

Interrupted noise exposures: Threshold shift dynamics and permanent effects

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A parametric study of the reduction of threshold shift (toughening phenomena) that takes place during the course of an interrupted noise exposure is described. 266 chinchillas randomly assigned to one of 32 experimental groups were exposed to one of the following: a 400-Hz narrow-band impact noise having a center frequency of 0.5, 1.0, 2.0, 4.0, or 8.0 kHz and peak sound-pressure levels of 109, 115, 121, or 127 dB. The impacts were presented for 5 d, 24 h/d or for 20 d, 6 h/d. Corresponding pairs of exposures had equal energy. Group mean noise effects were estimated from pure-tone thresholds obtained from inferior colliculus evoked potentials and from surface preparation histology. The threshold shift (TS) toughening phenomena is shown to occur in response to all stimuli that produce a TS and at all audiometric test frequencies. The amount of toughening, which is limited to less than 35 dB, varies with noise frequency and intensity. Based on group mean data the auditory system is not protected from the permanent effects of an interrupted noise exposure as a result of the toughening effect but rather differences in permanent effects between the 5- and 20-d exposures are attributed to the spreading of the exposure energy over an extended period of time. © 1998 Acoustical Society of America. [S0001-4966(98)06206-7]

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INTRODUCTION

The ISO-1999 (1990) document, relating levels of noise exposure to an estimated noise-induced hearing loss (NIHL) in the exposed population, uses an energy metric to organize the exposure data and an age correction (dB) that, when subtracted from hearing thresholds, yields NIHL. The energy approach to the standards document has been questioned by Bies and Hansen (1990) who showed that an alternate formulation is consistent with the demographic data base and by Kraak (1981) whose approach is consistent with that of Bies and Hansen. Similarly, there are many examples in the literature that demonstrate, on the basis of experimental evidence, the limitations of an energy metric (Lei *et al.*, 1994). The ISO approach to an age correction has also been questioned on methodological grounds by Bies and Hansen (1990) and by Humes and Jesteadt (1991) and most recently on experimental grounds by Mills *et al.* (1997). The approach to the interaction between noise and other threshold-elevating variables (e.g., age) suggested by Humes and Jesteadt is conceptually consistent with the approach of Bies and Hansen.

Experiments involving noise exposure paradigms that modulate postexposure threshold shifts (TS) (temporary or permanent) further question the suitability of an energy metric for noise exposure standards. One class of such experiments is typified by the exposure paradigms used by Canlon *et al.* (1988) and are referred to as “conditioning” or “priming” experiments. In this paradigm a continuous low-level noise, that produces little or no TS, is used to alter the susceptibility of the cochlea (i.e., usually to reduce its susceptibility to noise or to “toughen” it) prior to further experimen-

tal noise treatment. A second class of TS-modulating experiments is typified by the interrupted exposure paradigms used by, for example, Clark *et al.* (1987), Subramaniam *et al.* (1991a), and Hamernik *et al.* (1994). In this paradigm, a noise of sufficient intensity, presented to an experimental animal on a daily repeated cycle, produces a TS following the first day of exposure. Threshold shifts measured on subsequent days of the exposure sequence have been shown to decrease relative to the initial TS. This reduction of TS, despite a continuing daily exposure regime, has been called a cochlear toughening effect and the exposures referred to as “toughening” exposures.

A fundamental issue that appears throughout the toughening literature is the extent, if any, of the protection from permanent noise-induced changes afforded to the auditory system by the toughening phenomena as a result of an interrupted noise exposure. This issue has at least two different but related facets: (1) Does a population exposed to an interrupted noise that produces toughening develop less or more permanent threshold shift (PTS) than a matched population exposed to an uninterrupted noise of the same total energy? That is, is the ear that is being gradually toughened by a noise protected from that noise? In the absence of any toughening effects the interrupted paradigm would generally be expected to produce less permanent auditory system changes than the equivalent uninterrupted exposure (Ward, 1991). (2) Is the cochlea, toughened by an interrupted noise exposure and subsequently exposed to a more traumatic noise, affected less by the traumatic noise than an untoughened cochlea?

This latter question is addressed in a number of papers where the answer is arguably equivocal. The earliest reference to the issue of just such a protective effect can be found in the Miller *et al.* (1963) paper in which the noise-toughened cat cochlea was shown to be affected by a high-

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level noise to the same extent as the untoughened cochlea. More recently, Subramaniam *et al.* (1993) showed that, under some conditions, the cochlea toughened by a low-frequency, interrupted noise did not provide any protection from a subsequent high-frequency [4-kHz octave band noise (OBN)] exposure, instead the 4-kHz exposure produced an exacerbation of both PTS and outer hair cell (OHC) loss. However, protection from a low-frequency noise exposure was reported by, for example, Campo *et al.* (1991) and McFadden *et al.* (1997). A confounding factor in both of these papers was that when statistically less PTS was found in the toughened ears there was no protective effect on the OHC population as measured by conventional cochleograms. With this inconsistency the standard “escape clause,” that more subtle sensory cell damage must be present that is not seen in the light microscopic analysis, is invoked. The effect of an impact noise exposure on the noise-toughened cochlea was explored by Roberto *et al.* (1996) and by Henselman *et al.* (1994). In the former paper, the protective effects, if any, were inconsistent, while in the latter very large protective effects were observed in both the PTS and sensory cell data. The McFadden *et al.* (1997) paper presents a good overview of most of the literature on this topic.

Since one might expect that the underlying mechanisms of these two classes of TS-modulating experiments (i.e., priming and toughening) have some processes in common, the effects produced by each should mutually interact. The extent of the interaction, however, has not been sufficiently studied. The efforts of Roberto *et al.* (1996), to first prime the cochlea with a low-level noise followed by an interrupted noise which was known to also toughen the cochlea, yielded inconsistent results. Following a similar protocol, Dagli and Canlon (1997), using otoacoustic emissions metrics, showed that a primed cochlea responds differently to an interrupted noise than does an unprimed cochlea.

The question of whether the cochlea that is gradually being toughened by an interrupted noise is in fact being protected from that same noise has had only limited attention. In the Clark *et al.* (1987) paper the interrupted exposures that produced a toughening also resulted in less hearing and sensory cell loss than an equal energy control group. However, the effect was small, the experimental conditions were limited, and the group sample sizes were small. Furthermore, whether the reduced permanent effects were the result of a toughened cochlea or just the moderating effect of the noise interruption as is often seen following interrupted exposures (e.g., Ward, 1991) that produce no toughening is not clear. The toughening phenomena produced by an interrupted noise exposure has also been shown to be manifested in physiological data (single unit and whole nerve action potential measures) (Sinex *et al.*, 1987; Boettcher *et al.*, 1992). However, the relation of the physiological data to the status of the sensory epithelium is also not clear. Boettcher *et al.* (1992), for example, show a continuing increase in OHC pathology despite a nearly complete recovery of the AP thresholds thus indicating that despite the recovered AP, the final condition of the cochlea will be altered.

The modulation of TS during an interrupted noise exposure is further complicated by the frequency and intensity

parameters of the stimulating noise and the audiometric test frequency used to monitor the effects (Subramaniam *et al.*, 1991a, b). The mechanisms responsible for the toughening phenomena are not known, however, the mechanical properties of the OHC system and the efferent systems have been shown to play a role (Zheng *et al.*, 1997).

In the present paper, we present data from a parametric experimental design involving 32 different exposure conditions and 266 subjects. The presentation and discussion of the group mean data address the following issues: (1) The applicability of the equal energy concept to interrupted noise exposures; (2) the relation among stimulus frequency, energy, audiometric test frequency, and the amount of toughening; and (3) the extent of the protection from permanent noise-induced changes afforded to the noise-toughened cochlea.

I. METHODS

Summary data from 135 chinchillas exposed to an uninterrupted, 5d, asymptotic threshold shift (ATS) producing impact noise and 131 chinchillas exposed to an equivalent energy, 20-d, interrupted impact noise are used to assess the three issues identified above. Brainstem (inferior colliculus) auditory evoked potentials (AEP) collected from monaural chinchillas were used to estimate pure-tone thresholds and surface preparation histology was used to quantify sensory cell populations. A narrow-band transient (impact) noise, of varying intensity and center frequency (CF), was used to probe the extent of the toughening phenomena. Details of the experimental methods, beyond those that are presented below, can be found in Ahroon *et al.* (1993).

A. Noise exposures

Thirty-two different noise exposures were used; 16 were used to produce different ATS conditions and 16 similar exposures, having equal energy but presented on a 20d interrupted schedule, were used to induce toughening. The exposures consisted of narrow-band impacts (NBI) 400-Hz wide, having center frequencies of 0.5, 1.0, 2.0, 4.0, and 8.0 kHz. The NBIs were presented at a rate of 1/s, 24 h/d for 5 d or 6 h/d for 20 d. Peak sound-pressure levels (SPLs) were 109, 115, 121, or 127 dB. All noise stimuli were generated digitally using a virtual instrument developed using the LabView™ software package. A fixed-length pulse was fed through a 4th-order bandpass Butterworth filter. The resulting waveform was played through the computer's sound output and fed to an AB International Precedent Series 900A amplifier. The output of the amplifier was fed to either a JBL model 2445J speaker with model 2360H horn and model 2360T transition piece (1-, 2-, and 4-kHz CF impacts); Electro-Voice dual DH1Amt-16 transducers with MTA-22 transition piece and HP640 horn (8.0-kHz CF impacts), or an Electro-Voice TL550D speaker system (0.5-kHz CF impacts). Table I shows the experimental groups and the number of subjects in each group. Figure 1 shows the relative spectrum and temporal waveform of each NBI at the 121-dB peak SPL. Waveforms and spectra at other levels were qualitatively similar.

TABLE I. Experimental groups: number of animals in each group exposed to the narrow-band impacts (NBI) for 5 or 20 d having the indicated center frequencies (CF) and peak sound-pressure levels (SPL).

NBI CF (kHz)	5-d exposures dB peak SPL				20-d exposures dB peak SPL			
	109	115	121	127	109	115	121	127
0.5	...	10	5	6	...	9	9	6
1.0	10	9	9	10	9	9	9	9
2.0	...	9	9	5	...	9	9	6
4.0	...	9	9	9	...	9	9	8
8.0	9	9	8	...	6	9	6	...

During exposure, individual chinchillas were confined to cages (10×11×16 in.) with free access to food and water. A maximum of six animals was exposed at a time. Peak SPLs in the exposure field were uniform to within less than 2 dB.

B. Threshold testing procedures

Thresholds for all audiograms were measured at octave intervals from 0.5 to 16.0 kHz. The mean of three threshold determinations measured on different days defined each animal's pre-exposure audiogram. A complete audiogram was measured once daily during each of the five exposure days of the ATS exposure paradigm and the average daily TS established the mean ATS levels. For the 20-d interrupted exposure paradigm a complete audiogram was measured prior to and immediately following each daily 6 h exposure in order to establish the magnitude and time course of the toughening. The amount of toughening at each audiometric test frequency was defined as the difference between the TS measured at a given frequency following the first day exposure (TS₁) and the mean of the thresholds measured following exposure on days 16, 18, and 20 (TS₁₆₋₂₀). Following a 30-d postexposure recovery period thresholds for both sets of animals were measured again on different days and averaged for each animal to establish PTS. PTS was defined as the difference between the 30-d post- and pre-exposure audiograms.

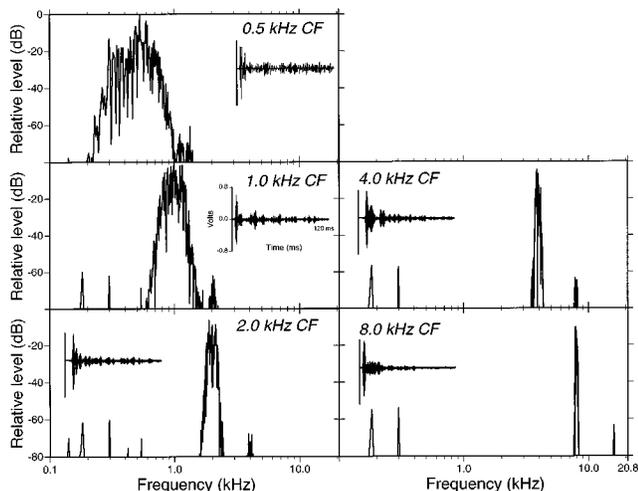


FIG. 1. The relative spectrum and waveform of each of the 400-Hz narrow-band impact stimuli. Peak SPL for each waveform shown is 121 dB. Spectra and waveforms for the other impact levels were qualitatively similar. The ordinate of the time waveform is calibrated at 1 V=125 dB.

C. Histology

Following the last AEP test protocol, each animal was euthanized under anesthesia and the right auditory bulla removed and opened to gain access to the cochlea for perfusion. Fixation solution consisting of 2.5% glutaraldehyde in veronal acetate buffer (final pH=7.3, 605 mOs) was perfused through the cochlea. After 12 h of fixation the cochlea was postfixed in 1% OsO₄ in veronal acetate buffer. Surface preparation mounts of the entire organ of Corti were prepared and inner and outer hair cell (IHC, OHC) populations were plotted as a function of frequency and location using the frequency-place map of Eldredge *et al.* (1981). For purposes of this presentation, sensory cell population data is presented as group averages taken over octave band lengths of the cochlea centered on the primary AEP test frequencies.

II. RESULTS AND DISCUSSION

A. Pre-exposure thresholds

The group mean pre-exposure thresholds are shown in Fig. 2. The large open symbols connected by the solid line in this figure represent the mean AEP thresholds of 924 non-noise-exposed monaural chinchillas from our laboratory. The dashed lines represent one standard deviation above and below the mean thresholds. The 16 group means for subjects exposed to the 5-d ATS or 20-d interrupted exposures are indicated by small points in the upper and lower panels of this figure, respectively. Only five of the 192 group means (32 groups×6 frequencies) differed from the laboratory norm by more than one standard deviation and none exceeded two standard deviations from the mean. Since the audiometric dependent variables used in this study are threshold shifts (as opposed to shifted thresholds) the small differences in group mean pre-exposure thresholds should not affect the overall conclusions drawn from this data base.

B. Threshold shifts and sensory hair cell losses

The correspondence between the group mean TS generated during the 5- and 20-d exposure paradigms for all the groups is shown in Fig. 3, where the group mean TS measured immediately following the first 6-h exposure (TS₁) of the interrupted paradigm is compared with the group mean ATS produced by the corresponding, equivalent energy, uninterrupted exposure for each of the NBIs at each AEP test frequency. [In this and in some of the subsequent figures standard error (SE) bars are indicated. When an SE bar is not

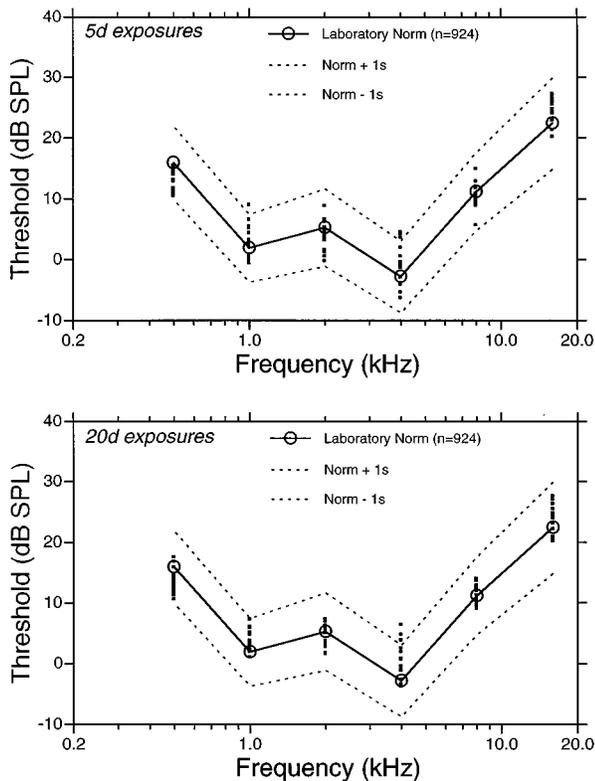


FIG. 2. Group mean pre-exposure auditory evoked potential audiograms for the 16 groups exposed to the 5-d uninterrupted noise (upper panel) and the 16 groups exposed to the 20-d interrupted noise (lower panel) compared with the laboratory norm ($n=924$). The dashed lines indicate one standard deviation above and below the laboratory norm.

present, the SE was less than or equal to the size of the symbol representing the datum point.] The mean ATS is defined as the average of the five TSs that were measured on each of the five days of the uninterrupted exposure. As expected, TS_1 is in general less than or equal to the ATS level. That is, the mean ATS level sets the upper bound for TS_1 . At a number of exposure conditions and AEP test frequencies mean ATS and TS_1 are equal, reflecting the observation of Blakeslee *et al.* (1978) that the ATS level can be reached rapidly using high-level impact stimuli; often during the first hour of exposure. Both sets of exposures produced TSs consistent with stimulus parameters; group mean TS_1 and ATS increased with increasing stimulus energy and TSs occurred at audiometric test frequencies appropriate to the impact center frequency.

Figures 4, 7, and 8 provide some perspective on the nature of the data base that was reduced in order to produce the remaining figures. Figure 4(A) and (B) show the group mean TS at the 4.0- and 8.0-kHz AEP test frequency immediately prior to (open symbols) and following (closed symbols) each of the 6-h exposures to the 1.0-kHz NBI at 127-dB peak SPL. Figure 4(C) and (D) show a comparable data set from the 4.0-kHz NBI at 121-dB peak SPL. Clearly seen in these plots is the regular and generally systematic decrease in TS (toughening) with increasing repetitions of the 6-h exposure. In each panel the amount of toughening [i.e., $TS_r = (TS_1 - TS_{16-20})$] is indicated, where TS_{16-20} is the mean TS measured following days 16, 18, and 20. Exposures to the higher frequency impacts (i.e., the 4.0- and 8.0-kHz

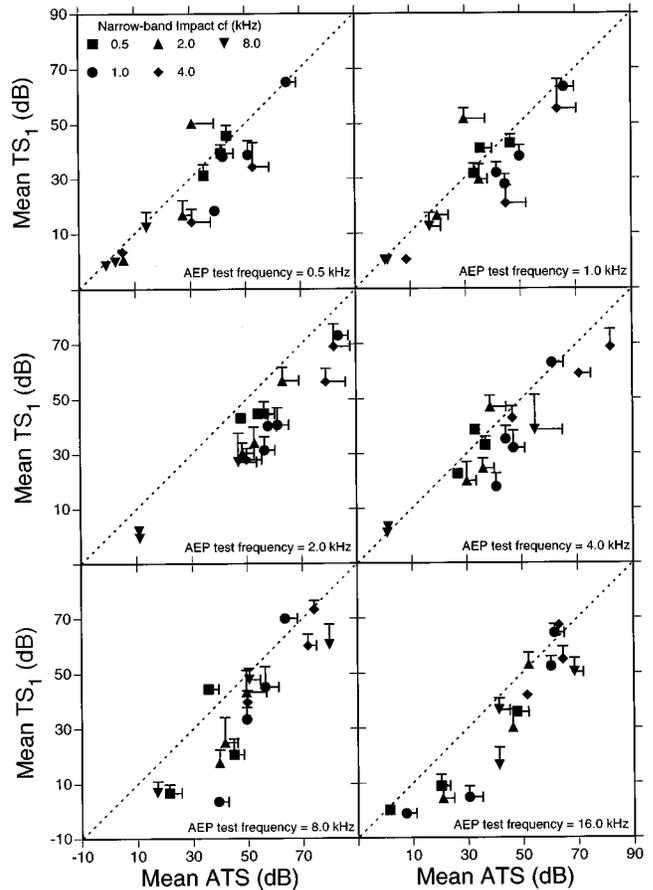


FIG. 3. The correspondence between the group mean threshold shift measured immediately following the first 6-h exposure (TS_1) of the 20-d interrupted exposure paradigm and the mean asymptotic threshold shift (ATS) produced by the equivalent energy uninterrupted 5-d exposure. Each of the six audiometric test frequencies is shown in a separate panel and symbols identify each of the five narrow-band impact stimuli. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

NBIs), produced a TS recovery (toughening) effect that took place at a slower rate than it did for the lower frequency NBIs. In fact, it appears that after 20 d, TS is still decreasing for some exposure conditions. Thus in some limited number

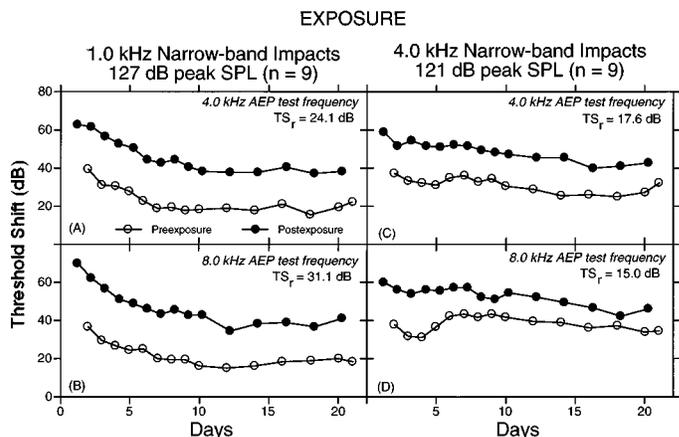


FIG. 4. Group mean threshold shifts measured immediately prior to and following the 6-h exposures on the days indicated during the 20-d exposure. Examples of data measured at the 4.0- and 8.0-kHz AEP test frequencies from two different exposure conditions are shown. The amount of toughening, TS_r , defined as $TS_1 - TS_{16-20}$ is indicated in each panel.

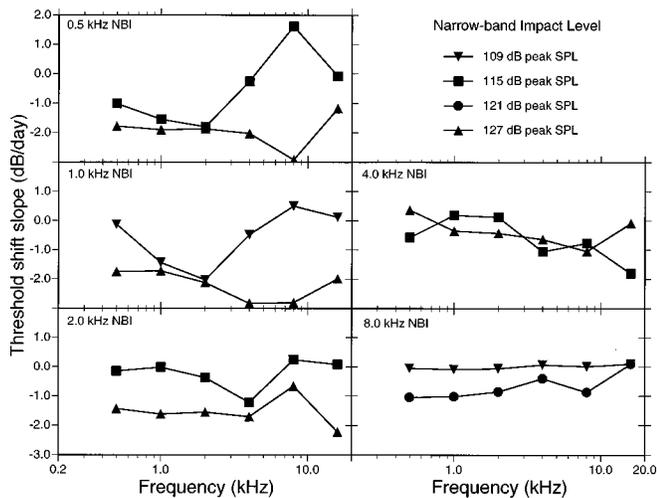


FIG. 5. Slope of the regression line drawn through the group mean threshold shifts measured following each of the 6-h exposures over the first 10-d of the exposure sequence. Slopes are plotted against AEP test frequency. Each panel presents data from one of the narrow-band impact (NBI) stimuli at the highest and lowest peak SPL used for that NBI.

of conditions our TS_r may be underestimating the maximum TS_r that might be achieved with that particular stimulus if the exposure was allowed to continue. Subramaniam *et al.* (1991b) also indicate differences in the rate at which toughening progresses but, unlike the present results, their results using 0.5- and 4.0-kHz CF octave band Gaussian noise stimuli indicate that the TS decline takes place more rapidly for the high-frequency stimuli.

Figure 5 provides an estimate of the rate at which toughening occurs at different AEP test frequencies as the NBI stimulus frequency and intensity are varied. This figure plots the slope of the daily postexposure TS, obtained from the linear regression line on the group mean TS values over the first 10 d of the interrupted exposure. Clear from this figure is the generally reduced slopes, or slower development of toughening, as the NBI stimulus frequency is increased or peak NBI levels are decreased. Slope data for only the high and low extremes of NBI peak SPL are shown. The slope data at other intensities were generally intermediate to those shown in Fig. 5. For the lowest intensity NBIs at some AEP frequencies either there was no TS or no toughening effect (i.e., a zero slope). Interestingly, at some of the lowest intensities there were some AEP frequencies that, rather than showing toughening, showed a group mean growth of TS (a positive slope) as the exposure was repeated. In most cases for which this occurred the effect, while consistent over the 20-d exposure period, was small amounting to less than a 10-dB growth. The single exception is the group exposed to the 115-dB peak SPL, 0.5-kHz NBI, which at the 8.0-kHz AEP frequency, showed about a 20-dB growth in the group mean TS. This is shown in Fig. 6 along with the group mean TS function, measured at 2.0 kHz, that showed the typical toughening effect. This result for the 8-kHz test frequency is consistent with the findings of Sinex *et al.* (1987) and Boettcher *et al.* (1992). On the basis of the group mean data it is clear that all AEP test frequencies that are affected by the noise are not necessarily toughened by the noise. In indi-

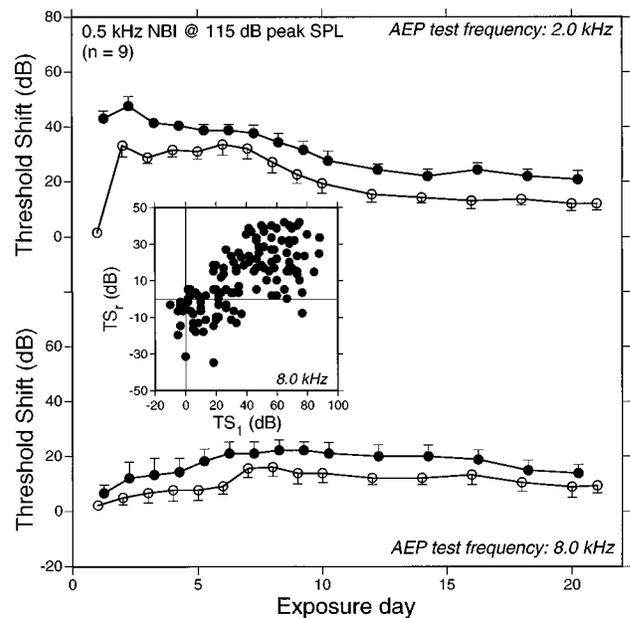


FIG. 6. Examples of group mean threshold shifts measured at the 2.0- and 8.0-kHz AEP test frequencies, prior to and following the daily 6-h exposures to the indicated narrow-band impact (NBI) stimulus. Examples were chosen to illustrate different threshold shift dynamics at different AEP frequencies within a single group. The inset shows the individual animals ($n = 131$) TS_r at the 8.0-kHz test frequency as a function of TS_1 for all NBI interrupted exposures. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

vidual subjects such frequency-specific differences in TS dynamics during an interrupted exposure can be very dramatic as seen in the inset of Fig. 6. The inset shows the TS_r versus TS_1 data measured at the 8-kHz AEP frequency for all 131 chinchillas that received one of the interrupted exposures. Data at the 8-kHz AEP test frequency were chosen for illustrative purposes since this was a frequency that was generally affected by all of the NBI stimuli. The data at the other frequencies are similar. At any given value of TS_1 there is considerable variability in TS_r . Interesting is the observation that for $TS_1 < 20$ dB a number of subjects show a growth of TS (i.e., a negative TS_r). Considerable variability in individual responses was also reported by Hamernik *et al.* (1994). The daily pre-exposure TS generally followed a time course during the 20-d exposure that was roughly parallel to that of the daily postexposure TS.

Figure 7(a), showing the group mean data from the 127-dB peak SPL, 1.0-kHz NBI exposures, compares the ATS level at various AEP test frequencies with TS_1 , and with TS_{16-20} . Toughening, TS_r , is seen to clearly exceed 30 dB at 8.0 kHz (i.e., the distance between the open and closed circles). In this example all audiometric frequencies have been toughened 20 dB or more. Panel B of this figure shows the mean PTS for these two equal energy groups. A two-way analysis of variance with repeated measures on one factor (frequency) indicated no differences in the levels of PTS (main effect: $F = 0.126$, $df = 1/17$, interaction: $F = 0.508$, $df = 5/85$). Panel C presents the profile of the mean OHC loss averaged over octave band lengths of the basilar membrane which, as with the PTS, shows no statistical difference between the two groups (main effect: $F = 0.518$, $df = 1/17$; in-

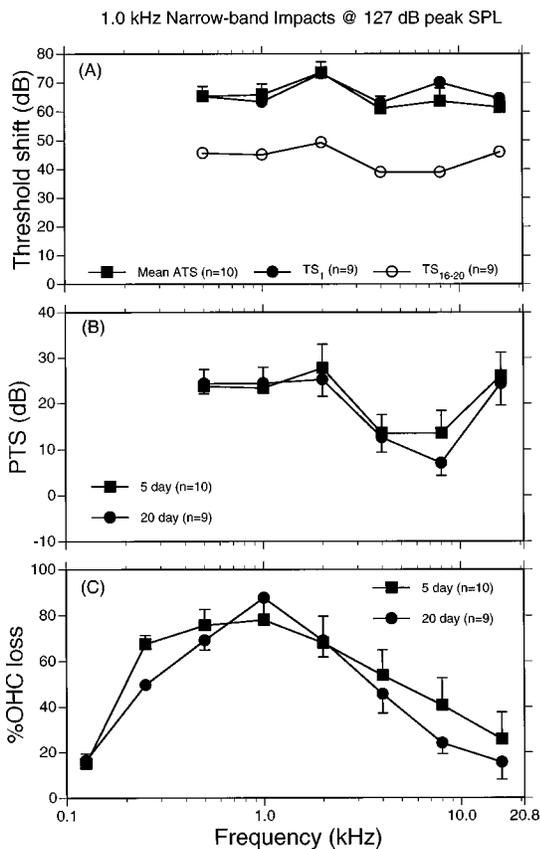


FIG. 7. A comparison of group mean audiometric and histological data from the 5-d and 20-d exposure to the indicated narrow-band impact stimuli. (A) Mean asymptotic threshold shift (ATS), the threshold shift immediately following the first 6-h exposure (TS_1) and the mean of the threshold shifts measured over days 16–20 (TS_{16-20}) of the interrupted exposure measured at each audiometric test frequency. Toughening is identified by the dB difference between the filled and open circles. (B) Permanent threshold shifts (PTS) at each audiometric test frequency for the two groups. (C) Percent of outer hair cell (OHC) loss over octave band lengths of the basilar membrane centered on the audiometric test frequencies. Despite the toughening there is no statistically significant differences in PTS or OHC loss between these two groups. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

teraction: $F = 1.361$, $df = 7/119$). This pair of exposures produced high levels of TS, PTS, and considerable sensory cell loss. Despite these severe noise-induced changes the toughening phenomena was robust across a broad range of AEP frequencies. In this case the toughened cochlea did not gain any advantage (protection).

A somewhat different set of results is seen in Fig. 8. (These two sets of examples were chosen to illustrate the different conclusions one can draw from a limited set of experimental conditions.) Figure 8 shows a parallel set of data for the pair of 121-dB peak SPL, 4.0-kHz NBI exposures. The profile of TS_1 and ATS is consistent with the level and CF of the stimulus. For this exposure TS_1 is less than the level of ATS, by from 10 to 22 dB, across all test frequencies, and a 15- to 20-dB toughening effect is seen between 4.0 and 16.0 kHz. A striking difference between the data in Figs. 7 and 8 is seen in the PTS and OHC losses for the two groups. The 4.0-kHz NBI interrupted exposure has produced statistically significant less permanent change (PTS: $F = 8.991$, $df = 1/16$, $p < 0.05$; OHC: $F = 4.935$, $df = 1/16$, p

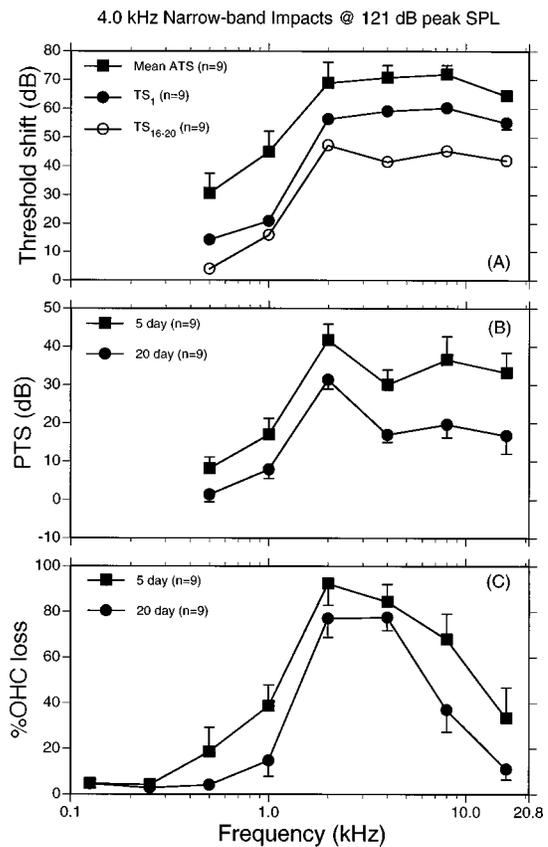


FIG. 8. A comparison of group mean audiometric and histological data from the 5- and 20-d exposure to the indicated narrow-band impact stimuli. (A) Mean asymptotic threshold shift (ATS), the threshold shift immediately following the first 6-h exposure (TS_1) and the mean of the threshold shifts measured over days 16–20 (TS_{16-20}) of the interrupted exposure measured at each audiometric test frequency. Toughening is identified by the dB difference between the filled and open circles. (B) Permanent threshold shifts (PTS) at each audiometric test frequency for the two groups. (C) Percent of outer hair cell (OHC) loss over octave band lengths of the basilar membrane centered on the audiometric test frequencies. There is a statistically significant difference in the PTS and OHC loss between these two groups. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

< 0.05). [The interactions of exposure group and frequency were not statistically significant (PTS: $F = 1.068$, $df = 5/80$; OHC: $F = 1.372$, $df = 7/112$.)] One might infer from the 10- to 22-dB difference between ATS and TS_1 that such differences in permanent effects might indeed turn out to be the case. However, other groups having similar TS_1 and ATS differences show no such differences in PTS or OHC losses. The results from the pair of groups shown in Fig. 8 are the only set of results showing such relatively large and consistent differences in permanent changes. The only other data in the literature that is somewhat related to the experimental conditions reflected in Fig. 8 are to be found in Subramaniam *et al.* (1992) where a 4.0-kHz OBN at 85 dB SPL was used to toughen the cochlea in an interrupted exposure paradigm. When the toughened subjects were exposed 5 d later to a 4.0-kHz OBN at 100 dB SPL for 48 h the toughened subjects showed more PTS than, and about the same sensory cell loss as, the controls. Since the opposite results were found for low-frequency exposures (Campo *et al.*, 1991) the differences were attributed to differences in the base–apex re-

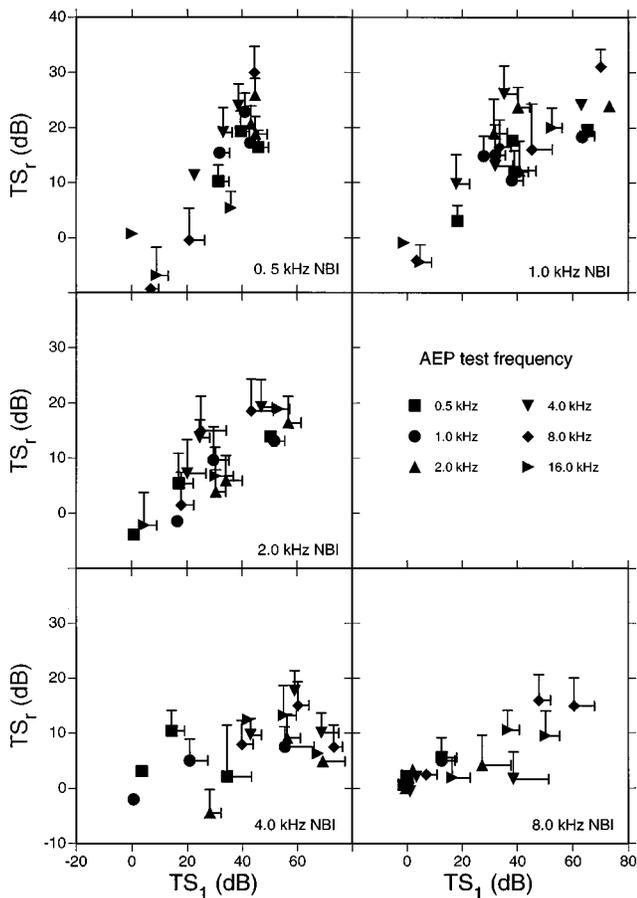


FIG. 9. The relation between the group mean amount of toughening (TS_r) and threshold shift (TS_1) measured immediately following the first 6-h interrupted narrow-band impact (NBI) exposure for each NBI exposure with audiometric (AEP) test frequency as a parameter. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

sponses of the cochlea. However, using the same paradigm but with only an 18-h recovery between the toughening and the traumatic exposures, Subramaniam *et al.* (1992) measured about 18 dB less PTS in the toughened cochleas. This latter result is somewhat consistent with the singular results shown in Fig. 8.

C. Effects of NBI frequency and intensity on TS_r

For each experimental group, data such as that presented in Figs. 7 and 8 have been reduced in an effort to extract some of the basic trends from the large mass of available data. The effects of exposure stimulus (NBI) frequency and intensity on toughening at the various audiometric test frequencies can be estimated from Fig. 9 where TS_r is shown plotted as a function of TS_1 for each NBI with AEP test frequency as a parameter or from Fig. 10 where TS_r is shown plotted as a function of TS_1 for each AEP test frequency with NBI CF as a parameter. Although NBI intensities are not specifically coded in the symbols of Figs. 9 and 10, the effect of NBI level is well ordered with respect to TS_1 and should pose no difficulty in interpretation. The following points can be made from Figs. 9 and 10:

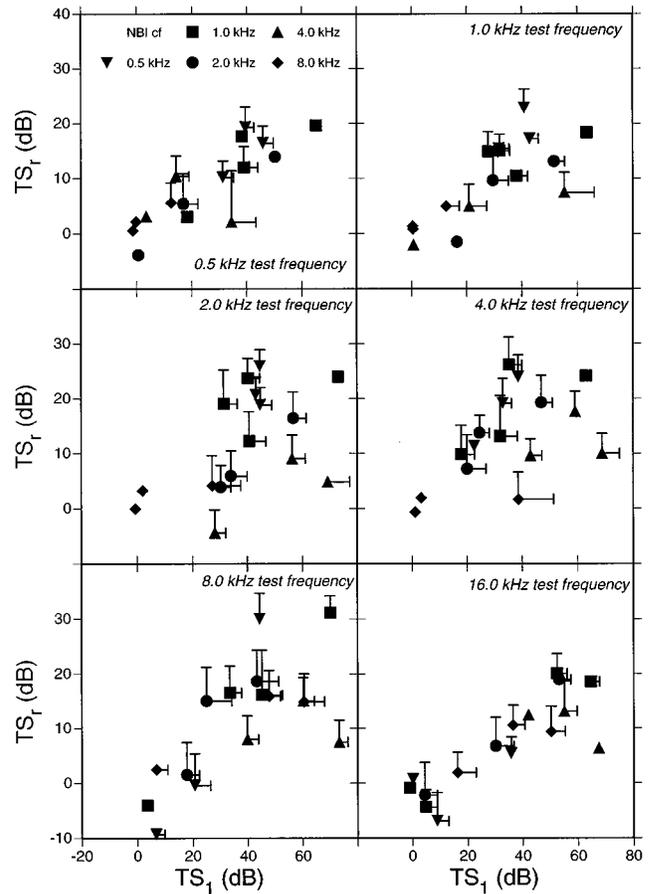
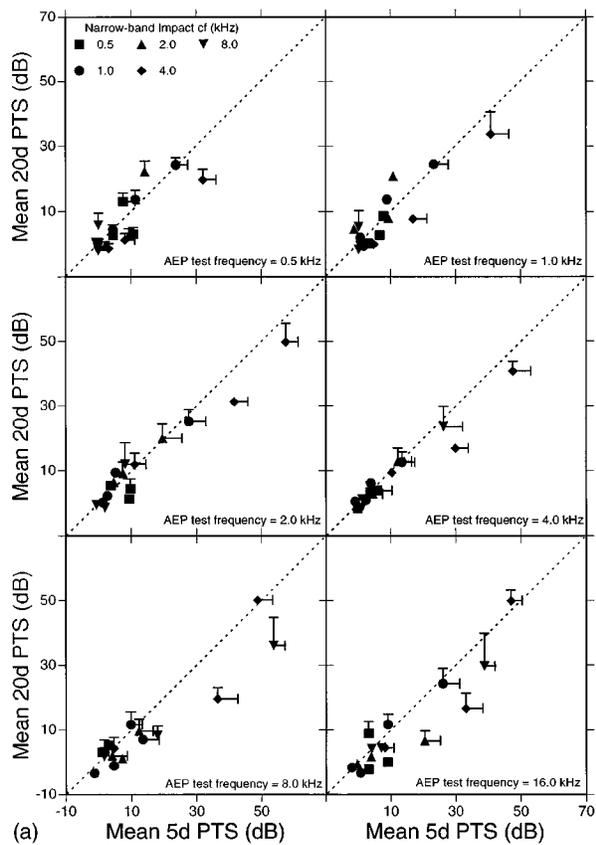


FIG. 10. The relation between the group mean amount of toughening (TS_r) and threshold shift (TS_1) measured immediately following the first 6-h interrupted narrow-band impact (NBI) exposure for each audiometric (AEP) test frequency with NBI center frequency (NBI CF) as a parameter. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

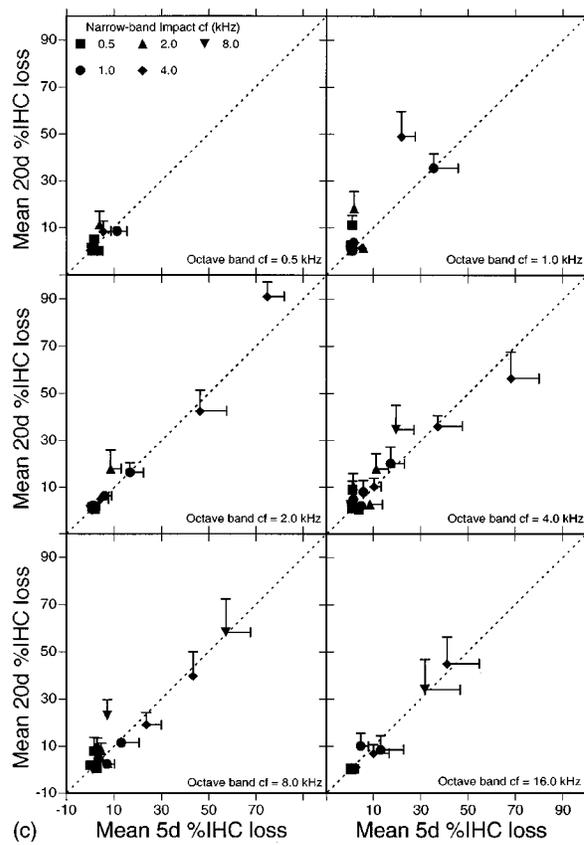
(1) Toughening is seen to be a general phenomena associated with all the AEP test frequencies and can be evoked by a broad spectral range of noise stimuli although much less so as the NBI CF is increased. This might be expected considering the increasingly restricted spread of excitation on the basilar membrane as NBI frequency is increased. Clark *et al.* (1987) have indicated that maximum TS_r is to be found a half-octave above the stimulating noise. Inspection of Fig. 9 or 10 indicates that AEP test frequencies as much as several octaves above the frequency of the stimulating noise may experience maximum or near maximum TS_r .

(2) Generally, as the level of the noise stimulus increases, TS_r increases although there is the suggestion in some of the intensity series and at some AEP test frequencies that TS_r begins to decrease for stimulus levels that produce a TS_1 greater than about 50 dB.

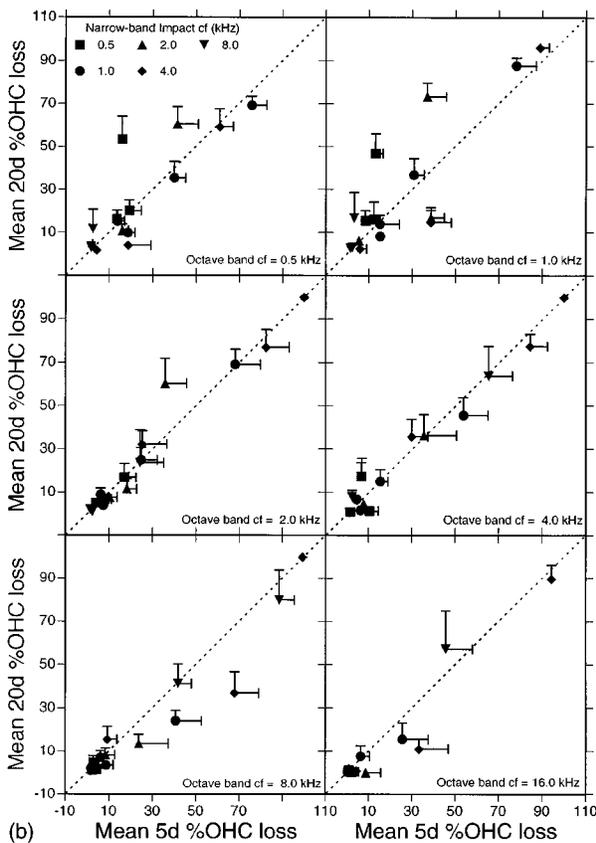
(3) For different NBIs that produce the same TS_1 at a given AEP test frequency a large difference in TS_r can be produced. Consider, for example, that both the 121-dB, 8.0-kHz NBI and the 127-dB, 0.5-kHz NBI produce a 40-dB TS_1 at 4.0 kHz. However, the former produces no TS_r while the latter produces a TS_r of more than 25 dB.



(a)



(c)



(b)

FIG. 11. A comparison of group mean PTS (panel a) and OHC and IHC loss (panels b and c) from the 5- and 20-d exposure to the indicated NBI impacts. Error bars represent one standard error of the mean. If error bars are not present, the standard error was less than the width of the symbol.

D. Evaluation of the equal energy/equal damage concept

Since corresponding pairs of groups, from the interrupted and uninterrupted exposure, received equal energy ex-

posures an evaluation of the equal energy principal was performed. Figure 11(a)–(c) show the relation between the PTS, OHC, and IHC for corresponding pairs of equal-energy exposures (i.e., 5 versus 20 d). Symbols reflect the narrow-band

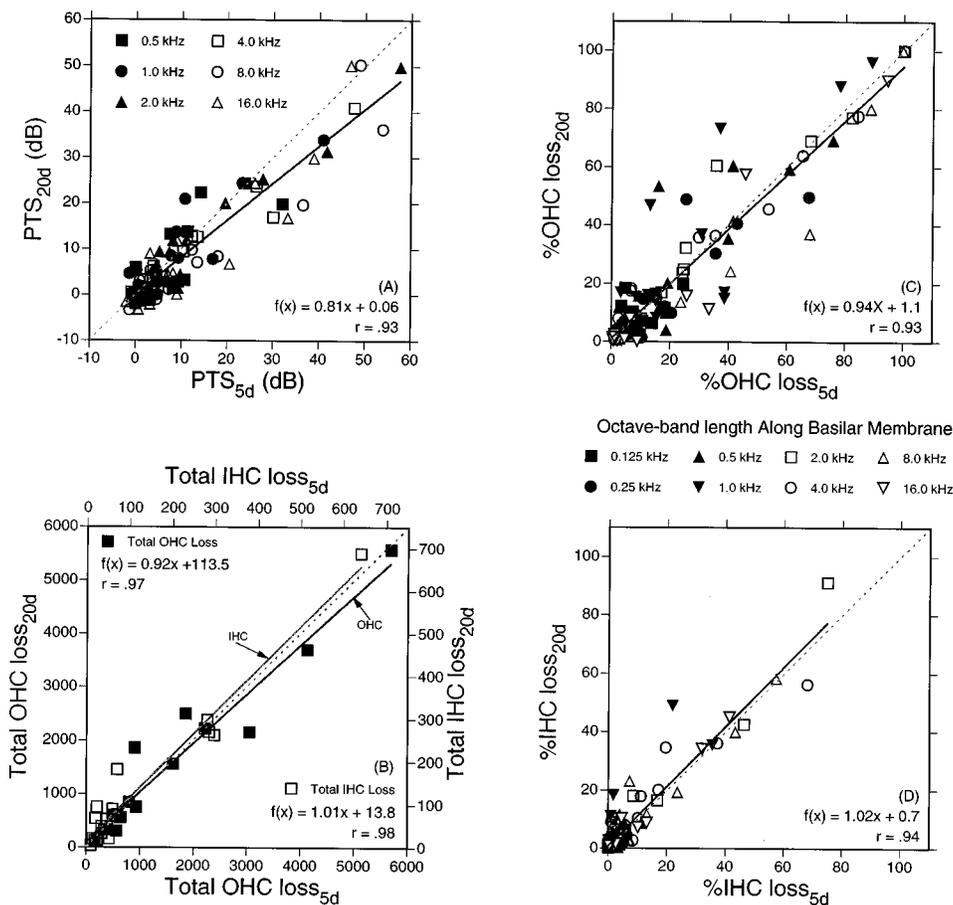


FIG. 12. A comparison of the group mean permanent audiometric and histological changes produced by each of the equal energy pairs of impact noise exposures. (A) Relation between permanent threshold shifts produced by the 20-d interrupted exposures (PTS_{20d}) and that produced by the 5-d exposures (PTS_{5d}). The symbols code for AEP test frequency. (B) The relations between total loss of outer and inner hair cells (OHC, IHC) for each of the corresponding exposures. (C) The relation between the percent OHC loss estimated over octave band lengths of the basilar membrane at the indicated center frequencies for corresponding pairs of exposures. (D) The relation between the percent IHC loss estimated over octave band lengths of the basilar membrane at the indicated center frequencies for corresponding pairs of exposures. In each of the above plots the equation for the linear regression line $f(x)$ and the correlation coefficient (r) are given.

stimulus used and each panel gives either the PTS measured at the indicated AEP test frequency or the sensory cell loss within the indicated octave band length of the cochlea. The frequency-distance translation was made using the data of Eldredge *et al.* (1981). From these figures there would appear to be very little and in many cases no difference in the permanent effects elicited by corresponding pairs of equal energy exposures. The data in Fig. 11 were replotted as shown in Fig. 12 and subjected to statistical analyses.

Figure 12(A) shows the group mean PTS, measured at each of the AEP test frequencies, for the groups exposed to the 5-d, uninterrupted and 20-d, interrupted exposures. OHC and IHC sensory cell loss data is similarly plotted either as total cochlear losses in panel (B) or as frequency-specific octave band losses in panels (C) and (D). Less PTS and sensory cell loss produced by the interrupted noise exposures should yield a linear regression line with a slope less than 1.0 describing points below the diagonal. The results of linear regression analyses of each of these data sets are indicated in the corresponding panels of Fig. 12. The analyses indicated that the predictor and criterion variables were all highly correlated. Thus, as expected, the permanent effects produced by corresponding pairs of equal energy exposures are highly

correlated with correlations ranging from 0.93 (PTS) to 0.98 (total IHC loss). An analysis of the regression line slope for the comparison of PTS ($\beta_1=0.81$) revealed a slope significantly different from $\beta_1=1$ ($t = -5.559$, $df=94$, $p<0.05$), indicating that PTS in the 5-d exposure was generally greater than for the 20-d exposures. The analyses of the slopes for each of the four sensory cell loss variables were not statistically significantly different from the diagonal (%OHC: $t = -1.879$, $df=126$; %IHC: $t=0.719$, $df=126$; total OHC: $t = -1.258$, $df=14$; total IHC: $t=0.083$, $df=14$). Thus the 20-d interrupted exposures resulted in slightly lower permanent threshold shifts than the 5-d exposures, and no difference in the extent of sensory cell losses.

E. Is the toughened cochlea a protected cochlea?

Figure 13 summarizes the relation between TS_r and any protective effect induced by TS_r , where protection is defined in terms of PTS as the difference, at each audiometric test frequency, between the PTS produced by the uninterrupted, 5-d exposure and that produced by the 20-d, equivalent energy interrupted exposure, that is, $[PTS_{5d} - PTS_{20d}]$. In terms of sensory cell loss protection is similarly defined as

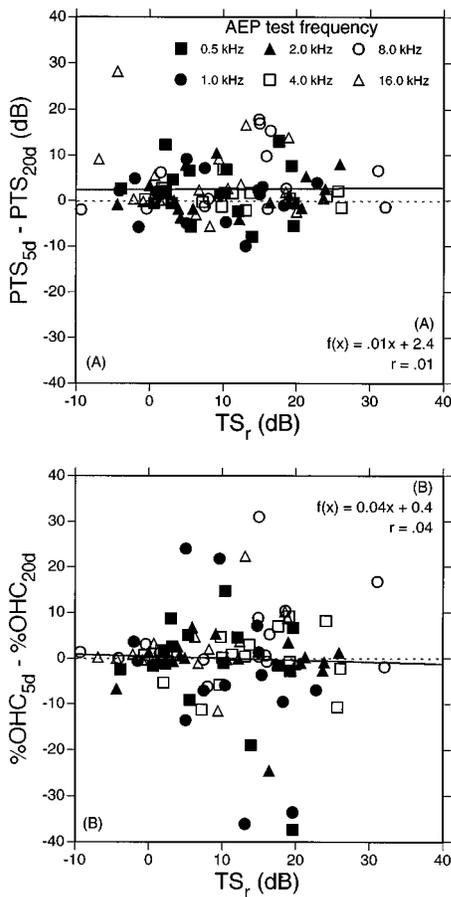


FIG. 13. The protective effect of toughening on the auditory system as a function of the amount of toughening (TS_r). Protection in terms of audiometric variables is defined as the difference between the permanent threshold shift produced by the 5-d exposure and the 20-d exposure ($PTS_{5d} - PTS_{20d}$), and in terms of histological variables as the difference between the outer hair cell loss produced by the 5- and 20-d exposures ($OHC_{5d} - OHC_{20d}$). In each of the above plots the equation for the linear regression line $f(x)$ and the correlation coefficient (r) are given.

$[\%OHC_{5d} - \%OHC_{20d}]$ computed across adjacent octave band lengths of the basilar membrane centered on the AEP test frequencies. The data points in this figure are derived from Figs. 9 and 11. Plotted in this format, a protected cochlea as a result of toughening should result in data points above the zero horizontal line. Analysis of these data using linear regression shows that there is a very low correlation between TS_r and the metrics that we have used to define protection. Neither correlation was statistically different from zero. Furthermore, a statistical analysis of the PTS regression shows that its slope is not significantly different from zero ($t=0.137$, $df=94$), but that the y intercept ($\beta_0 = 2.4$ dB) is statistically different from zero ($t=2.543$, $df=94$, $p<0.05$). A parallel analysis of the percent OHC data revealed that neither the slope ($t=-0.357$, $df=94$) nor the y intercept ($t=0.262$, $df=94$) were significantly different from zero.

A protective effect, as a consequence of an interrupted noise exposure, is achieved by either (1) decreasing the susceptibility of the system to permanent noise-induced effects (i.e., increasing the system's resistance to noise; toughening) or (2) delivering a given amount of energy to the system over

an extended time course thus allowing recovery processes to intervene during the quiet interludes. The data in Fig. 13 indicating no correlation between TS_r and $(PTS_{5d} - PTS_{20d})$ and $(OHC_{5d} - OHC_{20d})$ suggests that the operative mechanism for any protective effect is that associated with the spreading of energy over time rather than a toughening of the cochlea. This conclusion is further strengthened by the high correlations shown in Fig. 12. Thus an auditory system toughened by noise is not necessarily a protected system.

III. CONCLUSIONS

The foregoing analysis of an extensive set of group mean data from animals exposed to a variety of interrupted noises has served to confirm and extend a number of the results that have recently appeared in the literature on the toughening phenomena. We have shown that toughening, TS_r , is a general cochlear phenomena that can be measured at all audiometric test frequencies provided that a sufficient TS_1 is produced by the noise exposure stimulus. TS_r generally increases with an increasing TS_1 (or equivalently with an increasing exposure SPL). There is, however, the suggestion that for large values of TS_1 , the amount of toughening will begin to decrease. The magnitude of TS_r and the number of audiometric frequencies showing a TS_r is very dependent on the frequency content of the noise stimulus, where lower frequency stimuli are more effective in the production of TS_r .

Across the range of audiometric test frequencies, within an exposure group, the TS_r variable can take on both positive and negative values indicating that while thresholds at some audiometric test frequencies are getting better (being toughened) others are getting worse as the exposure repeats.

Perhaps the most significant aspect of these results is that, based on group mean data, there was no correlation between the amount of toughening and the extent of the permanent noise-induced changes. However, relative to the equal-energy control groups, the interrupted exposures produced slightly less PTS but no differences in sensory cell losses. Taken together these results suggest that a toughened cochlea is not necessarily a protected cochlea and that the concept of equal energy-equal damage is overly conservative for interrupted exposures that allow for recovery processes to intervene between exposures cycles.

IV. ANIMAL USE

The care and use of the animals reported on in this study were approved by the SUNY Plattsburgh Institutional Animal Care and Use Committee. In conducting the research described in this report, the investigators adhered to the *Guide for Care and Use of Laboratory Animals*, as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources Commission on Life Sciences, National Academy of Sciences-National Research Council, revised 1985.

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Interrupted noise exposures: Threshold shift dynamics and permanent effects

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