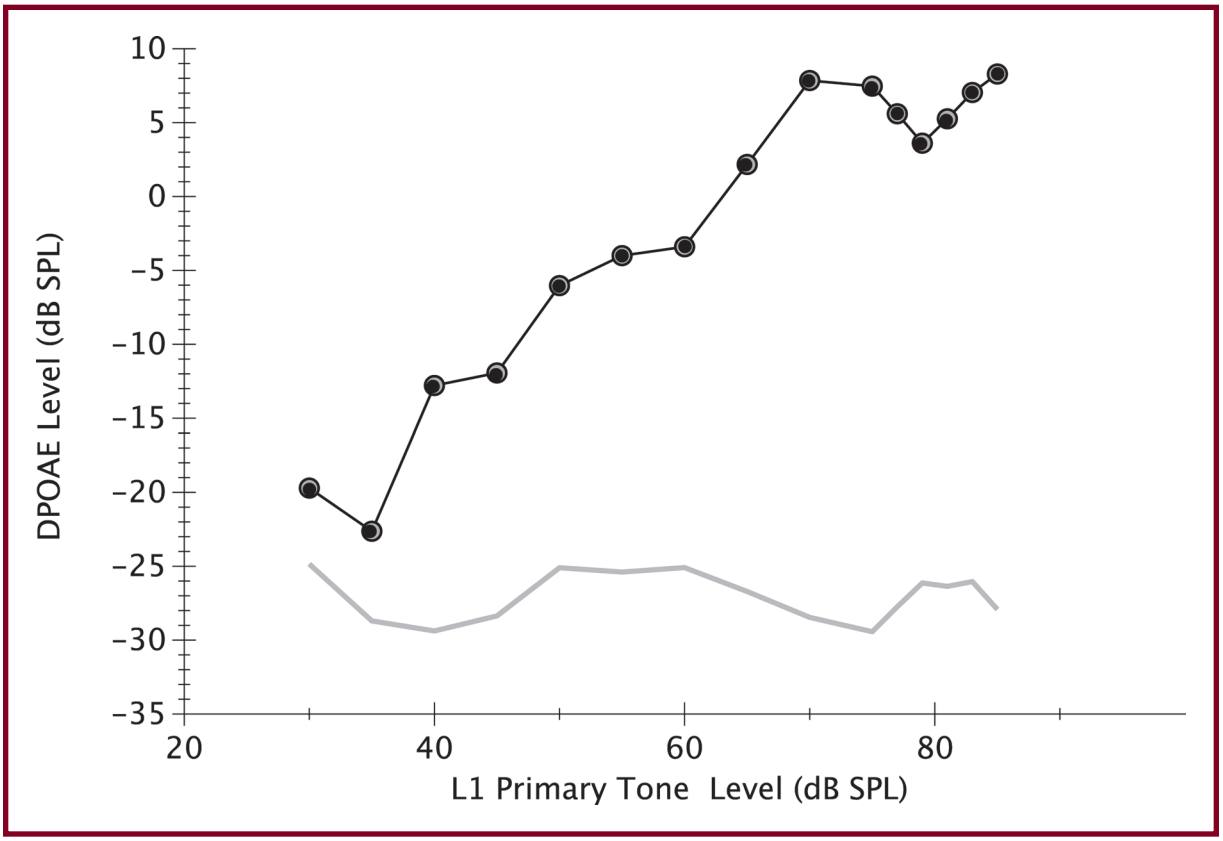

Figure 5–19. DPOAE Input/Output (I/O) graph at f_2 = 3000 Hz. DPOAE amplitude typically grows linearly at low stimulus levels and saturates at moderate-to-high levels. The gray line depicts the mean noise floor.

Efficacy of DPOAEs in Detecting Hearing Loss

Early work by Lonsbury-Martin and Martin (Lonsbury-Martin et al., 1990; Lonsbury-Martin & Martin, 1990; Martin et al., 1990) defined the basic features of DPOAEs in normal-hearing adults and preliminarily probed the impact of hearing loss on the response. They found that the normal adult DP-gram generally peaks in the low frequency range (1500 to 2000 Hz), often shows a dip in the mid-frequencies then peaks again around 4000 to 6000 Hz. The shape of the DP-gram roughly mimics the audiometric configuration when hearing loss is present and there is a rough correlation between DPOAE amplitude and audiometric threshold; the better the audiometric thresholds, the higher the DPOAE amplitude. The infant DP-gram shows slightly higher levels than the adult response, a more flat amplitude configuration and little or no drop-off in the high-frequency range (Abdala et al., 2008; Lasky et al., 1992; Smurzynski et al., 1993).

A few years after these initial observations, a series of reports from Gorga and colleagues quantified the efficiency of DPOAEs in detecting hearing loss with large groups of normal- and hearing-impaired individuals. DPOAE amplitude and SNR were able to separate normal-hearing from hearing-impaired ears with a hit rate (i.e., accurate identification of hearing loss) of ≥90% at 4000 and 8000 Hz and somewhat reduced accuracy at 2000 Hz (Gorga et al., 1993). At frequencies below 2000 Hz, DPOAEs could not distinguish reliably between normal-hearing and hearing-impaired ears. Measures of DPOAE SNR performed better than measures of amplitude. The DPOAE SNR that optimizes detection of hearing loss varies depending on test frequency and on what is considered an acceptable rate of error. For example, if a larger SNR is required to estab-

lish DPOAE presence (let's say ≥10 dB), there is an increased chance of classifying a normal hearer as hearing impaired (false positive) but the hit rate for actual hearing loss will be high. Conversely, a liberal SNR (≥3 dB) might miss individuals with mild hearing loss (false negative) while minimizing the false positive rate. Anecdotal evidence suggests that most audiology clinics apply a DPOAE SNR criterion in the range of 3 to 9 dB to establish response presence.

A second investigation studying more than one thousand ears with and without hearing loss (Gorga et al., 1997) confirmed that hearing-impaired ears generally have lower level DPOAEs than normal ears, although considerable overlap was noted between groups, especially in the low-frequency range. DPOAE SNR performed better than absolute amplitude at detecting hearing loss between 1500 to 6000 Hz as long as the loss was ≥25 to 30 dB HL. Test accuracy improved somewhat when DPOAE data were added at adjacent frequencies (re: test frequency), a second distortion product ($2f_2–f_1$) was considered and when regression analysis was conducted using DPOAE variables in combination (Dorn et al., 1999; Gorga et al., 2000, 2005). At present, this type of multivariate analysis of DPOAE test results has not been incorporated into the audiologic test battery.

Although the DP-gram became the most recognizable face of clinical DPOAE testing, the utility of the DPOAE I/O function (see Figure 5–19) has also been probed. Several investigators have reported differences between DPOAE level saturation (i.e., the primary tone level at which DPOAE amplitude plateaus) in hearing-impaired and normal-hearing listeners. Additionally, correlations have been reported between DPOAE threshold, slope of the I/O function and audiometric threshold (Dorn et al., 2001; Kummer et al., 1998) although the predictive strength of these associations for individual patients has not been been promising. There have been some innovative attempts to predict audiometric threshold by fitting regression lines to the DPOAE I/O function and extrapolating thresholds from the linear fit (Boege & Janssen, 2002; Gorga et al., 2003; Janssen et al, 2005); however, again, their successful application to individual patients remains tenuous. Because DPOAE I/O functions are not adultlike in infants (Abdala, 2000; Abdala & Keefe, 2006), any efforts to apply this index to the pediatric population for hearing assessment would require age-specific normative data. At this time, DPOAE I/O functions have not been regularly implemented in the audiology clinic and the DP-gram remains the most widely applied and interpreted DPOAE metric.

A caveat must be included in any discussion of past work defining the efficacy of the DPOAE in hearing loss detection. The DP-gram, as described and reviewed in the preceding studies, plotted DPOAE level as a function of primary tone frequency in one-half or one-third-octave intervals across the audiometric frequency range. The alternating pattern of DPOAE level known as *fine structure* was not measured. Thus, the response amplitude (and SNR) applied in diagnostic decision making for any of these studies might have been measured at DPOAE fine structure maxima, minima or at intermediate frequencies as shown in Figure 5–20. In cases of normal hearing and severe hearing loss, this imprecision may have had little influence on diagnosis. However, it is not possible to rule out this potential confound or to accurately predict the impact it might have had on past DPOAE work.

OAE Interpretation

The interpretation of clinically recorded OAEs is most productive when the tester considers a combination of factors and extends his/her diagnostic conclusion beyond a simple absent or present distinction. Whether the audiologist is conscious of this process or not, the initial present/absent label is typically augmented by a host of other considerations that enhance the diagnostic process greatly.

The OAE Is Absent

The OAE is absent if it does not manifest adequate SNR (≥3 to 9 dB) across most of the frequency range and, for CEOAEs, if whole-wave reproducibility is below 50%. With an "absent" OAE, the clinician asks him or herself a series of questions before deciding that a hearing loss is indeed present: "Was the test session of adequate quality to ensure a reliable result?" and "Were there low levels of ambient noise in the test room and/or biological noise from

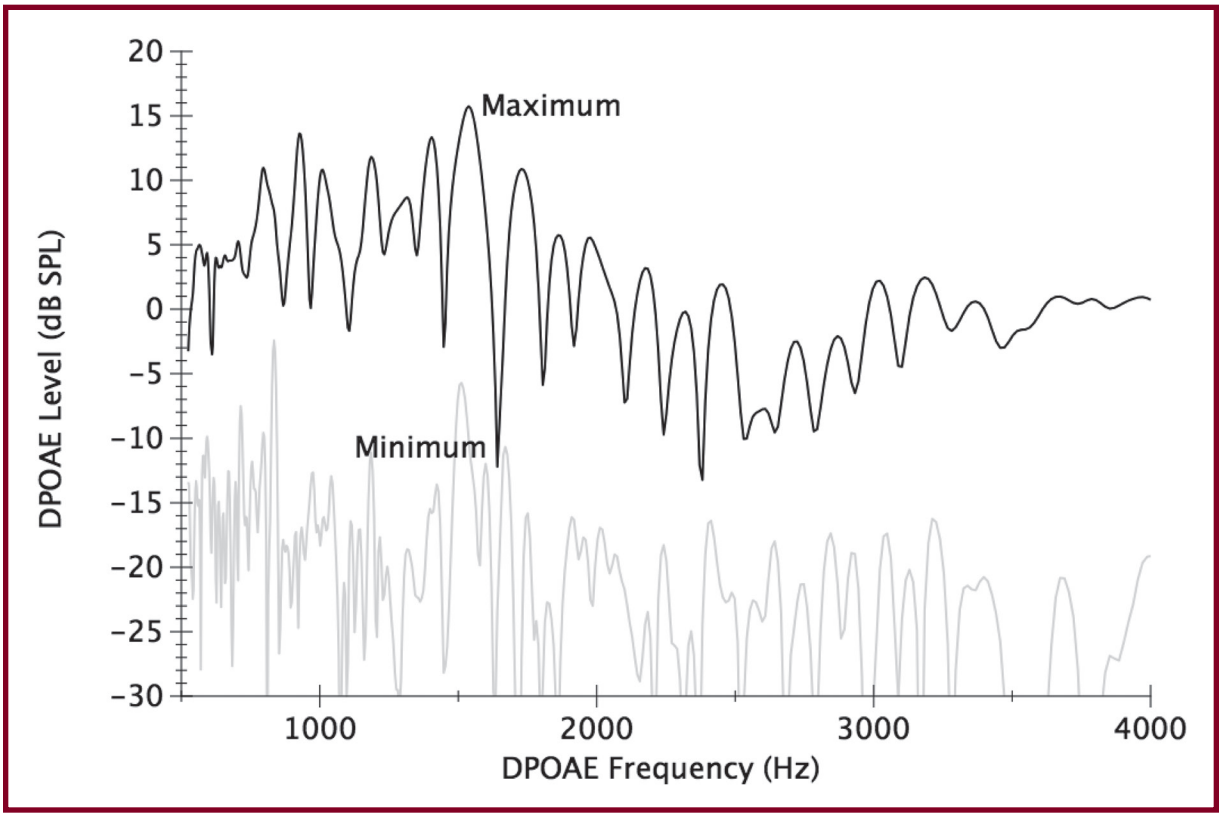

Figure 5–20. DPOAE fine structure (*black line*) and noise (*gray line*) from one normal-hearing adult. When recorded at fine frequency intervals, DPOAE level exhibits quasiperiodic maxima (*peaks*) and minima (*valleys*).

the patient?" Additionally, "Was the probe snug in the ear canal and was it stable for the duration of the test?" and "Was the equipment in good repair and functioning properly?" If the answers to these questions are affirmative, then an absent OAE can be associated with hearing loss of at least mild-moderate degree. Combined with a reported history (by parent, care-giver or self), a clinician might make some preliminary judgment about the severity of the hearing impairment. The final step is to decide upon the tests necessary to define the type, degree, and configuration of hearing loss.

If the answer to the above questions is not an emphatic "yes," an inexperienced clinician could easily mistake an undetected OAE due to elevated noise as a hearing loss when the appropriate outcome under these conditions would be: *Could not test*. This means: "We don't know if there is an OAE present because test conditions precluded us from reliably gathering this information." The *Could not test* outcome is common in pediatric audiology and serial test sessions to assess hearing are routine with infants and children. The costly (and anxiety-provoking) diagnostic procedures that follow a true absent OAE result need not be implemented until a reliable measure of cochlear function is obtained. If a clinician is lacking experience to adequately judge the quality of an OAE evaluation, several indices included in commercial OAE systems can help: the noise floor, the number of sweeps rejected, the stability of the probe fit and the time elapsed during the test.

The OAE Is Present

An OAE is present if it has sufficient SNR to distinguish it from the noise floor and for a CEOAE, if its whole-wave reproducibility is >50%. If an OAE is

determined to be present, it should be further categorized as: "Present and normal" or "Present but abnormal."

A. *The OAE is present and normal.* Present and normal indicates that: (i) the SNR was high at 75 to 80% of frequencies (or frequency bands) tested. It is not unsual for a normal ear to have an absent OAE at one or two points, especially at the low frequencies for children due to elevated noise, or at high frequencies for adults due to decreased amplitude associated with aging; (ii) OAE amplitude was within the range expected for the subject's age. A 1-month-old is expected to show levels between 5 and 30 dB SPL across frequency whereas a middle-aged adult might have OAE levels between –2 and 10 dB through mid-frequencies with reduced amplitude at high-frequencies; (iii) for CEOAEs, whole-wave reproducibility was between 80 to 100%. Both (i) and (ii) conditions should be met for the DPOAE to be considered present and completely normal and all three conditions for the CEOAE to be considered normal. The present and normal result is not equivocal and can be clearly associated with normal cochlear function, which typically is associated with normal hearing. The exception is when an atypical (e.g., Verpy et al., 2008) or auditory-neural deficit is present. In these rare cases, OAEs can be present and normal although hearing is not. The presence of normal OAEs in conjunction with a reliable report of perceptual and language difficulties, should prompt suspicion and further testing.

B. *The OAE is present, but is abnormal.* An OAE can be present because it has sufficient SNR to be distinguished from the noise floor but its parameters do not conform to those observed in normal-hearers. Unfortunately, in the audiology clinic this category is sometimes overlooked. The two most common examples of present but abnormal are: (i) the OAE is either low in amplitude considering the patient's age and/or (ii) the OAE is present in only a restricted frequency range. An astute diagnostician will be concerned about either outcome and investigate further. Applying this diagnostic label requires the audiologist to be familiar with normative ranges of OAE amplitude for different age groups. This will allow the tester to recognize, for example, that a 1-month-old (with normal middle ear function) should not have –2 dB SPL OAEs across the frequency range *even if the SNR is 10 dB.* SNR is not the only criteria in establishing an OAE to be present and normal. A second, more murky "present but abnormal" scenario includes an OAE with adequate SNR in a restricted frequency region. The OAE might be present at 2000 and 3000 Hz, indicating that the cochlea is functional (i.e. generating distortion and/or reflection) in an abbreviated region only. This result suggests a non-flat audiometric configuration.

With either *present but abnormal* result or a combination of both, the audiologist should probe further. If the test session was mediocre in quality, he or she might schedule a repeat OAE evaluation to replicate the result. The present OAE that is not normal might be the best indicator of mild hearing loss since OHC integrity is sufficient to produce an emission, but the OAE is sparse. Figures 5–21 and 5–22 provide examples of present but abnormal DPOAEs (DP-gram) and CEOAEs from pediatric patients. The results are not normal because they are present in only a restricted frequency range and in the case of the DP-gram, are abnormally low in level.

Updating Clinical OAE Protocols

Given our current understanding of OAE generation, it may be time to review and update the OAE protocols typically applied in the audiology clinic for the assessment of hearing. The OAE taxonomy

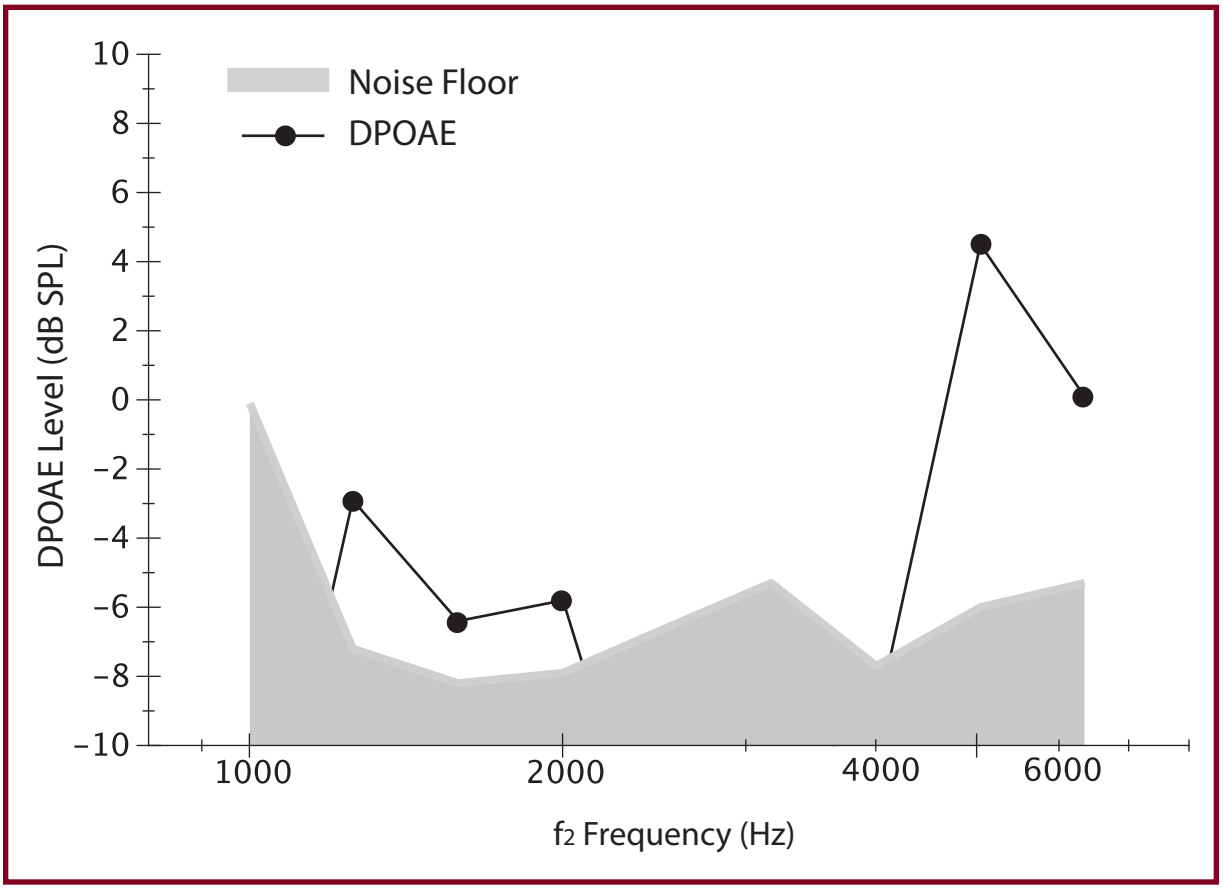

Figure 5–21. DP-gram from a 6-year-old showing present DPOAEs from 5000 to 6000 Hz only, and marginal responses between 1000 and 2000 Hz. This result would be classified as *present but not normal.*

outlined in the first section of this chapter predicts that reflection and distortion components will show differences in their sensitivity to cochlear pathology (Shera & Guinan 1999). The low-level reflection source OAE will theoretically diagnose pathologies affecting cochlear amplifier function more effectively than a distortion-source emission. These types of pathologies might include presbycusis or ototoxicity, for example. If we discover this to be the case, it would be wise to record CEOAEs or SFOAEs to detect these auditory deficits rather than DPOAEs. However, it is not known whether a present reflection OAE is sufficient to classify cochlear function as normal or whether a fully healthy cochlea will always manifest nonlinearity and generate distortion. Before updating clinical OAE protocols in any definitive way, it would be beneficial to know whether each emission type gauges the integrity of distinct cochlear properties.

In the future, an audiologist may be able to utilize the unique sensitivity of each OAE source, either by recording both CEOAEs and DPOAEs on each patient or by "unmixing" DPOAEs to simultaneously collect both types of emissions. This will allow the clinician to observe the effect of pathology on each emission source independently. At present there are many unanswered questions: If both components of the DPOAE are present but the relative contribution of one source is greatly reduced (or augmented), is this diagnostic for auditory pathology? Can we say the cochlea is normal if only distortion is present but no reflection (i.e., there is no fine structure)? Can we

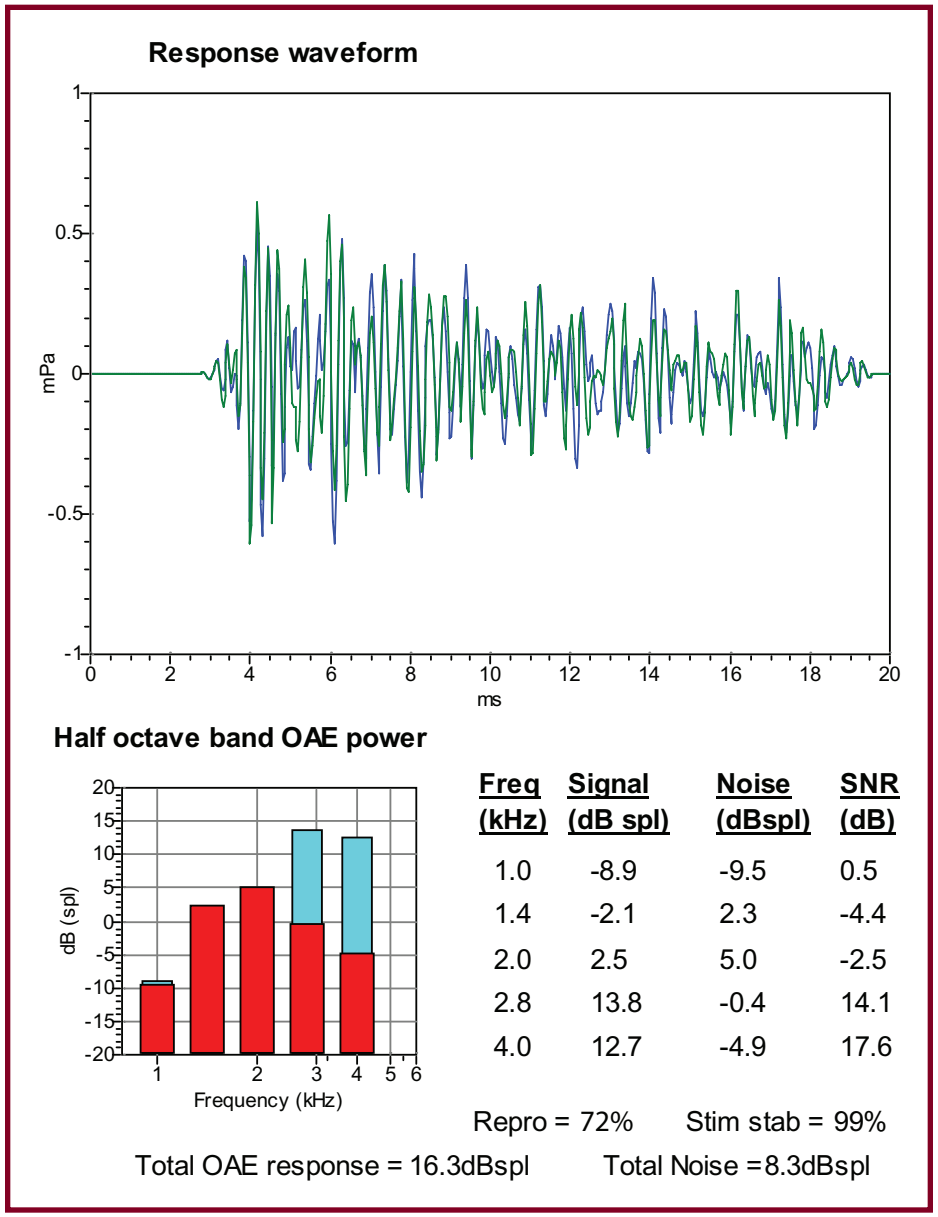

Figure 5–22. CEOAE result from a 2-year-old with present emissions in bands centered at 2800 and 4000 Hz only (as determined by SNR, see lower panel). Whole-wave reproducibility (Repro) is 72%. As can be seen from the superimposed green and blue time-averaged waveforms, reproducibility was poorest in the low-to-mid frequency range (between 12 and 20 ms). This result would be classified as *present but not normal*.

implement measures of DPOAE phase to provide diagnostic information about hearing rather than relying solely on measures of response magnitude? These are intriguing and clinically relevant questions that have yet to be addressed. When research empirically defines the effect of mild-moderate hearing loss of differing etiologies on independent emission sources (and on OAE phase), it might be possible to update and refine OAE testing protocols to improve diagnostic acumen.

Some preliminary attempts have been made to consider the impact of "unmixing" DPOAE components on clinical hearing assessment (Dhar & Shaffer, 2004; Johnson et al., 2006, 2007; Mauermann & Kollmeier, 2004; Mauermann et al., 1999; Shaffer et al., 2003). Mauermann and colleagues (1999) chose specific configurations of hearing loss to isolate contributions to the DPOAE. They determined that if the distortion region around f_2 was healthy, even if the reflection site at $2f_1–f_2$ was not, DPOAEs could be recorded but would show no fine structure. If the reflection site was intact, fine structure was always present even if hearing thresholds were mildly elevated around the DPOAE generation site at f_2. Thus, the f_2 site is clearly critical to the generation of the DPOAE. As convention, the DP-gram probably does well to plot DPOAE amplitude as a function of the f_2 frequency, and to consider the f_2 frequency as the site of hearing assessment.

Several studies have utilized a suppressor tone to control reflection contributions to the DPOAE in normal-hearing and hearing-impaired adult subjects (Dhar & Shafer, 2004; Johnson et al., 2006, 2007). Although suppression effectively isolated the generation source in some cases, it had highly variable effects on DPOAE fine structure from one individual to the next. It does not appear that suppression is viable as a quick, clinical tool for obtaining single-source distortion products in humans. Additionally, controlling component source did not improve overall accuracy in the detection of hearing loss and sometimes worsened it.

Mauermann and Kollmeier (2004) separated DPOAE components using inverse FFT and time-windowing. The IFFT technique has been successfully applied in a number of investigations. They generated single-source DPOAE I/O functions in normal hearers and found that, with decreasing stimulus level, contribution from the reflection-source emission increased. When the reflection source was removed, distortion-only I/O functions manifested fewer notches and reduced variability. The single-source distortion I/O function might be better suited for predictions of hearing threshold than standard, composite DPOAE I/O functions. However, the predictive value of any single-source DPOAE test to assess hearing has yet to be established. Research in this area is warranted to inform and update current OAE hearing assessment protocols and to bridge the gap between recent theoretical advances and clinical practice.

Alternative OAE Applications

Although the primary application of OAEs in the audiology clinic is to detect and preliminarily define hearing loss, they have also been applied for other diagnostic and/or scientific purposes. Some of these applications have made it into routine service delivery such as newborn hearing screening; whereas others remain experimental at present, such as OAE-based measures of the medial olivocochlear reflex.

Neonatal Hearing Screening

OAEs offer a potent tool for the screening of newborn hearing shortly after birth and prior to hospital discharge. The objective of hearing screening is quite different from that of diagnosis. Screening is conducted to identify *suspected hearing loss* and not to confirm the presence/absence of hearing loss or define features of the loss. Of the infants who do not pass the initial OAE hearing screen, it is understood that most will have normal hearing upon further testing. In trying to meet the underlying philosophical mandate, the OAE screening protocol is much abbreviated and automated to provide a rapid, categorical pass/refer distinction (the word "fail" is understandably not popular among parents of newborns and has been replaced in screening vernacular with the term "refer").

An abbreviated OAE test can be achieved in various ways: the OAE can be recorded at only one stimulus level, the time segment sampled post-stimulus can shortened, a fixed number of limited trials can be recorded and an automated pass-fail criterion can be applied. A DPOAE-based screening protocol might include testing at f_2 frequencies of 2000, 3000, and 4000 Hz only and a CEOAE screen might include a time-averaged waveform sampled for only 12 ms (versus 20 ms in diagnostic mode). The OAE screen is typically performed by a tester who is not a hearing specialist, necessitating an automated

pass/refer outcome based on SNR. By making the test simple and rigid, tester time (which translates to cost), and the influence of tester experience, is minimized. OAEs are ideal for hearing screening because they require little subject preparation, involve rapid averaging and can provide the categorical pass/refer distinction required for a screen.

It is not clear whether distortion or reflection OAEs provide a more accurate indicator of hearing status at birth. A large-scale investigation of three hearing screening tests (ABR, CEOAE, and DPOAE) conducted in nearly 5000 newborns determined that hearing loss could be detected equally well with a CEOAE screen at 80 dB pSPL or a DP-gram recorded with primary tone levels of 65 (L_1) and 55 (L_2) dB SPL (Norton et al., 2000). This lack of distinction between tests suggests that distortion- and reflection-source emissions are equally effective for hearing screening.

Monitoring Ototoxicity

OAEs have proven to be useful in monitoring the effects of ototoxicity on cochlear function. Most of these investigations have focused on the aminoglycocide family of antibiotics and more recently, on platinum-based chemotherapy drugs for cancer. There are numerous intrinsic limitations in conducting this kind of research. Since these experiments are conducted on sick patients, dosages and testing intervals are controlled by medical and safety guidelines and not by research protocol. Therefore, only *general* conclusions can be drawn from the collective body of literature.

Early studies using OAEs to monitor ototoxicity found that long-term aminoglycocide regimens (between 7 and 29 days) produced decreases in serially monitored CEOAE amplitude and overall waveform reproducibility; whereas short term dosages (<7 days) showed no difference in CEOAE features over the course of treatment (Stavroulaki et al., 1999). Interestingly, OAE changes were not accompanied by concomitant changes in the audiogram or ABR thresholds suggesting that OAEs provide a more sensitive indicator of ototoxicity than conventional threshold tests. A later study from this same research group (Stravroulaki et al., 2002) concluded that high-frequency DPOAEs were most sensitive to aminoglycocide-induced cochlear damage and were more effective indicators of ototoxicity than standard audiometry.

Some investigators have suggested that DPOAE latency and threshold might be more sensitive to aminoglycocide ototoxicity than response magnitude but this tack has not been pursued (Katbamna et al., 1999). Others have failed to find consistent effects of aminoglycocides on DPOAEs. Intratypmpanic gentamycin given for the treatment of Ménière disease, for example, did not alter audiometric thresholds or DPOAE features in adult patients 3 months after treatment (Perez et al., 2004). Additionally, a group of control and term infants treated with aminoglycocides to rule out sepsis showed comparable OAE and audiometric findings (Ruggier-Marone & Schochat, 2007). These negative results might suggest that DPOAEs are insensitive to aminoglycocide ototoxicity. However, an alternative interpretation is that the prophylactic regimen given to high-risk newborns is not ototoxic and produces little change in OHC function. Because the crucial variables of time-interval and dosage cannot be manipulated for research, it is difficult to accurately compare results among studies.

Drugs in the platin family are also ototoxic. As with aminoglycocide research, most investigators have concluded that DPOAEs are the earliest and most sensitive indicators of ototoxic damage induced by cisplatin and that they best gauge platin-induced declines in cochlear function (Biro et al., 2006; Dhooge et al., 2006; Stavroulaki et al., 2001). A recent, fairly comprehensive study compared the sensitivity of DPOAEs to aminoglycocide- and platin-induced ototoxicity (Reavis et al., 2008). The DPOAE was reduced or absent in 64 of 82 ears following treatment with either drug. Sensitivity of the DPOAE to ototoxic effects was unrelated to drug type. DPOAEs performed best when there was limited pre-exposure hearing loss, when the drugs produced large changes in the DPOAE and when DPOAEs were measured at frequencies >2500 Hz. Consistent with other reports, changes in audiometric threshold and DPOAE level did not always correlate in a predictable way.

Cumulatively, this body of literature suggests that: (1) high-frequency DPOAEs are most sensitive

to changes in cochlear function produced by ototoxic effects regardless of drug type and (2) changes in OAEs precede changes in the audiogram for conventional audiometric frequencies (through 8000 Hz), providing an early warning sign of cochlear damage. Given their distributed source and the mixed nature of the DPOAE, drug effects on DPOAE level cannot be easily associated with focal pathology at a corresponding characteristic frequency along the cochlear map. In the future, it would be of value to assess whether DPOAE component separation might enhance the sensitivity of current protocols monitoring the effects of ototoxic drugs on hearing.

Diagnosing Auditory Neuropathy

OAEs have been useful as one part of an audiologic battery applied to diagnose auditory neuropathy (AN). Patients with AN show preserved cochlear receptor function combined with impaired IHC synapes or auditory nerve function. The pathophysiology is thought to involve primary demyelization or axonal disease (Starr, 2001). The two major sequelae associated with neuropathies of the auditory nerve are disruption of temporal synchrony and reductions in the number of conducting fibers due to axonal loss. In patients with AN, neurons discharge in a temporally irregular fashion making it difficult or impossible for the auditory cortex to translate sound into meaningful patterns.

A typical patient with AN has present OAEs (sometimes robust, sometimes reduced in level and spectral content) and cochlear microphonics, combined with absent or grossly abnormal brainstem function as measured by the ABR, middle ear muscle reflex, and the medial olivocochlear reflex (For more information on these auditory responses and on AN, see Chapters 4 and 6). Patients with AN also have elevated audiometric thresholds, often with an erratic or atypical audiogram configuration and disproportionately poor monosyllabic speech discrimination scores. The feature that distinguishes AN from sensory loss is normal cochlear function in the presence of abnormal auditory-nerve function. Clearly, OAEs form a critical component of the AN diagnostic battery by establishing functional OHCs. In fact, AN undoubtedly existed long before we named it; audiologists must have considered it a perplexing sensory hearing loss with disproportionate effects on speech and language and on the ABR. The ability to easily and rapidly record a preneural, cochlear response like OAEs, in combination with the ABR, has made the diagnosis of AN definitive.

Measuring the MOC Reflex

The olivocochlear system contains efferent fibers that course from the olivary complex at mid-brainstem level to the sensory cells of the cochlea or the afferent fibers at their base. The medial portion of the olivocochlear tract contains large myelinated fibers that predominantly innervate the OHCs (Fex, 1962). When this medial bundle is stimulated electrically in laboratory animals, cochlear output is altered (as typically evidenced by a reduction in OAE amplitude) as is the firing rate of afferent auditory nerve fibers.

The MOC reflex can be recorded in humans using OAEs. Broadband noise will activate medial efferents and OAE measurements can provide evidence of altered cochlear output consequent to this activation. Each OAE-based MOC paradigm has its advantages and disadvantages as clearly described in an excellent review by Guinan (2006). SFOAEs may provide the most easily interpreted MOC reflex because they come from a focal, frequency-specific region on the basilar membrane and are thought to reflect cochlear amplifier function. However, SFOAEs are also challenging to record because the response overlaps with the stimulus both temporally and spectrally. CEOAEs have been used to elicit the MOC reflex (Collet et al., 1990) but also present their difficulties. The broadband click stimulus is a strong elicitor of the MOC reflex and this muddies the interpretation. Additionally, CEOAEs are most typically measured with nonlinear averaging (Bray & Kemp, 1987) which reduces the magnitude of the OAE-based MOC reflex. Finally, because of the broadband nature of the stimulus and response, CEOAE-based measures of MOC activation are not frequency specific. Depending on the objectives of the tester, this may or may not be a disadvantage.

DPOAEs have also been recorded with contralateral acoustic stimulation to assess the MOC

reflex. One of the major disadvantages of this paradigm is that the DPOAE is a mixed response including two sources with distinct generation mechanisms. This complicates matters. However, there are established methods for separating the two DPOAE components and assessing the effects of contralateral noise (i.e., efferent activation) on each source separately. Recent experiments applying the IFFT for component separation have shown that contralateral noise alters the reflection component of the DPOAE more than the distortion component (Abdala et al., 2009; Deeter et al., 2009). This is expected, given that the low-level reflection source is most sensitive to cochlear amplifier function, which is modulated by the MOC efferents.

Because MOC activation alters DPOAE components differently, DPOAE amplitude can sometimes be enhanced rather than suppressed when contralateral noise is presented. At minima in DPOAE fine structure, dual emission sources are 180 degrees out-of-phase, partially cancelling the OAE response recorded in the ear canal. If contralateral acoustic stimulation (CAS) presented to activate the MOC reflex alters the reflection component more than it alters the distortion component, *it will shift the phase relationship between the two sources*. This shift releases phase cancellation at frequencies around fine structure minima and in doing so produces an abrupt increase in DPOAE level, sometimes as marked as 15 to 20 dB. Figure 5–23 shows DPOAE fine structure recorded with and without CAS; the MOC reflex (the difference between no-CAS and +CAS conditions) is superimposed in gray. Clearly, episodes of DPOAE level enhancement are noted around fine structure minima when efferents are activated. The enhancement appears to be an artifact of component mixing and does not reflect an MOC-mediated increase in the gain of the cochlear amplifier.

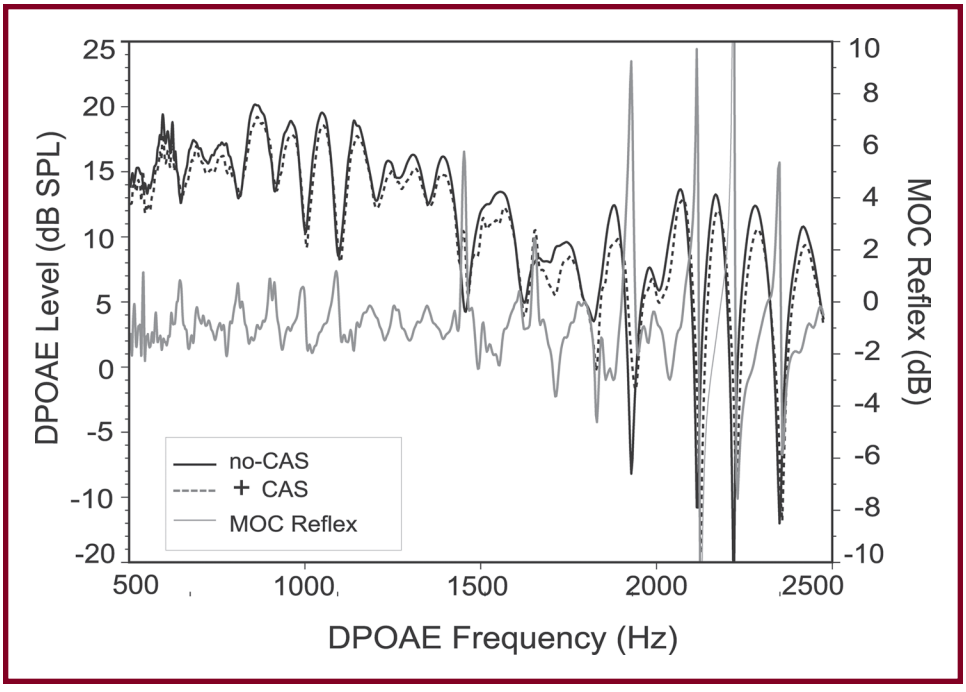

Figure 5–23. DPOAE fine structure with (*dashed line*) and without (*black line*) contralateral acoustic stimulation (CAS) to evoke the medial olivocochlear (MOC) reflex. The MOC reflex is displayed in gray (RE: right axis) as the difference between black and dashed lines. When CAS is presented, DPOAE amplitude around fine structure minima is enhanced (see sharp spikes). In contrast, at maxima DPOAE amplitude is reduced by the MOC reflex. Enhancement is likely an artifact of mixing between DPOAE components.

It is possible to mitigate the effects of this potential confound in DPOAE-based measures of the MOC reflex by measuring only when DPOAE components are adding constructively (i.e., at fine-structure peaks). At peak frequencies, an MOC-mediated reduction in either component will still produce an overall decrease in DPOAE level. This index should be a gross indicator of the strength of the MOC reflex. The MOC reflex measured in this manner (at peaks in DPOAE fine structure only) is reliable and averages ~1.5 to 2 dB in normal-hearing adults (Figure 5–24). This relatively new paradigm using DPOAE fine structure to measure the effects of the MOC reflex is a concrete example of how enhanced understanding of OAE sources theory can lead to an improved auditory probe. It is hoped that in the future the field can move toward a clinical measure of the MOC reflex. This index of cochlear modulation could identify individuals uniquely vulnerable to noise damage or possibly account for perceptual deficits not easily explained by the conventional audiogram.

Question 3

Are spontaneous OAEs in any way related to tinnitus?

Answer 3

Generally, no. Studies indicate that only a small percentage (perhaps 5%) of tinnitus subjects can trace their "ringing in the ears" to spontaneous OAEs (Penner, 1990). However, tinnitus is often associated with clinical or subclinical damage to the cochlea, damage that affects and can be detected using OAEs.

BACK ON YOUR CASE

At last we return to your waiting patient. Recall the (perhaps not so) hypothetical facts of the case: A youthful mouse complains of reduced sound

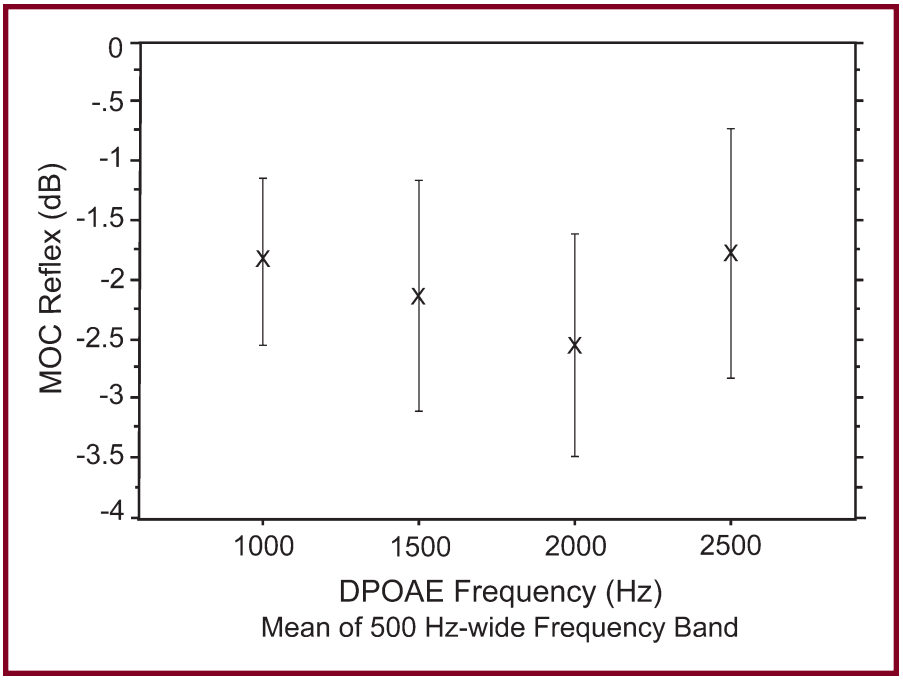

Figure 5–24. Mean MOC reflex recorded at DPOAE fine structure peak frequencies only in 15 normal-hearing adults. Overall mean MOC reflex was –2.05 dB (negative numbers are used to denote the effect as inhibitory). Error bars represent ±1 SD.

tolerance and inaudible Tartini tones. Your audiologic tests reveal normal pure-tone audiograms and ABRs, reduced loudness discomfort levels, no DPOAEs, and unusually large CEOAEs. Now that you have been chewing on it for a while, and have been reminded of a few mechanisms and applications of OAEs, can you make sense of the case?

In light of the implication that measurement methods matter, perhaps you immediately notice that you need more information to interpret the CEOAEs. What was the protocol? You check your records and determine that they were measured with the linear protocol. To determine whether the protocol makes a difference, you measure CEOAEs again using the nonlinear protocol. Sure enough, the results are very different. With the nonlinear protocol *there are no CEOAEs at all!* Can you construct a hypothesis consistent with all these facts? (Spoiler alert: the authors sketch out some possible ideas below. You, and probably the mouse, will be better off if you think of your own.)

After thinking it over, perhaps you propose the following hypothesis for your not so hypothetical case. Perhaps you suggest that the mouse carries a newly uncovered mutation in a gene — call it *Dpless*, because the phenotype shows no distortion products — that affects OHC stereocilia and modifies the OHC force-displacement transduction function so that it looks something like that illustrated in Figure 5–25. The solid gray line shows the sigmoidal curve that characterizes the transduction curve in a normal mouse (see Figure 5–12). The dashed curve shows a schematic of your hypothesized curve. It has roughly the same asymptotes at the extremes of bundle displacement, but in between the shape is different. In particular, the central portion is now very close to a straight line.

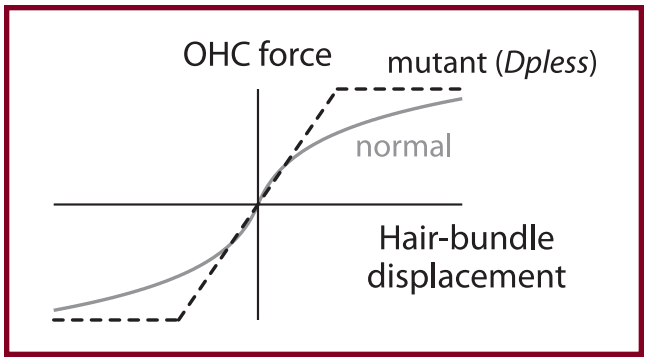

Figure 5–25. Hypothetical OHC transduction function in normal and *Dpless* mice.

As you see it, your hypothesized *Dpless* transduction curve has two important features relevant to the case. First, the mutation preserves the slope of the curve near the origin. Therefore, at low levels a given bundle displacement produces the same amount of OHC force in both cases. As a result, the amplifier gain near threshold is the same as normal. (Note that at higher levels, the amount of force produced by *Dpless* OHCs is actually greater than normal.) Second, the straight line greatly extends the hair cell's linear range of operation.

Can your hypothesis account for all the facts of the case? If not, which facts remain unexplained? Can you suggest ways the hypothesis might be tested further? Can you think of biophysical mechanisms that might modify the transduction curve in the way you propose? When thinking about this last question, it might help to remember that the idealized transduction curves shown in Figure 5–25 result from the total, summed current that passes through the many individual transduction channels in a hair bundle. Normally, the hair bundle moves as a unit so that the transduction channels at the tips of the stereocilia tend to open and close together (Karavitaki and Corey 2011). What might happen if the mutation were to cause the stereocilia in a bundle to move more independently, so that each of the many transduction channels had, in effect, a different operating point? We'll let you think about those issues on your own. After all, the mouse is your patient and *Dpless* is your hypothesis. But like Stuart Little at the end of his book, we are optimistic. Although this chapter may have seemed long, the sky is bright and we somehow feel you are headed in the right direction.

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