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Early identification of a hearing impairment should lead to early intervention and thus the chance for a child to reach his/her optimum level of speech, language, academic, and social development. ASHA, in 1989, advocated auditory brainstem response testing (ABR) as the screening method of choice for neonates. Recently, more interest has been directed toward the possibility of otoacoustic emissions (OAEs) being used clinically to evaluate cochlear function due to the rapid administration and objective, frequency-specific information provided (Lonsbury-Martin and Martin, 1990; Probst, et. al., 1991; Glattke and Kujawa, 1991; Martin, et. al., 1990). OAEs are low- level sounds produced by vibratory motion in the cochlea (Zizz and Glattke, 1988). OAEs have been grouped into two different types, spontaneous otoacoustic emissions (SOAEs) and evoked otoacoustic emissions (EOAEs). SOAEs occur in the absence of an initial acoustic stimulus to facilitate their production, thus the term spontaneous (Kemp, 1979). EOAEs are the result of external acoustic stimuli being presented to the ear. The normal cochlea responds to the presentations by emitting OAEs (Glattke and Kujawa, 1991). Three different types of EOAEs have been described.

1. **Transiently Evoked Otoacoustic Emissions (TEOAEs)**, are produced in response to a short duration stimuli, such as a click or tone burst (Kemp, 1978).

2. **Stimulus-Frequency Evoked Otoacoustic Emissions (SFOAEs)**, occur in response to a pure tone stimulus. The emission is of the same frequency composition as the eliciting stimulus (Kemp and Chum, 1980).

3. **Distortion Product Otoacoustic Emissions (DPOEs)**, are produced by tonal stimuli (Kemp, 1979). Unlike the SFOAEs, DPOEs do not occur at the stimulating frequency. The frequency at which the DPOE is produced is related by a mathmatical formula to the frequencies of the two primary stimuli (f_1 and f_2).

Although click-evoked OAEs have been used for screening (White, et. al., 1993), little published data is available for distortion product otoacoustic emissions (DPOEs) in neonates. This study was designed to examine the following:

1. Preliminary measures of sensitivity and specificity of DPOE as compared to ABR and otoscopy.

2. DPOEs in three subgroups of neonates. (1) Neonates who passed the ABR (otoscopic exam not considered) (2) Neonates who passed the ABR and otoscopic exam (3) Neonates who failed the ABR

3. Assessment of presentation level of f_1 and f_2 for 2 and 4 kHz to determine the optimal level for screening of neonates. Compare these levels with previous study by Bonfils and Avan (1992).

METHODS

Subjects

The sujects in this study were 31 (17 male, 14 female) neonatal intensive care unit (NICU) patients between the age of 35 and 44 weeks post-conception. Due to experimentor error (1 ear) and lack of subject cooperation (1 ear) data in this paper is based on 60 ears. Subjects included were recruited from those referred for ABR testing based on the High-Risk Registry (Joint Committee on Infant Hearing, 1982, 1990). If parents consented (see Appendix A for informed consent procedure) DPOEs were tested based on availability of the test equipment and personnel.

INSTRUMENTS

Subjects underwent ABR, DPOE testing, and received an otologic exam by a validated otoscopist. DPOEs were obtained using the Otoscan program, provided by Glen Martin and his colleagues, with the Macintosh II ci computer. Stimuli were delivered via ER2 insert receivers. Levels above 75 dB SPL were not used due to the concern of undue noise exposure and the possibility of waking or startling the neonates. An ER-10B low noise microphone was used to measure the DPOEs and noise floor. DPOE ($2f_1$-f_2) "audiograms" were obtained with an f_2/f_1 ratio of 1.21 at 75 dB SPL from 1077 to 6066 Hz. DPOE ($2f_1$-f_2) input-output functions were obtained with the same f_2/f_1 ratio from 75 to 25 dB SPL at 1.5, 2, 3, and 4 kHz. The ABR was recorded using a

Madsen 2250 with a click stimulus (centered at 2 kHz) presented at 70 and 30 dB nHL. Both the ABR and DPOEs were obtained in a quiet room adjacent to the NICU.

DATA CLASSIFICATION

ABR

ABRs were classified as pass or fail. The criteria for being considered a pass was a repeatable response at 30 dB nHL.

Otoscopy

The validated otoscopist classified his findings as either clear, inconclusive, or fail. For this study, inconclusives were grouped with the fails.

DPOE

DPOE "audiograms" were classified as pass or fail based on visual inspection of the data. DPOEs were visually inspected to see if emissions were clearly separate from the noise floor measures. If separation occured the ear was considered to have passed; on the other hand, if the emissions intermingled with noise floor measures the trial was classified as a fail. Visual inspection was more stringent than the "3 dB above noise floor" rule used by others. I-O functions were assessed for 1.5, 2, 3, and 4 kHz. A detection threshold at each frequency was determined as the point where the distortion-product was $\geq$3 dB above noise floor (see Fig 7) and remained $\geq$3 dB above the noise floor for the remainder of the function. Based on three presentation levels (65, 70, and 75 dB SPL) I-O functions were categorized as rising, roll-over, or plateau. If the final three points were within 3 dB of each other, the function was considered to be a "plateau". Functions exceeding the 3 dB limit were classified as "rising" and those decreasing beyond the 3 dB limit were considered to be "roll-over" functions.

RESULTS

Sensitivity and specificity calculations were made with DPOEs as the screen and ABR as the diagnostic standard (see Figure 1).

As shown in Fig. 1 DPOE provided sensitivity of 50% and a specificity of 60%. The sensitivity level is affected by two neonates (4 ears) who failed the ABR screen but passed the DPOE screen.

For individuals who passed the ABR screen, Fig. 2 shows the relationship between otoscopic exam and DPOE. Comparison of DPOE with otoscopic exam indicates a sensitivity of 76% and a specificity of 80% for DPOE.

The incidence of DPOEs in neonates who passed the ABR screen at 30 dB nHL varied as a function of both presentation level of f_1 and f_2 in dB SPL, and geometric mean frequency of f_1 and f_2. Table 1 depicts the incidence of DPOEs in normal hearing neonates (those who passed ABR at 30 dB nHL without consideration as to otologic findings), neonates who had normal hearing by ABR but failed the otologic exam, and neonates who failed the ABR screen at 30 dB nHL.

DPOE detection thresholds were measured at four frequencies. The average detection threshold for neonates at 1.5, 2, 3, and 4 kHz is shown in Table 2.

As described previously in the data classification section, each input-output (I-O) function was classified as rising,plateau, or roll-over. Examples of each can be found in Fig. 7. The frequency destribution of the I-O types is displayed in Table 3.

DISCUSSION

One would expect a level III NICU, to which all our subjects were admitted, to have a higher incidence of neurologic impairments than a well baby or level I or II nursery. Neurologic disorders interfere with ABR testing but not with DPOE. Thus, false positive ABR fails can be expected in a level III NICU. Follow-up testing of the two neonates who failed the ABR screen but passed the DPOE screen, indicates that both are neurologically impaired. These two infants (4 eaars) reduced the sensitivity in the pilot data reported here. Others have reported cases in which ABRs were failed due to neurologic reasons rather than hearing sensitivity (Norton, 1993). At this point in time,

ABR is the standard test; however, it is an indirect measure of hearing sensitivity which relies on neurologic integrity of the auditory system.

The specificity of DPOEs for this pilot data was 60%. This is low; however, DPOEs are being used as a screen because they are rapid and less costly than ABR. Individuals who fail DPOE will be followed-up with another test such as ABR which has a higher sensitivity and specificity.

Middle ear problems may interfere with DPOE measurements more so than ABR measures. When obtaining DPOEs, the stimulus has to go through the middle ear structures just like in ABR testing, but in order to measure the DPOE the sound "echo" has to come back out through the middle ear. The amplitude of the emissions are so small that this double interference may eliminate them or make them undetectable. For this reason, DPOEs were compared with the otologic exam to see if the neonates who passed the ABR screen and failed the DPOE could have been affected by middle ear pathologies observed by the otoscopist. With a sensitivity of 76% and a specificity of 80%, it seems possible that some of the DPOE fails that passed ABR could have been due to existing middle ear pathologies. Thus, if early detection of middle ear pathology is deemed desirable DPOEs have an advantage over ABR.

DPOE data for the neonates of the current study were compared with Bonfils and Avan (1992) adult data in Figures 3-6. In our study, the incidence of DPOEs for neonates is lower than the incidence found by Bonfils and Avan for adults at 2 and 4 kHz. At 1.5 kHz, both neonates and adults reached 100% at around 60 dB SPL. It appears that with neonates a higher presentation level is needed to obtain the same incidence of DPOEs.

Testing neonates at frequencies 1.5 kHz and below is difficult due to the interference of the noise floor. Only 12 DPOEs from the original 60 ears were valid at 1.5 kHz. Given the limits of currently available equipment, I-O DPOE screening should be limited to 2-6 kHz. Testing at lower frequencies is unreliable and time consuming.

Depending on the frequency, DPOEs are present only 50% of the time in neonates at levels between 50-60 dB SPL (see Table 2). The level used to obtain DPOEs should not be less than these levels. A wide range of variability is present for detection thresholds in neonates. At every frequency, at least one subject has a detection threshold as low as 25 dB SPL and with the exception for 1.5 kHz at least one subject has a detection threshold as high as 70-75 dB SPL. For this reason, there will always be some neonates missed by DPOE screening due to the fact that the presentation level may not be high enough to elicit an emission. This is why DPOEs are being proposed as a screen and not as a final measure of hearing sensitivity.

The majority of I-O functions (see Table 3) have a rising configuration at presentation levels of 50-75 dB SPL. This suggests 75 dB SPL may not be too high a level for presenting f_1 and f_2 for the majority of neonates. However, 75 dB SPL does exceed the levels (up to 60 dB SPL) at which the outer hair cells are able to act as a cochlear amplifier (Popelka, 1993 personal conversation). At levels above 60 dB SPL the inner hair cells are stimulated directly (Popelka, 1993 personal conversation). Further study is needed to determine a level between 55 and 75 dB SPL that can be supported as a presentation level for obtaining DPOEs.

Further research is needed in the area of DPOEs. More subjects need to be incorporated in the studies in order to obtain more reliable data. Longitudnal studies are needed to assess how DPOE measures relate to the final diagnosis of hearing status.

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Table 1. Incidence of DPOEs as a function of primary (f_1 and f_2) presentation levels

Geometric Mean	No.	Incidence, % Presentation level dB SPL										
f_1 and f_2,	Ears	25	30	35	40	45	50	55	60	65	70	75
kHz		**Normal Subjects**										
1.5	12	8	8	8	25	50	67	83	100	100	100	100
2	32	15	18	24	36	45	52	76	91	91	97	97
3	25	4	4	4	12	24	32	40	52	72	92	92
4	40	5	5	5	8	18	30	40	58	73	83	90
		Normals minus Otoscopic Fails										
1.5	12	8	8	8	25	50	67	83	100	100	100	100
2	26	15	19	27	42	50	58	73	92	92	96	96
3	19	5	5	5	16	32	42	53	63	74	95	95
4	29	7	7	7	7	17	34	45	59	79	90	93
		ABR Fails (>30 dB nHL)										
1.5	0	0	0	0	0	0	0	0	0	0	0	0
2	2	50	50	50	50	100	100	100	100	100	100	100
3	3	0	0	0	0	33	67	67	67	67	67	67
4	4	0	0	0	0	25	50	50	50	50	50	50

Table 2. Average detection threshold for neonates at 1.5, 2, 3, and 4 kHz.

1.5 kHz	(12 subjects)	average 48 dB SPL	(range 25-55)
2 kHz	(32 subjects)	average 47 dB SPL	(range 25-70)
3 kHz	(23 subjects)	average 57 dB SPL	(range 25-70)
4 kHz	(36 subjects)	average 57 dB SPL	(range 25-75)

Table 3. Distribution of Input/Output curve classifications at 2 and 4 kHz..

	Rising	Plateau	Roll-over
2000 Hz	12	6	2
4000 Hz	15	1	1
	27	7	3

ABR Results

		Fail	Pass
DPOE Results	**Fail**	**4**	**19**
	Pass	**4**	**29**

Sensitivity = 50%
Specificity = 60%

Figure 1. Sensitivity and specificity, with DPOEs as the screen and ABR as the diagnostic standard.

Otoscopic Exam

		Fail	Pass
DPOE Results	**Fail**	**13**	**7**
	Pass	**4**	**28**

Sensitivity = 76%
Specificity = 80%

Figure 2. Sensitivity and specificity, comparing otoscopic exam and DPOE.

Incidence of DPOE s at 1.5 kHz

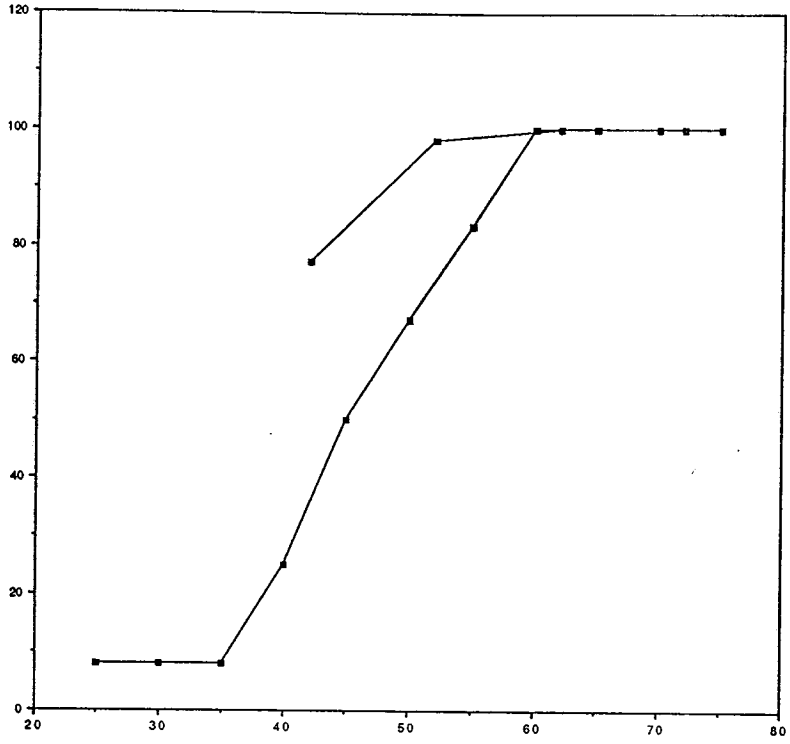

Figure 3. dB SPL

Incidence of DPOE s at 2 kHz

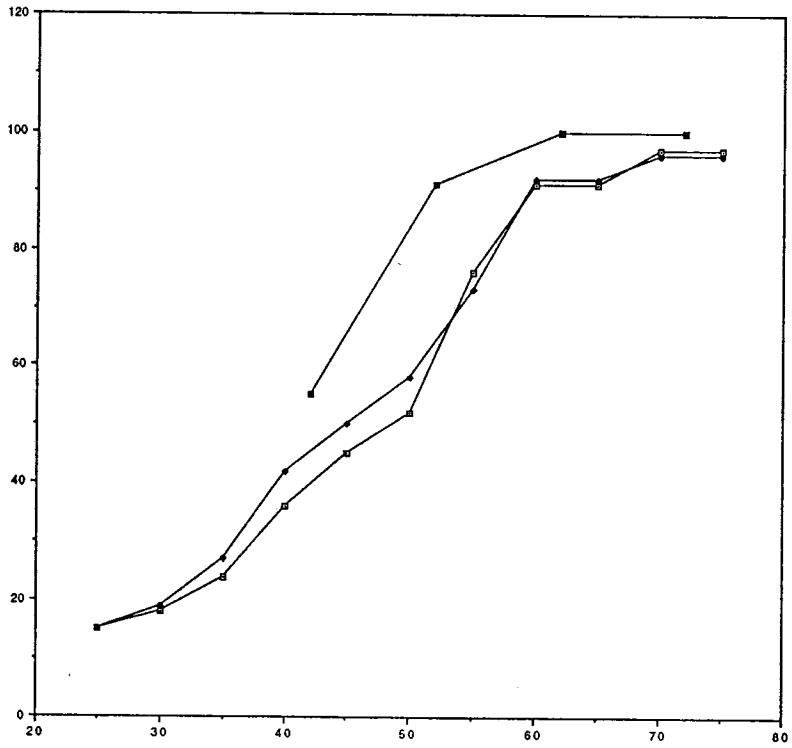

Figure 4. dB SPL

Incidence of DPOE s at 3 kHz (Bonfils-Avan showed no data for 3 kHz)

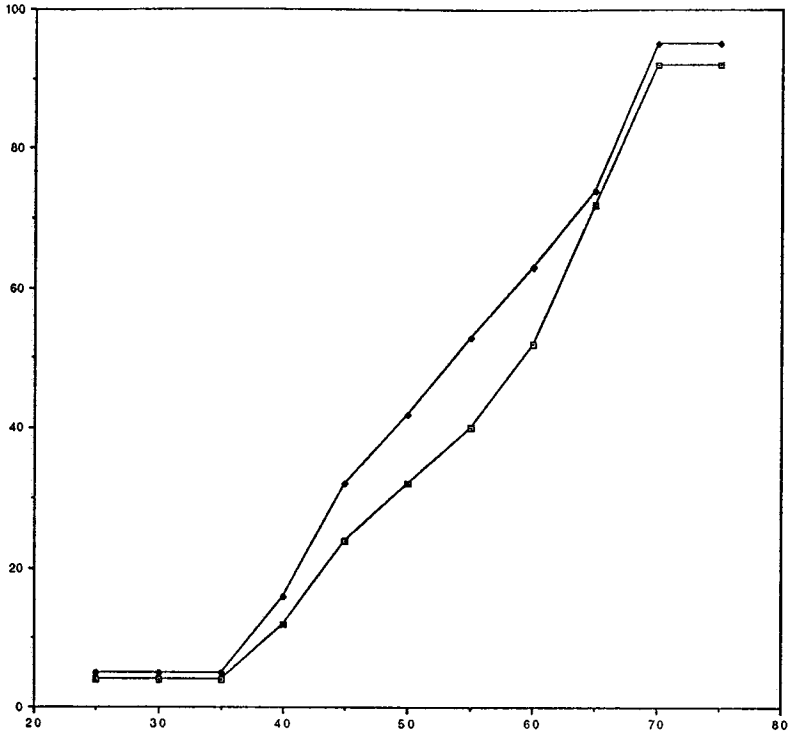

Figure 5.

Incidence of DPOE s at 4kHz

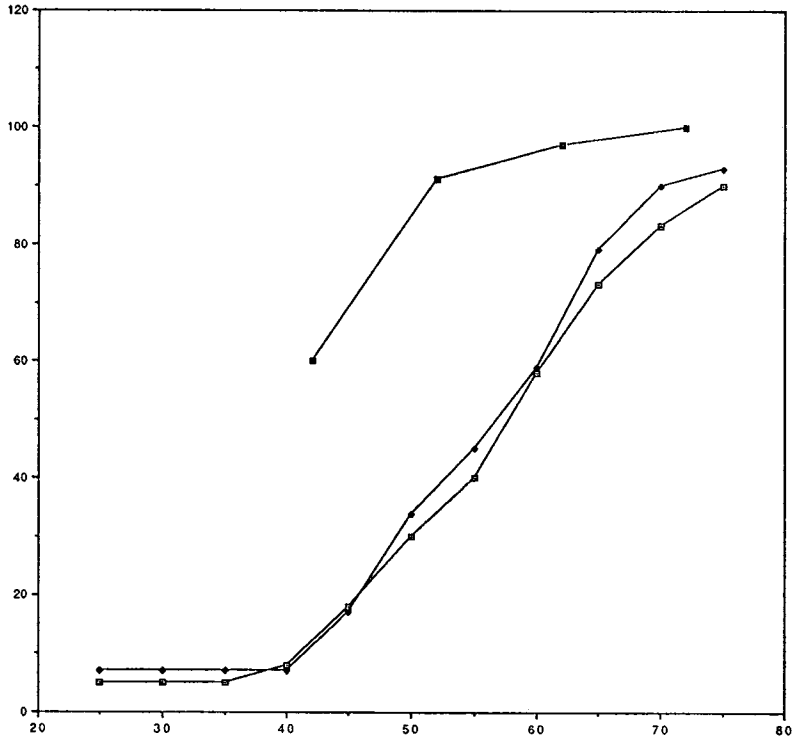

Figure 6.

Sample Input-Output Functions of Neonates

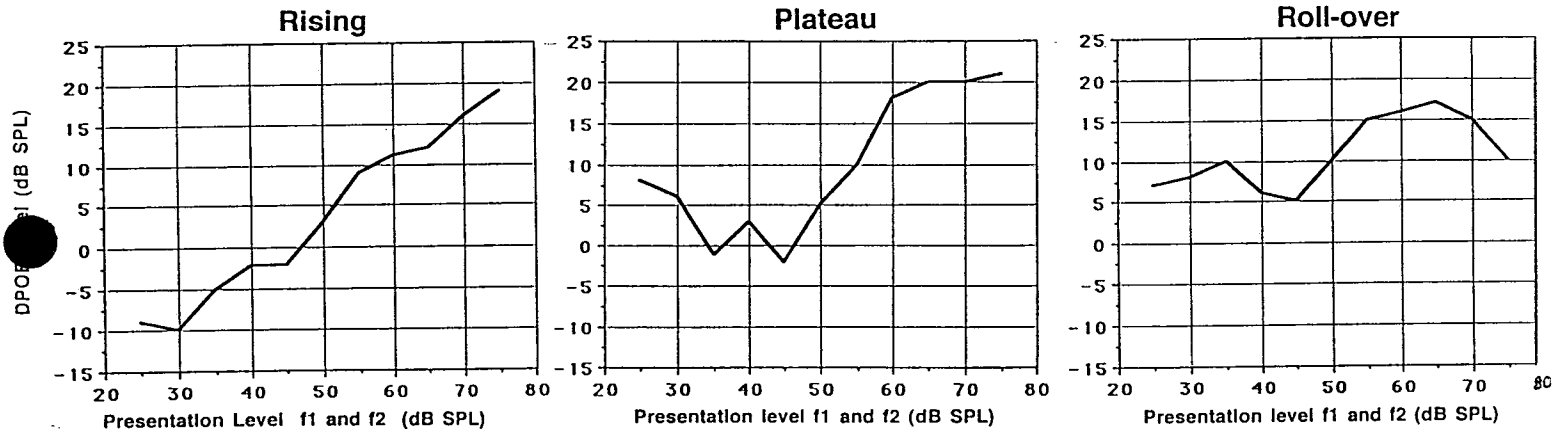

Figure 7

WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
AT WASHINGTON UNIVERSITY MEDICAL CENTER

Barnes Hospital
Children's Hospital
Other Facility: _____

PEDIATRIC
INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES

Participant _____

Principal Investigator Roanne Karzon, Ph.D.

Human Studies Committee Approval Number 90-243

Title of Project:

Measurement of distortion product emissions in patients in the neonatal intensive care unit.

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1. I have been asked to give my permission for my child to participate in a research project conducted by Dr. _____ and/or assistants. The overall purpose of this research is:

To develop an accurate cost-effective method for screening the hearing of infants.

2. My child's participation will involve the following:

Measurement of Distortion Product Emissions (DPE). DPEs are measured by presenting sounds to the infant through a soft plastic tip placed in the infant's ear canal. A special microphone measures the sound echoes coming back out. Pneumatic otoscopy will be carried out to look for any visible signs of ear disease. Pneumatic otoscopy is performed by placing a plastic cone in the infant's ear. A light shines through the cone and gentle puffs of air are generated to see how well the eardrum moves. Approximate test times are 10-15 minutes for DPE and 3-5 minutes for pneumatic otoscopy.

Appendix A. Informed Consent Form.

3. I understand there are certain risks and discomforts that might be associated with this research:

There are no health risks associated with the DPE hearing test or for pneumatic otoscopy in the subjects selected for this study. Any discomfort due to placement of the plastic tips and cones will be remedied by repositioning the tips and cones. Testing for DPE must be conducted while the infant is physically not active, preferable during natural sleep.

4. I understand that the possible benefits to my child or society from this research are:

DPE may become a more efficient means of screening hearing in infants. If it proves accurate and cost effective, it may be possible to screen hearing in all newborns rather than only those with high risk factors. Infants receive a hearing screen and otologic examination and parents will be notified of the test results.

5. I may choose not to allow my child to participate in this research; whatever my decision, it will not at any time affect the commitment of his/her health care providers to administer optimal care. I also understand that the following alternative(s) is/are available:

ABR screen as ordered by the patient's physician. An ABR (auditory brainstem response) test measures the electrical activity of the brainstem in response to click sounds. The electrical activity is measured through surface electrodes (disposable) placed behind each ear and on the forehead. The click sounds are presented through a disposable plastic tube placed in the ear.

6. I understand that the investigator(s) and the University will take all reasonable measures to protect the confidentiality of my child's records and his/her identity will not be revealed in any publication that may result from this project. The confidentiality of my child's records will be maintained in accordance with applicable state and federal laws. I understand there is a possibility that my child's medical record, including identifying information, may be inspected and/or photocopied by officials of the Food and Drug Administration or other federal or state government agencies during the ordinary course of carrying out their functions. If participation is in a sponsored research project, a representative of the sponsor may inspect these research records.

7. I understand that participation is voluntary and that I may refuse to allow my child to participate and/or withdraw my consent and discontinue participation in the project or activity at any time without penalty or loss of benefits to which my child is otherwise entitled.

8. I understand that the investigator is willing to answer any inquiries I may have concerning the research herein described. I also understand that I may ask questions or state concerns to the University's Chairman of the Human Studies Committee, 362-3244.

9. I understand that the University will provide immediate medical treatment in the event that a physical injury results because of my child's participation in this project. I also understand that ordinarily the University will not be financially responsible in case of injury.

IF APPLICABLE

10. To the best of my knowledge, my daughter is not pregnant. If she does become pregnant while a participant in this research project, I will notify the principal investigator. This information will help the investigator provide the best care for my daughter and her unborn child.

11. I will be informed of any significant (major) new findings developed during the course of my child's participation in this research which may have a bearing on my willingness to allow him/her to continue in the study. I understand that the investigator may choose to withdraw my child from this research project if at any time circumstances arise which warrant doing so.

12. I have received a copy of this informed consent which I have read and understand. I hereby consent to my child's participation in the research described above.

_____
(When Applicable)
Parent or legal guardian's signature on participant's behalf if participant is less than 18 years of age or not legally competent. (Blood drawing only: Less than 17 years of age)

_____
Participant's Signature when Appropriate

_____
Investigator's Signature

_____
Phone number

_____
Relationship to Child

_____
Witness' Signature, if witness is present

Date: _____

REGARDING CHILDREN SEVEN YEARS OF AGE AND OLDER

In our best judgement, we believe that requiring the signature of the patient is not appropriate in this particular instance. He/she understands the procedures and/or therapy and its potential risks and benefits, in our opinion, in a manner appropriate to his/her age.

(physician and parent/guardian should initial)

_____
Physician

_____
Parent/Guardian

This form is valid only if the Human Studies Committee Stamp of approval is shown below. Approval is for one year unless otherwise stated.

APPROVED BY
THE HUMAN STUDIES COMMITTEE (IRB)
JUN 16 1992
VOID ONE YEAR FROM ABOVE DATE