

EFFECTS OF INTENSE ACOUSTIC NOISE
ON COCHLEAR FUNCTION IN INFANT AND
ADULT GUINEA PIGS

By

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Chairman: Donald C. Teas
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Brain stem responses (BSR) to filtered acoustic clicks were obtained from four groups of guinea pigs, two newborn and two adult, with chronically implanted recording electrodes. One adult group and one newborn group were exposed to two hours of a 108 dB SPL narrow band of noise centered at 4 kHz. The two other groups served as controls. After one month following the exposure, BSRs were again obtained, the animals sacrificed and the cochleae prepared to determine the number of missing hair cells. Threshold, response amplitude and response latency values were analyzed for the N_1 and P_4 waves of the BSR for all animals. Preexposure results indicated that while the N_1 response functions in the adult and newborn groups were generally similar, the P_4 functions differed between the two groups. Postexposure results indicated a greater N_1 and P_4 threshold shift

for the exposed newborn group in response to the 6 kHz filtered click than for the adult group. In addition, the postexposure N_1 and P_4 response amplitude functions of the newborns showed a greater relative decrease in response to the 6 kHz filtered click than did the adult functions. Postexposure latency measures did not indicate differences between the groups although the latencies of N_1 and P_4 in response to the 1 kHz filtered click were longer at higher click intensity levels than those obtained prior to the noise exposure. Histological analysis failed to show any differences in the number of missing hair cells among the exposed adults and newborns. The results of this study are discussed in relation to maturation of the auditory system, effects of noise on the BSR and susceptibility to noise-induced hearing loss.

CHAPTER I

INTRODUCTION

Modern man pays a price for technological progress in the form of industrial and environmental related health disorders. The effects of noise on the auditory system are of considerable interest today and have been studied since the early 19th century. Fosbrooke (1831) identified individuals suffering noise-induced hearing loss on the basis of their exposure to weapon fire and forge operations. Yoshii (1909) was able to identify the hair cell region of the cochlea as the principle site of noise-induced damage. Investigations through the 1950's were directed toward the quantification of cochlear damage as a function of stimulus intensity and frequency (Crowe, Guild and Polvogt, 1934; Davis, Derbyshire, Kemp, Lurie and Upton, 1935; Lurie, Davis and Hawkins, 1944; Wever and Smith, 1944; Davis and Associates, 1953; Wever and Lawrence, 1955). Throughout the last several decades the effects of noise upon cochlear electrophysiology have received attention (Eldredge, Bilger, Davis and Covell, 1961; Price, 1968, 1972, 1974; Simmons and Beatty, 1962; Benitez, Eldredge and Templer, 1972; Mitchell, Brummett and Vernon, 1973; Eldredge, Mills and Bohne, 1973) as has the normal anatomical and physiological development of the cochlea (Nakai and Hilding, 1968; Pujol and Hilding, 1975).

The efforts of these and many other investigators have added much to our knowledge of the effects of intense noise on the auditory system. We know, for instance, that the cochlear structures principally

affected by high noise levels are the outer hair cells (Lurie et al. 1944; Davis et al. 1935). As the intensity or duration of the noise increases the extent of injury increases and may include other structures such as the inner hair cells and afferent nerve fibers. It is generally accepted that the location of damage within the cochlea is related to the frequency of the stimulus. High frequency, high intensity noise causes damage to the basal end of the cochlea whereas lower frequency noise affects more apical portions of the cochlea (Wever and Smith, 1944). It has also been shown that damage to the structures of the cochlea results in electrophysiological changes such as a decrease in the magnitude of the cochlear microphonic (Price, 1968, 1972, 1974) and in the whole-nerve action potential (Mitchell, Brummett and Vernon, 1973, 1977). Although the effects of noise on cochlear structure and function have been well studied and documented, the specific mechanisms of cochlear damage remain unresolved.

Spoendlin (1976) suggested that the specific mechanisms of noise-induced cochlear damage are a function of the intensity of the stimulus and its duration. Spoendlin described two critical intensities with respect to their effect upon the cochlea. Below 90 dB (critical intensity I) there appears to be little structural damage regardless of the duration of the exposure. Above 130 dB (critical intensity II) the structures of the cochlea undergo severe irreversible damage even with very short durations. As the duration of the exposure increases at 130 dB and above, the damage to the cochlea does not increase in proportion to the duration. The mechanism of damage at these levels is apparently mechanical as evidenced by separation of the organ of

Corti from the basilar membrane. The hair cells in the detached portion often have a normal looking appearance. The motion of the basilar membrane at high intensities is apparently so violent that the organ of Corti separates from the membrane. Between these two critical intensities (90-130 dB) the duration of exposure is an important consideration. As duration increases for moderately intense stimuli, cochlear damage increases. The specific mechanisms of damage between the two critical intensities have been the subject of considerable investigation (Spoendlin, 1970, 1971; Ward and Duvall, 1971; Beagley, 1965; Lipscomb and Roettger, 1973; Bohne, 1972, 1976).

One theory proposes that cochlear damage to moderately intense noise is the result of what Spoendlin (1976) calls metabolic decompensation. Hair cells examined after noise exposure show damage that is consistent with the effects of changes in the metabolic activity of the cells. These changes include distortion or swelling of the cell bodies (Spoendlin, 1970, 1971) fusion of stereocilia (Spoendlin, 1971; Ward and Duvall, 1971) and an increase in the number of lysosomes in the outer hair cells (Beagley, 1965; Ward and Duvall, 1971). A second theory suggests that vascular changes occur as a result of noise exposure resulting in an interruption of blood supply, oxygen and nutrients to the cells. Lipscomb and Roettger (1973) found evidence of constriction and decrease in red blood cells in the vessels below the basilar membrane following noise exposure. Spoendlin (1971) discovered swelling of the afferent nerve fibers following noise exposure. This finding is similar to that seen after an interruption of the blood supply to the cochlea.

A third theory, the Ionic Theory, as proposed by Bohne (1972, 1976) suggests that damage to the structure of the organ of Corti is caused by the communication of perilymph-like fluid of the organ of Corti (low potassium, high sodium ion content) with endolymph of the scala media (high potassium, low sodium ion content) through the normally impermeable reticular lamina. Bohne theorized that noise exposure somehow increases the permeability of the reticular lamina resulting in communication of the two fluids. To test her hypothesis, Bohne exposed chinchillas to a one hour exposure of 108 dB SPL octave band noise centered at 4 kHz and sacrificed the animals at different postexposure intervals to determine the course of injury over time. She discovered that while there was little evidence of damage shortly after the exposure (< one hour) at one month postexposure there was total degeneration of a 1 mm segment of the organ of Corti approximately 4 mm from the base. Bohne discovered small holes, the size of missing hair cells, in the reticular lamina two hours postexposure which were large enough to allow leakage of the endolymph into the organ of Corti fluid spaces. These holes later healed resulting in scars formed by the enlarged phalangeal processes. Some indirect support for Bohne's theory is provided by Goldstein and Mizukoshi (1967) who suspended outer hair cells in artificial endolymph and perilymph and found swelling in those cells placed in the endolymph whereas those cells placed in the perilymph retained their shape. Stronger support is provided by Duvall, Sutherland and Rhodes (1969) who nicked the endolymphatic surface of the organ of Corti and discovered increasing damage to the ultrastructure of the organ of Corti as the time increased following the procedure.

A second unresolved issue in noise-induced hearing loss is the possibility that susceptibility to noise-induced trauma varies among organisms within the same species. There is, as yet, no way to determine susceptible individuals within a population. As a result, those susceptibility studies which have been particularly valuable have dealt not so much with individual as with group susceptibility. The target for several of these investigations has been the very young.

Falk, Cook, Haseman and Sanders (1974) exposed two-day, eight-day and eight-month old guinea pigs to 30 hours of white noise at 119-20 dB SPL and found that the younger animals suffered significantly greater pathology as measured by hair cell loss. Price (1976) found a greater loss of cochlear microphonic (CM) as measured at the round window among kittens than among adult cats after an exposure to an intense 5 kHz pure tone for 50 minutes. The correlation between histological results and the CM measurements were somewhat inconsistent but the overall results suggested a positive relation between the two measures. Bock and Saunders (1977) proposed a critical period theory to explain the results of a study in which hamsters, 27-55 days of age, appeared to exhibit an increased susceptibility to noise trauma as measured by CM sensitivity. The authors suggested that there may be developmental changes in the young cochlea which increase the susceptibility to noise trauma. Danta and Caiazzo (1977) exposed newborn and adult guinea pigs to a 115 dB SPL narrow band of noise centered at 4 kHz for one hour and discovered an increased susceptibility to temporary threshold shift (TTS) among the newborns as measured behaviorally. Dodson, Bannister and Douek (1978) in attempting to simulate incubator conditions in a newborn nursery, exposed one week old guinea pigs to

white noise at 76 dB SPL for seven days. They found appreciable loss of outer hair cells in these animals as compared with a control group. These results suggest that young organisms may be more susceptible to noise-induced hearing loss than adult specimens. Of particular significance is the case of human infants remaining for weeks in incubators. If infants show similar susceptibility, these individuals may be undergoing noise-induced damage to cochlear hair cells.

The basis for noise-induced permanent hearing loss is structural damage to the fine detail of the organ of Corti. Only in recent years, with the use of electron microscopy, has the fineness of detail required to effectively study noise-induced damage become sufficiently documented. It is hair cell damage that must be assessed in noise trauma and the central question is the relation between hair cell damage and the parameters of the traumatic stimulus. However, hair cell damage can only be assessed post-mortem. If one could determine the relation between an ante-mortem assay of hair cell loss, an estimate of the state of hair cell integrity might then be possible. For this reason, there has been much interest in studying response activity in preparations subjected to stimuli which were chosen to induce acoustic trauma. One might expect, for example, that behavioral threshold would be a good correlate for hair cell damage if we assume that behavioral thresholds accurately reflect the integrity of cochlear structures. However, Eldredge, Mills and Bohne (1973) showed that in the chinchilla there was a poor correlation between threshold sensitivity and hair cell loss.

The CM discovered by Wever and Bray (1930) and defined by Saul and Davis (1932) has been used frequently as an index for noise-induced cochlear damage. The CM is a stimulus-related cochlear potential with waveform which duplicates the displacement-time pattern of the cochlear partition (Dallos, 1973). The input-output function of the CM is characterized by three segments. The first segment is a linear one in which output voltage is directly proportional to the stimulus intensity. CM output has been measured as low as .005 mv (Wever, 1966). The second segment is characterized by a departure from linearity toward the maximum output of the CM. The third segment consists of a roll-over effect in which increases in stimulus intensity result in decreases in CM output. The CM has traditionally been measured by two techniques: a single electrode placed on or near the round window (RW), and the differential recording technique (Tasaki and Fernandez, 1952) which utilizes two active electrodes placed in the same cochlear turn. The RW technique has the advantage of relative ease of recording but it has a serious drawback in that, in the case of low frequency stimulation, it cannot be determined whether the electrode is picking up proximally or distally generated CM. Another problem with the RW technique is that the electrode picks up the whole-nerve action potential (AP) with the CM. Under many stimulus conditions it is difficult to visually separate the two responses which originate from different anatomical sources. The differential electrode technique, on the other hand, permits the study of locally generated CM and the separation of whole-nerve AP and CM components but it requires a more surgically invasive technique than RW recording. Unfortunately, RW recordings tend to yield little

difference in the reduction of CM sensitivity as a function of test frequency (Simmons and Beatty, 1962; Price, 1968). In noise exposure experiments (Smith and Wever, 1949; Price, 1968) the frequency at which maximum depression of the CM occurred tended to be below the exposure frequency. Durrant (1976) concludes that, ". . . the loss of CM sensitivity and maximum output appear to be rather limited indicators of the detailed mechanisms involved with acoustic trauma, based on currently available data" (p. 192).

In contrast to the CM, the neural responses may be a more sensitive index of the degree of and perhaps the location of noise trauma (Davis and Associates, 1953; Benitez, Eldredge and Templer, 1972; Mitchell, Brummett and Vernon, 1977; Pugh, Horowitz and Anderson, 1974). The use of the eighth nerve action potential to gain frequency specific information was earlier felt to be limited since the prevailing thought was that the response reflected only synchronous activity in the basal portion of the cochlea. Analysis of the whole-nerve response with analytic procedures shows that some resolution of frequency representation can be obtained. The use of tone-pips (Davis, Fernandez and McAuliffe, 1950), filtered clicks (Aran, 1971; Zerlin and Naunton, 1975), click-pips (Coats, 1976) and selected masking of broadband click evoked AP (Teas, Eldredge and Davis, 1962; Eldredge, Mills and Bohne, 1973) have enabled investigators to obtain substantial frequency specific information from the whole-nerve response. The whole-nerve AP appears to correlate well with anatomical data. Eldredge and his associates (1973) concluded that, "The close rank order correlation between loss of whole-nerve AP . . . and the loss of hair cells is very gratifying in terms of a quest for reliable physiological indices

of injury. The N_1 peak voltages as a function of input sound pressure may be a more sensitive index for loss of hair cells than any measure of threshold simply because this function examines responses over a wider dynamic range" (p. 79).

The whole-nerve response in man is recorded most clearly with a transtympanic electrode resting on the promontory. The response can also be recorded with a wick electrode in the external auditory meatus, but with some loss of clarity. The whole-nerve response is also included in the Brain Stem Response (BSR) as wave I.

Jewett and his associates (Jewett, Romano and Williston, 1970; Jewett, 1970; Jewett and Williston, 1971), recording from the vertex of the scalp, described a series of waves consisting of seven peaks which appeared in the first nine msec after the onset of a click stimulus. Their evidence strongly suggested that wave I was generated by the eighth nerve while waves II through VII represented auditory evoked brain stem activity. The waves have since been referred to as the Brain Stem Response.

In an attempt to correlate the individual waves with specific brain stem structures, Lev and Sohmer (1972) recorded intracranially in cats and concluded that waves I through V represented activity of the cochlear nerve, cochlear nucleus, superior olivary complex, and the inferior colliculus (waves IV and V) respectively. Buchwald and Huang (1975) dissected various auditory brain stem structures in the cat and came to similar conclusions regarding the generator sites of the BSR with the exception that wave IV appeared to represent activity in the ventral nucleus of the lateral lemniscus. In a similar investigation, Henry (1979) concluded that the sources of the BSR in the

mouse closely resemble those in the cat.

Wave V is of particular interest as it is the most prominent peak when recorded from the human scalp. Recent investigations have attempted to demonstrate relationships between wave I and wave V (Elberling, 1976; Klein and Teas, 1978). Elberling has shown that, regardless of the intensity, the latency of wave V varies as a constant (4.2 - 4.4 msec) when compared to the latency of wave I for a 2 kHz acoustic transient. Elberling suggests that this relationship is indicative of the close approximation of frequency specificity between the two waves. The significance of this relationship is two-fold. First, the clinician's task for measuring responses close to threshold is made easier with the larger wave V and secondly, information may be obtained which can add to our knowledge concerning the relationship between peripheral and central auditory processing.

The use of BSR is rapidly becoming a valuable objective method for differentially diagnosing auditory pathway disorders (Sohmer, Feinmesser and Szabo, 1973; Sohmer, Feinmesser, Bauberger-Tell, Lex and David, 1972; Berry, 1976; Davis, 1976; Davis and Hirsh, 1977). At present, however, few studies have investigated the effects of intense noise on these brain stem neural potentials.

In one study, Sohmer and Pratt (1975) studied the effects on the BSR in human subjects produced by noise exposure. The noise produced a temporary threshold shift (TTS). The BSR to a click showed a greater latency and amplitude change for the earliest negative deflection (N_1) than the later waves which showed little change in the TTS condition. The authors suggested that this finding indicated that TTS is a peripheral, electrophysiologic event.

As humans cannot be used in permanent threshold shift (PTS) studies, the guinea pig has long been considered one of the animals of choice for several reasons: low cost, ease of procurement, surgical accessibility of the auditory structures, and as Davis and Associates wrote in 1953, "In any extrapolation of . . . data to the problem of acoustic trauma in man we can probably assume with some confidence that the organ of Corti in man has about the same mechanical strength that it has in the guinea pig. The size and structure are very similar, particularly if we compare the corresponding regions that are most sensitive to the same frequency. For given amplitudes of movement of the footplate of the stapes we should expect rather similar injurious effects on the hair cells and similar probabilities of mechanical failure of supporting structures" (p. 1188). The use of the guinea pig also has produced considerable data of intrinsic interest quite apart from their direct applicability to man. That is, the principles of function are also of interest.

The purpose of this study was to contrast the effects of noise which produces PTS on the BSR's of newborn and adult guinea pigs. Specific data are presented on (1) the effect of age on the susceptibility to noise-induced hearing loss as measured by the BSR, (2) on the effects of PTS on the amplitude and latency of the early and late waves of the BSR and the relations among these waves, (3) on the correlation between noise-induced changes in the early and late BSR and hair cell loss, and (4) on the suitability of filtered clicks as a frequency-specific stimulus.

CHAPTER II
METHODS AND PROCEDURES

Animals

Four groups of guinea pigs, 16 animals, were used. Five animals were in the adult experimental group (305-957 gms) and five animals were in the newborn experimental group (96-112 gms). Three animals were in the adult control group (407-508 gms) and three animals were in the newborn control group (107-132 gms). In this study an animal under 72 hours of age was considered newborn. The adult animals were procured, fed, and managed by the Animal Resources Department of the University of Florida and caged in a laboratory. The newborns were born in this room and stayed with their mothers. The ambient noise level in the room was approximately 48 dBA and consisted mostly of animal vocalizations and movement within the cages. No frequency analysis of the ambient noise was done.

Normal auditory acuity was determined by the presence of Pryor's Reflex (this reflex was often weak and/or missing in the newborns), normal otoscopic examination and acceptable BSR (first negative wave) threshold to broad band clicks. Pilot studies had determined this threshold to be approximately 30 dB SPL \pm 5 dB.

Surgical Procedure

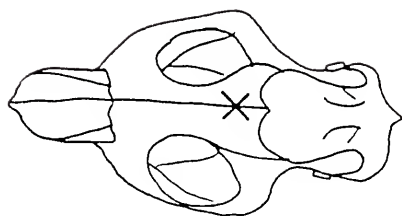
The animal was anesthetized with Nembutal (0.5 cc/kg of body weight). A supplemental dose (1/3 of initial dose) was given after two hours if the animal showed signs of discomfort or excessive

movement. Temperature and heart rate were monitored continuously. Temperature was maintained between 36-38° C. In order to eliminate the contribution of the contralateral ear to the BSR the test ear (Taniguchi, Murata and Minami, 1976; Teas and Nielsen, 1975) the left cochlea was destroyed by rupturing the round and oval windows transtympanically and draining the cochlear fluids.

Under clean, non-sterile conditions, a 2-3 cm anterior to posterior incision was made along the midline of the scalp. After the tissue was retracted to expose the skull, one hole was drilled at the parietal crest and another was drilled approximately 3 mm superior to the external auditory meatus (EAM). In the adults, mounting screws (0.80" x 1/16") were screwed into these holes and platinum wires were wrapped about each screw (.008" diameter + .003" diameter teflon coated except for 2 mm of its tip). In the newborn, the tips of the electrodes were inserted directly into the drilled holes since the newborn skull was too thin to accept the screws. With the wires attached to a small socket, the implant was fixed onto the skull with cranioplastic cement. Figure 1 illustrates the location of the electrodes in the skull. Soon after implantation was completed the animals were returned to their cages (the newborns to their mothers) and allowed to recover approximately 48 hours before BSR measurements were made.

One postsurgical complication found during pilot studies was that vestibular disturbances due to the contralateral labyrinthectomy could be so severe that feeding is inhibited. This occurred in one newborn animal which eventually died despite attempts at supplemental

Figure 1. Location of electrodes in the guinea pig skull. The electrodes were positioned in the areas indicated with a cross mark. One electrode was placed approximately 3 mm superior to the external auditory meatus (upper view), the other at the midpoint of the parietal crest (lower view).

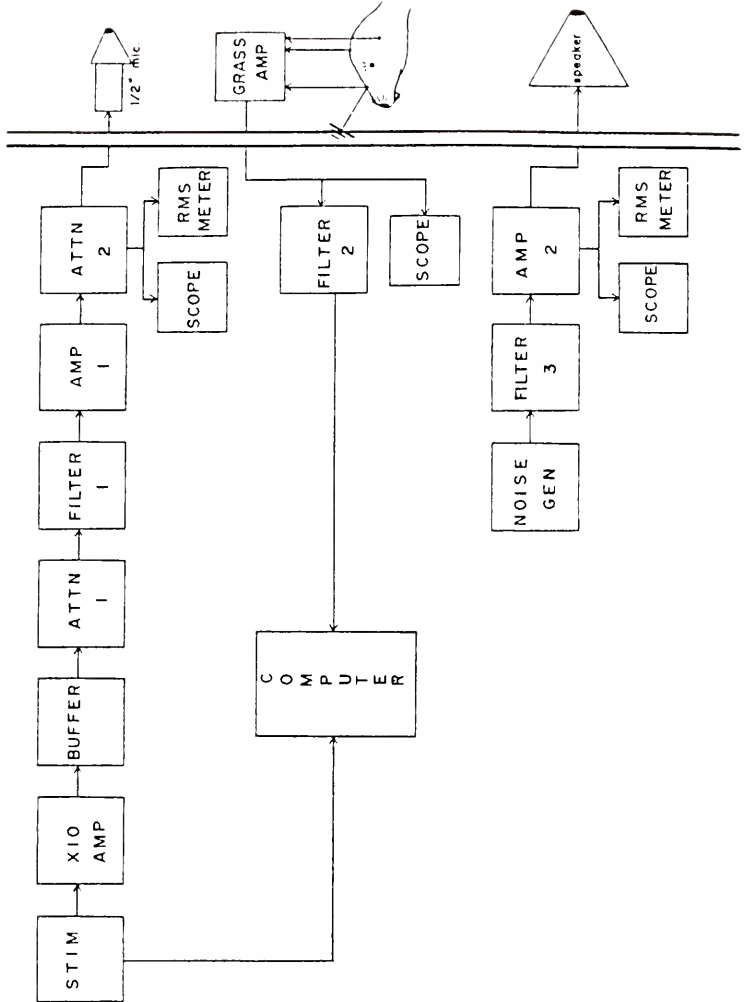


feeding. It was found that if damage to the non-test cochlea was kept to a minimum, the animals would quickly recover from vestibular problems (nystagmus and loss of balance). Another complication was the loosening and eventual loss of the implant plug in the newborn animals as a result of a rapid skull growth during the one month postexposure period. This problem was solved by periodically adding a small amount of cranioplastic to the perimeter of the implant during the one month period.

Signal Generation

A simplified block diagram illustrating the equipment used in this study is shown in Fig. 2. A Grass stimulator produced the square wave pulse which had a repetition rate of 10 pulses/sec and a duration of 120 msec. After being delivered to a buffer, attenuator and mixer, the signal was amplified (McIntosh, MC 40) attenuated and fed into an IAC single wall, sound-treated room enclosed by a concrete block wall. The filtered clicks were generated by activating a band-pass filter (Krohn-Hite, 3100) with the pulse. The filter cutoffs were adjusted to produce the desired waveform of approximately four cycles in length with its plateau being reached within the second cycle. The filter imposed a frequency dependent delay between the synchronizing pulse and the signal at the transducer which ranged from .18 msec for the filtered click (FC) centered at 8 kHz to .89 msec for the 500 Hz centered FC. All latency measures reported in this study are corrected for this filter delay. The filtered clicks drove a Bruel and Kjaer (B&K) 1/2 in condenser microphone (type 4133) coupled to the opening of the guinea pig's EAM by a 1 mm diameter speculum. The spectra of

Figure 2. Simplified block diagram of the stimulus generating and response recording equipment.



the filtered clicks (Fig. 3) were found by measuring the acoustic output from a speculum with a 1/8" condenser microphone (B&K 4138) connected to a sound-level meter (B&K 2209) with 1/3 octave filter (B&K 1616). The output of the meter was fed to a graphic level recorder (B&K 2306) which plotted the data semi-automatically. The spectra were corrected for ear canal effects as measured previously in this laboratory (Teas and Nielsen, 1975) and for the difference in repetition rates used for calibration (90/sec) vs. the rate used during the experiment (10/sec). The spectrum SPL at the ear drum at 0 dB attenuation was determined by subtracting $10 \times \text{Log}$ of the bandwidth (bandwidth being determined at 6 dB down from the peak) from the averaged SPL values of those data points within 6 dB of the peak.

Noise Stimulus Generation

The stimulus for the narrow band noise exposure was generated by a Grason-Stadler 455C Noise Generator. After being filtered (Krohn-Hite, 3100) and amplified (McIntosh, 4C40) the filtered noise was delivered to an Altec, 802 D acoustic transducer whose cone was placed 2 cm from the EAM of the animal. The signal was calibrated before and after each exposure by a Ballantine, 320A True RMS meter and by a B&K Precision Sound Level Meter (model 2209) with a 1/2 in condenser microphone (type 4135) placed at 0° incidence to the center of the cone's opening. The spectrum of this noise is shown in Fig. 4.

Recording

The two leads from the skull implant were connected to a Grass, model HIP511B high impedance cathode follower connected to a Grass P5 Series AC Preamplifier (gain set at 10k, band passed from 30 Hz to

Figure 5. Spectral characteristics of the FC's used in the experiment. Signals were measured at the speculum opening with a B&K 4138 1/8" condenser microphone coupled to a B&K 2209 sound level meter with 1/3 octave band filter. Frequency analysis was performed by means of a B&K 2306 graphic level recorder. The SPL measurements for this and all figures are referenced to .0002 dyne/cm².

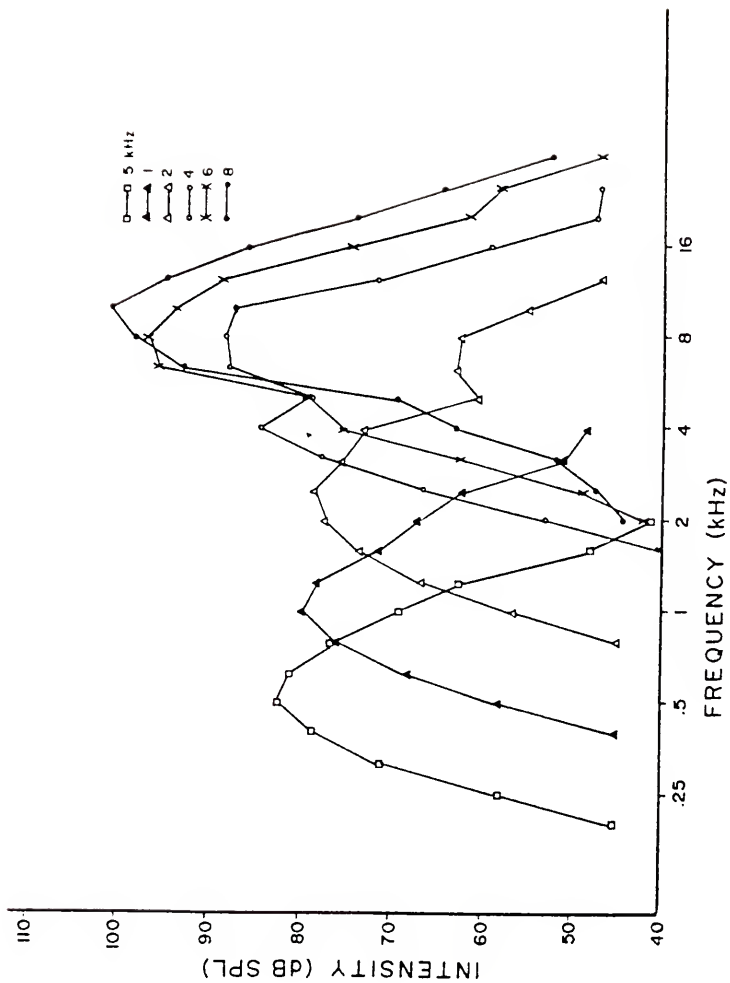
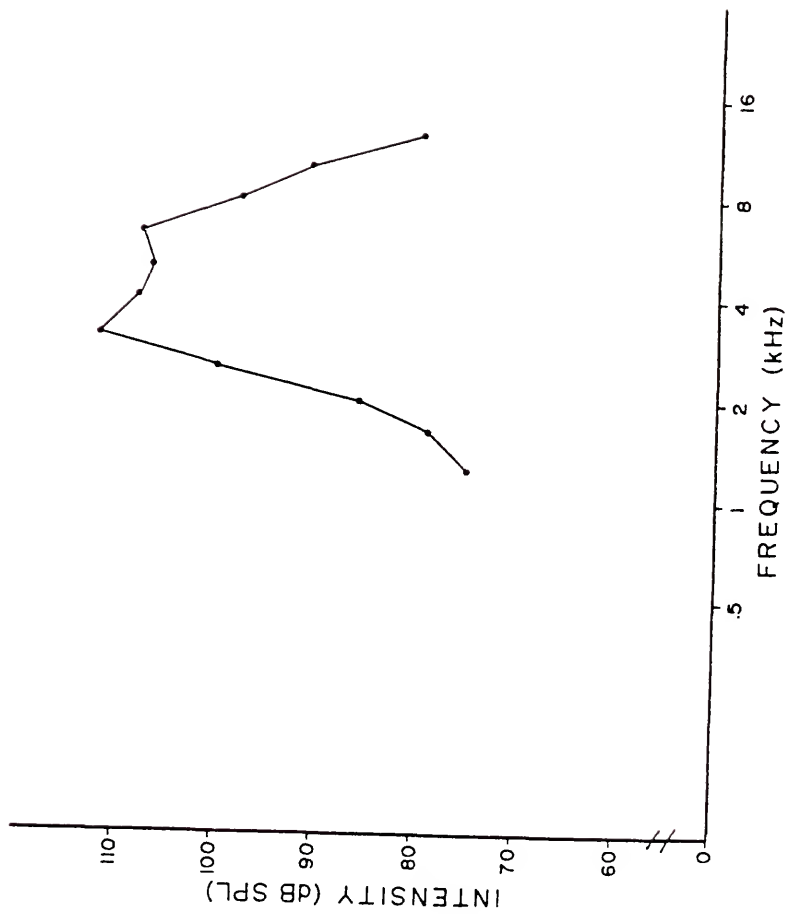


Figure 4. Spectral characteristics of the 108 dB SPL narrow band of noise centered at 4 kHz used for the exposure stimulus. The noise was measured before and after each exposure session with a B&K 4135 1/2" condenser microphone coupled to a B&K 2209 sound level meter with 1/3 octave band filter. Frequency analysis was performed by means of a B&K 2306 graphic level recorder.



3 kHz) and Krohn-Hite model 3100 filter (also band passed from 30 Hz to 3 kHz). The head holder served as ground. The filtered response was delivered to the A/D converter (40 μ sec bin width) of a Computer Automation mini-computer which performed the averaging of the BSR activity. The single responses were monitored on the Tektronix 565 oscilloscope to note changes in the waveform which would indicate equipment malfunction or excessive movement.

Procedure

The animal was placed in a head holder immediately after the anesthetic had taken effect and the implant was connected to the cathode follower. After the speculum had been placed into the opening of the EAM, intensity functions were performed with broad-band, 0.5, 1, 2, 4 and 8 kHz filtered clicks in that order. As the signal to noise ratio was poorest at the lowest frequencies, the averages tended to be satisfactory at these low frequencies while the animal was most heavily anesthetized. Intensity of the clicks was varied from 0 dB of attenuation to threshold, in 6 dB steps, for each stimulus. At 0 dB attenuation the calculated SPL was 89 dB at 8 kHz, 86 dB at 6 kHz, 75 dB at 4 kHz, 70 dB at 2 kHz, 77 dB at 1 kHz and 82 dB at 500 Hz. The attenuators were linear over the range utilized. The number of responses averaged for each stimulus varied depending upon the intensity and CF of the stimulus. This number ranged from 32 responses for the higher frequency FCs at 0 dB of attenuation to 2038 responses at threshold. Threshold was determined as the point between the level at which the response was just visually detectable in the average and the level at which it was no longer visually

detectable for 2048 repetitions. The responses were recorded on data cassettes for later processing.

After completion of the baseline measurements, the experimental groups were exposed to a narrow band of noise centered at 4 kHz at 108 dB SPL for two hours. Following the four-week interval, input-output functions were again performed, the procedure for which was identical to that described for the baseline measurements. A four-week interval was selected as there is no indication of additional anatomical damage beyond this time in the chinchilla (Bohne, 1976) and pilot work did not indicate additional damage as measured electrophysiologically in the guinea pig.

Histology

Immediately following the one month postexposure measures, the cochleae were processed for analysis by surface preparation (Engstrom, Ades and Anderson, 1966; Smith and Vernon, 1976). The animals were administered an overdose of Nembutal IP. As soon as respiration ceased, the animals were decapitated and the temporal bones removed and placed in vials of formalin fixative. Under a dissecting microscope at 12X magnification, the bulla was opened to expose the cochlea. A small hole was made in the apex and the cochlear windows were carefully ruptured to allow gentle perfusion of fixative throughout the cochlea by means of a Pasteur pipette. The perfused cochlea remained in fixative for at least 48 hours. After two 10 minute rinses in phosphate-buffered solution, the cochlea were gently perfused several times with 1 percent O_5O_4 for 2 hours. After removal of the O_5O_4 , the cochlea were rinsed twice with 35 percent alcohol, twice with 50

percent alcohol (at 5 minutes per rinse) and left to stand, and refrigerated in 70 percent alcohol until dissected.

Dissection was performed under a stereomicroscope. Beginning at the apex and continuing through the upper three turns, the bone portion of the cochlea was removed, followed by the stria vascularis and tectorial membrane. The organ of Corti was separated from the osseous spiral lamina with a capsule knife in 1/2 to full turns and placed in a vial of glycerol. The section was then placed in a drop of glycerol centered on a glass slide, covered with a glass cover slip, and sealed with permount. Due to the tenacity with which the organ of Corti adheres to the spiral ligament in the basal turn, the capsule knife was used to separate the organ of Corti from both the ligament and lamina. The tissue was carefully lifted out from the base in 1/4 turn sections for mounting.

The specimens were viewed under phase-contrast microscopy at 1000X magnification. Missing hair cells were counted for each turn.

CHAPTER III

RESULTS

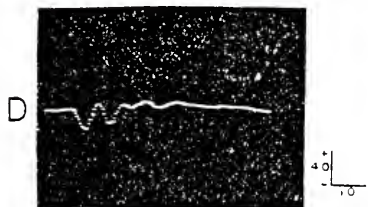
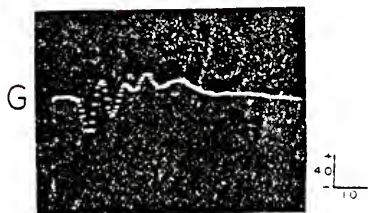
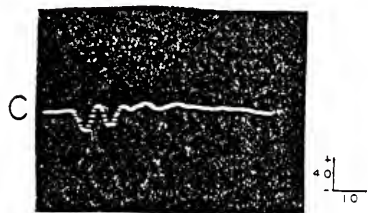
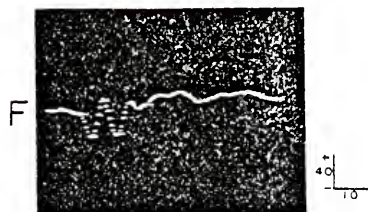
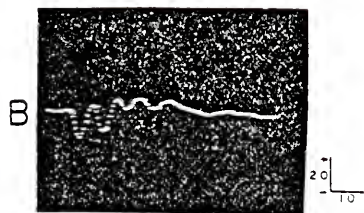
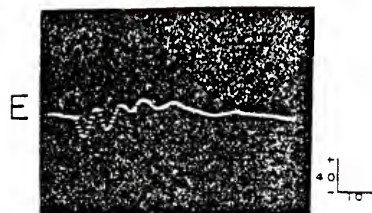
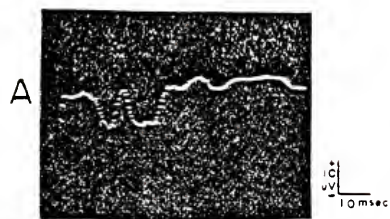
The results of this study are presented in preexposure and post-exposure sections. Within each section the threshold measures and the effects of frequency and intensity upon response amplitude and latency will be shown. Histological results will be presented in a final section. Except for the threshold measures, where data are presented for all filtered clicks, the results will focus upon the responses to the 1 kHz and 6 kHz FC's. Response amplitude and latency contrasted sharply as a function of click intensity and in the effects of the noise exposure for these two signals. Responses to the 4 and 8 kHz FC's were often similar to those of the 6 kHz signal. The 500 Hz FC often elicited a small dynamic range and the 2 kHz FC contained strong resonant energy at 4 kHz (Fig. 3).

Preexposure

Response Waveform

The BSR waveform is shown in Figure 5 and consists of four positive and four negative peaks. The parietal lead was positive with reference to the EAM. For the purpose of this study the first negative peak (N_1) and the fourth positive peak (P_4) were analyzed as they were the earliest and latest waves that varied systematically and consistently in amplitude and latency with changes in stimulus intensity. A cursor was used to measure peak amplitude and latency

Figure 5. Representative BSR waveforms produced by FC's of different center frequencies. A, 500 Hz; B, 1000 Hz; C, 2000 Hz; D, 4000 Hz; E, 6000 Hz; F, 8000 Hz; G, broad-band. All waveforms are shown at 0 dB of attenuation. The number of average responses varied from 32 for waveforms C thru G to 128 for waveform A.



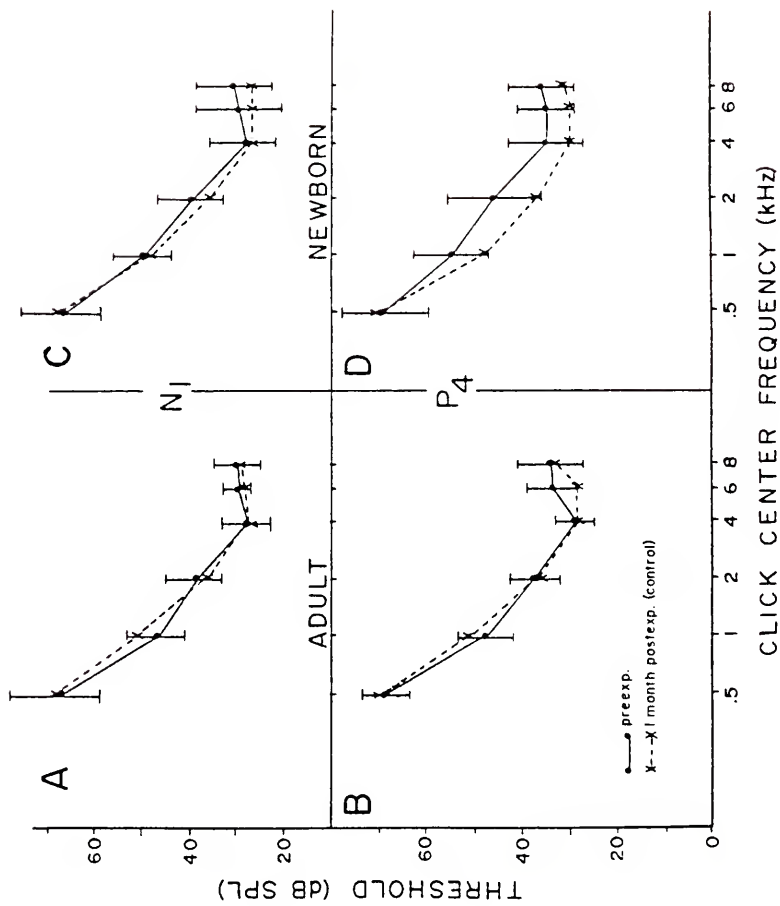
values. Amplitude of N_1 was measured from baseline to its most negative value and the amplitude of P_4 was measured from the most negative value of N_3 to the most positive value of P_4 . Latency was measured from the onset of the signal at the transducer to the N_1 and P_4 peaks at their most negative and positive amplitude values respectively.

In one pilot study electrode locations were varied. As the more caudal electrode was moved away from the external canal to more medial positions, the amplitudes of the later BSR waves increased. For this study the electrode configuration was chosen (Fig. 1) in order to emphasize the amplitudes of the earliest BSR waves. The waveforms in Figure 5 show that the amplitudes of the N_1 , N_2 complex are larger than the later deflections. However, the latencies could be read easily with the cursor at all locations in the BSR waveform.

Threshold

Figure 6 illustrates the mean N_1 and P_4 preexposure threshold values and ± 1 Standard Deviation (SD) for each FC. The solid line in each pair of curves represents the averaged responses of 5 experimental plus three control animals. The broken line represents the averaged responses of the three control animals measured 1 month following exposure of experimental animals. Thus, the threshold measurements over time are stable and the control group measures appear to be valid estimates of preexposure sensitivity. In all cases thresholds measured 1 month following exposure were within 1 SD of the preexposure threshold values. However, the P_4 thresholds of the newborn control animals measured 1 month after birth showed a decrease in

Figure 6. Average preexposure N_1 and P_4 thresholds as a function of FC center frequency. The thresholds of the 8 adult (5 experimental and 3 control) animals and 8 newborn (5 experimental and 3 control) animals are represented by solid lines. The thresholds of the 3 adult and 5 newborn control animals measured 1 month following exposure of the experimental groups and are represented by broken line. Panels A thru D illustrate the following response thresholds: Adult, N_1 ; Adult, P_4 ; Newborn, N_1 ; Newborn, P_4 . Vertical lines show 1 SD from the mean.

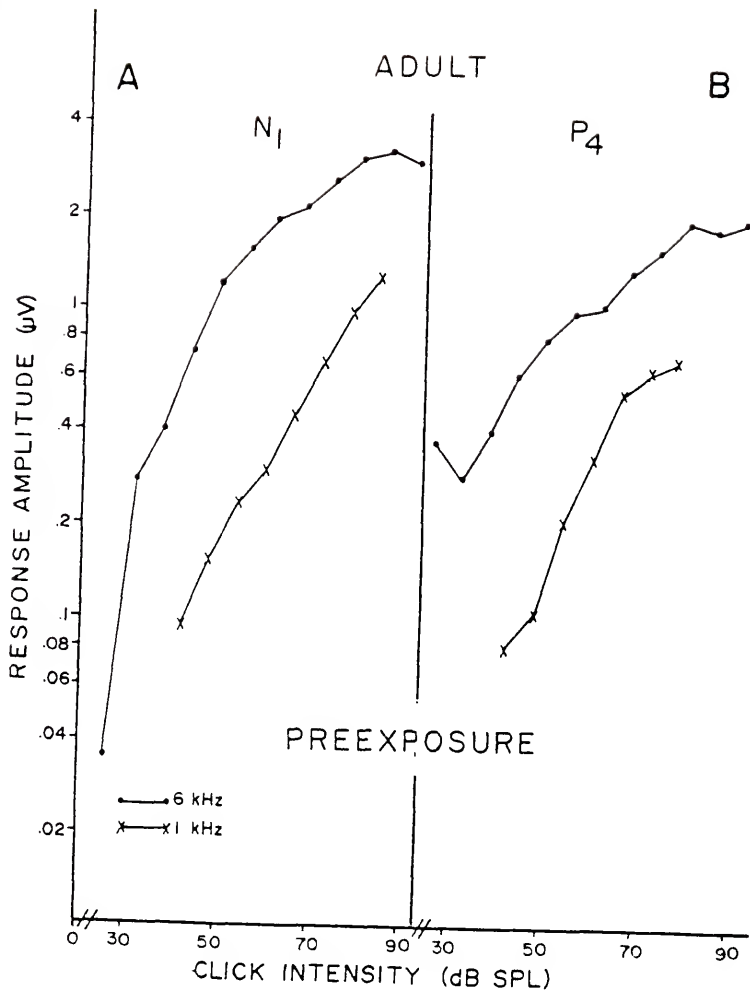


threshold for frequencies of 1 kHz and above. The average decrease in thresholds to the 5 filtered clicks (from 1 kHz to broad band) was 3.1 dB. There was no change in threshold for the 0.5 kHz FC. No differences occurred in threshold for P_1 in the adult control group and only a slight difference occurred in the N_1 responses in the newborn control group. All four sets of curves showed maximum sensitivity to the 4 kHz FC, and there was a tendency for the thresholds to higher FC's to be slightly higher. The most extreme difference in the visual detection level among the frequencies of the FC's occurred in the adult group for P_4 which showed a difference of 6 dB between 4 and 6 kHz. With the exception of the P_4 response from the newborn group, the absolute threshold levels for N_1 and P_4 were very similar among the newborn and adult animals. The maximum threshold values were approximately 67-69 dB SPL at 500 Hz and decreased to a minimum of 28-29 dB SPL at 4 kHz. The mean P_4 threshold values of the 8 newborn animals for FC's of 1, 2 and 4 kHz were 3 to 4 dB higher than the adults. The thresholds of the 3 newborn control animals measured one month later, however, were consistent with all other threshold measurements.

Effects of Frequency and Intensity on N_1 and P_4 Response Amplitudes

Figure 7 illustrates the preexposure response amplitude vs. signal intensity for the N_1 (Fig. 7A) and P_4 (Fig. 7B) peaks produced by the 1 kHz and 6 kHz FC's averaged over the 8 adult animals. Figure 7A shows that N_1 rises very steeply for the first 6 dB above threshold and then more gradually with increases in intensity of the 6 kHz FC. The N_1 response to the 1 kHz FC requires greater intensity for

Figure 7. Average preexposure response amplitude in the adult group (N=8) as a function of click intensity. Panel A illustrates the N_1 amplitude function; Panel B, the P_4 amplitude function. The solid circles represent response to the 6 kHz FC; the cross marks, responses to the 1 kHz FC. See Figure 9 for variance data.



detection and is lower in amplitude at all intensity levels above threshold. At suprathreshold intensities response magnitude increases at a slower rate for the 1 kHz FC than for 6 kHz. The intensity functions for P_4 contrast with those for N_1 . The threshold for the P_4 responses are the same as for N_1 . Except near threshold, the amplitudes of the P_4 responses are lower than the N_1 responses at respective intensities, probably because of the electrode configuration used. The slope of the function of P_4 , 6 kHz is less than that for the 1 kHz FC, but its maximum response is greater.

The intensity functions for the newborn group are shown in Figure 8. The functions for N_1 compare well with those for the adults. However, those for P_4 differ in some respects. The response magnitudes and the slopes of the intensity functions are lower. Unlike the adult responses there is little difference in slope between the 1 and 6 kHz FC's for the P_4 responses.

Figure 9 shows the coefficient of variation (CV) for the pre-exposure response amplitude as a function of click intensity for the 1 kHz and 6 kHz FC's. The CV's for the adult animals (Fig. 9A) in response to 6 kHz are nearly 1.0 near threshold and decreases to about 0.5 by 18 dB above threshold and remains at about that level throughout the intensity range. For 1 kHz, the threshold is higher and the CV varies around the 0.5 value throughout the intensity function. The CV's for N_1 and P_4 responses are similar in the adult. The CV's for newborns are shown in Figure 9B. The wide variation in CV for the responses from newborns contrasts with the consistency shown by the adults responses. In a broad sense the CV's for the two responses, N_1 and P_4 , to each stimulus resemble each other.

Figure 8. Average preexposure response amplitude in the newborn group (N=8) as a function of click intensity. The legend is the same as that for Figure 7.

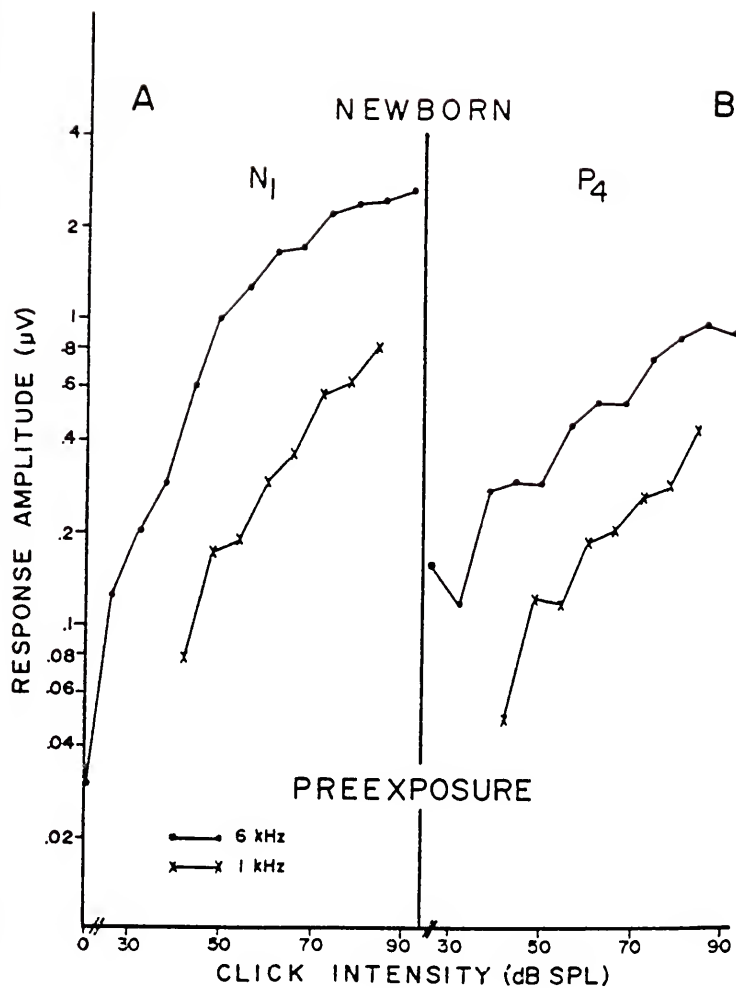
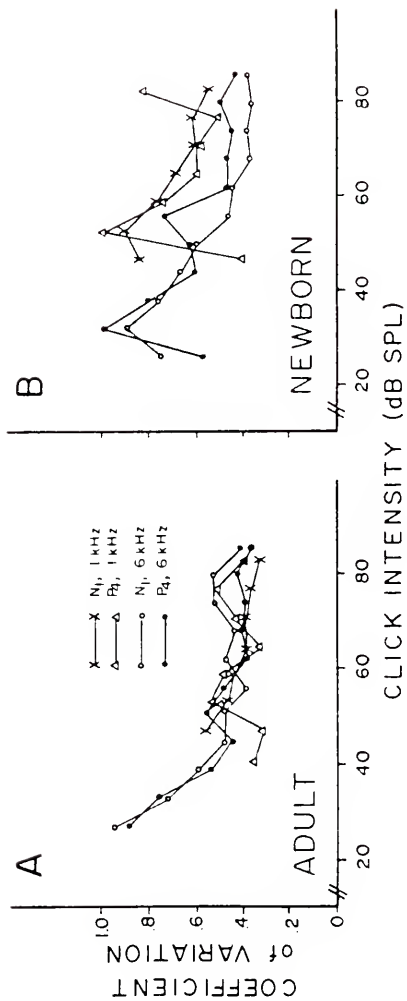


Figure 9. Coefficient of variation for response amplitude as a function of click intensity for the adult group (Panel A) and the newborn group (Panel B). $N=8$ for both groups.



For 1 kHz, N_1 and P_4 show maximum variation at 53 dB SPL. For 6 kHz each response shows a peak at 32 dB SPL. However, there are also differences between N_1 and P_4 and, in general, the variation in responses from the newborns is relatively large.

Effects of Frequency and Intensity on N_1 and P_4 Response Latencies

Response latency is reported to be a very stable measure of N_1 and BSR while amplitude may vary due to electrode contact and other procedural effects. Figure 10 illustrates the response latencies for N_1 and P_4 for the 1 kHz and 6 kHz FC's from adults and newborns. The latencies for N_1 and P_4 are plotted on overlapping coordinates that have a constant 3.0 msec difference. The ordinate for N_1 ranges from 1 to 2.4 msec, and for P_4 from 4 to 5.4 msec. The changes in latencies with intensity of N_1 and P_4 are similar in the adult responses. For the 1 kHz FC the average difference between N_1 and P_4 for the adult group is 3 msec, for the infant group it is 3.13 msec. For the 6 kHz FC the average N_1 and P_4 difference is 3.27 msec for adults and 3.34 msec for the newborns. However, the N_1 latency functions for the .5 kHz FC in adults and newborns have very similar values and, while an average difference is appropriate for the adults, for infants the N_1 and P_4 latency difference is larger at 68 dB than at 38 dB. No such divergence in N_1 and P_4 latency occurs for the 1 kHz FC. Apparently, P_4 lags the changes in latency of N_1 in the newborn group while for the adults, P_4 follows the latency decreases in N_1 as stimulus intensity increases. Figure 11 shows the functions in Figure 10 redrawn with the 1 and 6 kHz FC's as the parameter. For the responses from both the adult and the newborn, the latencies are similar when the stimuli are strong. The minimum latencies at 88 and

Figure 10. Average preexposure response latency as a function of click intensity and FC center frequency. Latency values for N_1 and P_4 are plotted on overlapping coordinates having a 3.0 msec difference. Solid circles represent the P_4 latency functions; cross marks, the N_1 latency functions. Panels A thru D illustrate, respectively, the following latency functions: Adult, 1 kHz; Adult, 6 kHz; Newborn, 1 kHz; Newborn, 6 kHz. N=8 for both groups. See Table 1 for variance data.

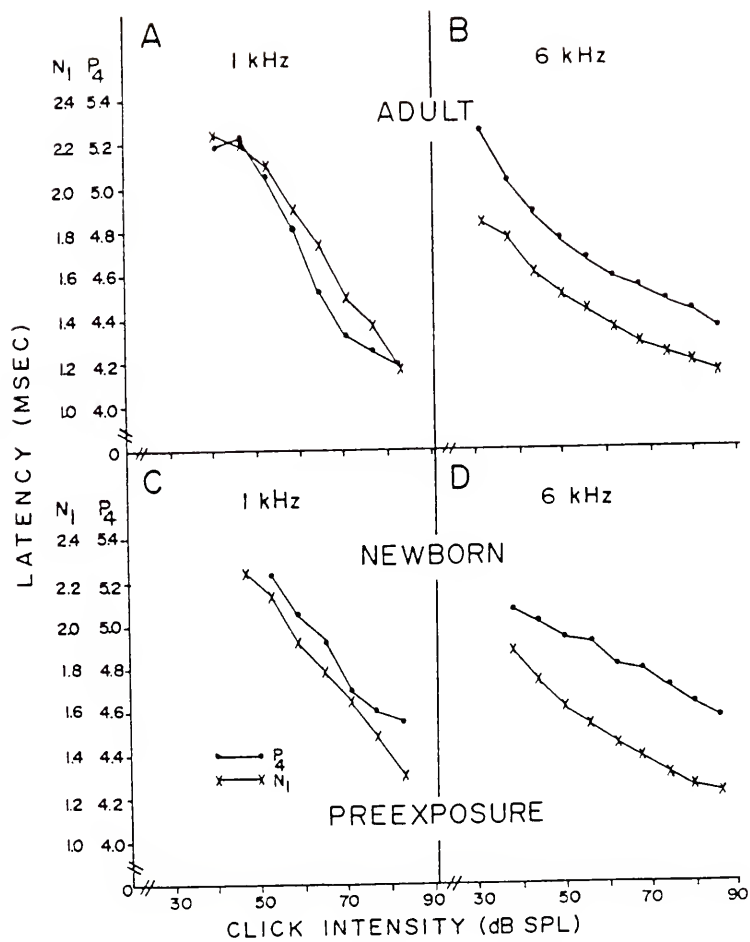
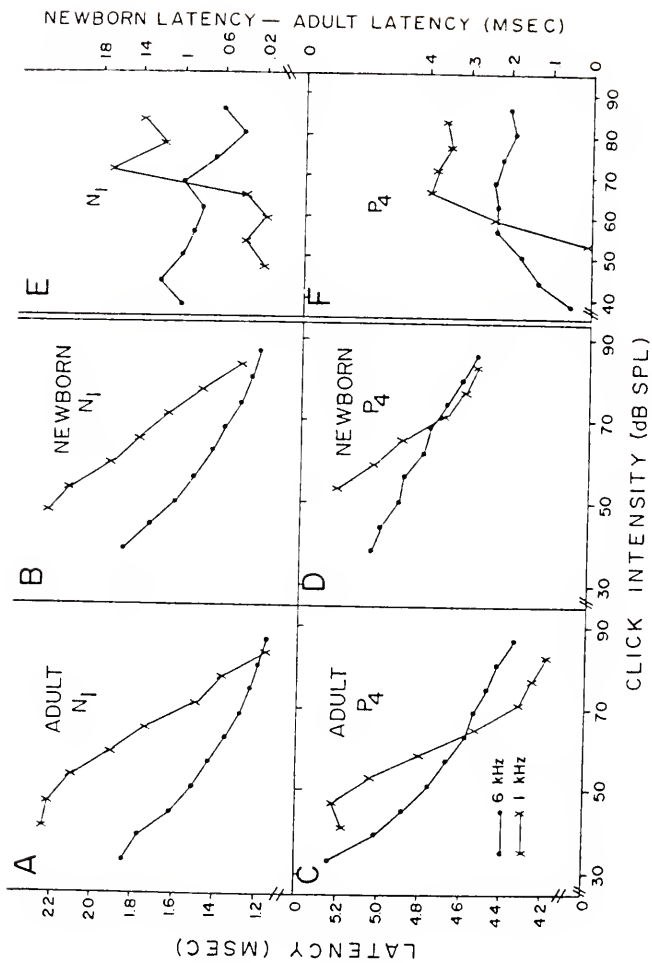


Figure 11. Response latencies of Figure 9 redrawn with the 1 and 6 kHz FC's as the parameter. Solid circles represent the averaged latency values in response to the 6 kHz FC; cross marks the averaged latency values in response to the 1 kHz FC. Panels A thru D illustrate, respectively, the following latency functions: Adult, N₁; Newborn, N₁; Adult, P₄; Newborn, P₄. Panel E shows the differences between the N₁ response latencies in the adults and newborns. Panel F illustrates the differences between the P₄ responses in the adults and newborns.



92 dB are slightly shorter in the adults than in newborns. On the right side of Figure 11, in panel E, the differences between the N_1 responses in adults and newborns for each signal are shown directly. All the infant latencies are longer than the adult but the differences for the 1 kHz FC below 66 dB are the smallest, i.e., the infant responses are most similar to the adult. Above 66 dB, the differences become larger abruptly, rising to 1.7 msec at 72 dB. For the 6 kHz FC, the infant responses gradually approach the adult values, i.e., the differences become less with increases in intensity.

For P_4 the latency functions for the two signals cross at about 64 dB. For signals greater than 64 dB, the responses to 1 kHz FC showed a shorter latency than those to 6 kHz, while at intensities less than 64 dB, P_4 for 1 kHz has a longer latency than for 6 kHz. The latency functions also cross for the infant responses, but the functions appear to be truncated, i.e., while the latencies for weak signals are similar to the adult latencies, the infant P_4 responses do not become as short as in the adults. The right-hand panel F shows the differences in P_4 responses between adult and newborn groups. As for N_1 , infant responses lag the adult. The sharp increase in P_4 delay for infants seen for N_1 is paralleled in the data on P_4 . However, the difference for 6 kHz is minimal at weak intensities and reaches a fairly constant value at 0.2 msec as intensity increases.

Table 1 shows the average SD for the N_1 and P_4 latency measurement for the adult and newborn groups. The overall variance was similar between the two populations (.227 msec for adults vs. .22

TABLE I

Averaged S.D. for N_1 and P_4 Latency Measurements (msec)

	<u>ADULT</u>		<u>NEWBORN</u>	
	N_1	P_4	N_1	P_4
1kHz	.259	.238	.210	.294
6kHz	.143	.266	.120	.256

msec for newborns). Within populations, N_1 latency displayed less variance than P_4 in both groups, the difference being larger among the newborns. Response variance to the 6 kHz FC was less than to the 1 kHz FC, for both groups.

The preexposure threshold, amplitude and latency data consistently illustrated that the N_1 response functions in the adult and newborn were generally similar whereas the P_4 functions differed between the two groups.

Postexposure

Effects of Noise on Threshold

Figure 12 illustrates the mean N_1 (Fig. 12A) and P_4 (Fig. 12B) threshold shift as a function of center frequency of the FC's for the two groups of guinea pigs. The solid lines represent the responses from experimental animals and the dashed lines represent control responses measured one month following exposure of the experimental animals. For both control groups, the threshold shifts for N_1 and P_4 were no more than ± 6 dB from their preexposure values. Figure 12A shows that the average threshold shift of N_1 for the adult experimental group increased with increasing center frequency for the FC to a maximum of 15 dB for the 8 kHz FC. The N_1 threshold for the newborn group also decreased with increasing frequency and exceeded the threshold shift in adults. The threshold shift for the newborns showed a maximum shift of 31 dB at 6 kHz. The shift in threshold for P_4 , shown in Figure 12B, shows the same trend of increasing shift with increasing center frequency of the FC. The P_4 threshold for newborns reached a maximum shift of 30 dB for the 6 kHz FC and the P_4 threshold for adults

Figure 12. Averaged threshold shift as a function of FC center frequency measured 1 month postexposure. Panel A illustrates the shift in N_1 ; Panel B, the shift in P_4 . Solid circles, exposed adult group; cross mark, exposed newborn group; open circle, control adult group; triangle, control newborn group. $N=5$ for the experimental groups and $N=3$ for the control groups. Variance data (Table 2) indicate that the means of the threshold shifts fall outside the standard deviation of the two groups for the 1, 2, 4, and 6 kHz FC for N_1 and for the 6 kHz FC for P_4 .

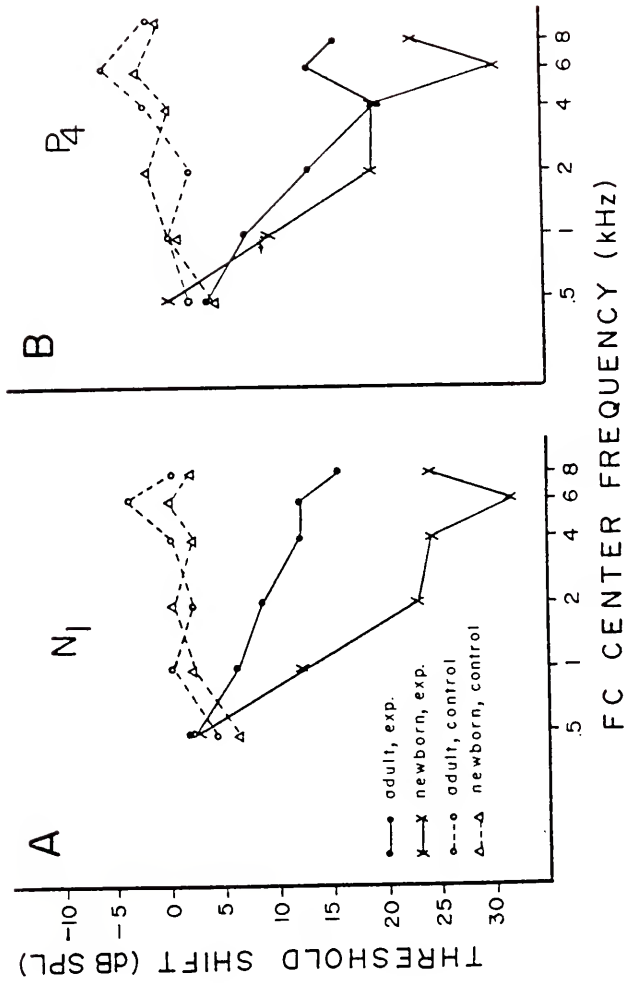


TABLE 2

Standard deviation for averaged postexposure threshold shift (dB SPL).

FC		N ₁ exper. (N=5)	N ₁ cont. (N=5)	P ₄ exper. (N=5)	P ₄ cont. (N=5)
0.5 kHz	Adult	±15	±6.9	±8	±3.4
	Newborn	13.8	0	14	6.9
1	Adult	6	0	4.9	0
	Newborn	7.3	3.4	6.8	6
2	Adult	6	3.4	9.5	3.4
	Newborn	8.7	0	8.8	3.4
4	Adult	5.8	0	8.6	9.1
	Newborn	6.1	6.9	8.8	6
6	Adult	7.4	3.4	5.5	6
	Newborn	10.3	6	8.1	6.9
8	Adult	11.2	6	11.8	3.4
	Newborn	15.6	3.4	15.5	3.4

reached a maximum shift of 19 dB at 4 kHz. Except for the 6 kHz FC, the difference between newborn and adult threshold shift was less for P_4 than for N_1 .

Effects of Noise Exposure on Response Amplitude and Latency

Response amplitude. Figures 13 and 14 illustrate the relations between postexposure response amplitude and signal intensity for the N_1 and P_4 peaks produced by the 1 kHz and 6 kHz FC's averaged over the five adult (Fig. 13) and five newborn (Fig. 14) experimental animals. The preexposure equivalent measures are shown in Figures 7 and 8. As in the preexposure amplitude functions, response amplitude was a continuously increasing function of stimulus intensity. The postexposure curves of N_1 for 6 kHz show a greater decrease in response amplitude from preexposure values than the curves for 1 kHz. Both intensity functions show a shift to the right, i.e., requiring greater intensities to reach a given amplitude, but the greatest change occurs for the 6 kHz curve. The response threshold to the 6 kHz FC is elevated and a larger response was required for detection. There is less postexposure change in the N_1 response amplitudes for the 1 kHz FC. The curves for P_4 (adults) show relations similar to those described for N_1 . For the newborns, however (Fig. 14), the postexposure curve for N_1 to the 6 kHz FC is shifted so far to the right that it coincides with the intensity function for 1 kHz, corresponding to the maximum threshold shift seen in Figure 12 (about 30 dB). Only very strong signals evoked P_4 responses in the post-exposed newborn.

Figure 13. Average postexposure response amplitude in the adult group (N=5) as a function of click intensity. See Figure 7 for comparison with preexposure functions and legend and Table 3 for variance data.

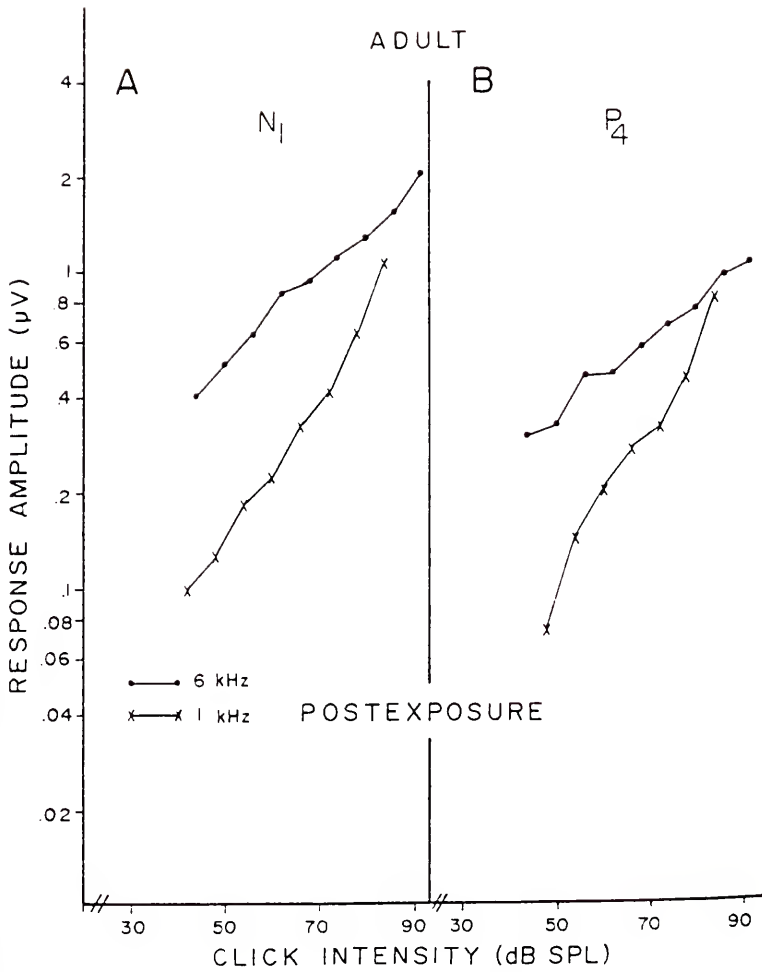


Figure 14. Average postexposure response amplitude in the newborn group (N=5) function of click intensity. See Figure 8 for comparison with pre-exposure functions and legend and Table 3 for variance data.

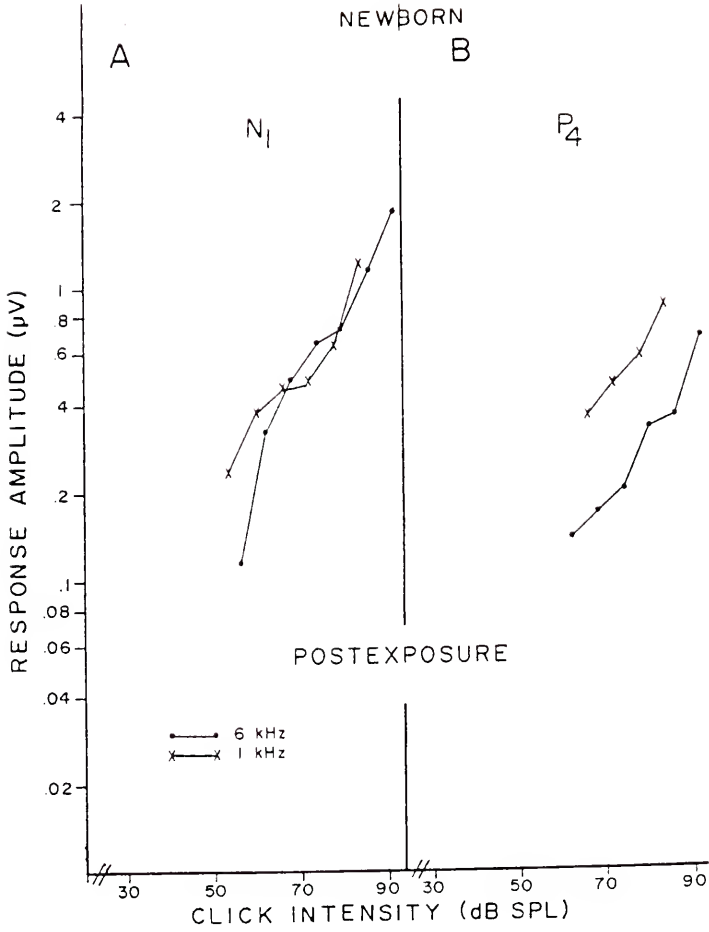


TABLE 3

Standard deviation for postexposure response amplitude (μV).

dB SPL	1 kHz (N=5)		dB SPL	6 kHz (N=5)			
	N_1	P_4		N_1	P_4		
41	Adult	<u>+.07</u>	<u>+.07</u>	38	Adult	<u>+.18</u>	<u>+.06</u>
	Newborn	-	-		Newborn	-	-
47	Adult	.07	.07	44	Adult	.34	.23
	Newborn	-	-		Newborn	-	-
53	Adult	.12	.1	50	Adult	.32	.45
	Newborn	.23	-		Newborn	-	-
59	Adult	.17	.27	56	Adult	.5	.63
	Newborn	.23	-		Newborn	.11	-
65	Adult	.23	.09	62	Adult	.54	.5
	Newborn	.41	.44		Newborn	.2	.12
71	Adult	.25	.2	68	Adult	.5	.68
	Newborn	.34	.35		Newborn	.52	.05
77	Adult	.34	.16	74	Adult	.39	.69
	Newborn	.74	.68		Newborn	.37	.1
83	Adult	.84	.43	80	Adult	.19	.66
	Newborn	1.31	1.15		Newborn	.58	.25
				86	Adult	.37	.58
					Newborn	.82	.16
				92	Adult	.57	.4
					Newborn	.71	.27

The differences in response amplitude between preexposure and postexposure conditions are shown in absolute values in Figures 15 A-D and in relative values in 15 E and F. Relative shift was computed by dividing postexposure response amplitude by preexposure response amplitude, subtracting the result from 1 and multiplying by 100 to obtain a percentage shift. The results shown in Figure 15 indicate that the noise exposure produced little change in the responses to the 1 kHz FC but substantial change in response to the 6 kHz FC. The absolute postexposure shift in the N_1 response to the 6 kHz FC was greater than that for the 1 kHz FC in both the adult and newborn populations. Similarly, response amplitude of P_4 showed a greater shift in response to the 6 kHz FC than to the 1 kHz in both groups but to a lesser amount than N_1 . Figures 15 E and F show the postexposure response amplitudes in relation to the preexposure control responses. The N_1 and P_4 response amplitudes to the 6 kHz FC in the newborn group decreased more than did the responses of the adults. Except at low intensities, the N_1 and P_4 responses decreased about the same amount in the newborn group whereas the N_1 response in the adults shifted more, relative to the preexposure control responses than did the P_4 response.

Response latency. Figure 16 illustrates the postexposure latencies vs. signal intensity for the N_1 and P_4 peaks produced by the 1 kHz and 6 kHz FC's averaged over the five experimental adults (Figs. 16 A and B) and five newborns (Figs. 16 C and D). The ordinate for P_4 is labeled so that there is a 3.0 msec constant between N_1 and P_4 . The corresponding preexposure measures are shown in

Figure 15. Absolute and relative postexposure amplitude shift as a function of click intensity. Panels A thru D illustrate, respectively, the following absolute shift functions: Adult, N₁; Adult, P₄; Newborn, N₁; Newborn, P₄. Solid circles, 1 kHz function; triangle, 6 kHz function; solid line, experimental group; broken line, control group. Panels E and F illustrate relative postexposure amplitude shift at 6 kHz for N₁ and P₄, respectively. Open circles, adult group; triangles, newborn group. N=5 for the experimental groups and N=3 for the control groups.

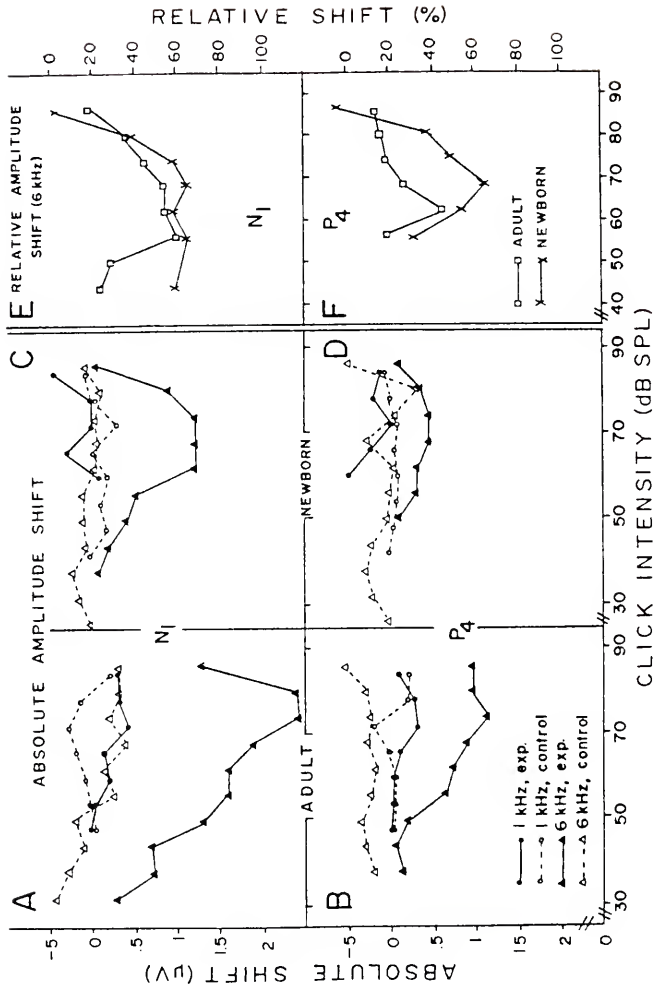


Figure 16. Averaged postexposure response latency as a function of click intensity and FC center frequency. See Figure 10 for comparison with preexposure functions and legend and Table 4 for variance data. N=5 for both groups.

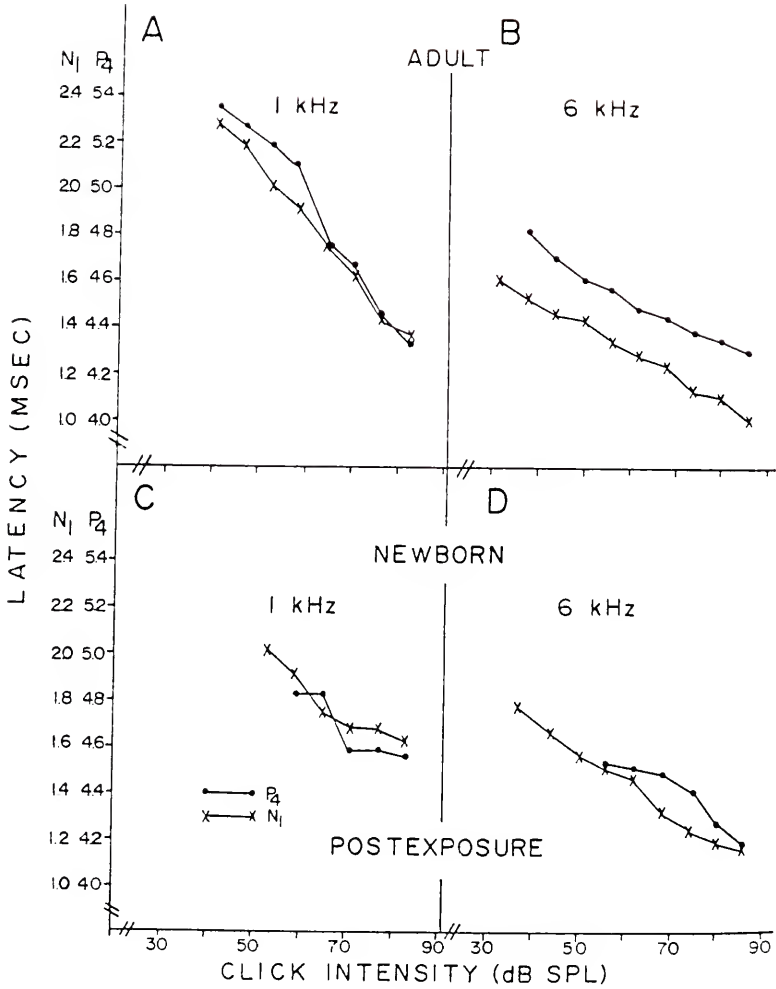


TABLE 4

Standard deviation for averaged postexposure response latency (msec).

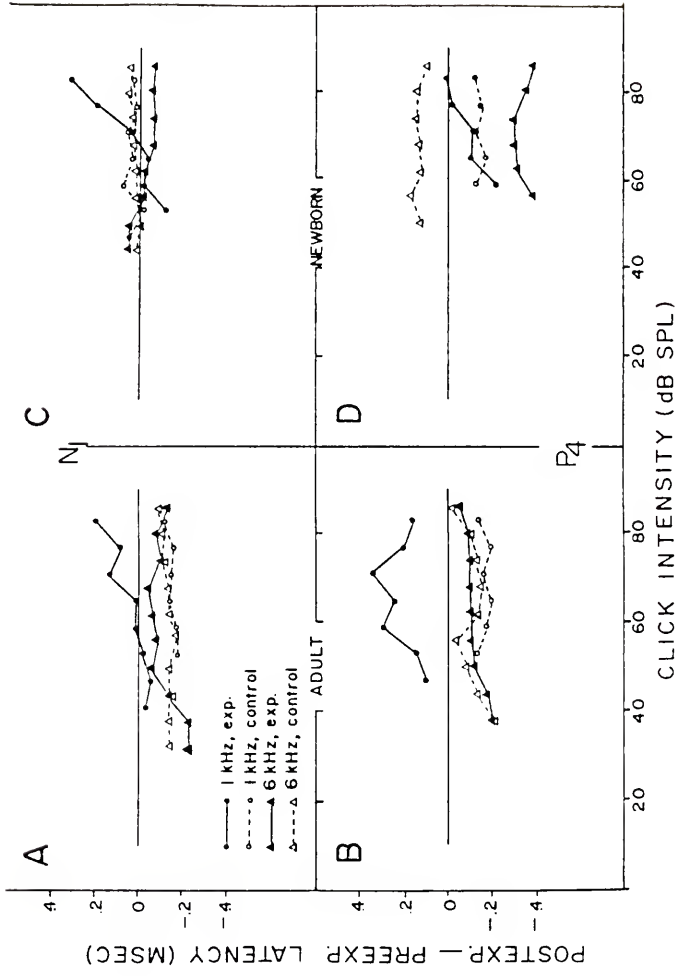
dB SPL	1 kHz (N=5)		dB SPL	6 kHz (N=5)			
	N_1	P_4		N_1	P_4		
41	Adult	$\pm .136$	$\pm .222$	38	Adult	$\pm .27$	-
	Newborn	-	-		Newborn	-	-
47	Adult	.114	.222	44	Adult	.121	.357
	Newborn	-	-		Newborn	.333	-
53	Adult	.171	.32	50	Adult	.088	.284
	Newborn	.236	-		Newborn	.382	-
59	Adult	.32	.494	56	Adult	.131	.355
	Newborn	.252	.253		Newborn	.389	-
65	Adult	.328	.291	62	Adult	.07	.298
	Newborn	.256	.256		Newborn	.455	.166
71	Adult	.337	.141	68	Adult	.09	.261
	Newborn	.42	.433		Newborn	.327	.186
77	Adult	.182	.199	74	Adult	.088	.191
	Newborn	.56	.482		Newborn	.285	.253
83	Adult	.171	.129	80	Adult	.06	.24
	Newborn	.437	.47		Newborn	.27	.439
				86	Adult	.067	.288
					Newborn	.195	.169
				92	Adult	.121	.336
					Newborn	.192	.499

Figure 10. As in the preexposure functions, response latency for all stimulus conditions was a continuously decreasing function of stimulus intensity. There are relatively fewer data points for the newborn population due to the restricted dynamic range caused by the increase in postexposure threshold.

The slopes of the postexposure response latencies from adult 1 kHz functions are not as steep as the corresponding preexposure curves (.016 msec/dB postexposure vs. .03 msec/dB preexposure). By contrast, the slopes of adult 6 kHz functions (Fig. 16B) for pre and postexposure are similar, but the postexposure latency values are shorter than the preexposure measures. It is difficult to observe definite trends in the postexposure response latencies for the newborn groups because of the relatively few data points. The postexposure latency function for N_1 in response to the 6 kHz FC (Fig. 16D) is very similar but earlier (shifted left) than the preexposure measure. The P_4 response latency function shows a large decrease in postexposure latency values throughout the intensity range and requires signals greater than 56 dB for detection.

The postexposure N_1 and P_4 shift in latency as a function of FC intensity is shown in Figure 17. Figures 17 A and B illustrate latency shifts in the adult and Figures 17 C and D show the shifts in the newborn group. The latencies for the control groups (dashed lines) decreased for both the 1 kHz and 6 kHz FC's. The N_1 and P_4 postexposure response latencies to the 6 kHz FC for adults and the N_1 responses in the newborns also decreased in latency by a similar amount. The latency of P_4 from newborns increased in the responses to 6 kHz. However, the postexposure latencies to the 1 kHz FC shows

Figure 17. Averaged postexposure-preexposure latency shift as a function of click intensity. Panels A thru D illustrate, respectively, the following functions: Adult, N1; Newborn, N1; Newborn, P4. Circle, 1 kHz; triangle, 6 kHz; solid line experimental group (N=5); broken line, control group (N=3).

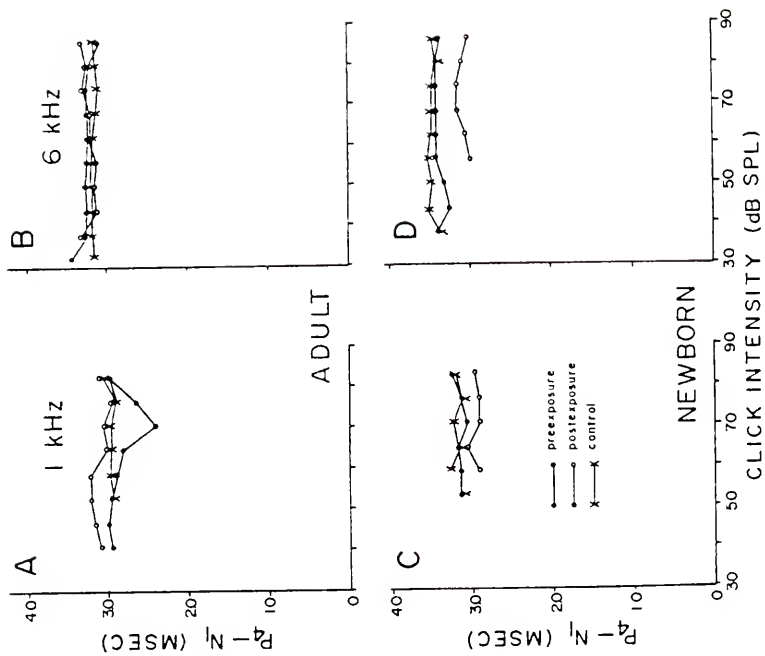


an increase in latency with increasing signal intensity for N_1 and throughout the intensity range for P_4 for both adult and newborns. Even though the N_1 response to the 1 kHz FC changed little in magnitude (Figs. 15A and 15C), the latency increase for the postexposure measures was consistent. The response latency to the 6 kHz FC also decreased but less than for the 1 kHz FC, even though the amplitude change was large. The P_4 functions in the newborn group (Fig. 17D) differ from the others in that there is a large decrease in latency for the experimental group in response to the 6 kHz FC as compared with the control group. Also, the response latency to 1 kHz decreased at all signal levels except at the highest intensity, although the function becomes less negative with increasing signal strength.

Figure 18 illustrates the $P_4 - N_1$ latency differences as a function of click intensity. For the adult responses to 1 kHz (Fig. 18A) the postexposure $P_4 - N_1$ differences are larger than the preexposure differences, but for the responses to 6 kHz (Fig. 18B) there is no change in the $P_4 - N_1$ latency differences. For the newborns (Figs. 18C and 18D) postexposure $P_4 - N_1$ differences are shorter than preexposure values for both stimuli. Although N_1 latencies for the adult responses to the postexposure 1 kHz FC were slightly longer than the preexposure latencies, a greater increase in latency occurred for P_4 . No systematic latency effect occurred for responses to the 6 kHz FC.

The latencies from newborns showed shorter $P_4 - N_1$ latency differences following exposure to the 4 kHz narrow band noise. The differences were consistent across the full range of intensities that

Figure 18. Averaged $P_4 - N_1$ latency differences as a function of click intensity. Panels A thru D illustrate, respectively, the following functions: Adult, 1 kHz; Newborn, 1 kHz; Newborn, 6 kHz. Solid circle, preexposure; open circle, postexposure; cross mark, control, measured 1 month following exposure to the experimental group. N=8 for the preexposure functions, N=5 for the postexposure functions and N=5 for the control functions.



could be measured. The $P_4 - N_1$ latency differences in response to the 1 kHz FC in the adult control group (Fig. 18A) (measured one month following the exposure) to the experimental group were longer than the preexposure measures at the higher signal intensities. As intensity of the stimulus decreased, the latency differences of the control group approached those of the preexposed experimental group. The $P_4 - N_1$ latency differences in response to the 6 kHz FC in the adult control and preexposure groups (Fig. 18B) showed little differences. Similarly, the $P_4 - N_1$ latency differences for the newborn control group measured one month following exposure to the experimental group were similar to the preexposure measures (Figs. 18C and 18D).

The postexposure electrophysiological data show that exposure to a narrow band of noise centered at 4 kHz produced a larger threshold and amplitude shift in the N_1 and P_4 responses to the 6 kHz FC than to the 1 kHz FC. The postexposure response latencies to the 1 kHz FC increased as compared to the response to the 6 kHz FC. The results also show that the newborn group experienced greater threshold and relative amplitude shift than did the adults.

Histology

Figure 19 is a photomicrograph of a healthy section of turn III of animal CI3, a control newborn animal. The three rows of outer hair cells, their stereocilia and supporting structures can be clearly seen. The inner hair cells are more difficult to see but their line of stereocilia are just visible. A damaged portion of turn II of animal EA6 is seen in Figure 20. Missing outer hair cells are visible in all three rows.

Figure 19. Photomicrograph of an undamaged cochlear section of the third turn of animal C13. OHC, outer hair cells; IHC, inner hair cells; N, nerve fibers. (X 630)

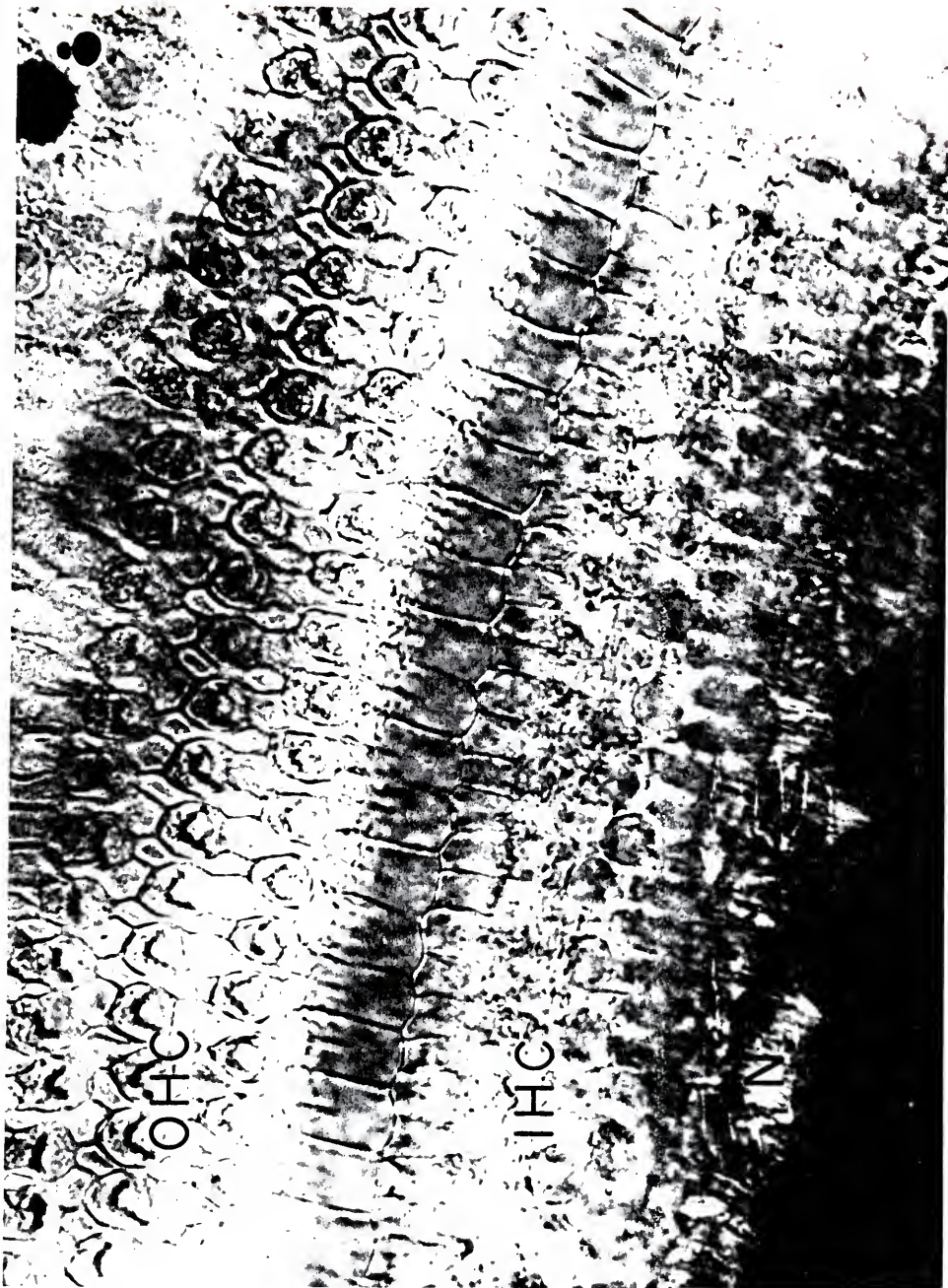


Figure 20. Photomicrograph of damaged cochlear section of the second turn of animal E.16. Arrows show location of missing outer hair cells (X630)

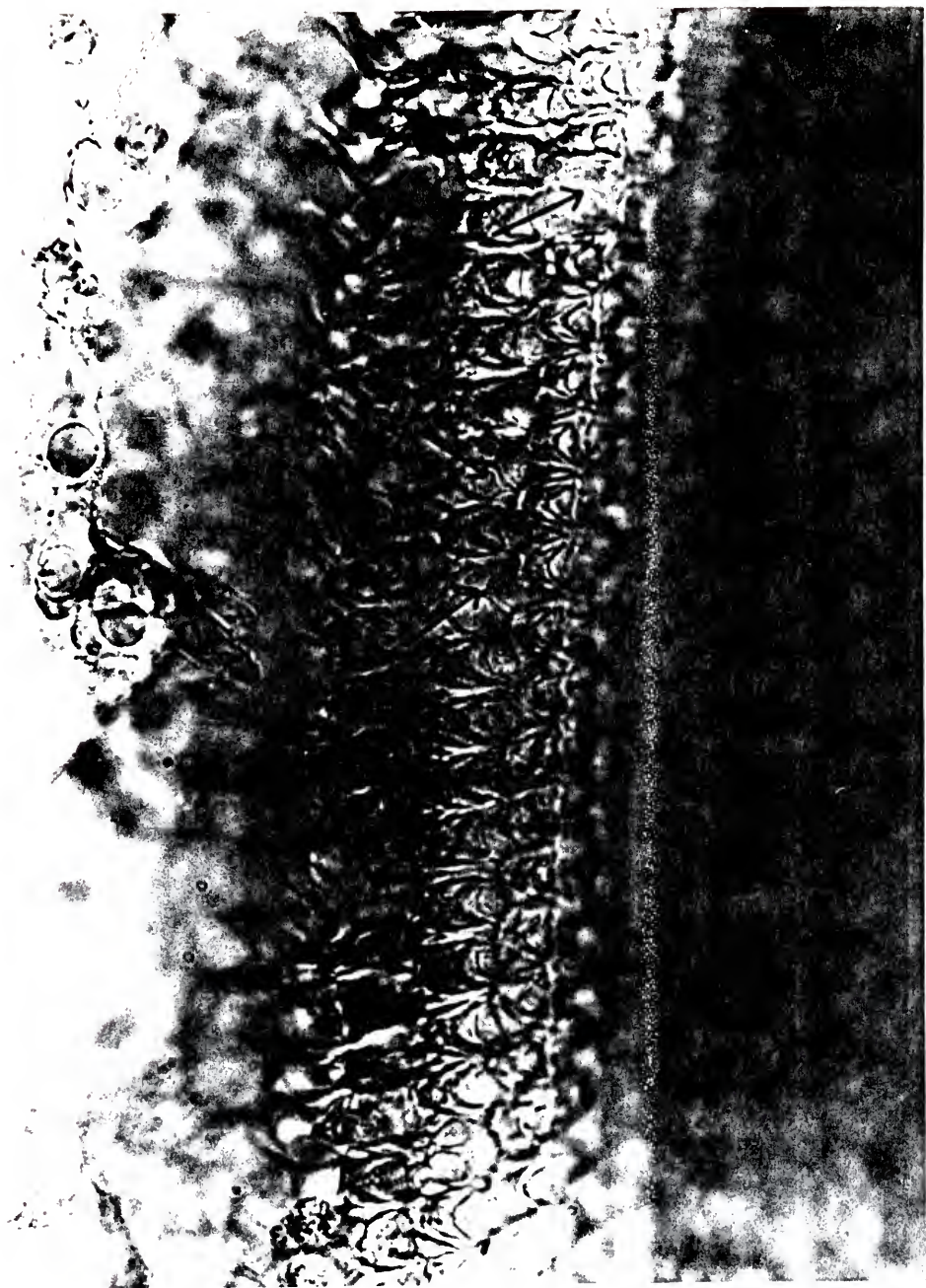


Figure 21 illustrates the averaged number of missing hair cells as a function of distance along the cochlear partition for the four categories of preparations. In general, both groups exhibited only minimal hair cell damage (in terms of missing cells). The adults (Fig. 21A) showed damage at the base in all four rows of hair cells with the amount of missing cells decreasing toward the apex. Outer hair cell row 3 exhibited the greatest amount of damage throughout most of the cochlea although the first outer hair cell row was the most damaged at the base. The newborn experimental group (Fig. 21B) exhibited maximum damage at the apex in the third outer hair cell row and minimum hair cell loss in the other turns and toward the base. The control animals showed very little hair cell loss throughout the cochlea.

There appears to be little correlation between histological and electrophysiological data. The newborn group showed greater postexposure threshold shift (Fig. 12) and relative amplitude shift (Fig. 15) than the adult group in response to the 6 kHz FC. The histological data, however, do not demonstrate greater hair cell loss for the newborns. On the contrary there are fewer missing hair cells toward the basal end of the cochlea for the newborns than for the adults. Much of the histopathology in the adult group was statistically influenced by one animal, EA6, which exhibited extensive hair cell loss in the lower turns. It is thought that this damage existed prior to exposure as EA6 was the oldest and largest (957 gms) animal used in this study. Furthermore, EA6 demonstrated minimal postexposure electrophysiologic changes. If the influence of EA6 is eliminated from the

Figure 21. Number of missing hair cells as a function of distance along the cochlear partition. Panels A thru D illustrate, respectively, the following groups: Experimental adult, experimental newborn, control adult, control newborn. Dashes, inner hair cells; solid line, outer hair cell row 1; dots, outer hair cell row 2; dots and dashes, outer hair cell row 3. N=5 for the experimental groups and N=3 for the control groups. See Table 5 for variance data.

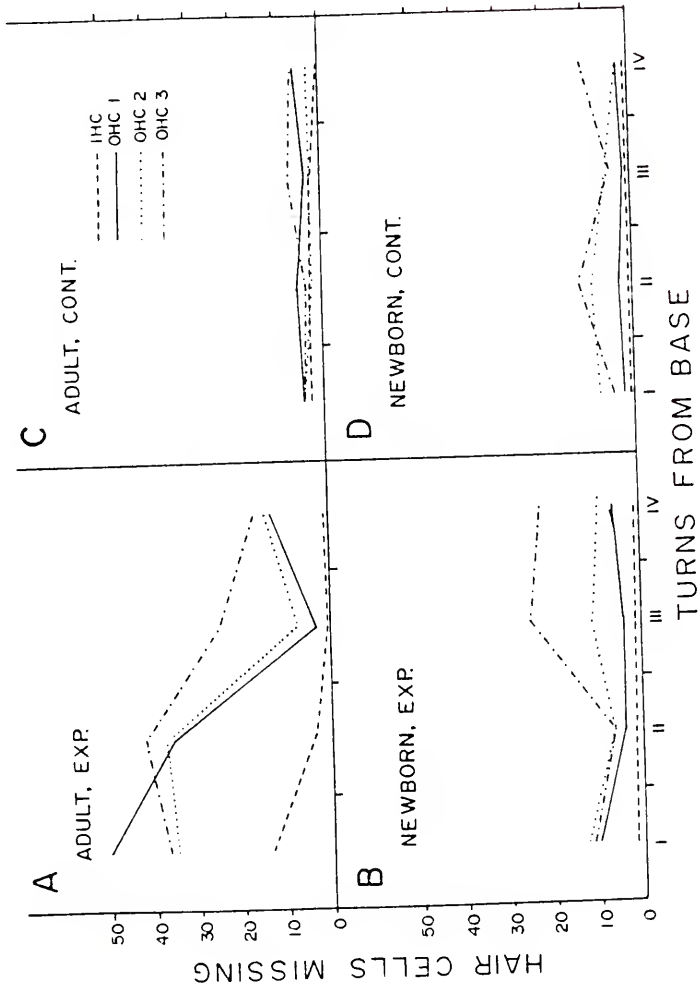


TABLE 5

Standard deviation for averaged number of missing hair cells.

Row	Newborn, exp. (N=5)	Newborn, cont. (N=3)	Adult, exp. (N=5)	Adult, cont. (N=3)
IHC	± 1.9	± 3.7	± 22.8	± 2.5
OHC 1	11.2	3.2	111.8	2.0
OHC 2	17.7	19.7	114.3	2.3
OHC 3	58.2	26.1	140.4	3.6

adult group, there is little difference between the number of missing hair cells for the two groups. There does not appear to be a systematic relationship between postexposure latency changes and hair cell loss. Figure 17 showed an increase in N_1 response latency in response to a 1 kHz FC for both the adult and newborn groups as compared with preexposure measures. The histological data in Figure 21 show maximum hair cell loss in the 3rd and 4th turns for the newborns and the 1st and 2nd turns for the adults. The histological data for the control groups are shown in panels 21C and 21D. Only minimal hair cell loss was seen for both the adult and newborn groups.

CHAPTER IV

DISCUSSION

Development of the Auditory System

Recordings of the BSR in humans and animals provide information concerning the maturity and integrity of the auditory system. The origins of the BSR peaks have been previously discussed. In the present study, N_1 as recorded in the adult and newborn guinea pig, is thought to represent the synchronous discharges of auditory nerve fibers. P_4 is thought to represent the synchronous discharges of more centrally located auditory neurons. The basis for these assignments of origin depend upon peak latency, increase in amplitude and decrease in latency with increasing stimulus intensity, and repeatability of the waveform. The difference in the number of peaks (4 in the present study vs. 5 in most human studies) may be due to electrode configuration (implanted) recording technique (differential), or species differences. Taniguchi et al. (1976) also recorded four positive peaks in the guinea pig utilizing a similar electrode configuration, and 4 peaks are seen in cat's responses (Buchwald and Huang, 1975).

The gross similarity of the waveforms recorded from the adult and newborn animal might suggest a high degree of auditory system maturity at birth. On closer inspection, however, differences are apparent in the latencies and amplitudes of responses from the two populations. The preexposure measures suggest an immaturity of the central auditory system of the guinea pig if P_4 is interpreted to represent brain stem

activity. Figure 6, for example, illustrates the similarity of threshold sensitivity for N_1 in the adult and newborn groups as contrasted with P_4 threshold sensitivity in newborn animals. P_4 is detectable at lower intensities as animals age and Figures 7 and 8 show greater response magnitudes for the P_4 responses in the adults than in the newborns. However, the N_1 response magnitudes are similar in the two groups. Preexposure latency measures (Figs. 10 and 11) also support the interpretation of developmental immaturity of higher auditory brain stem structures. The P_4 responses lagged the changes in N_1 latency as a function of increasing intensity in the newborn group, whereas P_4 followed the latency decrease in N_1 in the adult group.

The structural and physiological development of the peripheral auditory system of the fetal and newborn guinea pig has been well documented (Nakai and Hilding, 1968; Pujol and Hilding, 1973). In the latter study the investigators discovered synaptic bars and cisternae in hair cells opposite nerve endings, myelination of nerve fibers, increasing numbers of mature synapses, and integration of stria vascularis epithelium as indices of cochlear maturation of the fetal guinea pig. Physiological evidence of peripheral maturity which was reported included mature CM and whole-nerve action potentials at birth. Although the preexposure N_1 responses of the newborn animals in the present study suggest relative maturity of the peripheral auditory system, the evidence described above indicates less than complete maturity. For example, the N_1 response amplitude in the newborn animals is lower than that of the adult, particularly at high intensity levels (Figs. 7 and 8). Also, N_1 latencies in the

newborns were found to be longer than those of the adults (Figs. 10 and 11).

BSR investigations with human subjects have examined the relationship between chronological age and latency of the BSR waves as an indication of auditory system maturity. Hecox and Galambos (1974) found decreasing latencies in wave V responses to broad band clicks as the age of human infants increased from three weeks to 18 months. The authors suggested that incomplete myelination of the auditory system may be partly responsible for the longer latencies near birth. Salamy and McKean (1976) investigated the latency changes in wave I and in the I to V difference as a function of age in newborn to one year old human infants and interpreted their findings to suggest that maturation of the peripheral (Wave I) and the central (Waves I-V difference) auditory system occurred at different rates. The newborn's wave I reached adult latency by six weeks of age whereas central transmission latency did not reach adult values until one year of age. The authors suggest that the paucity of myelinated fibers in the inferior colliculus (Rourke and Riggs, 1969) may be responsible for the lengthened latency at birth. Starr, Anlie, Martin and Sanders (1977) measured BSR latencies in preterm and newborn human infants ranging in gestational age from 25 to 44 weeks and found, as in the other studies, a decrease in wave V and I to V difference with an increase in age. In the present study, maturation of the central auditory system is suggested by the decrease in P_4 thresholds in the one month control animals as compared with their thresholds as newborns (Fig. 6). Central auditory system maturation is not reflected, however, in the growth in P_4 response

amplitude in the one month control animals (Fig. 15). Nor does there appear to be any demonstrable decrease in latency of the P_4 response or decrease in the $P_4 - N_1$ latency difference in the one month control animals (Figs. 18C and 18D). There are several possibilities to account for these observations:

1. The change in electrophysiologic threshold is a more sensitive indicator of maturation in the central auditory system of the guinea pig than response amplitude or latency, or

2. Changes in response amplitude and latency are not seen in the guinea pig until after one month of age, or

3. The number of control animals was too small to demonstrate significant changes in amplitude and latency. There does, however, appear to be substantial evidence in the literature and in the present study to support the idea that the auditory system is not mature at birth and that the central system reaches maturity later than the periphery. Whether this delay is the result of incomplete myelination or some other developmental factor is yet to be determined.

Effects of Noise on the BSR

Few studies have investigated the effects of noise on the later BSR waves and the findings, thus far, are contradictory. Sohmer and Pratt (1975) in their temporary threshold shift (TTS) study found that the decrement of the later BSR waves was much smaller than the N_1 decrement. Babighian, Moushegian and Rupert (1975) also used noise which produced TTS and found a greater decrement in the collicular than in the peripheral response. TTS is a fatigue phenomenon and does not result in durable structural damage to the cochlea or nerve fibers.

Thresholds usually recover within several minutes. The effects of structural damage resulting from permanent threshold shift are lasting and apparently can be observed at higher levels in the auditory system. In addition, the frequency specific effects of noise exposure is seen for the P_4 as well as for the N_1 response, i.e., the greatest electrophysiologic changes in threshold, response amplitude and latency are seen in response to filtered clicks with a center frequency similar to that of the center frequency of the noise stimulus. These changes are observed in both the peripheral and central BSR waves. The decrease in postexposure response amplitude and, consequently, threshold sensitivity is thought to result from the disruption of the mechano-electrical coupling of the damaged hair cells to afferent 8th nerve fibers. This disruption results in a loss of synchronous firing of the nerve fibers with an accompanying decrease in whole-nerve AP magnitude and, apparently, in response magnitudes from brain stem locations.

The greatest decrease in threshold sensitivity and postexposure magnitude was found in response to the 6 kHz FC, near the center frequency of the noise stimulus whereas postexposure responses to the 1 kHz FC were not demonstrably different from preexposure levels. The value of the FC's to reveal the frequency-specific nature of noise-induced cochlear damage is also supported by the postexposure latency measures. Figure 17 illustrates the increase in postexposure N_1 latency with increasing click intensity in response to the 1 kHz FC whereas postexposure response latency to the 6 kHz FC showed little change. This finding supports the interpretation that at high intensities a 1 kHz FC stimulates nerve fibers toward the basal end of the

cochlea due to the wide traveling wave envelope (note the similarity of latencies at high intensities in response to the 1 kHz and 6 kHz FC in Fig. 11). When hair cells in the basal region are damaged by high intensity narrow band noise, a 1 kHz FC stimulates healthy hair cells more apically in the cochlea resulting in an increase in post-exposure latency measures. This finding also confirms the belief that the interpretation of responses to low frequency filtered clicks presents problems, particularly at high intensities since the responses include activity from basal locations in the cochlea.

Although this study was not able to confirm a simple pattern of extensive hair cell damage in the basal portion of the cochlea, neither have previous studies. Eldredge et al. (1973) discovered that the fractional loss of the whole-nerve AP in noise-exposed chinchillas significantly exceeded the fractional loss of hair cells. Apparently hair cell loss is not an accurate measure of cochlear damage. Bohne, Eldredge and Mills (1973) discovered the following characteristics of remaining hair cells in noise-exposed chinchillas: misshapen outer hair cells; loss of mitochondria; increase in vesicles, vacuoles and smooth endoplasmic reticulum in the efferent nerve fibers in the affected region. It is entirely possible that such changes occurred in the hair cells of the guinea pigs in the present study but were not observed under light microscopy.

Susceptibility

The findings of this study support the interpretation that the newborn guinea pig suffers greater noise-induced damage to the auditory system, as measured by changes in the BSR, than the adult animals.

The susceptibility of the newborn to noise-induced trauma is consistent with findings of previous investigations which compared hair cell loss between newborn and adult animals (Falk et al., 1974; Dodson et al., 1978; Bock and Sanders, 1977). It has been theorized that a critical period exists in the developing auditory system which makes the system unusually susceptible to the effects of noise (Bock and Saunders, 1977). In the guinea pig it appears that the first few days after birth are within this critical period. Although the guinea pig auditory system is relatively mature at birth there is considerable evidence, as discussed previously, that the system is still developing. An exposure to a moderately high level of noise for a sustained period of time is sufficient to cause more damage to the newborn than would ordinarily be experienced by an adult guinea pig. The cause of increased susceptibility in infants is now known. This increased susceptibility, however, has serious implications for newborn humans placed in incubators for extended periods of time. The noise levels in incubators vary greatly but can reach levels as high as 75-80 dB SPL. The source of the noise is usually the ventilation fan and the noise level is often intensified by the resonance effects of the closed chamber. Although these levels are not considered noise-hazardous by present damage-risk criteria, it must be remembered that these criteria were formulated for an adult population. The noise levels found in incubators may, in fact, present a potential hazard for the susceptible newborn. Another important consideration involves the finding that the effects of noise-induced trauma is reflected in the activity of higher brain stem structures. This observation also presents serious implications

for the infant as the central auditory system provides integrative functions that are important for signal recognition and language development.

This investigation, as well as others dealing with the problem of susceptibility, has presented evidence which indicates that the newborn auditory system is more susceptible than the adult's to noise-induced damage. Additional investigation needs to be conducted to determine a set of damage-risk criteria for the human infant.

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BIOGRAPHICAL SKETCH

Harvey Bruce Abrams was born on November 25, 1948, in Brooklyn, N.Y. He was graduated from Sheepshead Bay High School in June, 1966. In June, 1970, aided by a U.S. Office of Education Fellowship, he received the degree of Bachelor of Arts with a major in speech pathology and audiology from the George Washington University. Mr. Abrams received the degree of Master of Arts with a major of audiology in August, 1971, from the University of Florida. Aid afforded by a Social Rehabilitative Services traineeship enabled him to complete this aspect of his education. After serving four years as an audiologist in the U.S. Army, Mr. Abrams returned to the University of Florida in January, 1976, to pursue work toward the degree of Doctor of Philosophy with a major in speech, aided by a Veterans Administration Traineeship.

Mr. Abrams is an audiologist with the Veterans Administration Medical Center at Bay Pines, Florida. He is a member of the American Speech-Language and Hearing Association, the Acoustical Society of America and the Military Audiology and Speech Pathology Society.

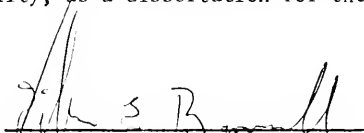
He is married to the former Catherine L. Breder of Washington, D.C., and is the father of three children -- Lydia, Jesse and Emily.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



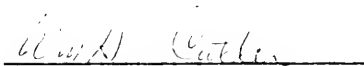
Donald C. Teas
Professor of Speech

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



William E. Brownell
Asst. Professor Neuroscience

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



William H. Cutler
Adjunct Asst. Professor, Dept.
of Speech

This dissertation was submitted to the Graduate Faculty of the Department of Speech in the College of Liberal Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Dean, Graduate School

UNIVERSITY OF FLORIDA



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