Anatomical Correlates of Functional Recovery in the Avian Inner Ear Following Aminoglycoside Ototoxicity

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Tucci and Rubel have demonstrated functional recovery of the chick cochlea following aminoglycoside ototoxicity. The cochleae of these same animals were examined by scanning electron microscopy (SEM) in order to further understand this recovery process.

Hatchling chicks were given daily doses of gentamicin for 10 days. Auditory-evoked potential measurements and examination of the cochlea by scanning electron microscopy were performed after survival periods of 5 days to 20 weeks.

After 5 days of gentamicin exposure, there was near complete basal hair cell loss associated with a high-frequency hearing loss. Apical progression of damage with a broad-band hearing loss occurred over 4 weeks. At 20-weeks, hair cell counts were normal with a small high-frequency hearing loss. Hair cell regeneration played a major role in the functional recovery of the cochlea.

INTRODUCTION

The production of inner ear sensory hair cells is complete early in embryogenesis in birds[1] and mammals,[2] including man.[3] Any postembryonic loss of cochlear hair cells due to noise exposure, ototoxic drugs, infections, or age was believed to be irreversible and associated with permanent hearing loss.

However, the literature does contain reports of hearing recovery following aminoglycoside ototoxic drug injury. Moffat and Ramsden[4] reported partial hearing recovery in one patient with a gentamicin-associated hearing loss. Fee[5] reports 55% of patients with an aminoglycoside-induced hearing loss demonstrated some improvement in hearing 1 week to 6 months following cessation of the drug therapy.

Recent studies in the chick auditory system may provide insight into the possible mechanisms of this recovery process. Indirect evidence suggesting the possibility of chick cochlear hair cell regeneration following aminoglycoside ototoxicity and noise exposure was first published in 1987.[6,7] Since that time, conclusive documentation of hair cell regeneration by DNA labeling studies has been reported following acoustic trauma in neonatal chicks[8,9] and sexually mature quail.[10] These regenerated hair cells appear to arise from a latent stem cell population (hyaline or cuboidal epithelial cells) and possibly from supporting cells.[9] In addition, anatomical recovery is nearly complete 30 days following noise exposure.[7,9,11] Following gentamicin-induced ototoxicity in the chick, hair cell numbers approach normal by 3 weeks after gentamicin exposure.[6] However, the anatomical changes seen with aminoglycoside ototoxic injury and recovery have not been well documented in the chick.

Tucci and Rubel[12] recently reported near complete recovery of auditory brainstem responses in chicks following gentamicin-induced hearing loss. Initially, the hearing loss was limited to the high frequencies, but progressed for 5 weeks following cessation of the gentamicin to involve the entire frequency range tested. By 20 weeks after gentamicin, the evoked potentials to low frequencies were essentially normal. A mild high-frequency threshold shift persisted, however.

The current study is an attempt to better understand the anatomical correlates to the recovery process. In addition, we hoped to determine the role hair cell regeneration plays in the recovery of hearing. To this end, the cochleae from the same animals used to study functional recovery were examined by scanning electron microscopy.

The methods and results of the evoked-potential testing previously reported[12] will be summarized to allow correlation with the anatomical findings.

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METHODS

Subjects for the physiological portion of this study were 80 newly hatched chickens (Hubbard × Hubbard). Experimental animals (N = 53) received one subcutaneous injection of gentamicin sulfate (50 mg/kg) daily for five (n = 10) or ten (n = 43) days. Control animals (N = 27) received no injections, and were raised and tested with experimental animals. No deaths which were attributed to the drug administration occurred, although body weight of the drug-treated chicks was substantially reduced (by almost 50%) as compared with age-matched controls at 4 weeks after the injections.

The ten animals that received only 5 days of gentamicin were all tested the day after drug treatment was completed. This experimental group (5–1-day) was included to determine how rapidly the drug administration produces hearing loss. In the 43 animals that received the full 10 days of gentamicin, evoked-potential hearing thresholds were measured at a variety of times following the drug administration. Testing was carried out either 1 week, 3 weeks, 4 weeks, or 20 weeks (range 16 to 20 weeks) following gentamicin injections.

The preparation and recording procedures are described in the previous report.[12] Briefly, animals were prepared for testing after adequate anesthesia was induced by injection of Equithesin (1.5 mg/kg) and ketamine hydrochloride (80 mg/kg). Anesthetics were supplemented throughout the recording session. The cartilagenous portion of the external auditory canal on the test side (arbitrarily selected) was removed to facilitate placement of the sound-delivery tube. The tympanic membrane was visualized under the microscope to ensure that it was intact. Pin electrodes (Grass Instrument Co., Quincy, Mass.) were implanted bilaterally through the skull, at a level just above the brainstem auditory nuclei (active and reference electrodes) and into the thigh muscle (ground electrode). Responses were amplified, filtered (30 to 3000 Hz band pass), digitized at a rate of 10 kHz, and averaged during 200 to 500 stimulus presentations.

Evoked-potential thresholds were measured for test frequencies ranging from 250 Hz to 4000 Hz, and for a 5000-Hz stimulus on the older animals. Tone bursts with four-millisecond rise and decay times and 10 milliseconds' total duration were delivered at a rate of five times per second. Stimuli were presented by a closed-tube delivery system, calibrated using a Bruel and Kjaer ⅛-inch microphone and a Hewlett-Packard (3561A) signal analyzer, so that all threshold data were recorded in decibel sound pressure level (dBSPL).

Thresholds were obtained by identifying the lowest stimulus intensity (within 5 dBSPL) that reliably evoked a response of at least twice the amplitude of the baseline variation. Preparation and threshold measurement typically required 2 to 3 hours per animal.

A sample of the experimental animals tested for evoked potentials (3 to 4 animals/group; n = 16) and two of their age-matched controls (n = 10) were chosen for the quantitative anatomical analysis presented here. Immediately following evoked-potential testing, while still under anesthesia, the chicks underwent bilateral cochlear perfusion (intralabyrinthine via the round window) with 3.5% glutaraldehyde in 0.1 M phosphate buffered saline (PBS; pH 7.4). After decapitation, the external auditory canals and cochlear ducts were opened and immersed in the same fixative at 4°C for 24 to 48 hours. The temporal bones were removed and the cochleae were exposed. The temporal bones were postfixed in 1% osmium tetroxide (in 0.1 M PBS) for 2 hours at room temperature.

The tissue was dehydrated in 70% ethanol at 4°C for 72 hours, followed by final dissection that included removal of the tegmentum vasculosum and the tectorial membrane. Dehydration was then completed through a graded ethanol series. The temporal bones were critical-point dried and sputter coated to 500 Å with gold palladium. Scanning electron microscopy was performed on a JEOL 35C electron microscope (15 kV accelerating voltage).

Tissue analysis was carried out in two phases. First, low-magnification (150×) montages of the entire sensory epithelium were constructed for each cochlea. This allowed gross identification of the region of damage induced by the gentamicin. Damage was defined as a gross disruption of the normal mosaic pattern of hair cells. This included regions of hair cell injury as well as hair cell loss. These low-magnification montages were used to quantify the total surface area of the sensory epithelium, as well as the area of damage using a Zeiss VideoPlan™ morphometric system. This provided quantification of the area of damage as a percentage of the total surface area of the sensory epithelium for each experimental cochlea.

In the second phase of tissue analysis, five regions of the sensory epithelium were chosen for sampling based on the total length of the cochlea as measured from the apex to the base (Fig. 1). Distances were normalized into a percentage of the total length with samples taken at 10%, 30%, 50%, 70%, and 90% of the distance from the apex. These locations corresponded to approximately the 250, 500, 750, 1500, and 4000 Hz regions of the cochlea,[16] respectively. At each sample location a higher magnification (1500×) montage was constructed across the sensory epithelium perpendicular to the long axis of the cochlea. This level of magnification allowed hair cell apical surface morphology to be examined.

Counts of normal, damaged, and regenerated hair cells were performed for a 50-μm wide strip at each sample location. Regenerated hair cells were identified based on the morphology of the apical surface. Cotanche[7] has previously described the phases of maturation seen in the regenerating hair cell stereociliary bundle. This process closely resembles embryonic hair cell stereocilia maturation.[13] A hair cell was not considered regenerated unless the stereocilia appeared immature or residual microvilli remained on the apical surface of the hair cell.

For comparison, the sampling procedure and hair cell counts were performed on age-matched control cochleae (n = 10) which had received no gentamicin treatment.

All experiments were carried out in strict adherence to the standards of animal care as specified by the National Institutes of Health (NIH publication No. 80-23, revised 1978).

RESULTS

Physiological Results

The evoked potential threshold data from these animals has been previously reported[12] and will be

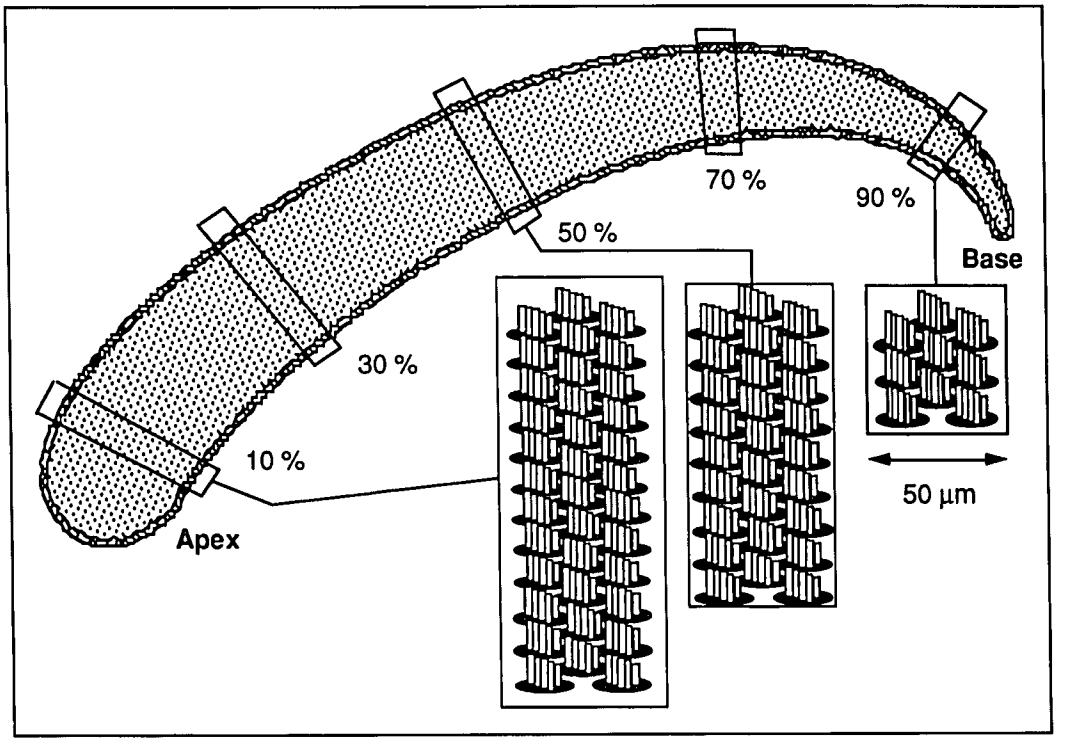

Fig. 1. Schematic representation of sample locations for high-magnification (1500×) scanning electron microscope (SEM) montages of the chick cochlea for hair cell counts and morphologic examination.

briefly summarized here.

Control animals. It has been reported[14] that hearing thresholds in the chick are adult-like at the time of hatching. However, thresholds measured from control animals at 6 days after hatching (5–1-day) were, on the average, 10 dB higher than those of animals tested at 1 to 4 weeks after treatment ($P<.01$). In addition, thresholds measured at 20 weeks were significantly better than those measured at 1 to 4 weeks after injection ($P<.05$). Because of these differences, the youngest (5–1-day) and oldest (20-week) experimental groups are compared with their own age-matched controls. Thresholds of all other experimental groups (10–1-week through 10–4-week) are compared, for each frequency, to the mean threshold of all age-matched control groups combined.

Experimental animals. Figure 2 shows the mean evoked-potential thresholds (± 1 SD) of experimental and control groups for each age group. A high-frequency threshold shift is evident in the 5–1-day group with progression over time. At 4 weeks after gentamicin administration, threshold elevation was seen across the entire frequency range tested. The threshold shift was significant ($P<.001$) for all but the 5–1-day experimental group. In this group the threshold shift was significant for frequencies above 1500 Hz ($P<.01$).

The threshold data for the animals tested 20 weeks (range 16 to 20 weeks) after injection are also shown in Figure 2. Hearing has essentially returned to normal at low frequencies, although a residual 15- to 30-dB high-frequency threshold shift is evident.

Anatomical Results

Control animals. The normal avian inner ear differs anatomically from that of the mammal. The sensory epithelium consists of a curvilinear sheet of hair cells which is narrow (5 to 6 hair cells across) at the base and wide (30 to 40 hair cells across) at the apex.[15] There are two hair cell types identified by their cross-sectional morphology. Tall hair cells occupy the superior edge of the sensory epithelium and have innervation patterns similar to mammalian inner hair cells.[15] Short hair cells are located more inferiorly and have innervation patterns similar to mammalian outer hair cells. Tall hair cells predominate at the apex, while short hair cells predominate at the base, with a transitional gradient between these extremes. When viewed by SEM the apical surface of normal mature hair cells is smooth except for the staircase organization of stereocilia (Fig. 6). The hair cells are divided by a thin band of microvilli at the apical surface of surrounding supporting cells. The result is a mosaic pattern of the sheet of hair cells.

There was no evidence of hair cell loss or injury in any of the control cochleae when examined by either the low-magnification or high-magnification montages. The hair cell density (but not overall number) has been shown to decrease during the postnatal period.[11] Therefore, for the purpose of hair cell counting, the youngest (5–1-day) and oldest (20 weeks) control animals were used as age-matched controls for their experimental counterparts. The middle-aged control groups (1, 3, and 4 weeks) were combined for purposes of comparison to the experimental groups.

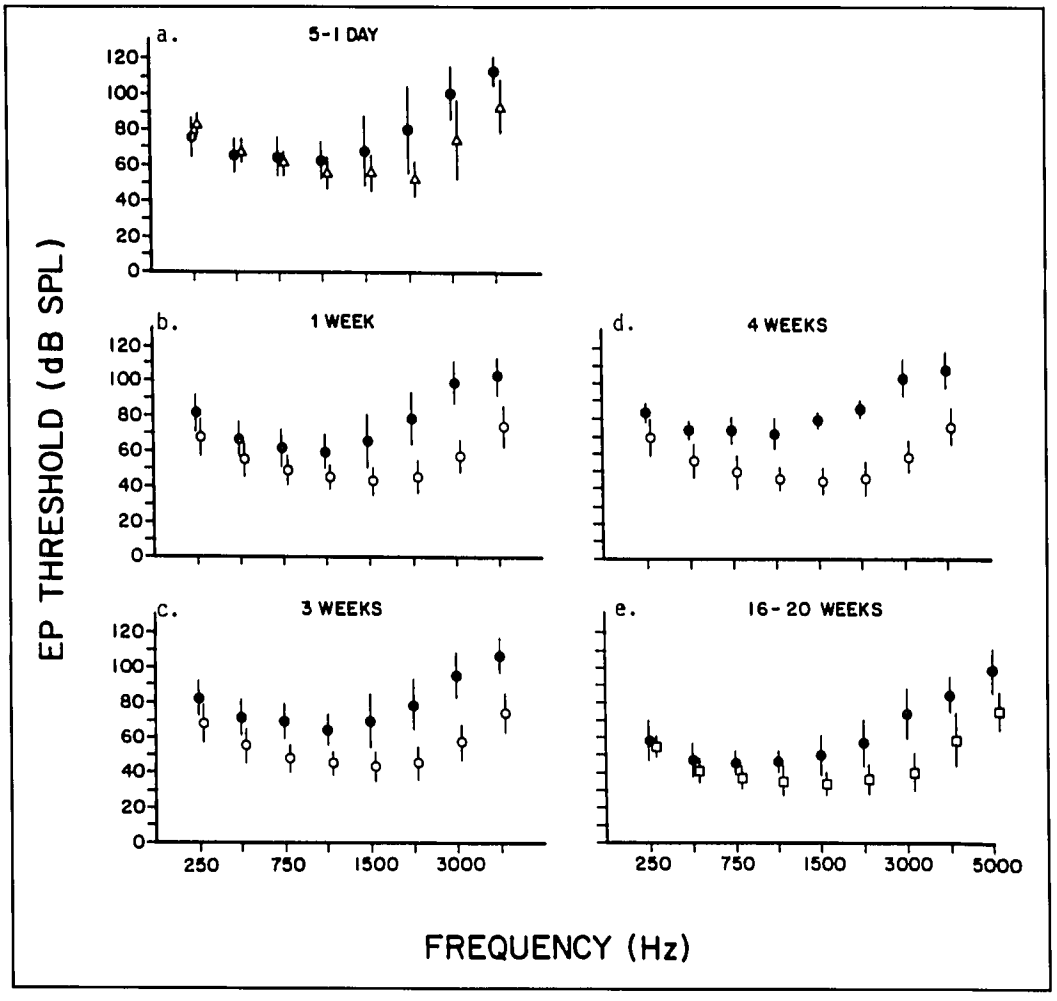

Fig. 2. Mean evoked-potential thresholds in dB SPL (± 1 SD) for experimental (filled circles) and control (open symbols) animals at survival intervals as shown. Control data are for 5–1-day (open triangles), combined 1-week to 4-week inclusive (open circles), or for 16- to 20-week (open squares) groups.

Experimental animals: Area of damage. Figure 3 summarizes the percentage of total surface area damaged (± 1 SEM) for each of the experimental groups. This is based on gross identification of injury using the low-magnification (150×) montages. The drawings below this plot represent the location of damage for one "representative" cochlea in each of three experimental groups.

A small basal lesion is present in the earliest group (5–1-day) accounting for 12.5% of the total surface area. Over time the area of damage spreads in an apical direction to involve the low- to mid-frequency regions of the cochlea and 58.2% of the total surface area by 4 weeks. In the 20-week group, most of the cochlea again appears grossly normal. However, the basal-most high-frequency region continues to show evidence of disruption of the normal mosaic pattern of hair cells.

Considerable variability between animals was observed in all experimental groups, but was most pronounced in the 1-week experimental group. Of the three animals examined, two showed minimal evidence of injury while the third had an area of damage greater than 15% of the total surface area. Review of the evoked-potential data for each of these individual animals revealed a good correlation between the physiological and anatomical findings; animals with minimal anatomical damage had near-normal hearing thresholds and those with significant anatomical injury had elevated hearing thresholds. Despite this variability the overall trend is quite evident.

Even at this gross level of analysis, the temporal pattern of injury identified correlates well with the temporal pattern of hearing threshold shift and recovery as seen in Figure 2.

Experimental animals: Hair cell counts. Hair cell counts were performed using the high-magnification montages. A normal cell exhibited a smooth, nonblebbed apical surface with normal stereocilia. A cell was considered damaged if there was any disruption of the stereocilia array or apical surface. Regenerated hair cells were identified by their small size, embryonic appearing stereocilia, and residual microvilli on the apical surface, as previously described elsewhere.[7]

The percentage of hair cells present in the 50-μm

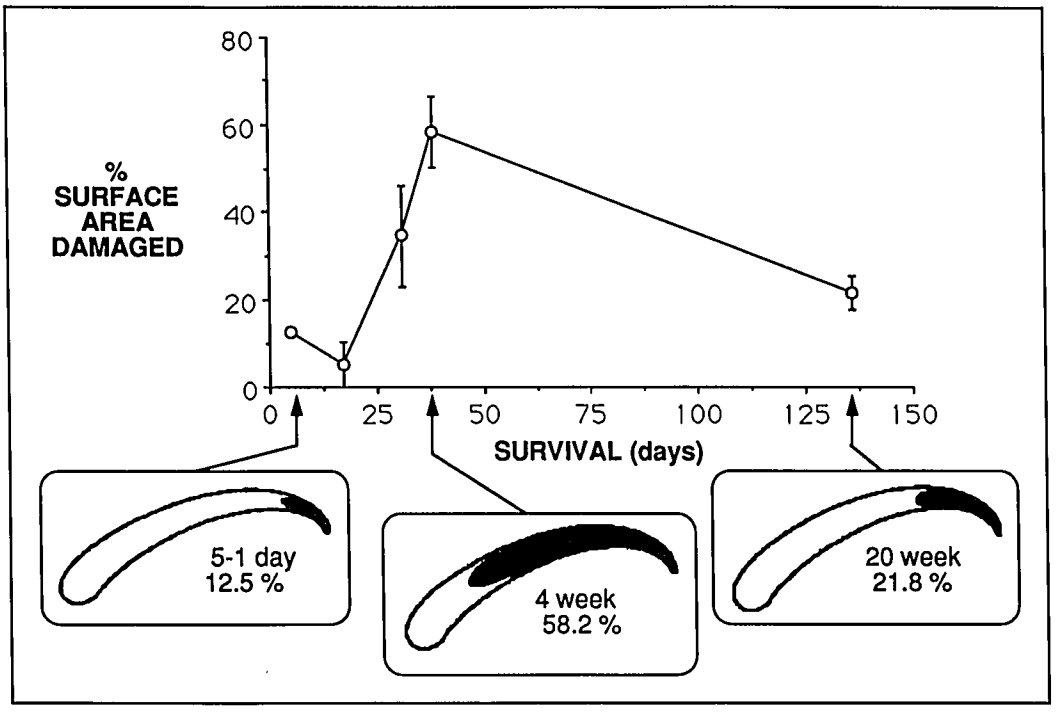

Fig. 3. Mean percentage (± 1 SEM) of total sensory epithelium surface area damaged by gentamicin as identified on low-magnification SEM montages. The lower schematics demonstrate the injury location in one cochlea from each of the three groups.

wide sampling areas (±1 SEM) when compared to age-matched controls is presented for each experimental group in Figure 4. Each sample location is represented as a percentage of the total length of the cochlea as measured from the apex. The counts shown in Figure 4 include all the hair cells present (normal, damaged, and regenerated hair cells).

There is an obvious loss of hair cells at the basal tip after only 5 days of gentamicin. This progresses in an apical direction to involve the midregion of the cochlea (50% distance from the apex) by 4 weeks after gentamicin. Again, considerable variability between animals is evident, especially in the 1 and 3 week groups.

By 20 weeks after gentamicin treatment, overall hair cell numbers have normalized, except at the apex where hair cell numbers were slightly higher than age-matched controls. There was no evidence of hair cell injury, loss, or regeneration in the most apical sample in any experimental animal, so the significance of this apparent increase in apical hair cell numbers at 20 weeks is not clear (Fig. 4).

Comparisons of Figures 3 and 4 indicate that the areas of injury identified on the low-magnification montages are, in fact, areas of partial to near-total hair cell loss. This again correlates highly with the evoked-potential findings.

To better appreciate the importance of hair cell regeneration in this recovery process, the results of three representative experimental groups (5–1-day, 4 weeks, and 20 weeks) are presented in a somewhat different format (Fig. 5). Hair cell counts have been normalized to a percentage of the total number of hair cells lost based on the numbers determined from age-matched controls. In Figure 5, the mean percentage of cells that are lost is plotted. Only mature (*i.e.*, normal or damaged) hair cells have been included (regenerated hair cells are not included) to better reflect the severity of gentamicin-induced hair cell loss. Thus, in Figure 5, 100% represents a total loss of the original complement of hair cells, while 0% represents no loss of hair cells. Most striking is the near-complete loss of hair cells at the basal tip (90% distance from the apex) after only 5 days of gentamicin. There continues to be a near-complete absence of mature hair cells at 4 weeks after gentamicin exposure, with a persistent 36% loss of mature-appearing hair cells at 20 weeks.

In addition, there is substantial loss of mature hair cells in the mid-to-apical regions of the cochlea at 4 weeks. By 20 weeks the number of mature hair cells in the midregions has returned to normal.

The number of regenerated hair cells (no mature or damaged hair cells) are shown as a percentage of the total number of hair cells in age-matched controls (Fig. 5).

At the basal tip (90% distance from the apex) in the 5–1-day group, 30% of the control number of hair cells have already been regenerated. Remarkably, this hair cell regeneration (5–1-day group) and differentiation has occurred in the face of ototoxic levels of gentamicin and while mature hair cells continue to be lost.

Further regeneration occurs over the next 4 weeks (52% of hair cells replaced at the basal tip). By

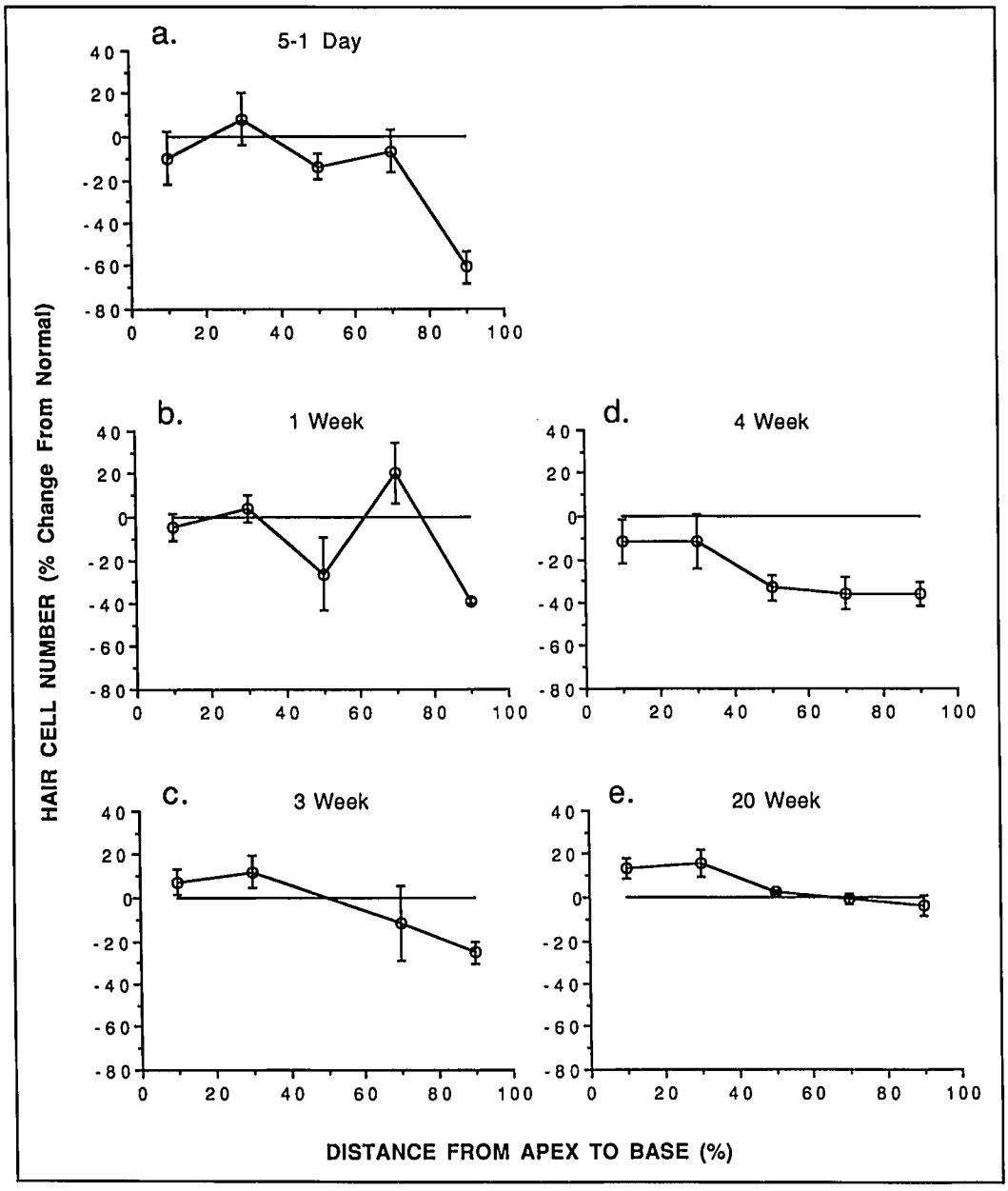

Fig. 4. Mean percentage (±1 SEM) of the total number of hair cells present in age-matched controls for each experimental group.

20 weeks, there is essentially complete recovery of hair cell numbers (Fig. 4). Of note, however, is that 35% of hair cells at the basal tip in the 20-week group are still immature enough to be identified as regenerated hair cells based on their morphology. This is not true for the mid-to-apical regions where mature cell numbers approach normal at 20 weeks.

Ryals and Rubel,[16] using pure-tone acoustic overstimulations to cause discrete lesions in the cochlea, have produced a frequency map for the chick cochlea. As anticipated, the basal regions were damaged by high-frequency tones and, progressively, apical regions were damaged by lower frequencies. Other studies have examined changes in the frequency map with age.[17,18]

For simplicity, this frequency map shift with age was ignored and the frequency map for a 30-day posthatch chick was used to correlate the degree of threshold shift with the number and condition of hair cells. The frequency that best corresponded to each of the locations sampled along the cochlea was calculated from this map.

The evoked potential data from the 5–1-day, 4-week and 20-week groups are represented as threshold shift for each of the locations of the cochlea that we studied anatomically. The isolated high-frequency threshold shift seen in the 5–1-day group corresponds to the basal hair cell loss. At 4 weeks, the threshold shifts involve all frequencies studied (Fig. 5). However, the hair cell loss does not extend com-

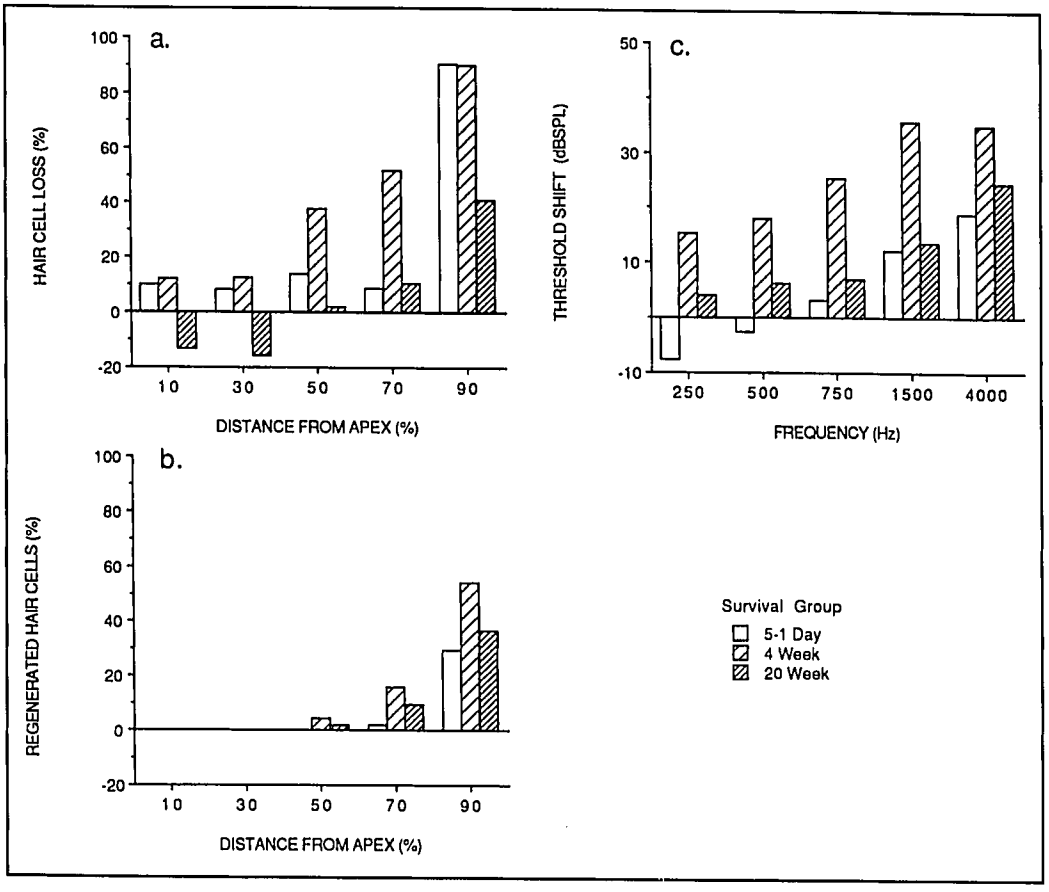

Fig. 5. **a.** Mean percentage of hair cell loss compared to age-matched controls counting only mature (normal or damaged) hair cells. **b.** Mean percentage of regenerated hair cells present as compared to total hair cell numbers in age-matched control. **c.** Mean threshold shift data (difference between experimental and control thresholds) at the frequencies corresponding to the sites of hair cell counts shown in a, b.

pletely to the apex. There are several explanations for this apparent contradiction: this area of the cochlea may, in fact, code frequencies below 250 Hz; the threshold shift may be due to a more central defect (*e.g.,* the hair cell–ganglion cell synapse); or, most likely, the evoked potentials preferentially test basal contributions, even to low-frequency stimuli.

Even 20 weeks after gentamicin exposure, there remains a high-frequency threshold shift despite normal numbers of basal hair cells (Figs. 4, 5). As described previously, however, a large proportion of the basal hair cells remain immature at this time and these may not be functioning normally.

Thus, hair cell loss is most severe at the basal tip. Although hair cell regeneration is complete in terms of overall numbers, there remains considerable immaturity of hair cells and not at residual high-frequency threshold shift found electrophysiologically in the long-term group. It is very possible that, with longer survival times, complete hair cell maturation may occur with normalization of evoked-potential thresholds.

Experimental animals: Hair cell morphology. Examples of hair cells from the basal region (90% distance from the apex) are shown in Figure 6. An example from a normal animal is shown, and the same region from three representative animals in experimental groups is also shown. The normal mosaic pattern of hair cell stereocilia has completely disappeared after 5 days of gentamicin. Only occasional surviving but injured mature hair cells persist (large arrow). The multiple, very small, embryonic appearing tufts of stereocilia on the regenerated hair cells are clearly visible (small arrows) throughout the region of hair cell loss.

By 4 weeks after gentamicin treatment, partial hair cell repopulation of the basal tip by regenerated hair cells is seen. These hair cells demonstrate varying degrees of maturity. Twenty weeks after gentamicin treatment, hair cell repopulation is completed. This is the least normal of our samples. In this extreme example, a significant degree of immaturity of most hair cells is seen (mature appearing hair cell = large arrow; immature appearing hair cells = small arrows). Other cochleae from this group appeared almost normal.

Examples from the midregion of the cochlea (50% distance from the apex) for these same four groups (control, 5–1-day, 4-week, and 20-week) are shown in Figure 7. There was no evidence of injury or loss after 5 days of gentamicin. Four weeks after gentamicin there is obvious hair cell injury with adjacent simultaneous hair cell regeneration. By 20 weeks, recovery is nearly complete with a fairly normal appearing sensory epithelium. However, occasional small, im-

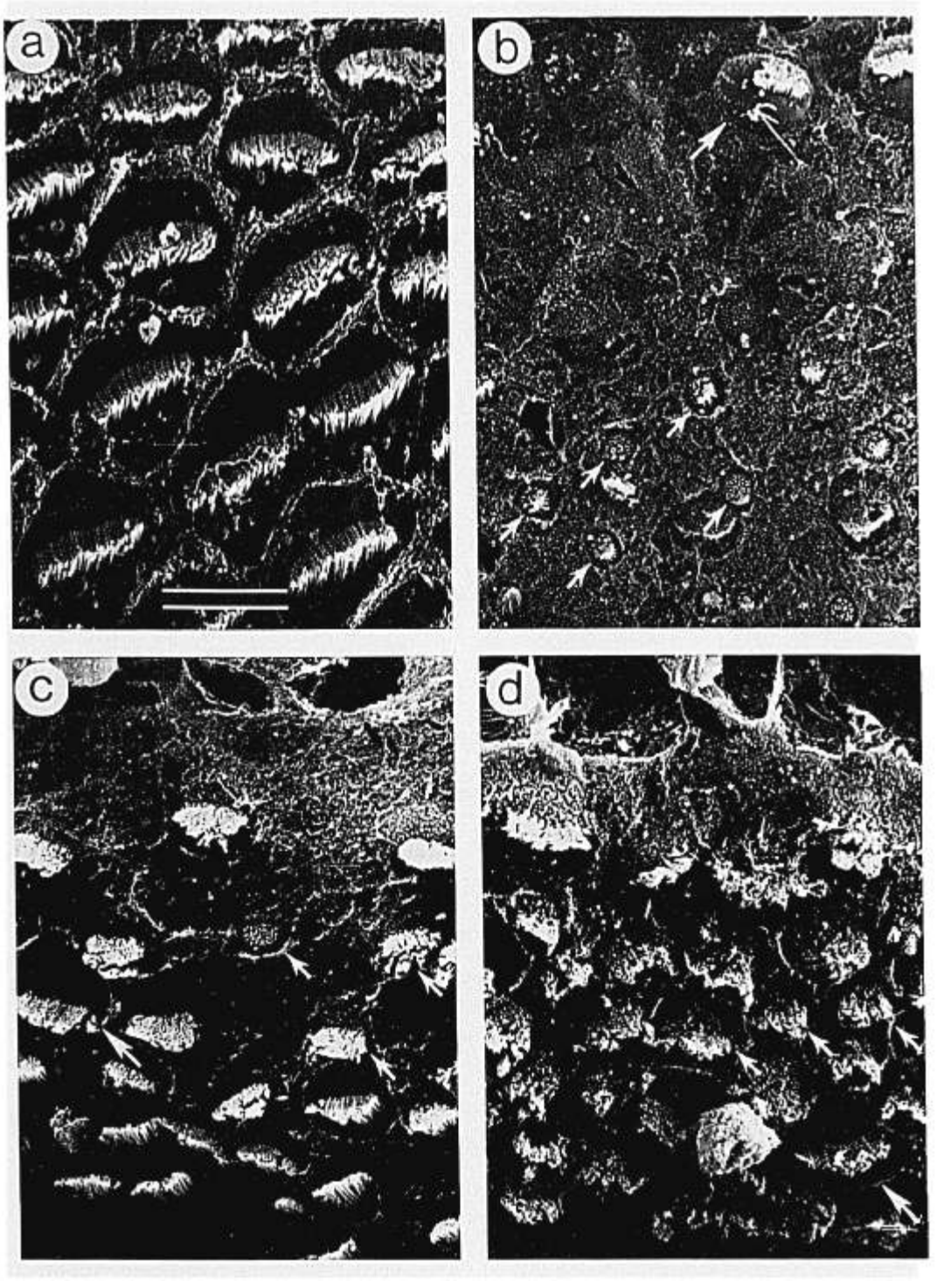

Fig. 6. SEM examples of the basal-most sample region (90% distance from the apex) in a normal control cochlea (**a**), 5–1-day cochlea (**b**), 4-week cochlea (**c**), and 20-week cochlea (**d**). Small arrows = regenerated hair cells; large arrows = mature hair cells. Bar = 10 μm.

mature hair cells are still visible nestled between the mature hair cells.

DISCUSSION

The avian cochlea has been shown to have remarkable anatomical regenerative capabilities following aminoglycoside[6] and acoustic[7,9,11] injury. This recovery occurs, at least in part, by the production of new sensory hair cells.[8–10] In addition, Tucci and Rubel[12] have reported near-complete functional recovery from a gentamicin-induced hearing loss. The goal of the present study was to correlate anatomical and functional data on damage and recovery in the same animals.

There was an immediate-onset (after 5 days of gentamicin) high-frequency hearing loss associated with almost complete loss of hair cells at the basal tip. The hearing loss progressed steadily for 4 weeks after

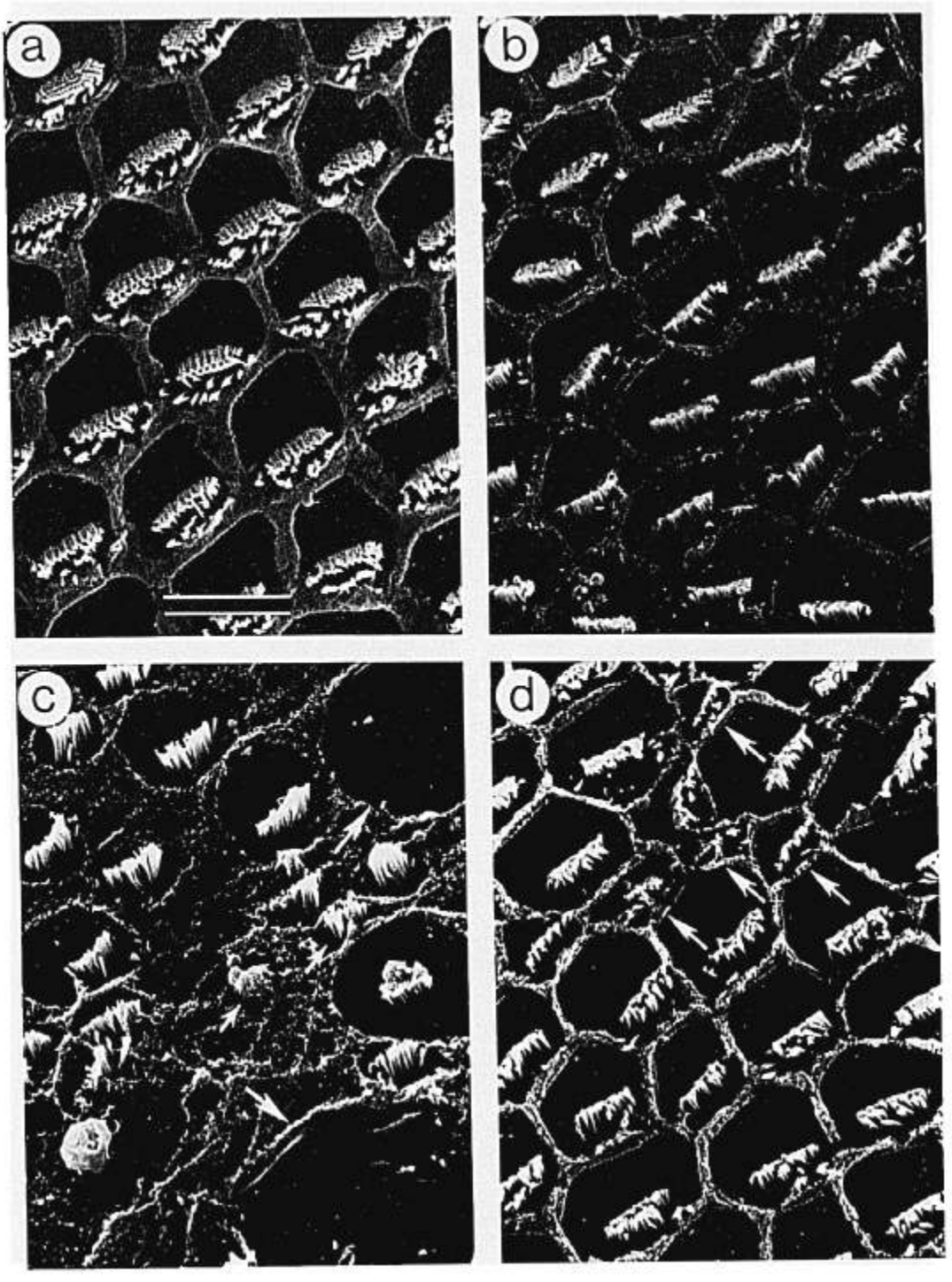

Fig. 7. SEM examples of the midcochlear region (50% distance from the apex) in a normal control cochlea (**a**), 5–1-day cochlea (**b**), 4-week cochlea (**c**) (small arrows = regenerated hair cells; large arrows = damaged hair cells), and 20-week cochlea (**d**) (large arrows = regenerated hair cells). Bar = 10 μm.

the termination of gentamicin administration to involve the entire frequency range tested. This correlated with a progression of hair cell injury and loss from the base toward the apex.

The same basal to apical progression of aminoglycoside-induced hair cell loss has been previously described in the chick[6] and in mammals.[17,18] The etiology of this pattern of injury is not well understood. Possible explanations include associated nephrotoxic effects with decreased drug clearance from the cochlea, organ-specific accumulation of the drug in the perilymph and cochlear tissues, selective uptake of the drug in the cochlea by basilar hair cells, and cochlear blood flow dynamics.

However, Dulon, *et al.*[20] have shown in guinea pigs that nephrotoxicity and ototoxicity from gentamicin are dissociated phenomena with no predictable interaction. Schacht,[21] in a recent review of the cellular mechanisms of aminoglycoside ototoxicity, provides a convincing collection of studies showing no

evidence for selective accumulation of aminoglycosides in the cochlear tissues or perilymph. Hayashida[23] showed diffuse uptake of gentamicin by all inner and outer hair cells following a single transtympanic injection. However, when the gentamicin was given intraperitoneally, there was only basal hair cell uptake. Conversely, Tran Ba Huy[22] found no such differential uptake by basal hair cells. Unfortunately, aminoglycoside distribution and uptake have not been studied in the chick cochlea to date.

In the present study, the basal region of the cochlea suffered 90% hair cell loss after only 5 days of gentamicin exposure. Despite this, evoked-potential threshold recovery was nearly complete by 20 weeks after gentamicin exposure. This was associated with normalization of hair cell numbers at all the sample locations. Thus, hair cell regeneration plays a major role in the anatomical recovery (hair cell number) and presumably in the functional recovery.

The residual 15 to 30 dBSPL high-frequency threshold shift in the 20-week group may be accounted for by the marked immaturity and disorganization of hair cells at the basal end (despite normal hair cell number). This high-frequency region is the site of the initial and most severe injury, yet it is the last to fully recover. The reason for this persistent hair cell immaturity is unclear. It may be the result of a drug-induced maturational slowing or arrest as the regenerated hair cells are exposed to residual gentamicin. Another possibility is that ongoing turnover of hair cells occurs in the basal region and regenerated hair cells continually die as they mature, only to be replaced by new hair cells. This seems less likely since damaged or dying hair cells in the basal region were not evident in tissue from the 4-week or 20-week groups in the basal region. It is entirely possible that, with longer survival times, complete maturation and functional recovery would occur.

One of the more intriguing findings of this study was the presence of regenerated hair cells at the basal tip after 5 days of gentamicin. This indicates that hair cell regeneration and differentiation can occur in the presence of ototoxic levels of gentamicin. Thus, these new immature hair cells must be resistant, at least initially, to the influence of the drug.

Schacht[21] has proposed a multistep model to account for the cellular mechanism underlying aminoglycoside ototoxicity. Initially, the aminoglycoside binds the outer plasma membrane of the cell. This binding displaces calcium and is reversible. The drug is then actively transported into the cell cytoplasm where it binds phosphatidylinositol biphosphate resulting in a lipid-drug complex. This disrupts a second messenger-signal cascade, plasma membrane integrity, actin polymerization, prostaglandin synthesis, and multiple other intracellular systems. These changes are felt to be irreversible.

It is possible that newly produced regenerated hair cells are not capable of active uptake of the gentamicin and, therefore, are protected from its irreversible side effects. As these cells begin to mature, however, they may begin drug uptake which then slows or halts the maturation process.

It is through the study of these molecular mechanisms that we may eventually be able to protect the cochlea from ototoxic insult. In addition, further insight into the mechanisms involved with triggering hair cell regeneration following injury may eventually provide the technology to induce hair cell regeneration in the mammalian cochlea and, thereby, provide a treatment for some forms of sensorineural hearing loss.

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Chicago Society Sets 1991–1992 Program Schedule

The Chicago Laryngological and Otological Society has announced its scientific program for 1991–1992.

On December 9, Timothy Hain, MD, of Northwestern University Medical Center will discuss "Head Shaking Nystagmus," and Drs. James Marks and Ralph Weichselbaum of Loyola University Medical Center and the University of Chicago Medical Center, respectively, will discuss "Radiation Therapy and the Otolaryngologist."

Drs. Michael Goldman and David Riesberg of the University of Chicago Hospital Medical Center will discuss "Osteo Integrated Implants on Craniofacial Rehabilitation" on January 6, 1992.

Also on January 6, Doran Ryan, DDS, MS, of the University of Wisconsin Dental School, will discuss "Temporomandibular Joint Syndrome—An Overview."

On February 3, 1992, Russell Kridel, MD, of the University of Texas Health Sciences Center, will talk about "Surgical Treatment of Septal Perforations" and "Tip Technique with the Open Rhinoplasty Approach."

Dr. Robert Jahrsdoerfer, University of Texas Medical School at Houston, will speak on "Surgery of Congenital Ear Malformation" on March 2, 1992.

The society's annual business meeting will be April 6, 1992, and the Annual President's Dinner will be May 16, 1992.

All scientific programs are held at the Chicago Athletic Association, 12 S. Michigan Ave., in Chicago.

For more information, contact Shirley Kennedy, 23 Dogwood Ct., River Oaks, IL 60409; or call (708) 841-1939.

Sinus Endoscopy Course Set at NYU

The NYU Medical Center's Post-Graduate Medical School is sponsoring a course, "Diagnostic and Operative Sinus Endoscopy," January 24–25, 1992, at the NYU Medical Center's Schwartz Lecture Hall.

The workshop will supplement traditional surgical approaches to sinus disease with new technology that may help previously unresponsive patients. Laboratory sessions are limited to 30 registrants on a first-come basis.

For more information, contact the NYU Medical Center, Post-Graduate Medical School, 550 First Avenue, New York, NY 10016; or call (212) 263-5295.