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The quantitative relation between sensory cell loss and hearing thresholds *

Roger P. Hamernik [1], James H. Patterson [2], George A. Turrentine [1] and William A. Ahroon [1]

[1] *Auditory Research Laboratories, State University of New York, Plattsburgh, New York, U.S.A. and* [2] *Sensory Research Division, U.S. Army Aeromedical Research Laboratory, Fort Rucker, Alabama, U.S.A.*

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On the basis of experimental data obtained from 420 noise-exposed animals (chinchilla), the amount of sensory cell loss has been quantitatively related to the amount of permanent threshold shift at eight audiometric test frequencies between 0.125 and 16 kHz. The noise exposures, which varied extensively in spectrum, intensity and duration, produced permanent threshold shifts that ranged from 0 to 70 dB across a broad range of test frequencies. These data show: (1) consistent outer hair cell losses with less than 5 dB permanent threshold shifts (PTS) across all the test frequencies; (2) the first approximately 30 dB of PTS is established by losses of primarily outer hair cells; (3) in regions of the cochlea that transduce frequencies higher than or equal to 2 kHz, the three rows of outer hair cells show the same degree of loss for a given PTS, while in the 0.5 to 1.0 kHz region of the cochlea, the third row of outer hair cells (OHC) consistently shows less loss than do rows one and two; (4) appreciable inner hair cell (IHC) loss does not begin to appear until PTS exceeds approximately 30 dB; (5) in the virtual absence of OHC, hearing thresholds are least sensitive to IHC loss in the octave band centered at 4 kHz, i.e., the 4 kHz region can be as functional as other areas of the cochlea in spite of a greater amount of damage. The quantitative relation between cell loss and PTS varies as a function of test frequency in an orderly fashion.

Sensory cell loss; Noise-induced permanent threshold shift; Hearing handicap

Introduction

The role of the inner and outer hair cells in hearing has been the focus of considerable attention since the two separate classes of sensory cells were first described. From the macroscopic perspective, quantitative relations between sensory cell lesions and hearing thresholds have varied considerably. As outlined below, one can find in the literature a variety of correlations, e.g., normal hearing in the presence of sensory cell lesions; abnormal hearing with no sensory cell loss, and various combinations of cell loss and hearing deficit. On the basis of individual animals having very nonhomogeneous pathologies, it may be overly optimistic to expect clear relations between sensory cell populations and a relatively gross measure of function, such as threshold. Furthermore, psychophysical thresholds reflect the totality of changes that have taken place at the periphery as well as centrally, and not simply sensory cell loss. Nevertheless, when relatively simple and consistent lesions are produced (e.g., Ryan and Dallos, 1975), there does appear to be some order to the relation between lesions and thresholds.

Lurie (1937), on the basis of guinea pig and cat experiments, was perhaps the first to suggest that the loss of outer hair cells (OHC) was correlated with approximately a 40 dB loss in pure tone threshold. Schuknecht (1953) essentially con-

Correspondence to: R.P. Hamernik, Auditory Research Laboratory, 107 Beaumont Hall, State University of New York, Plattsburgh NY 12901, U.S.A.

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firmed Lurie's results by concluding that a partial loss of OHC results in a hearing loss for the involved frequencies of less than 50 dB. Losses of greater than 50 dB were correlated with increasing losses of inner hair cells (IHC). Ryan and Dallos (1975) focused their attention primarily on the OHC, and on the basis of Kanamycin-induced basal lesions consisting of pure OHC losses in five chinchillas, concluded that 30 to 50 dB pure tone losses of thresholds were associated with total losses of OHC. Stebbins et al. (1979), using primates, were in essential agreement with these earlier studies. Thus, on the basis of guinea pig, cat, monkey, and chinchilla experiments, considerable evidence exists to equate OHC losses with the first approximately 40 dB of functional hearing loss (at least for the basal 80% of the cochlea (Smith et al., 1987)).

In contrast, the results presented in numerous other reports lead to conclusions that differed from the above. For example, Hunter-Duvar and Elliot (1972), and Schuknecht (1974) have shown 20 to 40 dB losses in thresholds without sensory cell loss; while Eldredge et al. (1973), Henderson et al. (1974), and Hunter-Duvar and Elliot (1973), among others, have shown essentially normal thresholds in the presence of outer hair cell lesions. A number of other studies with anomalous findings have appeared over the last 20 years or so. The human postmortem studies of Bredberg (1968) showed individual cases that could fit into any of the classes of results discussed above. Two factors which contribute to these differing classes of results are: (1) very small sample size upon which generalizations are formed, and (2) the very nonhomogeneous or diffuse nature of the pathology generated by some noise exposures. The approach to the data analysis used in this study would tend to obviate some of these factors and to allow generalizations to be made regarding the quantitative relation between hearing loss and cochlear sensory cell loss in large populations of noise damaged subjects. From these data an estimate of the probability of each of the above anomalous findings can be obtained.

Although much of the current emphasis in research in this area is aimed at uncovering the relation between subtle changes in sensory cell morphology and neural function (Liberman and Dodds, 1984a, b), there still may be useful information to be gleaned from correlations between sensory cell populations and psychophysical measures of hearing function. This paper presents the results of an analysis of the noise-induced permanent threshold shift (NIPTS) and sensory cell loss in 420 noise-exposed chinchillas. While, in part, these data recapitulate some of the conclusions of others, the conclusions here carry the weight of a large sample size. The data also provide a broader frequency and dynamic range over which interrelations between pathologies and hearing can be assessed.

Methods

These data were collected over a period of approximately five years using a relatively consistent set of experimental protocols which have been published elsewhere e.g., Henderson et al., 1983 and Hamernik et al., 1987. The animals generally varied in age from approximately 6 months to two years; however a small percentage was as old as 4 years. Each animal in this population study was made monaural by the surgical destruction of the left cochlea. Pure tone thresholds were obtained on most animals at 0.125, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 kHz using either behavioral or evoked response techniques. In some animals thresholds at 0.125, 0.25, or 16 kHz were not measured. The resolution of the evoked potential and behavioral threshold test system was ± 2.5 dB and ± 5 dB, respectively. All animals were exposed to a noise which varied from a very short duration, acute exposure at high intensity, to relatively long term (5 days), low-level exposures. The noises were varied: impulse noise and impact noise comprised the majority of exposure conditions ($\approx 75\%$), while the remainder were either continuous broad band noise, octave band noise, or combinations of any of these classes of noise. The noise levels varied from relatively low levels (80 dB SPL) to very high peak intensities of impulse noise (165 dB), while the energy spectra of the noises in the vast majority of cases ($> 95\%$) were confined to the 0.25 to 2.5 kHz region. These exposures caused a range of effects; from little or no hearing loss, to a severe, broadly distributed hearing loss. In all cases, NIPTS was measured

between 30 and 40 days following the termination of the exposure. The mean of at least three separate threshold determinations at each test frequency established both the preexposure and 30 days postexposure thresholds from which PTS was calculated. The difference between the postexposure and preexposure thresholds in each animal was used to establish each animals PTS.

Following the last postexposure threshold test, the animals were killed and the cochleas were prepared for standard surface preparation histology. Cytocochleograms were generated on each cochlea. The cytocochleogram was divided into bins representing octave band lengths of the cochlea with center frequencies at the audiometric test frequencies. Bin lengths were established using the frequency-place map for the chinchilla (Eldredge et al., 1981). For each octave bin, the total number of missing inner hair cells, outer hair cells, and outer hair cell loss by row (OHC_1, OHC_2, OHC_3), was tabulated. For each test frequency, the NIPTS and sensory cell loss data for each animal were entered into a DEC Micro PDP 11/73 computer for subsequent analysis and plotting.

Results

Cell loss was calculated on a percentage basis using the mean standard sensory cell populations established from 30 normal animals shown in Table I. The normative sensory cell populations that were used in the calculation of the percent sensory cell loss in the eight bins of the cochlea are in agreement with the figures presented by Bohne et al. (1982), and Santi et al. (1986). For the 420 experimental cochleas presented in this paper, the mean length was L = 18.533 mm with a standard deviation of 0.84 mm (max = 21.03 mm; min = 15.58 mm).

A preliminary analysis of the PTS-cell loss data was performed in order to obtain an estimate of the functional relation between PTS and sensory cell loss at each test frequency. Some of the results of this initial analysis are shown in Fig. 1. Each data point shown in this figure was obtained as follows: at a given test frequency, the sensory cell loss for all animals that showed a $X - 4 \leq \text{NIPTS} \leq X + 5$ (where $X = -5, 5, 15, \ldots 65$ dB) was obtained over the octave band length of the cochlea centered at that test frequency and averaged. The mean cell loss data was plotted as a function of NIPTS for each value of X. The bar through the data point represents the standard error of the mean, and the sample size (N) that generated that data point is located along the lower margin of the graph. The absence of a bar through a data point indicates that the standard error was less than the size of the symbol representing the point.

A visual inspection of these reduced data suggested the function that would best fit these data would be an exponential of the form:

$$Y(\%\ \text{cell loss}) = 100\left[1 + e^{\left(\frac{C-X}{B}\right)}\right]^{-1} \quad (1)$$

TABLE I

THE NORMAL SENSORY CELL POPULATIONS THAT WERE USED TO ESTABLISH THE % CELL LOSS IN OCTAVE BAND LENGTHS OF THE COCHLEA

Location (%) re: apex	CF (kHz)	Frequency range (kHz)	$\bar{L}$ (mm)	Mean No. of cells	
				IHC	OHC
0 – 7.45	(0.125)	0.123– 0.177	1.382	125	495
7.46– 20.68	0.25	0.178– 0.354	2.464	247	981
20.69– 34.18	0.50	0.355– 0.707	2.484	264	1053
34.19– 47.40	1.00	0.708– 1.414	2.451	240	930
47.41– 60.91	2.00	1.415– 2.028	2.505	255	1023
60.92– 74.41	4.00	2.029– 5.656	2.503	242	930
74.42– 87.91	8.00	5.657–11.312	2.503	250	930
87.92–100.00	16.00	11.313–20.840	2.241	250	930
		Total	18.533	1873	7272

These figures are means, based upon a sample of 30 normal chinchillas.

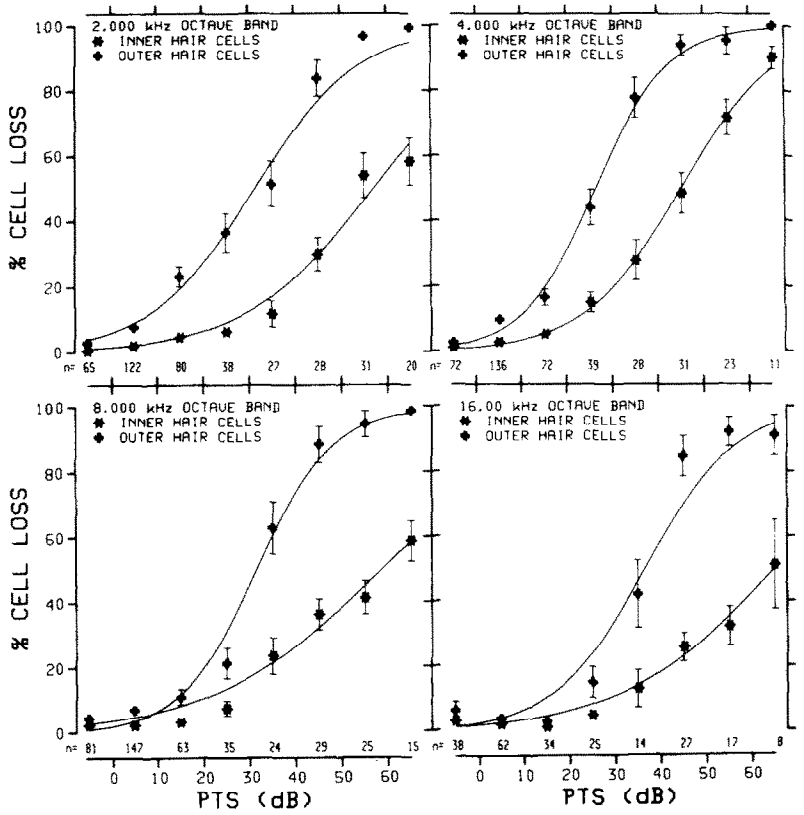

Fig. 1. The relation between percent inner and outer hair cell loss within the indicated octave band length of the cochlea and the mean noise-induced permanent threshold shift measured at the 2.0, 4.0, 8.0, and 16.0 kHz test frequencies. The solid line is a result of a least squares regression of % cell loss on PTS, and the symbols represent the reduced data points.

where B and C are empirically determined, frequency dependent constants, and X is the NIPTS. B (dB) is inversely proportional to the maximum slope of the exponential function and C (dB) is the point at which the gradient of sensory cell loss (i.e., the slope) reaches its maximum. Note that the inner and outer hair cells lost in a given octave band increase from roughly 30 to 70% in the range $C - B \leq \text{NIPTS} \leq C + B$. This exponential was converted into a linear form which allowed a simple linear regression analysis to be performed using a least squares approximation. Thus equation (1) can be written $Z = \gamma - \beta X$ where $Z = \ln [100/y - 1]$ and $\gamma = C/B$; $\beta = 1/B$. The solid line drawn through the reduced data points in Fig. 1 is the result of this least squares approximation.

The functional relation between NIPTS and cell loss described by equation (1) was fit to the entire set of raw data using a least squares analysis (see appendix A for a more detailed discussion of this analysis). The results of this analysis, along with the raw data, are shown in Fig. 2 for both the inner and outer hair cells. Since the regression line which ultimately generated the solid curves in Fig. 2 can be artifactually skewed by values of Y equal to zero or 100%, all experimental data for which Y was equal to zero or 100% were assigned values of 0.001% or 99.999%, respectively to obtain the equation of the regression line. The manner in which the constants B and C vary with frequency for both the IHC and the OHC is plotted in Fig. 3. For each frequency the best fit curves to the data computed using the approximate method of averaging the data within bins (Fig. 1), and the entire set of raw data (Fig. 2) produce qualitatively very similar functions at 0.5 kHz and above. Therefore, the constants B and C, which describe

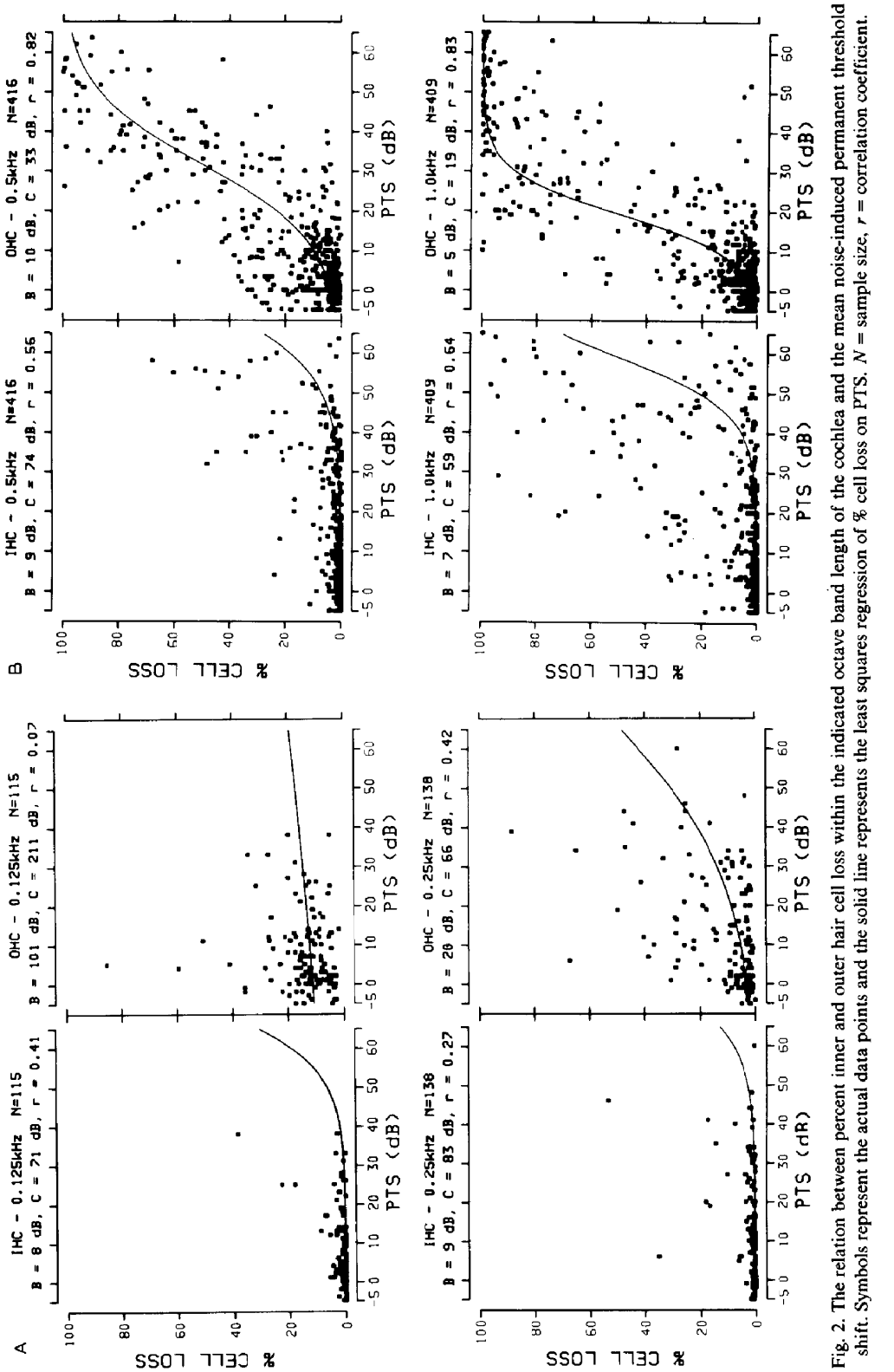

Fig. 2. The relation between percent inner and outer hair cell loss within the indicated octave band length of the cochlea and the mean noise-induced permanent threshold shift. Symbols represent the actual data points and the solid line represents the least squares regression of % cell loss on PTS. N = sample size, r = correlation coefficient.

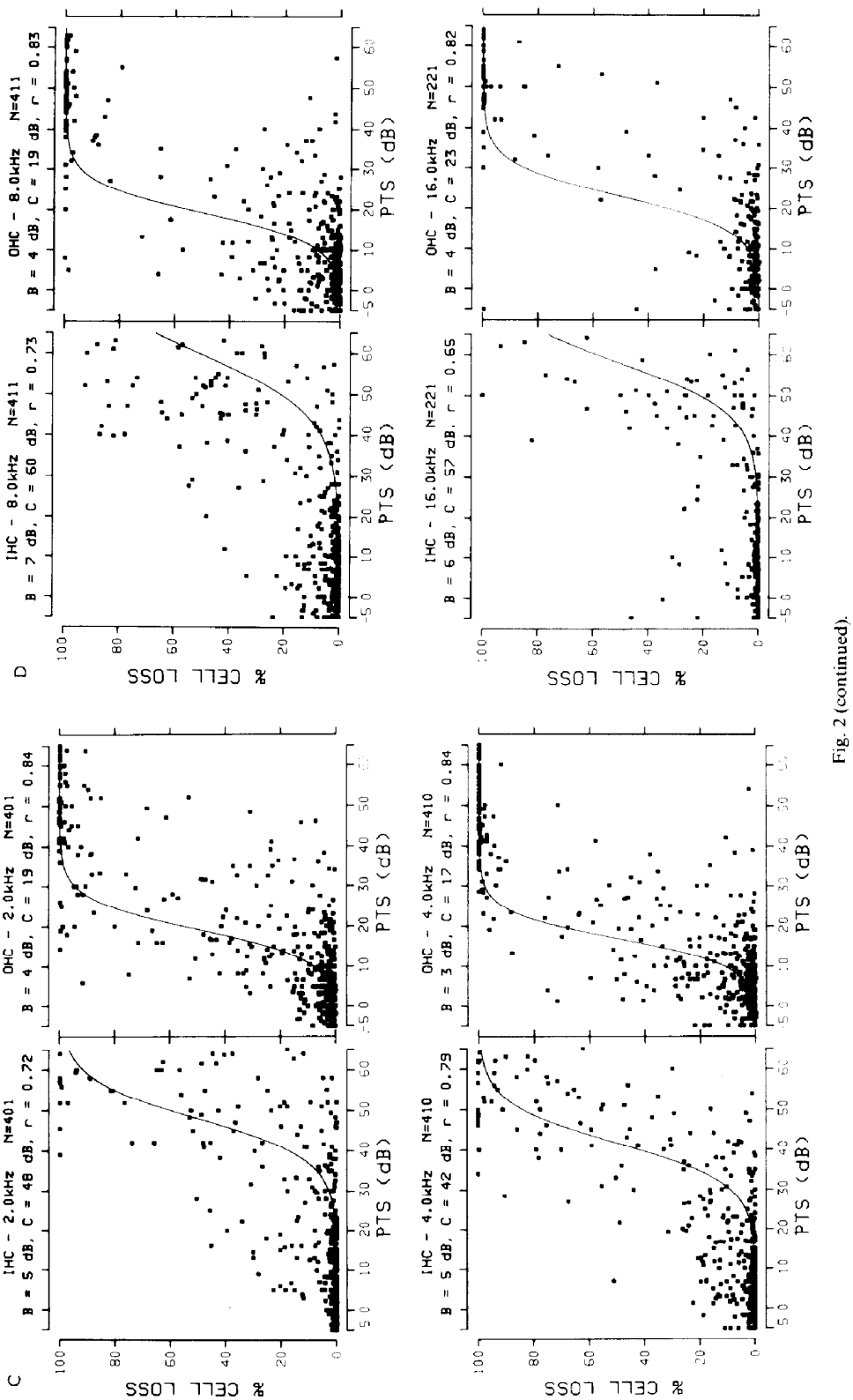

Fig. 2 (continued).

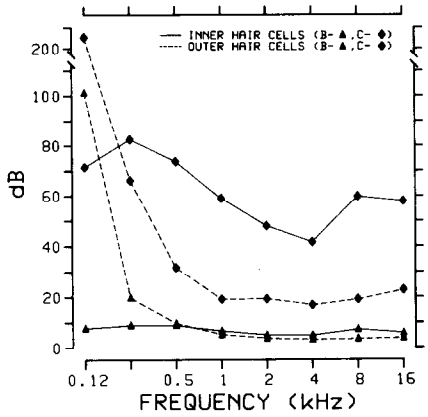

Fig. 3. The variation of the parameters B and C as a function of frequency for both the inner and the outer hair cells.

the curves which were fit with the approximate method, have not been shown.

The relation between the three individual rows of OHC and NIPTS was analyzed in a manner similar to that described for the data in Fig. 1, i.e., using the approximate method. The only statistically significant differences (t-test) among the three rows of OHC are shown in Fig. 4. Over an approximately 30 dB range of NIPTS (25 dB $\leq$ NIPTS $\leq$ 55 dB), only the OHC_3 at 0.5 and 1.0 kHz showed less loss on the average for a given NIPTS than did rows one and two. At all other frequencies, the percentage of OHC loss by row versus NIPTS was identical and is typified by the 4 kHz and 8 kHz data presented in Fig. 4.

The analytical representation of the data in Fig. 2 has been replotted in Fig. 5 as iso-NIPTS curves in order that the pattern of cell loss across the range of test frequencies can be visualized more easily. The following points can be made from this figure: (1) when there is no NIPTS, there is relatively little or no IHC and OHC loss; (2) less than 5 dB NIPTS at any frequency is reflected in a low level ($\approx 5\%$) of OHC loss and little or no IHC loss; (3) for low levels of NIPTS, the OHC lesion is most severe at 1 kHz; as NIPTS increases, a larger peak of OHC loss develops in the 4 kHz

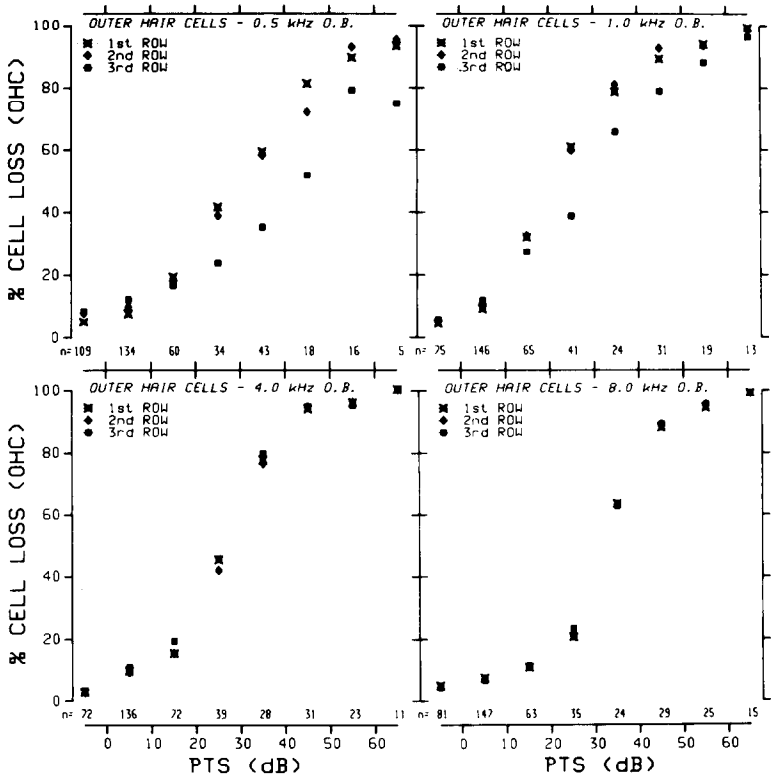

Fig. 4. The relation between the individual rows of outer hair cells and the amount of NIPTS at 0.5, 1.0, 4.0, and 8.0 kHz.

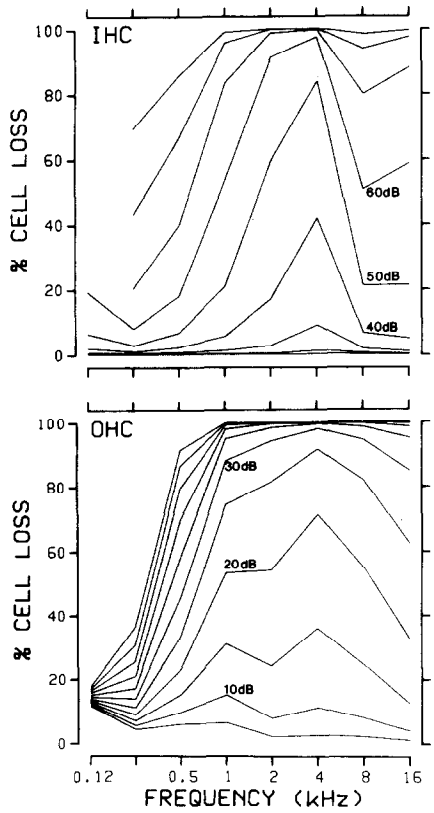

Fig. 5. An iso-NIPTS representation of the inner (upper) and outer hair cell loss (lower) as a function of audiometric test frequency. The IHC iso-NIPTS contours range from 10 to 90 dB in 10 dB intervals; the OHC iso-NIPTS contours range from 5 to 55 dB in 5 dB intervals.

region, while the iso-NIPTS contour is consistently depressed at 2 kHz; and (4) when NIPTS reaches approximately 30 dB, there is a clear tendency for IHC loss to develop at 4 kHz. This 4 kHz peak is dominant throughout the remaining IHC iso-NIPTS series.

Discussion

The detailed VIIIth nerve studies of Liberman and Kiang (1978), Liberman and Dodds (1984a, b), Salvi et al. (1982), and others, have shown a relatively precise relation between changes in neural responses and morphological changes of inner and outer hair cells in noise-exposed animals. On the other hand, correlations between auditory thresholds and cell loss have been quite variable. Thus, on the basis of physiological data, it would appear that the audiogram is not sufficient to characterize the unique distribution of sensory cell loss or pathology. However, it seemed reasonable to expect if a sufficiently large sample of NIPTS audiograms and cochleograms were to be assembled and analyzed, some meaningful trends would emerge. This was the primary reason why this data analysis was undertaken. Although the manner in which these data were analyzed neglects important known properties of the traveling wave mechanics that are reflected in threshold measurements, there is a satisfying order to the data that commands attention. The group results substantiate a close relation between a relatively normal (i.e. within 5% of the sensory cell population of the control values) OHC population and normal hearing thresholds across the 0.25 to 16.0 kHz test frequency range. However, consistently detectable OHC losses in the group data are apparent with less than 5 dB NIPTS at all audiometric test frequencies. This is especially noticeable at the 0.125 test frequency where OHC losses can be as high as 10%. The data further support the body of existing data referred to in the introduction which equates severe OHC pathology with the first approximately 30 to 40 dB of NIPTS.

The exponential function used to fit the experimental data provides a reasonable approximation to the data. This function, along with the empirically determined constants, B and C, which define the steepness of the function for a given frequency, can be used to explain all the features evident in the iso-NIPTS contours. The constants, B and C, may be useful indexes for comparing results across species. Also, in many experimental situations, frequently it is desirable to be able to estimate (even crudely) sensory cell losses from the audiometric data alone. On the basis of the orderly distribution of the analytical data shown in Fig. 5, we can at least roughly estimate the mean sensory cell loss (i.e., a mean cochleogram) for an experimental group of noise-exposed chinchillas on the basis of the audiometric data alone.

Throughout the literature on the effects of noise on sensory cell populations, various authors have commented on the relative susceptibility of the three rows of outer hair cells (Saunders et al.,

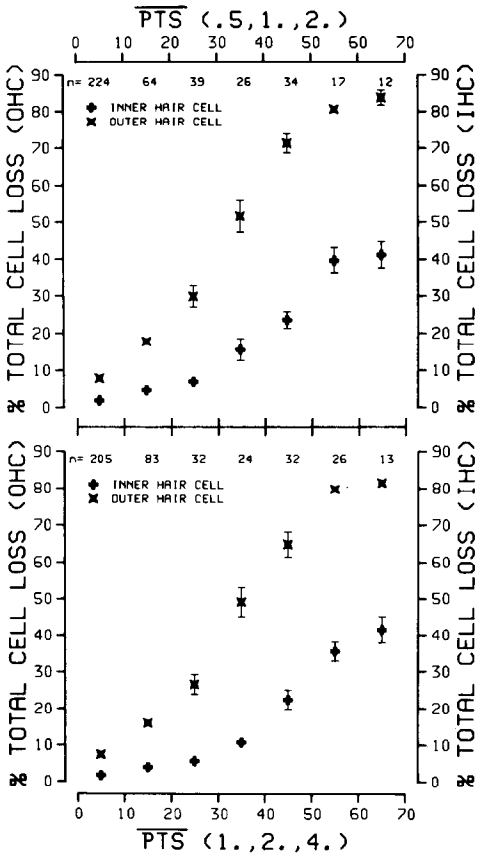

Fig. 6. Two examples of the manner in which the AA00 definition of hearing handicap can be translated into a morphological equivalent based upon NIPTS measured at 0.5, 1.0, and 2.0 kHz and at 1.0, 2.0, and 4.0 kHz.

1985). As with threshold and sensory cell correlations, there is no clear agreement on the contribution of the various rows of OHC to audiometric thresholds. The data presented in this paper show a statistically clear difference in the pattern of OHC loss for a given PTS only at 0.5 and 1.0 kHz where the third, or outermost, row of sensory cells shows consistently less damage for a given amount of PTS. These differences are significant only for the range of NIPTS between approximately 25 and 55 dB. Throughout the remainder of the cochlea, all three rows of outer hair cells would, on the average, appear to make an equal contribution to the noise-induced hearing loss.

One practical application of this type of database is shown in Fig. 6. The old AAOO (1959) recommendation defines hearing handicap on the basis of an average PTS measured at 0.5, 1.0, and 2.0 kHz. We have illustrated in Fig. 6 how this definition of handicap can be interpreted in terms of cochlear sensory cell loss. The mean PTS at 0.5, 1.0 and 2.0 kHz ($\overline{PTS}_{0.5,1,2}$) was calculated for each animal and the animals were sorted into consecutive 10 dB bins based on their $\overline{PTS}_{0.5,1,2}$. The total number of missing IHC and OHC throughout the entire cochlea for each animal in a particular bin was obtained from the cochleogram and the total mean sensory cell loss for that 10 dB bin was calculated. This exercise was repeated for $\overline{PTS}_{1,2,4}$, $\overline{PTS}_{2,4,8}$ and $\overline{PTS}_{0.5,2,4}$. The suprising feature of these data is the similarity of all four graphs, typified by the two examples shown in Fig. 6. The argument has been put forward that the definition of hearing handicap should include higher audiometric frequencies and thus make it a more sensitive indicator of the onset of handicap. The data in Fig. 6 can be used to assess, in quantitative terms, how to interpret the differences among these various proposed handicap definitions in terms of cochlear pathology, at least for the chinchilla.

Our approach to analyzing these data in the chinchilla was similar to that which was attempted by Bredberg (1968) in his human postmortem studies and by Miller et al. (1963) in their cat studies. The limited database in Bredberg's (1968) Fig. 96 has been replotted, along with the equivalent curve-fitted chinchilla data, in Fig. 7. The dashed line in this figure represents a curve fit (using the same function as in the chinchilla) to the Bredberg data after it had been collapsed into 10 dB bins as was done with the individual chinchilla data (Fig. 1). An interesting difference between the human and the chinchilla data is the difference in OHC loss for a given NIPTS at the low and high frequencies. For the low frequency data (250 Hz), the chinchilla consistently shows less sensory cell loss for a given hearing loss than the human, while the opposite is true for the high frequency (8 kHz) data. This would imply that for some midfrequency range, the relation between outer hair cell loss and NIPTS may be similar in the two species. While obvious parallels between the two sets of data are not apparent partially because of the very limited data in the Bredberg study, it is possible that if the scattered human

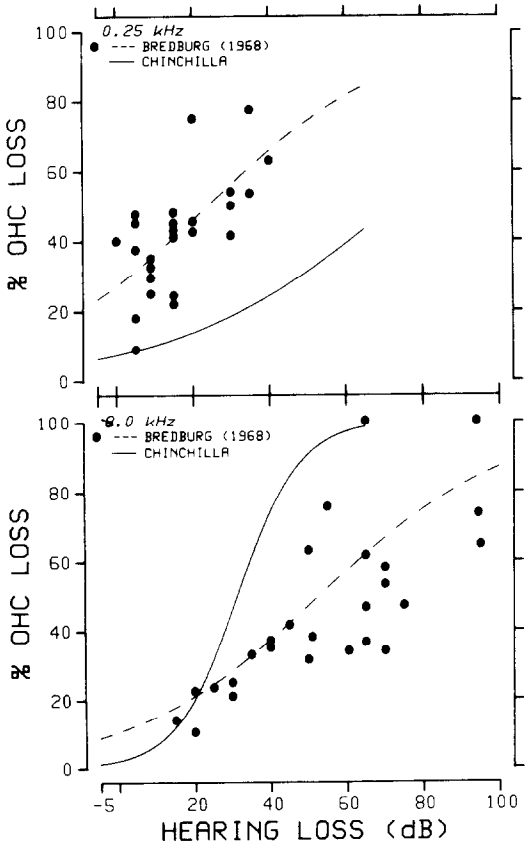

Fig. 7. A comparison of the human postmortem data of Bredberg (1968) and the chinchilla data at 0.25 kHz and 8.0 kHz. The curve-fitting parameters for the reduced Bredberg data are: At 0.25 kHz, $B = 24.5$ dB, $C = 24.0$ dB; at 8.0 kHz, $B = 8.2$ dB, $C = 31.4$ dB.

database can be organized, we may be able to develop an extrapolation strategy between the two species.

The iso-NIPTS curves shown in Fig. 5 bear a surprising similarity to the cat data (Fig. 35) of Miller et al. (1963). Again, direct comparisons are difficult because of the lack of quantitative sensory cell data in the Miller et al. study. In both the cat and the chinchilla, large amounts of NIPTS are associated with a relatively small amount of cellular damage at the very low frequencies. The reasons for this, that are presented by Miller et al. (1963), also apply to the chinchilla. Also the initial peak of injury in the Miller et al. study (presumable mostly OHC damage) occurs between 1 and 2 kHz in the cat, and at 1 kHz in the chinchilla. As larger values of NIPTS are approached, the severity of the sensory cell loss in both species shifts to the 4 kHz region of the cochlea. Considering the quite different nature of the noise exposures and the differences in the middle ear transmission characteristics of the two species, the overall congruence of the plotted data in the two studies is suprising.

In the chinchilla the highest density of myelinated nerve fibers, which presumably innervate the IHCs, is found near the 4 kHz region of the cochlea (Bohne et al., 1982). On the basis of the iso-NIPTS curves shown in Fig. 5, it would appear that for a given amount of hearing loss the 4 kHz region of the cochlea can sustain a greater IHC loss than can higher or lower frequencies. Keeping in mind that the OHC pathology is severe by the time noticeable losses of IHCs begin to occur at 4 kHz, the 4 kHz peak in the IHC contour may imply a redundancy in the innervation to the 4 kHz region of the cochlea. Alternately, the excessive damage to the IHC at 4 kHz may be a reflection of an altered mechanics induced by, e.g., what must be abnormal tectorial membrane attachments in the area (Zwislocki, 1982 and 1984) or changes induced by an abnormal efferent input to the already damaged OHC area (Patuzzi et al., 1984), both of which undoubtedly produce changes in the basilar membrane mechanics in that area (Cody and Johnstone, 1982). While Liberman and Kiang (1978) make the point there is no evidence to support the idea of a 'special weakness' in the 4 kHz area of the cat, they do indicate there appears to be 'something unique about the 3 to 4 kHz region' of the cochlea. While detailed quantitative data on the innervation patterns to the OHCs are lacking, the inverted 'W' pattern of the iso-PTS curves for the OHCs may also reflect differences in the innervation pattern to the OHCs in this region of the cochlea.

Acknowledgements

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Animal Use

In conducting the research described in this report, the investigators adhered to the 'Guide for Laboratory Animal Facilities and Care', as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

Appendix A

Note on the data analysis: Since the X (PTS) and Y (% cell loss) variables are not perfectly correlated, predictions of one variable from the other must use one of two regression lines. Conventional predictions of PTS use a least-squares regression of PTS on % cell loss, while a prediction of % cell loss would use the regression of % cell loss on PTS. Neither of these two lines, however, provide the best descriptor of the functional relationship between PTS and % cell loss. Predictions (between X and Y) based upon two regression lines introduce an unsatisfactory duality which could be avoided by focusing on a description of the data (i.e., a functional relationship) rather than on prediction. Traditional least-squares regression lines minimize the sum of the squared deviations of the observed point from the predicted line along either the Y (regression of Y on X) or X (regression of X on Y) axis. However, since neither PTS nor % cell loss are independent variables, the best descriptor would be one that minimized the error along both the X and Y axes simultaneously. A regression line may be computed that does, in fact, minimize the error along both directions by using the sum of the squared deviations of the perpendicular distance from the observed data point to the line of 'best fit'. Miller et al. (1963) on page 70 of their monograph have used such an approach. Our Fig. 2 shows the line of 'best fit' computed using the traditional regression of Y on X (% cell loss on PTS). As a result of the different scales employed on the X and Y axes, the regression of Y on X is virtually identical to the function derived by minimizing the sum of the squared perpendicular distance. Thus, we have chosen to present our data using a conventional regression analysis.

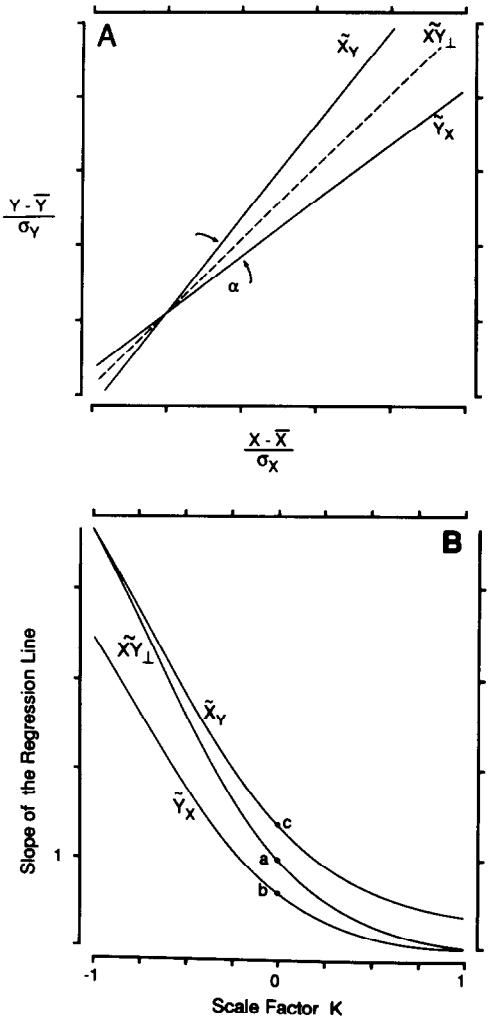

Fig. A-1. A schematic portrayal of the rational for using a least squares regression of % cell loss on PTS to describe the functional relation between these two variables.

The logic for using the perpendicular minimization scheme and the reasons that this procedure produces nearly the same function as that obtained for a regression of Y on X are presented schematically in Fig. A-1. When the X and Y data points are plotted on standardized axes, i.e.:

$$Z_Y = \frac{Y - \bar{Y}}{\sigma_Y} \qquad Z_X = \frac{X - \bar{X}}{\sigma_X}$$

the two regression lines ($\tilde{Y}_x$ and $\tilde{X}_y$) differ by some angle α, as shown in Fig. A-1 (A). This angle depends upon the correlation between the two variables Z_y and Z_x. It can be shown that when standardized axes are used, a minimization of the perpendicular distance produces a 'regression' line ($\widetilde{XY}_\perp$) that bisects α. However, consider what happens to the slopes of $\tilde{Y}_x$, $\tilde{X}_y$, and $\widetilde{XY}_\perp$ when the Z_x variable to multiplied by a scale factor e^k (i.e. $Z_x \cdot e^k$) where $-1 \leq k \leq +1$ (Fig. A-1 (B)). The variable e^k is a scale factor acting on the Z_x-axis alone. When $k = 0$, the axes are standardized and the slope of $\widetilde{XY}_\perp$ (point a) lies midway between that of $\tilde{X}_y$ (point c) and $\tilde{Y}_x$ (point b). Note that the distance between b and c is determined by the correlation coefficient. As k approaches 1, the slope of $\widetilde{XY}_\perp$ approaches that of $\tilde{Y}_x$, while as k approaches -1, the slope of $\widetilde{XY}_\perp$ approaches that of $\tilde{X}_y$, i.e., an expanded or compressed X-axis relative to the Y-axis affects the slope of $\widetilde{XY}_\perp$. For the experimental data presented in Fig. 2, the slope of $\widetilde{XY}_\perp$ is very close to that of the conventional regression of Y on X. Thus, the curves shown in Fig. 2 actually represent a very good description of the data while maintaining a conventional approach to regression analysis.

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