INTERNATIONAL ATOMIC ENERGY AGENCY
UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION
INTERNATIONAL CENTRE FOR THEORETICAL PHYSICS
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SMR.853 - 9

ANTONIO BORSELLINO COLLEGE ON NEUROPHYSICS

(15 May - 9 June 1995)

"The Ear and Hearing"

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These are preliminary lecture notes, intended only for distribution to participants.

THE EAR AND HEARING

INTRODUCTION

The inner ear detects --- and precisely encodes the frequency content and temporal structure of --- sound pressure waves that are transmitted to us from vibrating sources in our air environs. The inner ear is technically fascinating. It can detect and report to the brain a repertoire of half a million distinct tones over a frequency range extending from about 15 Hz (cycles per second) to 20kHz. It can reliably detect sound intensities that produce a few tens of **Angstroms** of motion of the ear drum, and can measure sound intensities over a billionfold range above this remarkably low threshold. It can encode the timing of input events with such precision that we can detect a shift of the location of sound that represents a difference of a few **microseconds** of time for sound waves arriving at our ears.

The hearing sense provides us with a continuously updated sound picture of the dynamics of our immediate environment, including near and distant objects in motion out of our field of view. It provides the primary inputs for speech and language understanding, and for establishing speech production in a growing child. The complexly manipulated sounds of music are a major source of human entertainment and pleasure. Given this behavioral importance, severe hearing losses have psychological consequences that are, in general, more devastating than are those following blindness. Hearing loss is commonplace. Nearly 30,000,000 individuals in the United States require sound amplification provided by the use of a hearing aid. More than 2,000,000 individuals have severe hearing losses resulting in limited speech understanding. About 300,000 Americans are completely deaf. More than 2,000,000 Americans have incessant ringing of their ears (**tinnitus**), and that problem largely incapacitates several hundred thousand of them. Because these problems develop progressively in life, hearing losses and tinnitus are special problems of our aged population: more than half of severely afflicted individuals are older than 65 years of age. There are also special risks to hearing presented in childhood, in part because of a high susceptibility to middle ear disease (>90% incidence of persistent middle ear infections = 'otitis media') in children between the ages of 1.5 and about 4 years. Undetected, uncorrected hearing deficits in young children substantially impede the development of their language and other cognitive skills, and result in an individual with a lifelong communication handicap. About 7,000,000 school-age children in the US have speech reception-based learning disabilities. Surgical procedures designed to protect the ear from damage or to improve or recover hearing are among the most common of procedures applied in Western medicine.

In the central nervous system, brain damage and stroke in auditory, speech and language brain areas of the cerebral cortex result in debilitating deficits of speech and language understanding or production for more than 500,000 individuals in the U.S. Central nervous system-based deficits in communication abilities arising in childhood (dysphonia, stuttering, et al.) that have ties to the human auditory sense are commonplace.

In this and in the following lecture, you shall be introduced to the special sensory organ of hearing, the cochlea, and to the 'central auditory nervous system' that processes and represents its complex outputs. In sequence of discussion: The path of delivery of sound into the inner ear will be described. The devolution of sound frequencies by the specialized mechanical structures of the inner ear will be explained. Mechanisms underlying the transduction of minute sound-generated mechanical signals into receptor potentials and coded action potential volleys by the receptor cells and ganglion cells of the inner ear will be reviewed. Principal origins of deafness arising from ear trauma or ear pathology will be briefly considered. Some modes of treatment designed to reverse or to ameliorate hearing losses or deafness will be discussed in terms of inner ear physiology and anatomy. Special features of the central auditory nervous system that relate to our abilities to locate environmental sounds and to understand complex signals like speech will be described. Some principles of organization of the auditory forebrain will be summarized. Strategies by which central hearing pathways are functionally assessed in humans will be discussed, with some consideration of the functional organization of this great central sensory system. Finally, some of the common consequences of central auditory nervous system injury will be briefly described.

SOUND TRANSMISSION INTO THE INNER EAR

Sound waves are pressure waves that are transmitted in the gaseous medium (air) in which we humans all swim. These pressure waves are complexly filtered by our external ears and conveyed through the external ear canal (**external meatus**), where they set the ear drum (**tympanic membrane**) located at the terminus of the external meatus into motion (see Figure 1). Three small bones (**ossicles**) situated in an air cavity behind the ear drum are coupled to the center of the drum; they follow eardrum motion, and by their arrangement, amplify

sound pressures as they deliver sound into the detection/analysis/transduction part of the inner ear, the **cochlea.**

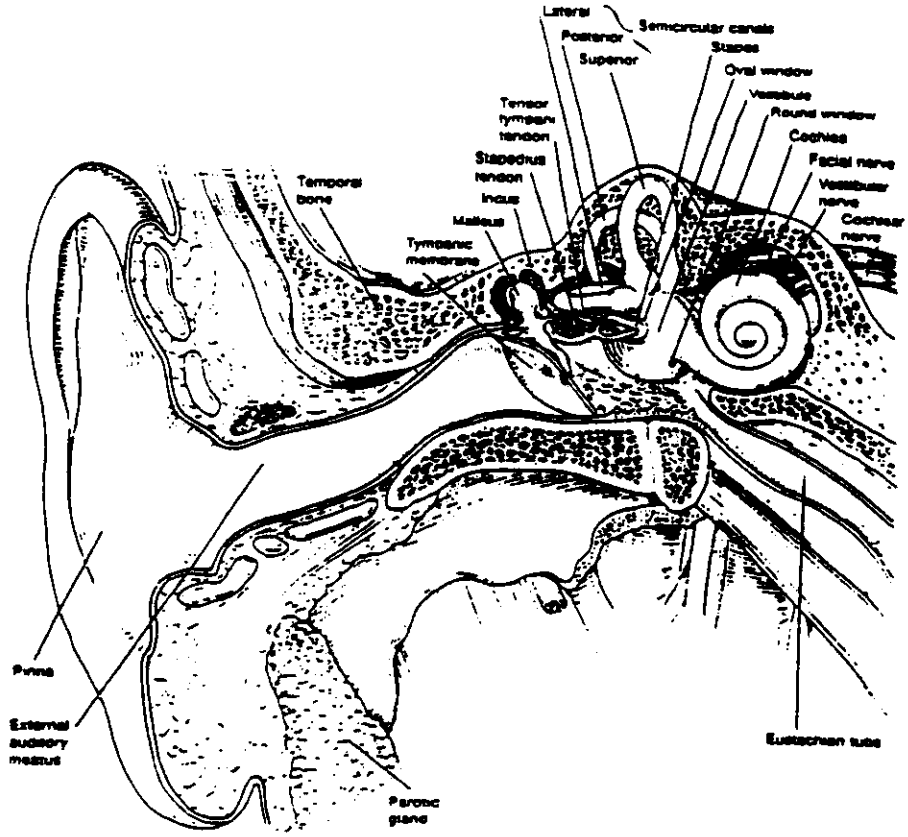

Figure 1. *Cutaway drawing of the external, middle and inner ear.*

Our external ears (**pinnae**) are antennae that reflect sound into our ear canals. The pinnae are motile in most mammals, in that case serving as actively controlled directional antennae. In both man and animals, the pinna surfaces reflect sounds differently when they arises from different locations around our heads. These differences in pinna reflections provide one of the fundamental sets of cues decoded by the brain for locating the origins of sound sources in our acoustic environment.

The **external auditory meatus** is about 2 centimeters long in humans. This long tube has a resonance that favors the transmission of sound energy in the range of 1000-2000 Hz, a critical frequency range for speech reception. The ear canal maintains the delicately mechanically poised tympanic membrane at a stable, warm temperature. Perhaps most importantly, it provides protection for this fragile membrane.

The translucent **tympanic membrane** is about 40 microns in thickness and about 9000 microns (9 mm) in diameter in the average adult human. It is set into motion by the succession of soundwave rarefraction-condensation pressure events. The envelope of ear drum motion includes all of the frequency components of incident sound.

The ossicles of the middle ear are a chain of three small jointed bones coupled at one end to the tympanic membrane, and at the other to a membrane on the inner ear chamber, called the **oval window** (see Figure 2). The largest ossicle, the **malleus**, terminates on the ear drum and couples to the second bone in the chain, the **incus**. The incus links to the smallest bone, the **stapes**, which is set in motion by tympanic membrane motion like a piston, to pump sound energy into the cochlea. This arrangement actually results in a roughly >100-fold amplification of sound pressure as sound passes across the middle ear. This gain almost exactly compensates for a 100-fold loss of sound pressure as it passes across the physical air-water interface, i. e., from air, into the fluid-filled inner ear. The gain of the middle ear arises from two affects:

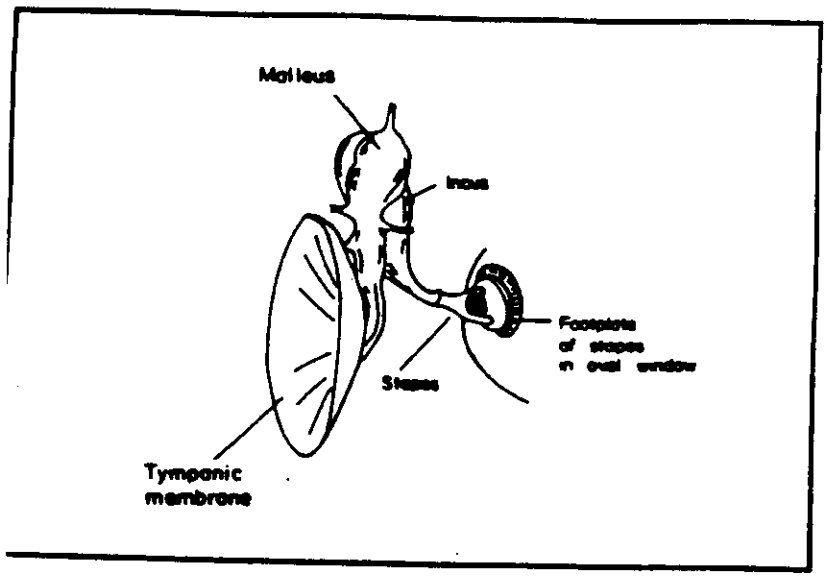

Figure 2. *Middle ear ossicles, coupling the sound-vibrating tympanic membrane and to the oval window membrane of the cochlea. Size differences between the eardrum and oval window and a lever gain of the ossicles results in a many-fold amplification of sound pressuresacross the middle ear.*

First, there is a lever ratio gain across the ossicular chain. Second, the tympanic membrane is many times larger in area than the oval window (Figure 2). The force/unit area (the pressure) is therefore magnified proportionally at the oval window.

The tendons of two small muscles, the **tensor tympani** and **stapedius**, insert on the malleus and stapes, respectively. These muscles are activated by intense sound (eg, as can be generated by a dental drill). Their activation results in a partial discoupling of the ossicular chain, and hence serve a protective function for the inner ear. However, because a muscle response involves a nervous system loop that takes tens of milliseconds to complete, they can provide no protection for damaging acoustic stimuli of sudden onset --- which, alas, are commonplace in modern society. With the exception of these highly nonlinear effects of the 'middle ear muscles' at high sound intensities, the translation of sound across the tympani membrane and ossicles is surprisingly linear, that is, is achieved with remarkably little distortion of the incident sound signal.

Pressure in the air-filled middle ear is equalized with that in the mouth by communication with the nasopharynx via a narrow, 3.5 centimeter long passage, the **eustachian tube** (see Figure 1). This middle ear drainpipe is sometimes blocked by a swelling of the tissues of the nasopharynx (e. g., with a head cold or allergies). The passage can also collapse with rapid changes in atmospheric pressure. The resultant higher pressure in the middle ear results in an unbalanced pressure environment for the tympanic membrane, and in a significant temporary hearing loss. The attendant stuffiness and hearing loss is overcome by again equalizing middle pressure with atmospheric pressure, induced by repositioning the mandible in deglutition or yawning, or by a successful Valsalva maneuver, which produces positive pressure in the nasopharynx that forces the eustachian tube to reopen.

CONDUCTIVE HEARING LOSSES

Anything that interferes with the transmission of sound to the cochlea results in a **conductive hearing loss.** Common causes of conductive hearing losses include blockage of the external ear canal (e.g., with impacted ear 'wax' = 'cerumen' or with a foreign body); perforation of the tympanic membrane; physical damage to, or disarticulation of the ossicles; fluid in the middle ear impeding ossicular motion often linked to an infection-based blockage of the eustachian tube and an active infection in the middle ear cavity; abnormal tissue growth in the middle ear (e.g., as in epithelial cell tumors called cholesteotomas, or that develops as a reaction to persistent middle ear infections); abnormal bony growth originating from the temporal bone impeding the motion of the stapes (e. g., as occurs in a disease called otosclerosis that affects about 1 in 1000 of us); among others. Severe conductive hearing losses result in a >100-fold change in hearing sensitivity, reflecting the loss of the amplification of sound energy provided by the ear drum and middle ear.

Conductive hearing losses occur in every individual in life. They are easily identified. The causes of conductive hearing losses can often be visualized directly by examination of the ear canal or translucent tympanic membrane. Conductive hearing losses are easily confirmed in hearing tests, and by measurements of eardrum and ossicle mobility and middle ear pressures called 'impedance tests'. Hearing sensitivity is evaluated behaviorally by contrasting hearing using the normal stimulation route (*air*), with hearing measured

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by coupling sound stimuli directly to the skull. With a conductive hearing loss, the former hearing test of course reveals a loss. At the same time, 'bone-conduction hearing', in which the delivery of sound to the cochlea bypasses the normal sound conduction pathway through the external and middle ears, remains normal.

Conductive hearing losses are usually correctable. Otologic surgeons have devised numerous procedures that are effective for reversing most conductive hearing losses. Even the most severe losses can be treated, for example, by inert prosthetic replacement of the ear drum and/or ossicles. The behavioral impacts of conductive hearing losses can also be reliably ameliorated by application of sound amplification hearing aids, as purely conductive losses are of limited severity and do not affect the sound-resolving capacities of the cochlea.

BASIC COCHLEAR ANATOMY

Before we consider how the cochlea encodes sound frequency content with such exquisite fidelity and sensitivity, it is useful to remind ourselves about basic anatomical features of the inner ear. A section through the middle of the snail-formed cochlea is shown in Figure 3. The cochlea is comprised of two fluid filled chambers (the **scala tympani** and **scala tympani**) that are coiled atop one another in a 2.75 turn spiral. A long thin, flexible membrane, the **basilar membrane**, separates these two spiralform chambers. The sensory organ, the **organ of Corti** rides upon this membrane. Together, they comprise the 'cochlear partition'. It is the basilar membrane, and thereby the cochlear partition, that is set into motion by sound. In turn, resonant mechanical effects originating in the organ of Corti (as we shall see below) dramatically alter the mechanical behavior of the basilar membrane by pumping mechanical energy back into it.

As described above, the stapes terminating on the oval window at the base of the scala vestibuli is the primary natural mode of delivery of sound energy into the cochlea. A second pressure-relieving membrane, the **round window**, is situated at the base of the scala tympani. The spiralling fluid channels of the cochlea, its scalae, are reduced in diameter as one progresses up the 3 - 3.5 cm long cochlear spiral. However, the basilar membrane - cochlear partition suspended between these spiraling fluid pipes actually progressively widens by about 4X as it ascends in the spiral.

Above the organ of Corti (see Figure 4), a one-cell-thick membrane (**Reissner's membrane**) walls off a special fluid compartment for the transducing surfaces of the receptor cells on the upper surface of this sensory epithelium. This fluid compartment, the **cochlear duct** or 'scala media' is walled off on all sides by the tightest of tight junctions in the human body. This is a necessity, because a special, high concentration potassium ion solution is created in this fluid compartment. The cochlear duct also has special mechanisms that precisely regulate osmolar pressures within it. The requirements for precise osmolar regulation of this fluid space, which also extends into the vestibular apparatus, are without parallel in the human body. It is believed to be achieved by special osmolality-sensitive glyco-protein secreting cells in the **endolymphatic sac**. Without it, the extraordinarily mechanically precise operations of the organ of Corti (and of the sensory structures in the vestibular apparatus) would not be possible.
The afferent fibers innervating the organ of Corti exit medially into the bony treestalk of the cochlear spiral (the **modiolus**), where their cell soma form a dense **spiral ganglion**.

MICROANATOMY OF THE ORGAN OF CORTI

A cross section of the organ of Corti is shown in Figure 5. A surface view of the special sensory cells of the organ, the hair cells, are shown at two levels of magnification in Figure 6. There are three rows of **outer hair cells** (OHCs) and a single row of **inner hair cells** (IHCs). There are altogether about 12,000 OHCs and about 3500 IHCs innervated by the axons of about 30,000 **spiral ganglion neurons** in each cochlea in man.

The tops of the cochlear hair cells are embedded in and form, with the tops of special supporting cells, a continuous stiff plate, the **reticular lamina**. The reticular lamina is supported by rigid microtubule-filled supporting-cell pillars. Some of these stiff rods form the distinctive 'arches of Corti' (triangular-shaped strutssee in Figure 4). There is one of these supporting arches for each inner hair cell. Other supporting cell rods are located between and just outside the three rows of outer hair cells. These supporting pillars of the organ of Corti should be regarded as skeletal struts. This structural arrangement insures that the upper surfaces of hair cells, at which mechanical-electrical transduction occurs, flawlessly track the movement of the vibrating basilar membrane.

Each hair cell has a staircase cluster of stereocilia (50-100 per hair cell in humans) that projects from the reticular lamina into the cochlear duct (Figure 4). The longest stereocilia of the rod-shaped outer hair cells are embedded in a membranous structure overlying them, the **tectorial membrane**. By contrast, the stereocilia of the flask-shaped inner hair cells are freestanding. Inner hair cell stereocilia are arrayed in a straight or slightly

curved staircase. Stereocilia of both OHCs and IHCs increase progressively in length from the base to the apex of the organ of Corti.

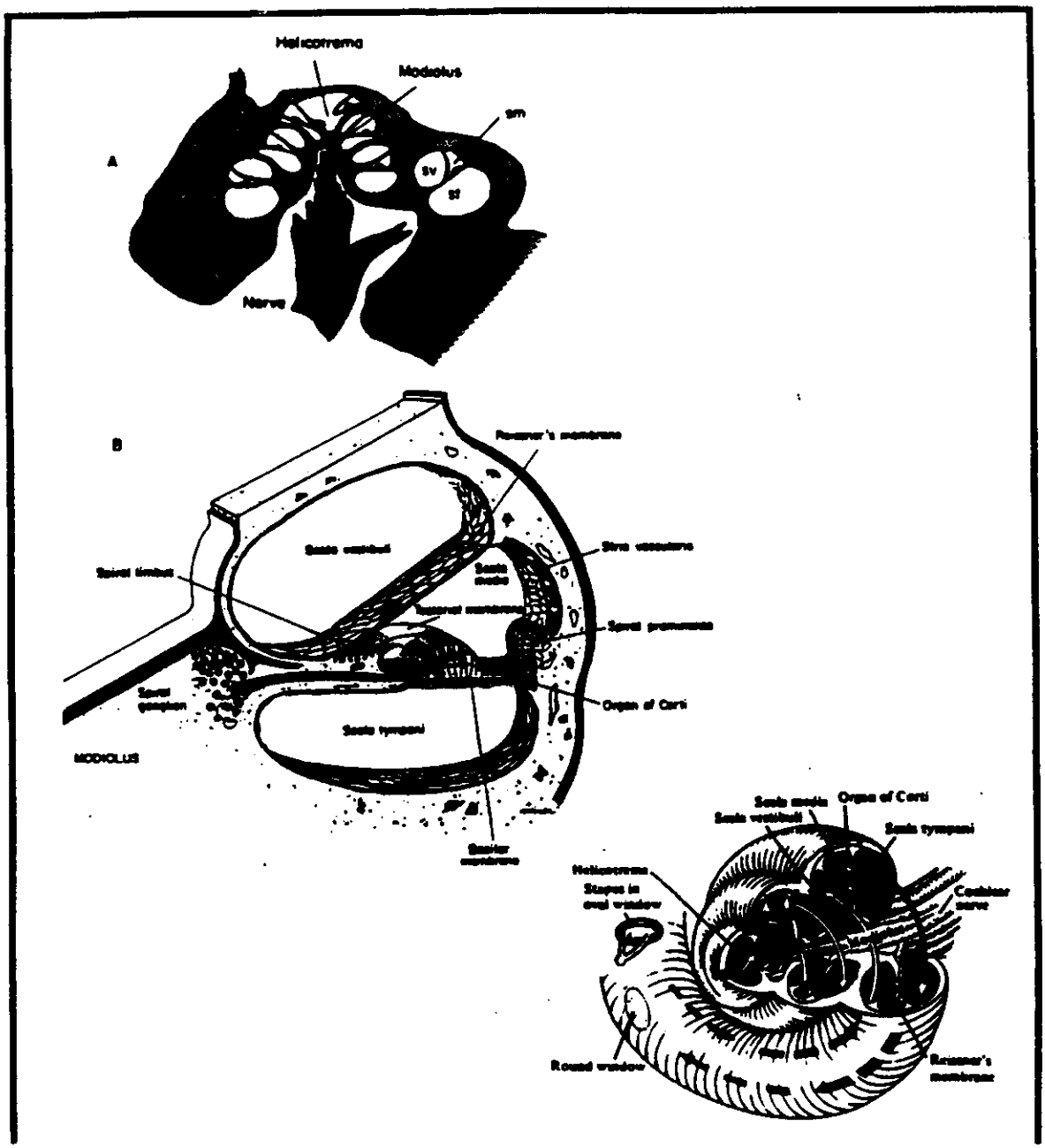

Figure 3. *A crossection through the center of the cochlear spiral buried in the petrous temporal bone is shown at the left (TOP). Bone is shaded. ST=scala tympani; SV = scala vestibuli; SM = scala media (cochlear duct). These three fluid-filled tubes are coiled together through 2.75 turns in a tight spiral (see cutaway drawing at the right). A magnified view of a short section of the spiral is shown at the bottom left. Note the organ of Corti riding on the basilar membrane, which together form the 'cochlear partition' that separates the spiralform cochlear scalae.*

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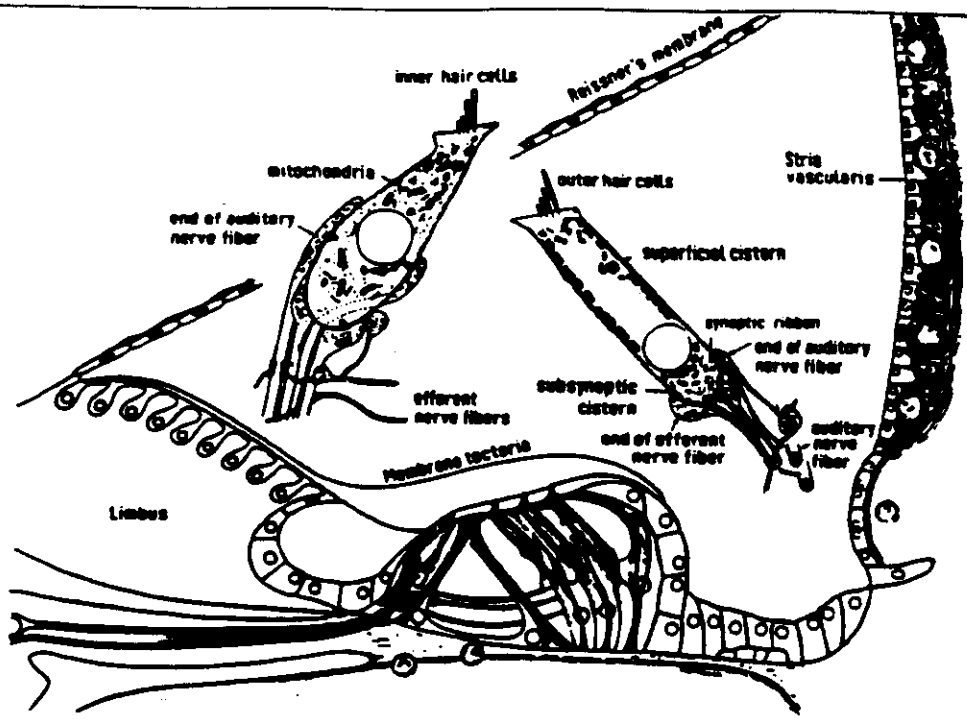

Figure 4. *Magnified view of a cross-section of the organ of Corti, with some microscopic details of outer and inner hair cells and their innervation. Note the staircase rows of stereocilia projecting from the tops of hair cells.*

Hair cell stereocilia are comprised principally of crosslinked, vertically-oriented actin filaments. Small filaments also extend between the tips of hairs situated adjacent to one another in different rows (see Figure 7). Each stereocilia narrows at its base, to form a "root" that projects down into the stiff cuticular plate at the top of the hair cell. Myosin is among the proteins identified in the zone of root insertion at the top of the hair cell. Stereocilia are stiff members; when deflected microsurgically they bend as a unit until, under relatively high forces, they snap. Their stiffness is 'reactive', that is, it changes dynamically when the stereocilia are bent. This reactive stiffness is a key to their active-resonance properties.

Both outer hair cells and inner hair cells have a number of small **afferent synaptic terminals** in their basal aspects. Terminal bars are seen in hair cells opposite these afferent boutons; presynaptic membrane specializations are seen; synaptic vesicles are actually seen only rarely. All physiological evidence is consistent with these synapses operating as conventional chemical synapses: Glutamate is the probable transmitter. Outer hair cells are marked by prominent **efferent synaptic terminals**, which dwarf afferent endings and cover a significant percentage of their bases. The morphologically more modest efferent endings on inner hair cells terminate presynaptically on ganglion cell afferent fibers. There are unusual smooth endoplasmic reticulum channels that encircle the hair cells and communicate with the Golgi apparatus and with other channels at the top of the hair cell. In outer hair cells, these channels are specialized subsynaptically beneath efferent terminals.

About 95% of the fibers of the spiral ganglion neurons terminate with a single bouton upon a single inner hair cell; each inner hair cell is synaptically coupled to the terminals of 8-16 spiral ganglion cells. About 5% of acoustic nerve fibers end upon the more numerous outer hair cells. A population of about a thousand efferent fibers arising in the brain stem project to the inner ear. About 500 of them terminate roughly directly on outer hair cells. The other 500 terminate of the afferent endings of inner hair cells.

COCHLEAR MECHANICS; MECHANICAL FREQUENCY REPRESENTATION

The great German physicist Georg Ohm was the first to argue (in 1843) that the cochlea sorts out and separately represents the different frequency components of complex sounds. He understood that our ability to simultaneously hear different sound frequencies indicates that the ear performs a kind of frequency analysis (to the physicist Ohm, a 'Fourier analysis') by which the energies at different frequencies are largely independently represented. His arguments provided much of the basis for the development of the **resonance theory of hearing**, introduced by the great 19th century physicist Herman von Helmholtz, in 1863. Helmholtz

postulated that a spatial resolution of frequency was produced by a series of resonators in the organ of Corti analogous to the strings of a piano, each of which selectively responds with a 'sympathetic vibration' at its natural resonant frequency. Lowest frequencies must be represented in the apex of the spiral, where the organ of Corti is paradoxically the widest (and resonating 'strings' can be the longest).

Helmholtz found support for his resonance theory of hearing in a brilliant set of experiments demonstrating the spectral resolving power of the cochlea. However, it became increasingly apparent over the ensuing decades that there was no obvious anatomical or physical basis for the existence of string-like resonators of the dimensions and under the tensions required for representing the wide frequency range of hearing.

Our understanding of the physical resolution of sound frequency along the length of the cochlear spiral was greatly advanced by a remarkable series of experiments conducted by George von Bekesy in the 1930s and 1940s, for which Bekesy was awarded the Nobel Prize. Bekesy demonstrated that a sound pressure wave introduced into the fluids of the cochlea gives rise to a **mechanical traveling wave** on the basilar membrane carrying the organ of Corti. This wave passes from the base of the cochlear spiral to its apex in humans in about 7 msec. For sound of any given frequency, it grows in amplitude as it moves toward the apex, reaching a maximum at a fixed position along the partition, and declining in amplitude still further toward the apex. Bekesy demonstrated that **each frequency component of sound generates maximal vibration at a given location along the basilar membrane,** with high frequencies thus resolved toward the base of the cochlear spiral, and low frequencies toward its apex.

How does this spatial mechanical resolution of different sound frequencies arise? Bekesy demonstrated that the basilar membrane is not actually under tension, as would be required for Helmholtz' 'string resonators'. On the other hand, **there is a continuous gradient in the STIFFNESS of the basilar membrane from the base to the apex of the spiral.** The resonant frequency is therefore continuously changing along the spiral. Highest frequencies generate maximum amplitudes of vibration at restricted locations within the narrower, stiffer basilar membrane sector at the cochlear base. Lowest frequencies generate maximum amplitudes of vibration at the wider and more compliant basilar membrane sector in the cochlear apex.

Thus, Bekesy confirmed Helmholtz' postulate that there must be an array of resonators spanning the frequency range of hearing and arrayed longitudinally in the cochlear spiral. He demonstrated that the resonator is actually continously varying, and does not have discrete, taut resonating elements, as Helmholtz believed. With sound stimulation, a traveling wave moves down this continously varying resonator because movement is initiated in successively more compliant basilar membrane sectors at successively later instances in time.

Bekesy was actually able to directly measure the compliance of the basilar membrane and the resolution of frequencies down its length in fresh human cadaver material. It took hearing scientists more than 30 years to repeat the most crucial of his experiments in living animals. Using ultrasensitive laser interferometry and Mossbauer radiation measurement techniques, contemporary scientists have been able to measure basilar membrane motion to near-threshold levels. At threshold, the hair cells are excited by vertical motions of the basilar membrane of approximately 5-10 Angstroms. There is a remarkably sharp spatial resolution of frequency — greater than 100 dB [i.e., a 100,000 change in effective sound pressures]/octave [i.e., with a doubling of the frequency] — in any resonating region of the basilar membrane. In the main, these contemporary studies have supported Bekesy's 'travelling wave theory of hearing', but they also added an important correction to it. **Basilar membrane tuning is far sharper in living cochleas than in dead ones** (Figure 4). **The sharpness of resonance tuning contributed by the basilar membrane is dramatically SHARPENED by ACTIVE resonators in the organ of Corti.** We believe that this active mechanical resonance is generated by the stereocilia of cochlear hair cells (see below).
Thus, Bekesy defined the location and nature of the basic resonance that underlies the mechanical devolution and representation of sound frequency in the inner ear. Upon receiving that basic mechanical signal, the living sensory cells of the organ of Corti, its hair cells, themselves greatly sharpen it mechanically, to create very narrowly 'frequency-tuned' resonators, not so very different from those described hypothetically by Helmholtz more than a century ago.

GENERATION OF RECEPTOR POTENTIALS IN HAIR CELLS

How are these mechanical events transduced to create a neural representation of sound frequency and timing?

The motion of the cochlear basilar partition leads directly to hair cell excitation. The cochlear hair cells have been termed 'directionally sensitive displacement detectors'. **The adequate stimulus for hair cell excitation is the bending of their stereocilia in a preferred (outward) direction.** Hair cells at any given position along the cochlear spiral move vertically, tracking the motion of the basilar membrane with high

fidelity. With this up-and-down motion of a cochlear hair cell, its stereocilia are deflected in an outward-then-inward cycle, because the basilar membrane and the tectorial membrane have different points of attachment (pivot points) on the modiolus. Thus, as illustrated in Figure 6, hair cell stereocilia are bent away from the central core of the spiral (the preferred or depolarizing direction) with an upward movement of the basilar membrane. With a

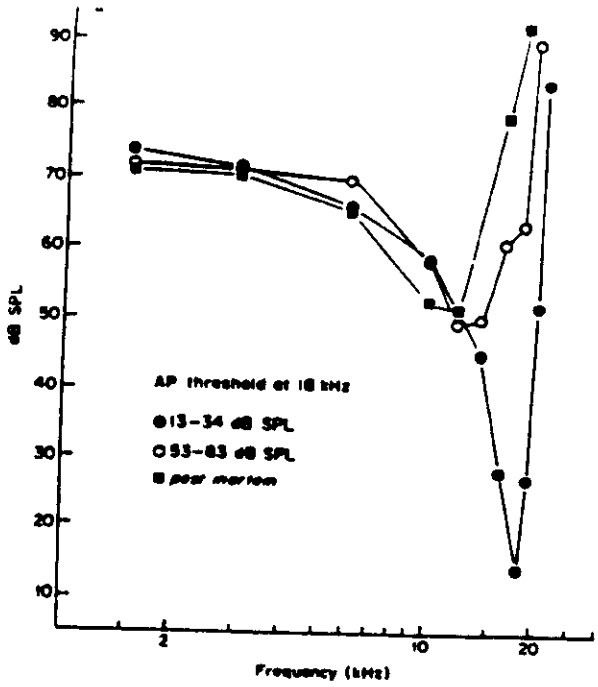

Figure 5. *Sensitivity for basilar membrane motion or for evoking a physiological response for a cochlear site resonating most strongly at 18kHz in a normal animal (filled circles), and after anoxia (open circles) and death (open squares). To derive these functions, the sound intensity (ordinate) required to evoke a constant-magnitude displacement or a constant-magnitude neural response is defined as a function of sound frequency (abscissa). In this typical 'cochlear tuning curve', note that the shallow mechanical peak contributed by the basilar membrane resonance evident in the deteriorated or dead ear is SHARPENED greatly around 18kHz by energy-dependent biological processes in the intact, healthy ear. This sharpening of mechanical resonance is attributable to an active process in the stereocilia of cochlear hair cells.*

downward movement, they are bent toward the central core of the cochlea (the non-preferred or hyperpolarizing direction). It might be noted that contrary to the drawing in Figure 6, the actual excursion of the hair cell stereocilia at highest sound pressure levels is probably of the order of a tenth of a micron -- which constitutes only a small fraction of the length of the longest stereocilia. The longest stereocilia of outer hair cells are embedded in the tectorial membrane but the inner hair cell stereocilia are freestanding. Inner hair cells are excited by transverse fluid motion in the fluid space beneath the tectorial membrane. By this arrangement, OHCs are displacement sensitive while IHCs are velocity sensitive.

The tops of hair cells and the rest of their surfaces are peculiar in that they have completely different

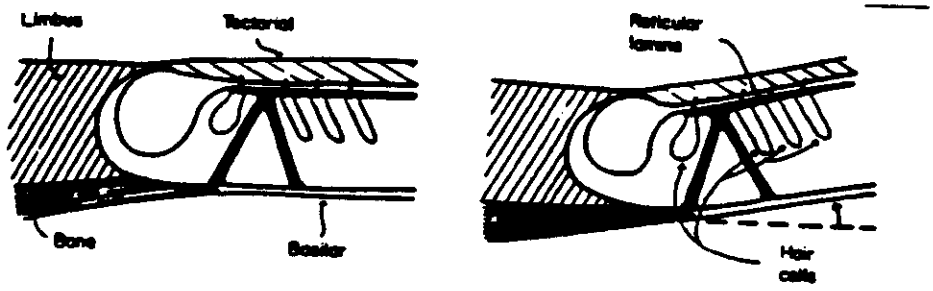

Figure 6. *The adequate stimulus for hair cell excitation is the bending of stereocilia in their 'preferred' direction. This occurs when the basilar membrane is elevated by the mechanical traveling wave, because of a different pivot point for the basilar membrane and tectorial membrane.*

extracellular ionic environments. All but the upper surfaces of cochlear hair cells are in a fluid similar in composition to cerebrospinal fluid (ionically like extracellular fluid everywhere), called **perilymph**. Perilymph also fills the scala tympani and scala vestibuli. The special fluid filling the cochlear duct, called **endolymph**, baths only the upper hair-bearing surfaces of cochlea hair cells. It is marked by an unusually high ionic concentration of potassium (about 140 mEq/L) and a very low concentration of sodium (about 5 mEq/L). As noted above, the endolymph is sealed off from other cochlear structures by tight junctions in Reissner's membrane and across the top of the reticular lamina. These are believed to be the most tightly sealed barriers to the movement of small ions in the body.

The unusual ionic constituency of the endolymph is actively maintained by a specialized secretory structure lining the outer wall of the scala media, the **stria vascularis**. The stria vascularis maintains not only the peculiar ionic constituency of the endolymph by pumping K+ into it, but also thereby, generates a +80 mV potential, the endolymphatic potential. The resting potentials of hair cells are of the order of -60 to -80 mV; thus, there is an remarkable 150 mV potential across the transducing surfaces of cochlear hair cells. By this arrangement, the cochlea is provided with an biological amplifier that increases the amplitude of receptor potential signals.

Before describing how a receptor potential arises in cochlear hair cells, it is of interest to briefly review several of their special accomplishments. First, as noted earlier, hair cells are incredibly sensitive mechanoreceptors, responding at threshold to vertical basilar membrane displacements of a few Angstroms. Second, there can be almost no energy loss in the inner ear; to account for the tuned responses of inner hair cells, virtually all sound energy entering the cochlea must be focussed to them. Third, the receptor potential has an alternating component that tracks the frequency of the basilar membrane with high fidelity all across the normal frequency range of hearing. The temporal response characteristics of this transduction process are unparalleled. How is this remarkable sensitivity and temporal fidelity accomplished?

In a brilliant series of experiments conducted over the past decade, Dr. A. James Hudspeth and colleagues demonstrated that the transduction channels are located at the tops of hair cell stereocilia; that the transduction channel number is approximately equal to the number of stereocilia; and that the receptor potential generated by channel opening is directly proportion to the numbers of deflected stereocilia. Work by Hudspeth and by other investigators have shown that the fine filaments between stereocilia of different rows are tied directly to the transduction channels: **Stretch of inter-stereocilia filaments results in a direct mechanical deformation = channel opening (Figure 7).** The filament is elastic, so that the channel closes with high fidelity as the stereocilia are bent back in the opposite direction in a normal cycle of motion. [This notion is sometimes called the 'trap-door hypothesis' of hair cell transduction.]

Hudspeth has actually measured the mechanical force it takes to open a 'trap door': 100 femtoNewtons. That's 10^{-14} Newtons! Other features of these transduction channels have been studied electrically, by recording intracellularly from hair cells *in vivo*, and by patch clamping isolated hair cells. *In vivo* recording experiments have revealed that the receptor potential tracks a sinusoidal (tonal) sound stimulus by a high-fidelity, alternating oscillation of the receptor potential (the **AC receptor potential**) at frequencies all across the normal range of hearing (see Figure 8). A **DC receptor potential** component is also present. It arises from a filtering of the AC response by the resistance/capacitance properties of the hair cell membrane, and is proportionally larger at proportionately higher stimulus frequencies. Impedance changes across the tops of hair cells track these intracellularly recorded receptor potentials. Both AC and DC responses are sharply tuned, i.e., respond only over a very narrow range of frequencies for any one hair cell except at high stimulus intensities. Indeed, this tuning precisely parallels measured vertical basilar membrane motions at corresponding resonance frequency locations. The tuned responses of OHCs and IHCs are almost identical.

Isolated hair cells from the hearing and vestibular organs in amphibians, turtles and lizards, and from the lateral line organs of toads and fishes have been extensively studied. These preparations re used because they allow the *in vitro* study of hair cell properties and/or because they provide special advantages of access or mechanical stability or stimulus presentation or size. They have directly confirmed the exquisite stereocilia displacement sensitivity of hair cells. Receptor potential responses have been shown to be highly directionally selective in all of these preparations (and in others). They have revealed that the channels on the tips of hair cells are nonspecific for small cations, with the main current borne by K+. A calcium-dependent K+ channel on the other surfaces of the hair cell accounts for the repolarizing phase of receptor potential generation.

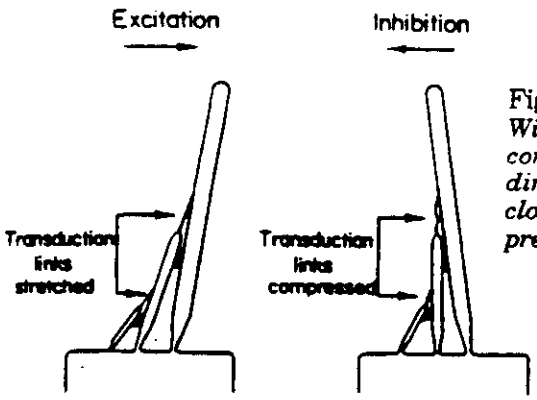

Figure 7. *Illustrating the 'trap-door' hypothesis' of hair cell transduction. With bending of the stereocilia in the preferred direction, filamentous links connecting the tops of stereocilia on different staircase rows are stretched, directly opening transduction channels. These filaments are springs that close more tightly when the stereociliar bundle is bent in the opposite, non-preferred direction, as at the right.*

MECHANISMS UNDERLYING MECHANICAL SHARPENING BY THE ORGAN OF CORTI

How are movement patterns in the organ of Corti sharpened by active biological processes in the cochlear hair cells? The exact basis of mechanical sharpening by the hair cells of the organ of Corti is unknown. It has now been demonstrated that: a) these mechanical effects are dependent upon intact hair cells; b) they involve active processes, i.e., are dependent upon normal hair cell oxidative metabolism; c) stereocilia have a reactive stiffness that is consistent with their operation as resonators; d) hypothetical stereocilia resonators vary systematically in their lengths, with the shortest and longest stereocilia located in the extreme basal and apical sectors of the cochlea, respectively; e) abnormal cochleae can spontaneously generate relatively loud tonal sounds (called **spontaneous acoustic emissions**), that manifest the presence of highly tuned oscillators in the inner ear; f) studies in turtles and lizards have shown that hair cells can resonate electrically, although the relationship between this electrical resonance and mechanical resonance is incompletely understood. Actin is a participant in mechanical effects in a number of other settings in cells, and the actin-loaded stereocilia are clearly implicated in this remarkable mechanical process.

EFFERENT CONTROL OF THE ORGAN OF CORTI

The stereocilia are not the only active mechanical machine in the organ of Corti. The outer hair cells are themselves contractile. Outer hair cells are constructed like little muscles. Their walls are lined with open Ca++ - loaded channels like the endoplasmic reticulum of muscles, and these channels are related to contractile proteins akin to those in smooth muscles. The cochlear efferents that terminate directly on these hair cells are coupled to these channels, which are specialized under efferent terminals. **When cochlear efferents terminating on outer hair cells are activated, outer hair cells CONTRACT.** This contraction also results in an inward movement of the entire stereociliar bundle, which lowers the tectorial membrane. Thus, under efferent control, the tectorial membrane is moved up and down like an elevator, altering the fluidic environment of inner hair cell stereocilia. While a description of these mechanical effects are too difficult to review in this forum, suffice it to say that an increase in cochlear efferent activity results in mechanical damping that attenuates the receptor potentials generated in the inner ear. Thus, central nervous system mechanisms establish a feedback control of inputs from this elaborate sensory organ, expressed in this elaborate, indirect mechanical form. Isn't nature wonderful! Studies indicate that this control operates in real life to suppress the cochlear representation of acoustic noise, while selectively conserving representations of novel or otherwise-behaviorally-important stimuli.

THE HAIR CELL-GANGLION CELL SYNAPSE; CODED REPRESENTATIONS OF SOUND BY AUDITORY GANGLION CELLS.

We have noted earlier that: a) inner hair cells have a sharply tuned receptor potential response, with responses closely paralleling the motion of the basilar membrane at the point at which they are located, but with an

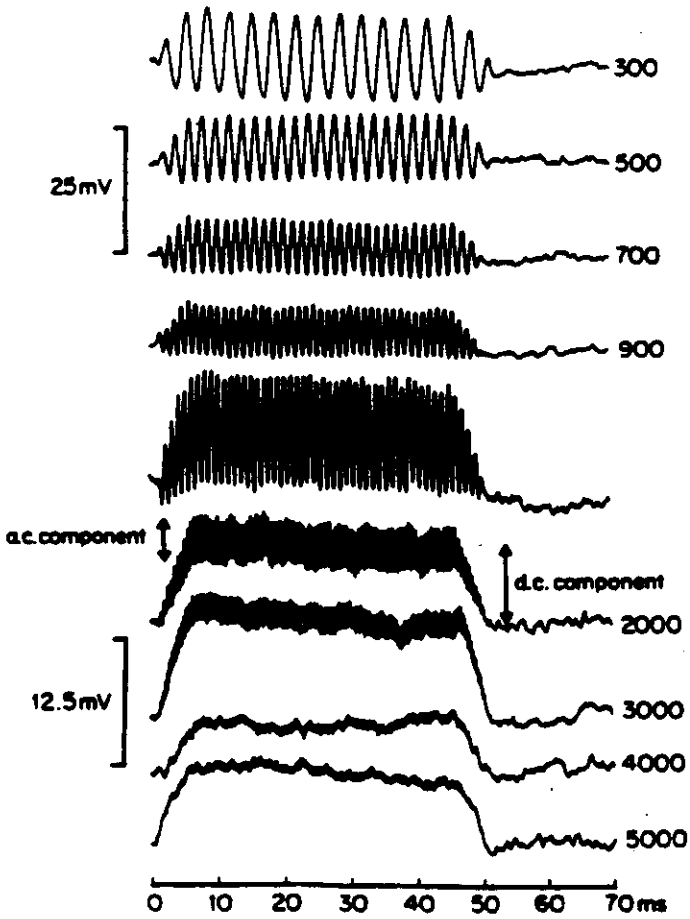

Figure 8. *Receptor potentials recorded from an inner hair cells excited by tonal stimuli ranging from 300 Hz to 5000 Hz. Note that the AC (alternating current) receptor potential dominates at low sound frequencies, while a DC (direct current, rectified) receptor potential is proportionately larger at higher sound frequencies. Also note the beautiful sinusoidal tracking of the motion of the basilar membrane by the AC receptor potential response.*

increasing DC potential component and decreasing AC component as stimulus frequency rises; and that b) most ganglion cells receive their input from a single inner hair cell. The hair cell - spiral ganglion cell synapse is morphologically unimpressive but functionally spectacular. Best evidence indicates that it is a conventional chemical synapse. It is marked by a high level of spontaneous activity during periods of quiet. With sound excitation, neuronal discharges very faithfully track hair cell potential changes. In fact if one examines: a) motion at a given point along the basilar membrane, b) receptor potential isopotential functions in the depolarizing direction, and c) discharges of spiral ganglion cells, THEY ARE VIRTUALLY IDENTICAL. Despite its modest appearance, **the representation of receptor potential fluctations in time by the trans-synaptic discharges of auditory nerve fibers are as precise as across any synapse in humans.**

At low frequencies of stimulation, where the AC component of the receptor potential is large, all or nearly all of the discharges of the ganglion cell occur in the best (depolarizing) half-cycle of the stimulus. Such action potential response patterns in auditory ganglion cells are therefore said to be 'rectified'. As sound frequency increases, the AC receptor potential component declines, and the discharges represent the stimulus frequency with correspondingly declining fidelity. However, these temporal details of sound stimuli still well represented at stimulus frequencies above 3000 Hz in humans.

Auditory ganglion cells have maximum firing rates of about 250 discharges per second. Their response to low frequency tonal stimulation follows a Poisson distribution: once they have discharged, there is a random probability of discharge on any subsequent stimulus cycle. No single fiber can represent a sound frequency by the timing of its discharges. However, because responses occur only during the excitatory half cycle up to frequencies of several KHz, **populations** of neurons can <u>together</u> very faithfully represent sound frequencies by their collective discharges (see Figure 9). The notion that sound frequency might be represented temporally by

populations of auditory nerve fibers is called the **Volley Theory** of frequency encoding. This hypothesis was originally stated as a 'telephone theory' of hearing by the great physicist Lord Rutherford in the late 19th Century, and with physiological evidence, later formally reformulated by an American scientist, E. Glenn Wever, in the 1930's.

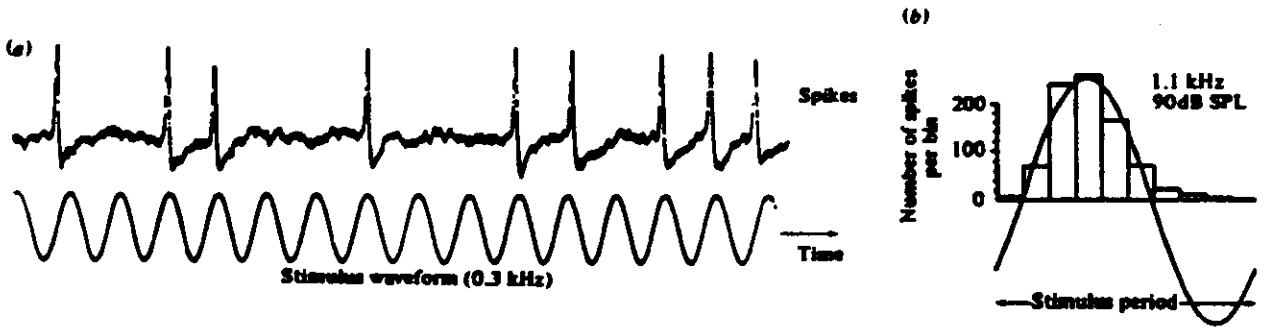

Figure 9. *Temporal encoding of sound frequency by auditory nerve fibers. When a neuron is stimulated by a tonal stimulus component, it responds only during the excitatory half cycle (corresponding to the upward half cycle of the basilar membrane, over which hair cells are depolarized) of the stimulus, as is shown for a raw spike trace at the top. The distribution of this typical neuron's responses as a function of stimulus cycle phase is shown at the lower left. Nearly all of its discharges fall in the best half cycle, and if averaged over many cycles, faithfully represent it temporally. Similarly, any small population of excited afferents (8-15 innervate every inner hair cell) will also faithfully temporally represent stimulus periodicity.*

Sound frequency is also encoded by its site of representation along the cochlear spiral: As acknowledged in the **Place Theory** of frequency encoding, originally stated by von Helmholtz, any given frequency is optimally represented by activity at a given location along the cochlear spiral.

In actuality, both the cochlear 'place' and precisely timed input 'volleys' contribute to the creation of a central nervous system representation of tonality or pitch. With any real acoustic stimulus, like a spoken word, a chirping bird or the sound of snoring in a lecture hall, there is a complex, continuous spatial AND temporal representation of the spectral content of sound distributed topographically across our auditory nerve arrays.

SENSORINEURAL HEARING LOSS

Cochlear hair cells are mechanically and chemically fragile, and lost hair cells are non-regenerable. Their loss results in a PERMANENT **sensorineural hearing loss** (sometimes called a 'sensory hearing loss'). Common causes of sensorineural hearing loss include exposure to damaging noise; infections that involve the inner ear, most commonly from an episode of a childhood disease like measles, mumps, chicken pox or meningitis, or from congenital syphilis; treatment with numerous ototoxic drugs, ranging from aspirin to widely-applied streptomycin-derivative antibiotics; vascular disease; physical trauma to the ear, e.g., from a blow to the head; and 'aging'. Hair cell loss is progressive, and is 'seeded' by initially-local organ of Corti damage. A significant

loss in childhood or early adulthood sets an individual up for later progressive hearing deterioration that can ultimately result in a completely dysfunctional ear.

Sensory hearing losses are usually defined by determining the magnitudes of elevation of hearing thresholds that cannot be accounted for by conductive hearing loss. Again, 'bone conduction' and 'air conduction' audiograms are obtained. If the loss is due to organ of Corti damage, there is an equivalent increase of both bone conduction and normal air conduction hearing thresholds.

Conventional sound-amplification hearing aids ameliorate the effects of a sensorineural hearing loss, but are of limited use when the loss is severe. With widespread hair cell loss, the basis of 'sharpening' of mechanical sound tuning dependent upon intact hair cells in the inner ear is lost. The practical consequence for a severe hearing loss patient is that a hearing aid can restore hearing sensitivity, but the ear can only create a detuned representation of sound to the brain, which is often uninterpretable. You will see many patients with detuned or limited-spectral-input ears in your career, marked by the report, "I can hear my wife (husband, daughter, friend) talking, but just can't understand what she (he, they) say." Hearing aid treatments are also limited by the fact that losses affect the hearing spectrum idiosyncratically.

A new, radical treatment for very severe sensorineural hearing loss patients pioneered at UCSF employs patterned electrical stimulation applied directly to the auditory nerve array to generate spatiotemporally patterned inputs from the ear that simulate those generated by normal speech. Thus, these cochlear prostheses replace (albeit crudely) the normal sound-to-patterned nerve response transduction function of the organ of Corti. These devices provide a restoration of hearing of intelligible speech for a high percentage of implanted subjects.

VESTIBULAR ORGAN ANATOMY AND FUNCTION

The sensory organ of the vestibular system is the labyrinth, which is continuous with the chambers of the cochlea. Hair cells are distributed in the labyrinth in five main patches, called maculae. Three are associated with semicircular canals; two with otolithic organs. The semicircular canals inform the organism about the direction and speed of any significant movement, and are used to coordinate head and eye movements. The otolithic organs, which include the utricle and saccule in humans, provide information about the static position of the head in reference to gravity, inform us as to which way is up.

The three semicircular canals are roughly circular fluid-filled tubes, oriented at right angles to one another. One is oriented approximately horizontally; the second roughly in the sagittal plane; and the third roughly in the frontal plane (see Figure 10). There is a swelling in each tube, its 'ampulla'. Within this swelling is a ridge, the crista (for 'crest'), which traverses it. This ridge is densely covered with about 2000 vestibular hair cells. Atop the long stereocilia of these maculae is a gelatinous structure, the cupula. The cupula completely blocks the canal, but can glide on its upper surface while maintaining a tight fluid seal. When the head is accelerated, fluid in the canal moves differential to the movement of the head, which results in a displacement of the gelatinous cupula, which deflects the stereocilia of all 2000 hair cells (Figure 11). All hair cells in each semicircular canal are oriented in the same direction. Thus, all are most favorably excited by head movement in one specific axis (in which the canal is oriented), and in one specific direction in that axis.

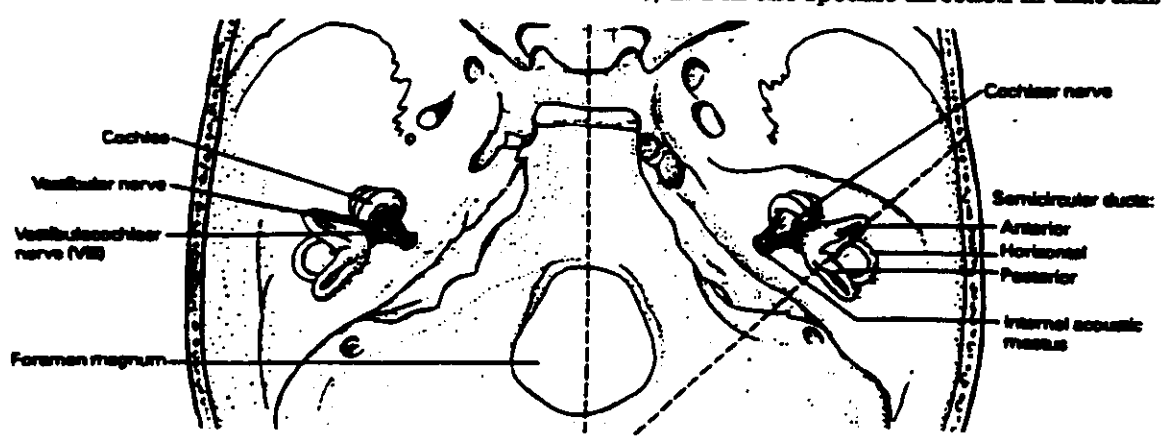

Figure 10 (from Kandel et al.)

It should be noted that the semicircular canals respond selectively to active head turning, and are NOT excited by movements of constant velocity or by static head tilt. The principle behind this effect is inertia of the

endolymph that fills the ducts. As the head begins to move, endolymph tends to stay at rest and exerts pressure on the cupula, thus bending the stereocilia. When the stereocilia bend in one direction, the hair cells are depolarized. When they bend in the opposite direction, the hair cells are hyperpolarized. With constant velocity motion, there is no longer any movement of the endolymph relative to the head. The cupula returns to its resting position by virtue of its own elastic properties, and the hair cells are returned to their normal resting potential. Deceleration can be as effective as acceleration in bending hair cells within the ampulla. Once the head stops moving, endolyph will continue to move for awhile in the same direction, and will displace the cupula by virtue of its inertia. Decelleration in one direction is therefore approximately equivalent to acceleration in the opposite direction.

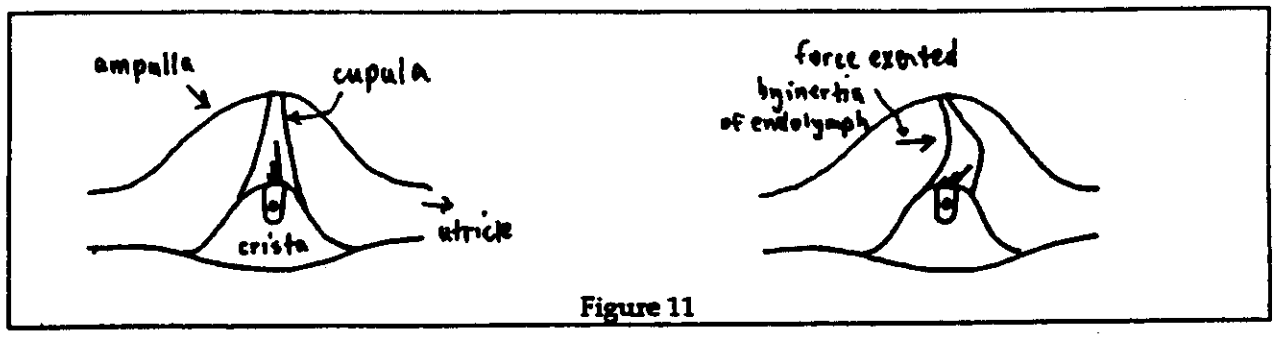

Figure 11

How can we know that we are moving at a constant velocity, or that our head is tilted relative to gravity? That information is signalled by our otolithic organs, the utricle and the saccule. The macula of the utricle is oriented in a roughly horizontal plane, and of the saccule in a roughly vertical plane. Both are comprised of several thousand hair cells. Atop these cells, embedded along with their stereocilia in an otolithic membrane (Figure 12A) is a rock! The rock (otolith) is comprised of calcium carbonate crystals produced by the cells of the membrane. They have a much higher specific gravity than the surrounding endolymph. Thus, any constant velocity stimulus or any head tilt will move the stone in relation to the hair cells of these maculae.

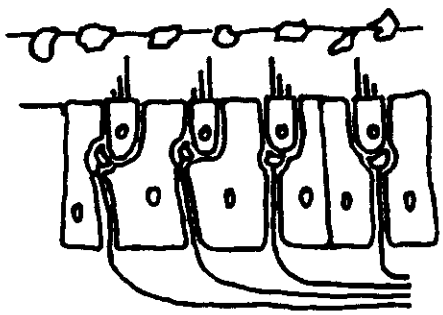

Figure 12A

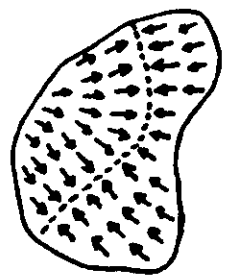

Figure 12B

How are different tilts or head positions encoded in these marvelous structures? The hair cells in both maculae are oriented in a pattern in which the directional selectivity changes across the center of each organ (Figure 12B). Thus, by reading which hair cells are depolarized and which are hyperpolarized by a given head tilt or velocity, the central nervous system can resolve the direction of tilt, or the velocity of movement.

OBJECTIVES:

1. Know the basic components of the outer, middle and inner ear.
2. Understand the main functional roles of the middle ear.
3. Know the origins of conductive and sensorineural hearing losses.
4. Understand the basic mechano-electrical transducing properties of hair cells.

5. Understand how sound frequency is represented in the cochlea, and by the patterned discharges of auditory nerve fibers.

6. Know the location of maculae (patches of hair cells) in the vestibular part of the inner ear, and the stimuli that depolarize hair cells in these maculae.

READING:

Nolte, J. 1993. The Human Brain, 3rd edition, Mosby, St. Louis, pp. 201-207.

Kandel, E.R., Schwartz, J.H., and Jessell, T.M. 1991. Principles of Neural Science, 3rd edition, Elsevier, New York, Chapter 32 (pp. 481-491).