# THE EAR'S GEARS: MECHANOELECTRICAL TRANSDUCTION BY HAIR CELLS

**Our senses of hearing and equilibrium depend upon biological strain gauges that can respond to mechanical stimuli of atomic dimensions and frequencies exceeding 20 kilohertz.**

A. J. Hudspeth and Vladislav S. Markin

Although we are generally unaware of the fact, our nervous systems constantly monitor a variety of mechanical stimuli. Neurons in the spinal cord and brain stem extend sensory terminals to the body's surface and there provide us with sensitivity to touch. Other such neurons measure the tension in and extension of skeletal muscles. Sensory cells of the autonomic nervous system detect pressures within the body's hollow organs, including blood vessels, the bladder, and the gut. The most sensitive of our mechanical receptors are hair cells, the sensory receptors of the internal ear. Such cells underlie our sensitivities to sound, to linear accelerations (including that due to gravity), and to angular accelerations.

This article reviews our understanding of mechanoelectrical transduction by hair cells. As used in sensory research, the term "transduction" encompasses more than the interconversion of energy, in this instance the conversion of mechanical stimulus energy into electrical energy. Sensory transduction includes the related processes of amplification and adaptation, both of which we touch upon here. For the most part we consider hair cells from various species and organs together, because those dedicated to hearing and those concerned with acceleration are similar in structure and in operating principles, and the form and function of hair cells have been highly conserved throughout vertebrate evolution.

## The internal ear

Housed in the hard temporal bone of the skull, a human internal ear contains six independent receptor organs, each sensitive to a specific type of stimulation. (See figure 1.) The spiral cochlea, the receptive organ for sound, provides information about the intensity and frequency content of airborne vibrations. (See the article by Jont B. Allen and Stephen T. Neely in PHYSICS TODAY, July 1992, page 40.) Because there are two cochleas, one on each side of the head, we can localize sound sources on the basis of phase and intensity differences between the signals reaching the two ears.

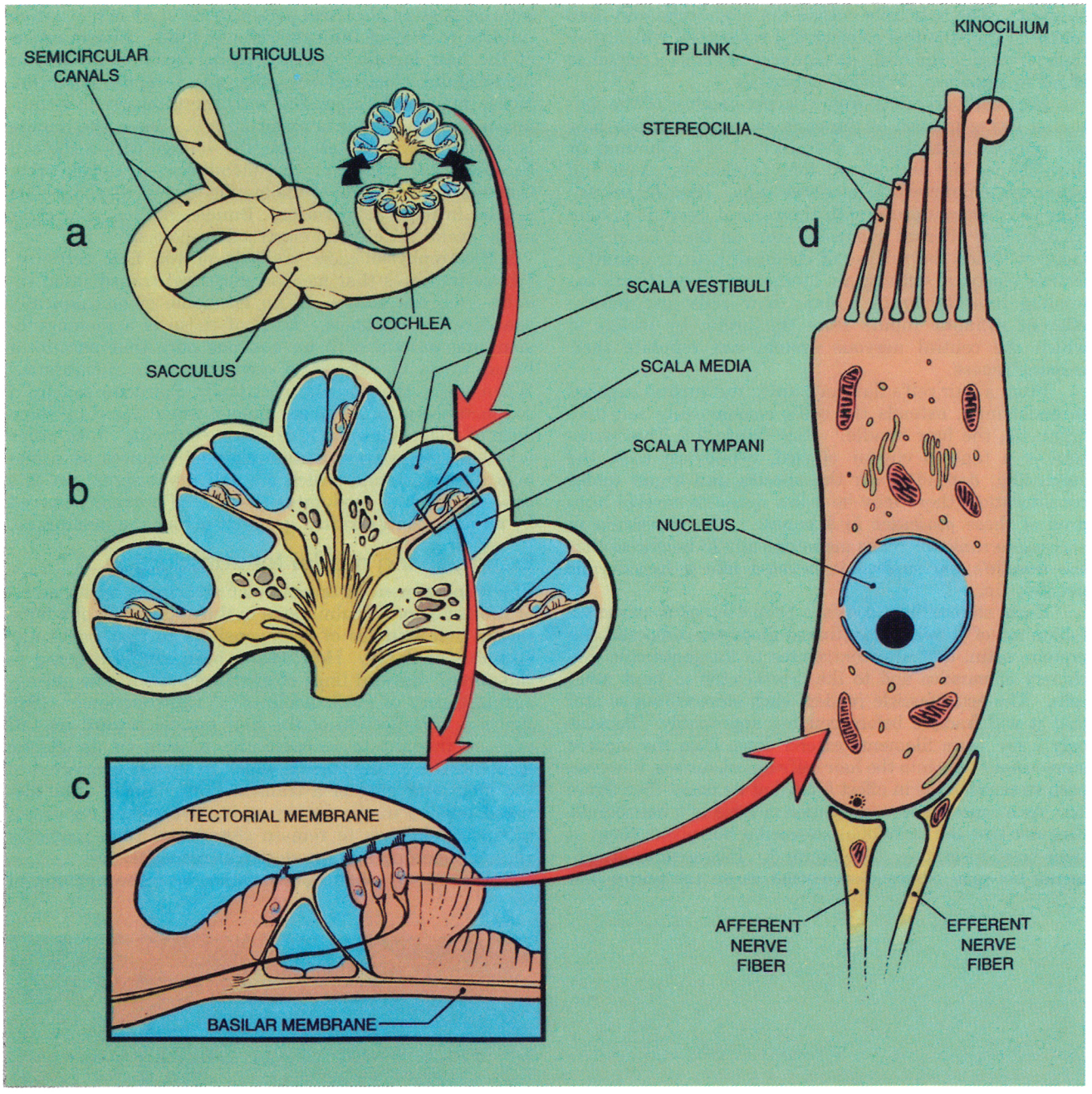
The internal ear contains a pair of detectors for linear acceleration—the sacculus and utriculus—which measure movements in respectively the vertical and horizontal planes. Because each of these organs provides a unique response to an acceleration in any orientation within a particular plane, the two organs together encode linear accelerations in any direction. The presence of a symmetrical pair of linear-acceleration detectors on the body's opposite side provides a degree of redundancy. Three semicircular canals within each internal ear monitor angular acceleration about mutually orthogonal axes. Taken together with their counterparts on the body's other side, these organs provide more than sufficient information for the unique decomposition of any angular acceleration.

The cells of the internal ear originate from the surface ectoderm of an embryo, a single layer of cells that also gives rise to the epithelial cells of the skin. The cells destined to form the ear invaginate from the embryonic surface to form a bilaterally symmetrical pair of pouches that subsequently pinch off from the surface. During the ensuing series of morphogenetic events, these rudiments are each partitioned to form the ear's six receptive regions. Each of these nascent organs comprises a continuous sheet of epithelial cells separating an interior cavity from the remainder of the extracellular space. By actively transporting ions and small molecules, these cells maintain within the ear's cavities a $K^+$-rich fluid environment, called endolymph, in which mechanoelectrical transduction takes place.

## The hair cell

Despite the apparent differences in their sensitivities, the organs of the internal ear all operate in fundamentally

**A. J. Hudspeth** is an investigator at the Howard Hughes Medical Institute and director of the Center for Basic Neuroscience Research at the University of Texas Southwestern Medical Center in Dallas, Texas. **Vladislav Markin** is a research professor at the Center for Basic Neuroscience Research.




**The internal ear** (**a**) includes the five acceleration-sensitive organs of the vestibular labyrinth and the cochlea, the detector of airborne sound. The sacculus and utriculus include respectively about 15 000 and 30 000 hair cells in planar sheets. The vertically oriented sacculus best detects up-and-down accelerations, while the utriculus is most sensitive to accelerations in the horizontal plane. Each of the three semicircular canals, which measure angular accelerations, consists of a fluid-filled tube interrupted by a gelatinous diaphragm into which insert some 7000 mechanically sensitive hair bundles. The spiraling cochlea (**b**) comprises three fluid-filled tubes separated from one another by a pair of elastic, helical partitions. Upon the thicker of these partitions, the basilar membrane (**c**), sits the organ of Corti, which includes 16 000 hair cells disposed in four rows. Each hair cell (**d**) is anatomically and functionally divisible into two regions. The hair bundle at the cell's top is the detector for mechanical inputs. The bundle contains numerous actin-stiffened stereocilia and may include a single true cilium at its tall edge. The cell's basolateral membrane surface is specialized for electrical amplification of the receptor potential and for synaptic transmission of information to afferent nerve fibers. Efferent nerve fibers, whose activity regulates hair-cell sensitivity, also terminate on the basolateral membrane.
**Figure 1**

the same way.[1] In each instance, the stimulus—sound, linear acceleration, or angular acceleration—is mechanical. This stimulus is transmitted through mechanical and hydraulic linkages to a set of receptor cells, the hair cells, dedicated to the detection of the relevant type of stimulus. The hair cells encode the magnitude and time course of the stimulus as electrical responses, which they then forward to the brain along nerve fibers as a sequence of nerve impulses, or action potentials.

Hair cells originate from specific patches of the epithelial lining in each of the ear's six organs. Each hair cell remains epithelial in character: it is a columnar or flask-shaped cell without the long extensions, axons and dendrites, characteristic of nerve cells. (See figure 1c.) Hair cells communicate with the central nervous system by means of afferent synapses, sites on their basal surfaces at which the release of chemical neurotransmitter evokes electrical activity in contiguous nerve fibers extending into the brain. Many hair cells also receive efferent synaptic inputs from the brain, by means of which the central nervous system can regulate their responsiveness.

From a hair cell's flattened apex, the surface exposed to endolymph, extends the cell's mechanically sensitive organelle, the hair bundle.[1] (See figure 2.) This structure is a tapered cluster of stiff, cylindrical rods, the stereocilia; depending on the species and organ under consideration, there may be a few dozen to several hundred of these processes in a bundle. The stereocilia in successive ranks increase monotonically in height so that the bundle's top surface is beveled like a hypodermic needle's tip.

Each stereocilium consists primarily of a paracrystalline rod of parallel, cross-linked filaments composed of a protein, actin, that also contributes to the contractile machinery of muscles and to the cytoskeleton in most other cells. The actin fascicle renders each stereocilium so stiff that it will fracture before bending appreciably. Because only a few actin filaments extend down from the tapered stereociliary base into the hair cell's apical surface, however, each stereocilium is in effect hinged at its base. (See figure 1c.) As a consequence, application of force to a hair bundle does not bow the individual stereocilia but pivots them at their basal insertions. (See figure 3.) Filamentous attachments between adjacent stereocilia cause the entire hair bundle to move as a unit, so that contiguous stereocilia slide along one another's lengths.

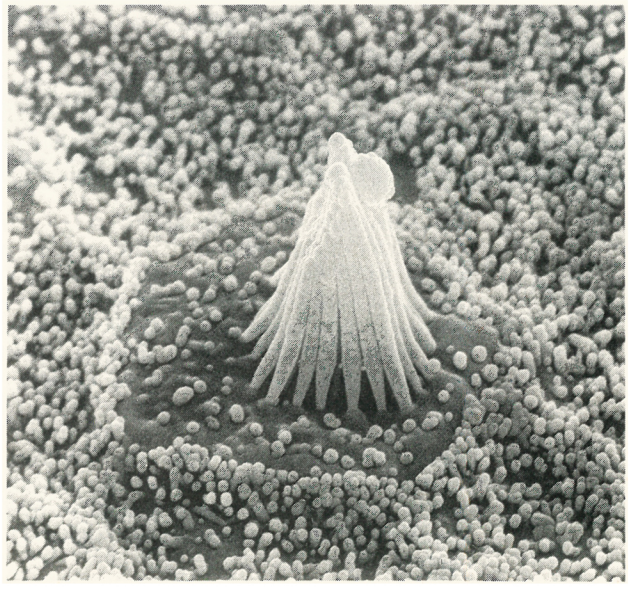
Like other cells, the hair cell has a resting potential: because of differences in ionic concentrations on the two sides of the cell's surface membrane, the fluid of the cell's interior is at an electrical potential about 60 mV negative relative to that of the extracellular fluid. Displacement of the hair bundle from its resting position evokes an intracellular electrical response, the receptor potential, whose magnitude is graded with the intensity of stimulation and ranges up to about 20 mV. When the bundle is moved toward its tall edge, the voltage within the cell becomes less negative: the membrane is depolarized. Conversely, deflection of the bundle toward its short edge results in hyperpolarization. Bundle motions at a right angle evoke little or no electrical response.[2]

Electrophysiological analysis of the hair cell's response indicates that mechanoelectrical transduction results from the activity of an ensemble of mechanically sensitive ion channels. Each of these is a membrane-spanning protein with an aqueous pore that permits a broad range of cations to cross the cell's membrane.[3] When open, the pore is electrically characterized by a conductance near 100 picosiemens; when closed by some form of molecular gate, it carries no current.[4] Like other ion channels, a transduction channel behaves as a biological transistor in which a small input signal, in this case mechanical, modulates the flow of current powered by an ionic concentration gradient across the membrane.

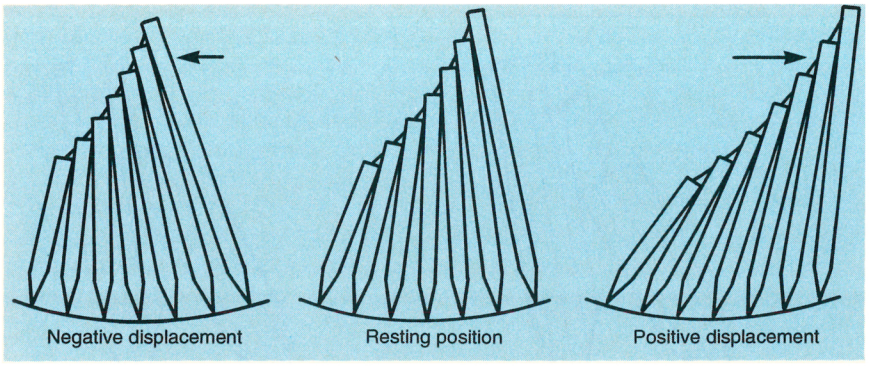
## Gating-spring model for transduction

The displacement of internal-ear structures by an acceleration or a sound culminates in the application of a force to the hair bundles of cells sensitive to that particular stimulus modality. How does a hair bundle respond to this force? Several lines of evidence support the gating-spring theory of mechanoelectrical transduction.[1,5] (See figure 4.) Deflection of the hair bundle toward its tall edge is thought to increase the tension in an elastic element, the gating spring, which in turn is connected to the molecular gate of a transduction channel. The elevated tension in the gating spring overcomes the gate's intrinsic tendency to remain closed and thus promotes channel opening and an electrical response.

The energy change associated with the opening of



**Hair bundle** from the frog's sacculus, here seen in a scanning electron micrograph, consists of about 60 stereocilia in ranks whose length increases monotonically up to 8 microns. Movement of the bundle to the right, toward its tall edge, excites the cell by depolarizing its membrane. Bundle deflection in the opposite direction evokes an inhibitory response. The hair cell is surrounded by the pebbly apical surfaces of nonsensory supporting cells. (Magnification, 5800×.) **Figure 2**




**Motion** of a hair bundle when stimulated by a mechanical force indicates that the individual stereocilia pivot about their basal insertions while remaining straight. Although a hair bundle can survive displacements as great as those shown, the loudest tolerable sound would move a bundle by only one stereociliary diameter. The gating-spring model supposes that mechanoelectrical transduction results from the longitudinal shear produced between adjacent stereocilia in a deflected hair bundle. During positive stimulation the tip link that connects two contiguous stereocilia is stretched and promotes opening of ion channels by pulling on a molecular gate. Negative stimuli relax the tip link and permit the closure of some of the channels that are open at rest. (Adapted from ref. 1.) **Figure 3**

each channel is $\Delta U = -Z\,(X - X_0)$, in which $X$ is the hair bundle's deflection from its resting position and $X_0$ is the bundle position at which half the channels are open. The parameter Z, the gating sensitivity, characterizes the mechanical responsiveness of the transduction process. At an equilibrium established a few milliseconds after the stimulus's onset, a channel's probability $p_o$ of being open is given by the Boltzmann relation

$$p_o = \frac{1}{1 + e^{\Delta U/kT}} = \frac{1}{1 + e^{-Z\,(X - X_0)/kT}}$$

Here $k$ is the Boltzmann constant and $T$ is the temperature.

The gating-spring theory was advanced to account for the relation between bundle displacement and electrical response. The formulation also accords with observations on the kinetics of transduction-channel gating.[5] Although it was but a hypothetical entity in the original proposal, the gating spring assumed a concrete form shortly afterward. Extracellular measurement of current flow through transduction channels indicated that the site of transduction is atop the hair bundle, near the stereociliary tips.[6] Electron microscope observations subsequently demonstrated that the end of each stereocilium is ligated to the longest adjacent process by a fine molecular thread, the tip link.[7]

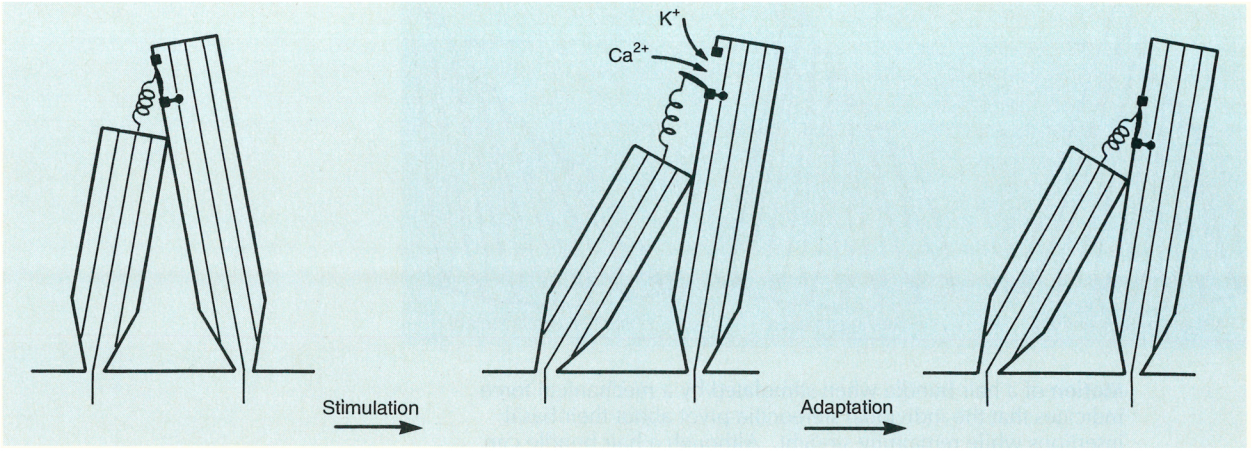
If it is attached to a transduction channel at either or both ends, this link could well serve as a gating spring. Pushing the bundle toward its tall edge, a positive displacement, causes shear between adjacent stereocilia that would extend the link and thus foster channel opening. (See figure 3.) Motion of the bundle in the negative direction, toward its short edge, would reduce the resting tension in the link and close channels. Orthogonal motion should have no effect on channel gating, as indeed it does not.[2] Identification of the tip link with the gating spring therefore not only renders the gating-spring model more concrete but explains why the hair cell's mechanical sensitivity is vectorial.

This direct, mechanical strategy for transduction confers upon hair cells two significant advantages that presumably have promoted its evolution and preservation. First, mechanoelectrical transduction is remarkably sensitive. There is no threshold that a stimulus must exceed to be detected; instead, an arbitrarily small stimulus produces a correspondingly diminutive response that can be discerned by averaging after a sufficiently long period. The other advantage of direct transduction is its great rapidity.[8] Each transduction channel makes transitions between its closed and open states at a rate dependent on a relatively low energy barrier,[5] on the order of the thermal energy $kT$. As a consequence a channel may clatter back and forth between its two states many thousands of times per second. Such a channel is poised to detect changes in tip-link tension that occur on a comparable time scale; for example, human audition extends to 20 kHz, and bats and whales can hear frequencies as high as 100–200 kHz.

## Adaptation to sustained stimuli

The hair cell's extraordinary sensitivity poses a question: How can the transduction apparatus avoid being overwhelmed by large stimuli? The cell's receptor potential is saturated by a brisk displacement of the hair bundle by only 100 nm toward its tall edge or by a still smaller motion in the opposite direction. Would not the transduction process become useless if a hair bundle were slightly displaced from its ideal set point?

Hair cells avoid saturation of their transduction capability by adaptation. If a hair bundle is deflected from its resting position and *held* at a different location, the position of maximal responsiveness migrates toward the bundle's new position.[9] Although such adaptation is not complete, it is effective: The transducer's set point can move more than 1000 nm in the positive direction and about 300 nm in the negative direction. Moreover, adaptation is relatively rapid; adjustment of the set point follows an approximately exponential time course, with a time constant near 25 msec. By acting as a high-pass filter, adaptation renders a hair cell insensitive to low-frequency stimuli. This loss of responsiveness is more than made up for, however, by the cell's ability to detect minuscule transient stimuli in the presence of large,




**Adaptation** of the transduction apparatus. During prolonged positive stimulation, the tip link's upper insertion slides down the stereocilium, reducing the tension in the gating spring and promoting channel closure. With prolonged negative stimulation, the insertion ascends the stereocilium, probably powered by myosin molecules, and increases tension in the tip link until channels reopen. (Adapted from refs. 1 and 10.) **Figure 4**

static backgrounds. The sacculi of frogs, for example, are sensitive to rapid accelerations smaller than 10 $\mu$m/sec$^2$ (about 1 microgravity) in the presence of a static gravitational acceleration over a millionfold as great.

Recent experiments have demonstrated that adaptation is the result of a unique mechanical process. (See figure 4.) When a hair bundle is pushed in the positive direction and held in place, shear between each pair of stereocilia increases the tension in the tip link that connects them. Adaptation occurs when the link's upper insertion slides down the side of the longer stereocilium, reducing the tension in the tip link. Adaptation to negative stimuli is accomplished by motion in the opposite direction: the link's upper insertion climbs up its stereocilium, retensioning a slackened link and restoring mechanical sensitivity to the hair bundle.[1,10]

Convoluted though the adaptation process may seem, several lines of evidence support the mechanism described above. As adaptation to a stimulus proceeds, a bundle's mechanical properties change strikingly. When a bundle is shifted in the positive direction and held in place, the force exerted against a stimulus probe declines by nearly half as the tip links relax.[11] Conversely, when the bundle is moved in the negative direction, the force exerted by the gating springs rises as the links are retensioned. In both instances there is good agreement between the time course of mechanical relaxation and that of electrical adaptation.

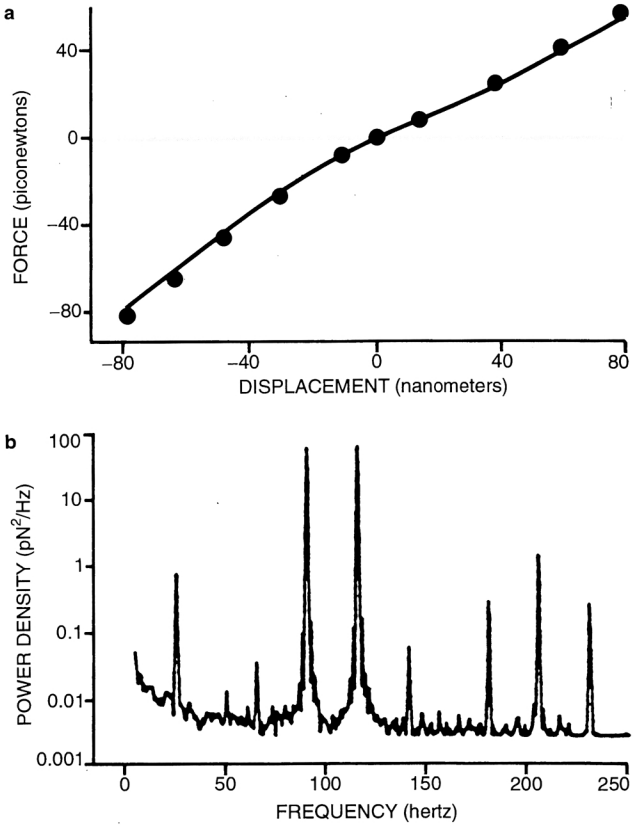
At least when it increases the tension in a tip link, movement of the link's insertion must involve the performance of mechanical work. What sort of motor might carry out this process? As noted earlier, the rigid core of each stereocilium consists of actin filaments. Such microfilaments are generally the substrate for the motion of molecules in the myosin family, one type of which mediates the contraction of muscles. Biochemical analysis discloses that hair bundles contain a smaller form termed myosin I. When observed by labeling with specific antibodies, these molecules are found to occur in appropriate positions to mediate adaptation: they lie in the stereocilia, largely in clusters near the stereociliary tips.[12] Although it seems likely that the myosin molecules congregate at the upper insertions of tip links, electron microscopy has not yet confirmed this.

Adaptation in mechanoelectrical transduction is a negative-feedback process set to maintain an approximately constant probability $p_o$ of a transduction channel's being open. The calcium ion $Ca^{2+}$, an ubiquitous intracellular messenger, serves as the feedback signal that informs the adaptation machinery of the appropriate tip-link tension. An open transduction channel admits a small quantity of $Ca^{2+}$ into the hair cell, along with a far larger amount of $K^+$. This ionic influx locally raises the intracellular $Ca^{2+}$ concentration near the transduction channel. A molecular $Ca^{2+}$ sensor, perhaps the protein calmodulin, is hypothesized to then bind $Ca^{2+}$ and modulate the activity of the myosin motor molecules. If the tip link's tension is high, augmented entry of $Ca^{2+}$ will "push in the clutch," allowing the tip link's insertion to slip down the stereocilium's flank. The consequent reduction in tip-link tension will then promote channel closure and a reduced $Ca^{2+}$ influx. Low tension in the tip link, on the other hand, will reduce $Ca^{2+}$ influx, activate the myosin molecules to ascend the stereocilium, and thus restore tension.[1,10]

Adaptation has been noted in the hair cells of amphibians, reptiles, and mammals, so it is likely a general feature of the mechanoelectrical transduction process.[10] In addition to maintaining sensitivity in the presence of large background stimuli, adaptation is probably necessary in setting an appropriate operating point for every hair cell. So sensitive is transduction that in the absence of adaptation, an error in stereociliary length of only 15 nm, or about 0.2%, would doom the associated transduction channel to be permanently open or closed. Adaptation fine-tunes the development of hair bundles by adjusting each transduction channel's range of sensitivity to coincide with the bundle's resting position.

## Sensitivity and nonlinearity

The hair bundle is so small and compliant that it exhibits significant Brownian motion. In fact, thermal background noise probably determines the practical limit to the sensitivity of hair cells. In an experiment with a laser differential interferometer,[13] it was found that the position of an unrestrained bundle's top fluctuates with a root-mean-square displacement of about 3 nm. However, temporal averaging of stimuli, especially periodic signals such as sounds, allows the ear to detect hair-bundle motions of 0.3 nm or less.




**Nonlinearity and its effect.** A hair bundle's stiffness varies nonlinearly with its position as a result of the opening and closing of transduction channels. When a bundle is driven by two simultaneous sinusoidal inputs, this mechanical nonlinearity in the relation between bundle displacement and restoring force (**a**) causes the ear itself to generate multiple, perceptible distortion products (shown in **b**) at frequencies other than the two used in stimulation. (Adapted from ref. 16.) **Figure 5**

Measurement of Brownian motion provides a means of estimating the hair bundle's stiffness $K_b$. Equating the bundle's mean elastic energy $K_b\langle X^2\rangle/2$ with the thermal energy $kT/2$, one can infer that this stiffness is about 350 $\mu$N/m near the bundle's resting position. The power-spectral density of fluctuations in bundle displacement displays[13] a high-frequency roll-off, characteristic of an overdamped harmonic oscillator, with a corner frequency near 450 Hz. The extensive damping of hair-bundle motion seems unfavorable because of the energy dissipation that accompanies movement of a bundle through the surrounding fluid. Many hair cells, however, among them the inner hair cells that are the principal receptors in the human cochlea, are actually driven hydrodynamically by motions of the surrounding fluid. That the bundle then oscillates together with this fluid implies that viscous damping is less of a problem than it might appear.

Mechanoelectrical transduction by means of gating springs has interesting mechanical consequences. If force applied to a bundle effects channel gating by a direct mechanical linkage, channel opening and closing should reciprocally affect the force exerted by the hair bundle. Measurement of a hair bundle's stiffness with fine glass probes confirms this reasoning. When abruptly pushed far in the positive direction, toward its tall edge, or well in the negative direction, toward its short edge, the bundle's instantaneous stiffness is nearly 1000 $\mu$N/m. Over a range of positions within a few tens of nanometers of its resting position, however, the bundle's stiffness is smaller by 30% to more than 50%. This diminution in stiffness is termed the hair bundle's gating compliance.[14]

The gating compliance is of the magnitude and spatial extent expected from the gating-spring theory.[1,14] On the basis of the model advanced above, the stiffness of the hair bundle is given by

$$K_b = K_g + K_s - \frac{NZ^2}{kT} p_o (1 - p_o)$$

in which $K_g$ is the stiffness component due to the gating springs, $K_s$ is the combined stiffness of the stereociliary pivots, and $N$ is the number of transduction elements. When the bundle is displaced far in either direction, the open probability $p_o$ approaches zero or unity and the last term essentially vanishes; the bundle's stiffness is then the sum of contributions from the gating springs and stereociliary pivots. Over the range of displacements for which channels are opening and closing, however, the final term asserts itself and the bundle's stiffness declines.

The observation of gating compliance not only lends support to the gating-spring theory but also provides information about the values of the model's parameters.[14] The data suggest that each hair bundle from the frog's sacculus contains only 40–80 transduction channels, or approximately one for each of the approximately 60 stereocilia. Each gating spring has a stiffness of about 500 $\mu$N/m, a value similar to that of a single molecule of an elastic protein. When a channel's aqueous pore opens, the molecular gate moves through a distance of roughly 4 nm; at the same time, the force in the associated gating spring declines by roughly 2 piconewtons.

## Distortion tones: Sounds that aren't there

Over the range of positions for which channels are gated, a hair bundle does not act as a Hookean spring. Instead, as the bundle's stiffness varies, there is a nonlinear relation between the external force $F_{ext}$ applied to the bundle and the ensuing displacement $X$:

$$F_{ext} = (K_g + K_s)X + C - Np_oZ$$

Here parameter $C$ embraces several constant terms. This nonlinearity may account for an interesting aspect of human hearing: the presence of phantom tones, or cochlear distortion products.

When listening to two sinusoidal tones of moderate intensity, one at frequency $f_1$ and the second at a greater frequency $f_2$, an observer may hear additional sounds of frequencies $f_1 + f_2$, $f_2 - f_1$, $2f_1 - f_2$, $2f_2 - f_1$, $3f_1 - 2f_2$, $3f_2 - 2f_1$ and so on. These phantom tones are sufficiently prominent that they have played a role in musical compositions and choral arrangements since their discovery in 1714 by the Italian violinist Giuseppe Tartini. Phantom tones arise within the cochlea. For distortion products to be observed, the two interacting stimulus tones must be presented to the same ear. Moreover, the perception of a particular distortion product may be eliminated by simultaneous presentation of a third tone, equal in frequency to the relevant phantom tone, whose amplitude and phase have been suitably adjusted. Measurements by laser interferometry show that phantom tones are actual mechanical oscillations upon the basilar membrane (the elastic partition on which the cochlear hair cells lie), produced by a nonlinearity in the cochlea.[15]

Gating compliance constitutes a mechanical non-

linearity that is a plausible source for phantom tones.[16] As a hair bundle is driven back and forth by simultaneous displacements at two frequencies, the force it exerts includes components at the various distortion-product frequencies. (See figure 5.) One may predict the magnitude and frequency of the distortion products by substituting the expression for two sinusoidal inputs into the above equation for hair-bundle force and expanding the result in a power series. The predicted pattern of distortion tones matches well the array of phantom tones observed by human listeners, supporting (though not proving) the idea that phantom tones arise from the hair bundle's mechanical nonlinearity.

## An aural amplifier

Although the basic steps of mechanoelectrical transduction by hair cells are satisfactorily understood, one major problem awaits a solution. Transduction by hair cells seems to be more effective than the processes we understand can account for; there appears to be an amplifier that augments cochlear sensitivity and thus reduces the effective threshold of auditory responses.

Three lines of evidence suggest that hair cells are not simply passive transducers but additionally serve as amplifiers of their mechanical inputs. First, a large body of physiological literature indicates that the mammalian ear is considerably more sensitive than would be expected from its structure.[17] The cochlea is inevitably a dissipative structure, for movement of its internal fluids causes energy losses due to viscous damping. The motion of the basilar membrane is nevertheless about a hundredfold greater than one would expect on the basis of most passive physical models. This observation has led to the suggestion that some structures within the cochlea supply energy to counter damping.

A second phenomenon suggestive of amplification by hair cells is that of evoked otoacoustic emission. If an ear is stimulated with an acoustical click, one or more bursts of sound emerge from the ear a few milliseconds later. These "echoes" occur far too late to represent the reflection of acoustical energy; instead, the cochlea emits sound when stimulated with a click. Continuous acoustical stimulation with one or several pure tones also evokes emissions, both at the primary frequency and at the frequencies of various distortion products.

The third indication of an active process in the cochlea is the occurrence of spontaneous otoacoustic emissions. When examined with a sensitive microphone, most human ears are found to emit sound energy continuously at one or more frequencies.[18] These sounds are not due to muscle activity, the usual source of fast biological motions: animal experiments reveal that the emissions persist after muscular paralysis or removal. The spontaneous sounds instead originate within the cochlea itself.

The site of the cochlear amplifier is almost certainly hair cells, probably of the class known as outer hair cells. These particular cells transmit little or no information directly to the brain, yet outnumber by a factor of three the inner hair cells that provide input to auditory-nerve fibers. Outer hair cells receive from the brain a copious efferent nerve supply, stimulation of which decreases the responsiveness of inner hair cells; moreover, destruction of outer hair cells reduces cochlear sensitivity, even though the inner hair cells and their innervation persist intact.[19]

Precisely how outer hair cells amplify the ear's vibrations remains uncertain. One possibility is that oscillatory forces produced by outer hair cells counter viscous drag. After isolating such a cell mechanically or by enzyme treatment, one can stimulate it by passing current across its membrane. Stimuli that depolarize the basal membrane surface of the cell cause abrupt contraction of the cell body, while hyperpolarization provokes elongation.[20] As required of a possible cochlear amplifier, responsiveness to exogenously imposed voltage changes extends to a frequency of several kilohertz.[21] In the intact ear, mechanical stimulation of the hair bundle might elicit the voltage changes that produce cellular movements. It is less clear, however, whether these voltage changes would suffice to evoke high-frequency movements. The capacitance and resistance of each hair cell's membrane constitute an electrical filter that attenuates high-frequency signals and thus reduces the drive applied to the electromechanical transducer.[21] Although this limitation argues against the proposed mechanism of mechanical amplification, it remains possible that outer hair cells *in vivo* are more responsive than the isolated cells studied to date.

Any oscillator driven by a periodic force may exhibit nonlinear behavior when its excursions become great. A peculiarity of cochlear function is that it is highly nonlinear at very low stimulus amplitudes, probably extending down to the threshold level. The ratio between basilar-membrane motion and sound pressure, for example, grows larger as the sound pressure decreases. This property implies that the greatest amplification occurs for the smallest inputs, a feature useful for enhancement of near-threshold stimuli. How the cochlear amplifier's gain is modulated with stimulus intensity is among the fascinating problems that remain to be solved.

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