First Quarterly Progress Report
NIH-DC-98-11

Effects of Remaining Hair Cells on Cochlear Implant Function

P.J. Abbas, C.A. Miller, J.T. Rubinstein, B.K. Robinson

Department of Otolaryngology - Head and Neck Surgery
Department of Speech Pathology and Audiology
Department of Physiology and Biophysics
University of Iowa
Iowa City, IA 52242

November 5, 1999

1 Introduction

With relaxed audiological selection criteria for cochlear implants, many patients implanted today have significant hearing prior to implantation (Risberg, et al., 1990; NIH Consensus Statement, 1995). As implant candidate selection criteria are relaxed further, the most obvious expansion of the patient cohort would include individuals with high frequency hearing loss and significant low frequency hearing. Histological studies in implanted animals suggest that hair cells apical to the implanted electrode array can survive over chronic periods of implantation (Ni et al., 1992; Xu et al., 1997). The possibility therefore exists that normal hair cell function apical to the implanted array could exist in implanted humans

If patients with significant hair cell function are implanted, an important issue is the extent to which the presence of hair cells impedes or assists with electrical hearing. Physiological studies of implanted animals have shown that viable hair cells respond to electrical stimulation. Furthermore, this response causes a pattern of nerve fiber activation different from that created by direct depolarization of auditory nerve fibers by electrical stimulation (Moxon, 1971). Thus, in electrically stimulated cochleae with intact hair cells, the neural representation of the stimulus would consist of components arising from both hair-cell mediated and direct-nerve excitation. The major goal of this research is to characterize the nature and interactions of these two responses, particularly as they may occur with patterned stimulation used by implanted cochlear prostheses.

Hair cells can be excited by three possible mechanisms. The first is through the normal acoustic transduction process; the second is through electrophonic hearing, i.e., electrically induced mechanical vibration of cochlear structures; the third is presumed to be through direct electrical stimulation of the inner hair cells. If the cochleae of patients with residual hearing can maintain significant hair cell integrity, it is important to define the extent to which these three response mechanisms could be manipulated so as to provide maximum benefit to implanted patients.

There are several possible ways in which hair-cell mediated responses might interact with direct depolarization of nerve fibers. One hypothesis is that the electrical stimulus encoding in nerve fibers with intact hair cells is adversely affected by excitation of the hair cells. Acoustic stimulation transduced through functional hair cells may conflict in some way with direct electrical stimulation and degrade the transfer of information. If that were the case in our hypothetical implant patient, it would be desirable

to maintain a functional separation between neurons stimulated electrically and those stimulated acoustically.

A second hypothesis would be that the presence of hair cells and/or the presence of acoustic stimulation actually improves the transmission of information via electrical stimulation of the cochlea. For example, the increase in the noisiness of the fibers due merely to the presence of a functional synapse could result in an increase in the information transfer in a process usually referred to as stochastic resonance (Morse and Evans, 1996; Moss et al., 1996; Rubinstein et al., 1999). This process takes advantage of the spontaneous activity present in nerve fibers with normal acoustic sensitivity and is thus a relatively passive intervention. It follows that the apical fibers may be particularly useful even if they are electrically stimulated by basal electrodes.

Finally, a third set of hypotheses states that controlled acoustic or electric activation of hair cells may be used to enhance the transfer of information provided by electrical stimulation. For instance, acoustic stimulation of apical fibers may improve the representation of the signal presented through electrical stimulation.

There are several general hypotheses concerning hair-cell mediated and direct-nerve excitation via electrical stimuli as well as potentially beneficial interactions between acoustic and electrical signals. To address these issues, we propose a sequence of experiments designed to first characterize the response patterns and interactions and then to explore techniques to best exploit them. These experiments employ both physiological measures and modeling of the effects of hair cells on the response to electrical stimulation. The initial experiments use measures of the electrically evoked compound action potential as well as measures of single fiber activity. In the course of this contract, a direct comparison will be made of the response properties with and without functioning hair cells as well as comparisons of the responses to electrical stimulation with and without acoustic stimulation.

2 Methods

We have performed a series of measures in several guinea pigs and one cat to date. Animals are anesthetized and monitored as previously described (Miller et al., 1998a).

2.1 Surgical procedures

The animals head is immobilized by a custom-designed fixture. The pinna is excised to provide consistent coupling of the earphone onto the external auditory meatus. To access the middle ear and auditory nerve, an incision (from midline, through bregma, and then laterally toward the jugular process) is made to expose the left posterior aspect of the skull. A small defect is made in the bulla to expose the base of the cochlea.

A defect is then be made in the skull to expose the auditory nerve using a posterior fossa approach. After surgical exposure, the head position is locked to allow placement of the earphone and stimulus and recording electrodes. A Beyer DT-48 earphone coupled through a speculum is placed into the ear canal. A Pt/Ir ball electrode with a rigid, insulated shank is used for EAP recording. It is placed in contact with the auditory nerve with a micromanipulator and connected to the positive input of a differential amplifier.

After initial acoustic measures, a small fistula is drilled in the bone adjacent to the round window to place an electrode into the scala tympani of the basal turn of the cochlea. A stimulating ball electrode is advanced through that opening such that the ball is inside the scala but not directly touching the spiral lamina or membranous structures. This approach is used to minimize trauma second to removal of the round window and to assure a stable electrical placement throughout the experiment.

2.2 Deafening procedures

To evaluate our hypotheses, several chemical treatments are used to either kill or temporarily disable hair cell function. A furosemide protocol which facilitates reversible loss of hair-cell function is based on procedures described by Sewell (1984). Furosemide is administered through a previously catheterized vein at an initial dose of 40 mg/kg. In other preparations we have used a combination of kanamycin and ethacrynic acid to permanently inhibit hair cell function (West et al., 1973; Brummett et al., 1979; Xu et al., 1993). This allows for comparisons of response properties with and without functional hair cells for an extended protocol of stimulus paradigms. An intramuscular injection of kanamycin (300 mg/kg) is administered, followed by intravenous injection of ethacrynic acid (20 +/- 5 mg/kg).

3 Results

The data presented in this first QPR are preliminary and were used as pilot experiments to develop the techniques needed for recording and to determine time course and effects of furosemide and ethacrynic acid/kanamycin deafening procedures. The experiments are used to validate the techniques and we view results as tentative at this point but several trends are worthy of note.

3.1 Acoustic and electric interactions

Figure 1 shows whole-nerve responses to a single monophasic electrical pulses (39 μs in duration) with and without acoustic masking noise presented to the same ear. Responses in the first column were recorded before any treatment, that is, with presumably normal-functioning hair cells. Recordings were made within a sound booth with no external acoustic noise stimulus present (i.e., 50 dB noise). These traces represent unprocessed waveforms in response to a cathodic stimulus. After the initial stimulus artifact, they show a large, early, negative peak at approximately 0.4 ms latency, followed by a second peak at approximately 1.2 ms. Based on these latencies, we attribute the first to direct nerve stimulation and the later peak to a hair-cell mediated activity. The ability of acoustic stimulation to mask this response was evaluated using wide-band noise. Responses with acoustic masking noise are shown in column 2 (i.e., wideband noise). The later responses are significantly decreased, while the effect on the early, direct-neural components is less. This trend is particularly evident for the responses to mid and low level stimuli.

Figure 2 quantifies some of these trends across stimulus level. The left graphs plots amplitude of the first peak with latency approximately 0.4 ms. Based on latency we interpret this response to be due to direct nerve stimulation and is therefore the standard EAP response. The right graph plots the amplitude of the peak with latency at approximately 1.4 ms, presumably electrophonic in origin. In each case the measured response amplitude is plotted for several levels of background noise as a parameter. Several trends are worthy of note. Consistent with other reported data on the electrophonic response (Yamane et al., 1981; Lusted and Simmons, 1988; McAnally and Clark, 1994), the elctrophonic response has a lowere threshold, but at high stimulus levels the amplitude is relatively small compared to the direct nerve response. We note in this animal the electrophonic re-

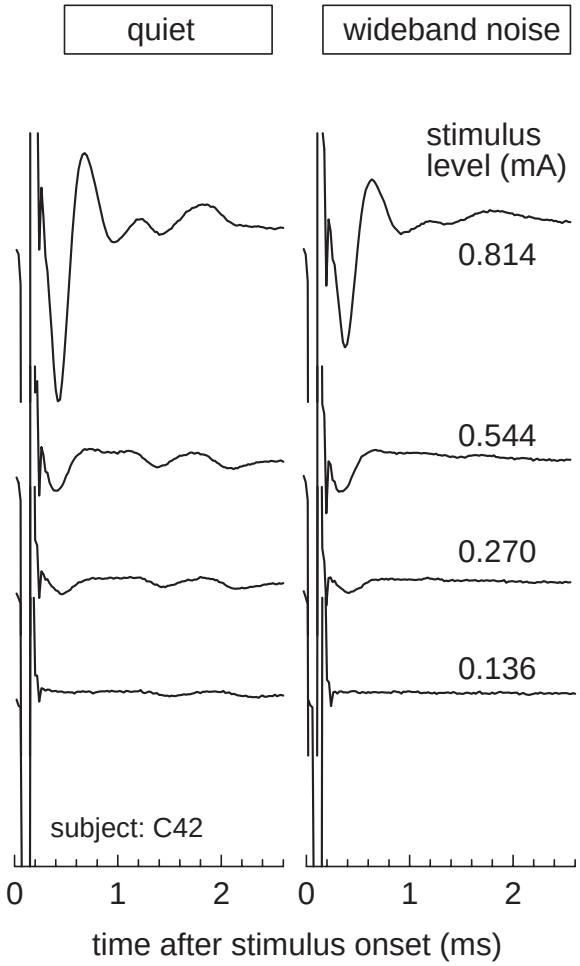
quiet
wideband noise
stimulus
level (mA)
0.814
0.544
0.270
0.136
subject: C42
0
1
2
0
1
2
time after stimulus onset (ms)

Figure 1:

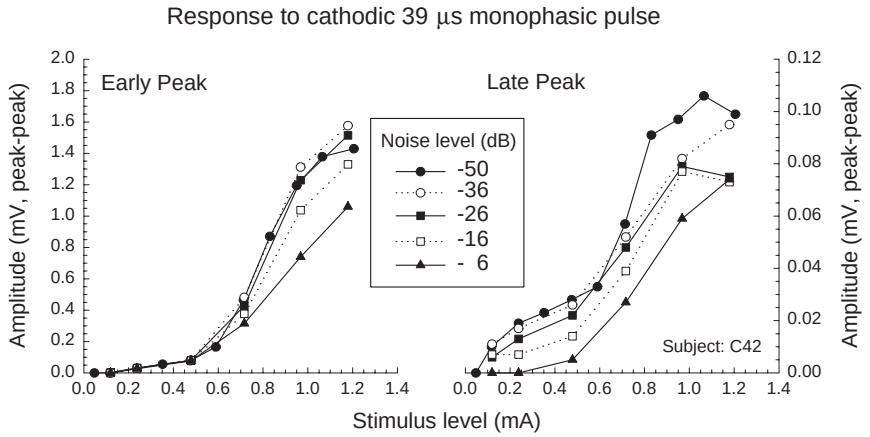

Figure 2:

sponse is strongly dependent on the level of the noise masker. Although the direct response shows a smaller effect of noise, there is a clear effect at the highest two levels noise used, suggesting that acoustic input can affect the direct nerve response. Also, at low stimulus levesl the noise masker is quite effective at eliminating the electrophonic response.

3.2 Effects of deafening procedures

Figure 3 also shows EAP traces in response to 39 μs monophasic pulses. In each of the three columns, the same stimulus levels were used, but experimental conditions were different. Responses in the first column are similar to those of Figure 1 recorded before any treatment and therefore assumed to have the effects of functioning hair cells. Here we show the later peak, which is susceptible to acoustic noise masking, is also vulnerable to disruptions in hair cell function. For our first chemical treatment we injected the animal with intravenous furosemide. The traces shown in the middle column were recorded after an initial dose of 40 mg/kg. These traces show a decrease in the later component that is similar that observed in the noise-masking experiment. At the end of the experiment, we administered intracochlear neomycin and observed the responses depicted in the last column of Figure 3. These responses similarly show a decrease in the later peaks, again suggesting that they are hair-cell mediated. In this animal we injected neomycin intracochlearly in order to permanently affect hair cell function. The later, electrophonic response is essentially completely eliminated; the initial peak

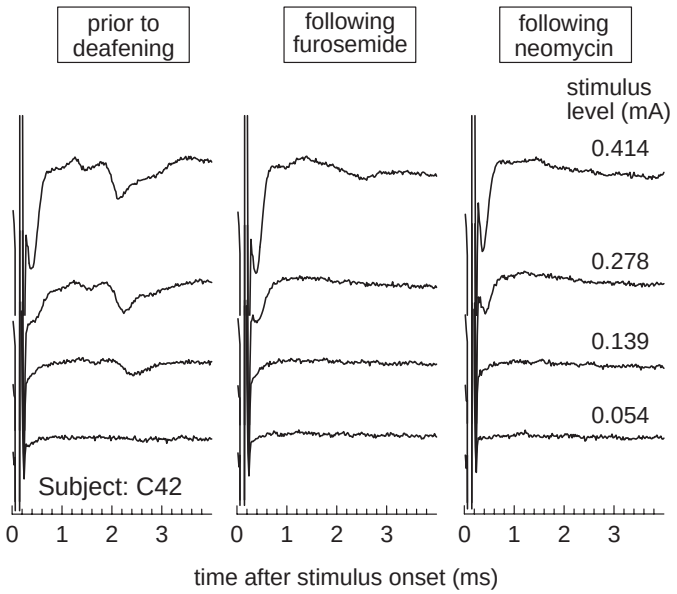

Figure 3:

attributed to direct nerve stimulation is slightly smaller but shows relatively normal growth.

We describe below preliminary data examining the effects of hair cell fucntion on growth of the EAP response to single pulses, as well as examining the temporal pattern of response to trains of pulses.

3.2.1 Responses to single-pulse stimuli

The amplitude of the EAP in response to single pulse stimuli is measured as a function of stimulus current level. Threshold, defined by the stimulus level evoking a criterion response amplitude, will provide a measure of stimulus efficiency. Input-output amplitude and the slope of that function relate to the extent of neural recruitment (Miller et al., 1999b) and provides a measure of the extent of spread of excitation across the nerve fiber population. Dynamic range, the range of stimulus levels between threshold and asymptotic response amplitude, relates to the range of usable stimulus levels available to recruit a population of nerve fibers. Based on known characteristics of the electrophonic response, we expect that these measures will be particularly sensitive to the presence of hair cells. Furthermore, we ex-

pect that such changes in sensitivity and dynamic range may be important in terms of perceptual characteristics in a cochlear implant (Brown et al., 1996; Brown et al., 1998).

The relative spread (RS) is a measure which characterizes the growth of firing probability of single fibers and is related to the stochastic characteristics of the response. As the fibers stochastic (or noise) properties increase, so does its RS value (Verveen, 1961). The growth of the EAP response may be dependent on the growth of individual neuron responses in the underlying active population, but the EAP characteristics are likely dominated by the distribution of single fiber threshold (Miller et al., 1998a,b; Miller et al., 1999b). It is of interest to evaluate the extent to which the presence of hair cells, which likely affect the stochastic properties of the neurons, has an effect on the EAP growth properties.

We have measured the responses before and after intracochlear neomycin injection in several animals. The growth functions (both threshold and slope) could be affected but the responses were quite variable. An important caveat in this method of deafening is that the stimulating electrode was removed and then replaced after neomycin injection. The repeatability of the responses are then dependent on reproducing the same electrode location.

In order to avoid this difficulty we have begun a series of experiments using the ethacrynic acid/kanamycin injection technique where we do not move the stimulating or recording electrodes. Figure 4 illustrates growth functions in response to single monophasic and biphasic pulses (39 μs in duration). Response amplitudes are illustrated for measures taken before and after this deafening procedure. In each case, the responses show a monotonic growth, in some cases reaching a saturation amplitude at high stimulus levels. In examining the response to both anodic and cathodic stimuli, there are several consistent trends. Growth functions obtained before deafening tend to have relatively lower thresholds and shallower slopes. These trends are consistent with a hypothesis that hair cells result in a more stochastic pattern (decreasing threshold). Since the pattern is less deterministic, the population response at high levels is less synchronous and therefore lower in amplitude. In addition, if there is stochastic background activity, each pulse will recruit fewer neurons and each will tend to have a smaller action potential due to refractory effects. The result would be a smaller EAP amplitude at higher levels with functional hair cells.

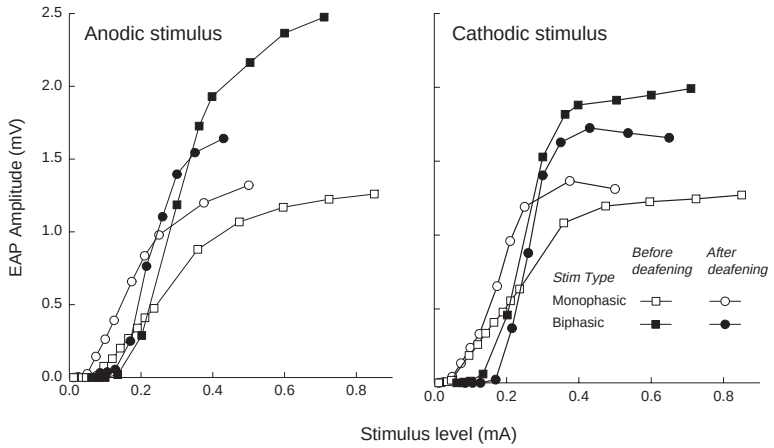

Figure 4:

3.2.2 Responses to pulse trains

Stimulation through an actual cochlear implant typically involves a complex pattern of stimulation, with multiple pulse trains presented to multiple electrodes. The sequence of responses to each pulse in a train becomes an important consideration in that this sequence of response amplitudes is often the basis of stimulus encoding. The presence of electrophonic responses as well as the additional noisiness that may be introduced by functional hair cells may have a significant effect on these properties.

In our previous work with deafened ears, we have measured EAP responses to trains of electrical pulses that are typically 100 ms in total duration. We have systematically examined the effects of stimulus and interpulse interval on the patterns of responses evoked by pulse trains (Matsuoka et al., 1998). The response amplitudes demostrated refractory properties in that the response to the second pulse was smaller than that to the first pulse. In addition, the response to successive pulses showed an alternating pattern which is highly dependent upon IPI, with the greatest degree occurring at short (1 ms) IPIs. This alternating pattern is attributable to the result of refractory recovery and stochastic effects. Based on comparisons to responses with acoustic stimuli (Smith et al., 1977; Smith and Brachman, 1982), we may expect that the adaptive properties of the response to electrical pulse trains may be affected by the presence of hair cells.

Response patterns that we have recorded from cats and guinea pigs (Mat-

suoka et al., 1998) are qualitatively similar to those from implant patients (Wilson et al. 1995; Wilson, 1997). We do, however, observe smaller amplitude alternations in our animal preparations. These differences may be due to stochastic properties of the stimulated neurons. Higher noise levels in the neural membranes of recently deafened animals may result in more stochastic response patterns. If hair cells increase the stochastic properties of neurons, we would expect smaller alternations and shorter persistence of the alternating pattern would result.

We have evaluated these properties in a preliminary way by presenting a series of constant amplitude pulses (100 ms in duration and 1 ms IPI). The response can then be measured in response to each pulse in the train. The left column in Figure 5 illustrates data collected beore deafening with kanamycin/ethacrynic acid. The right column illustrates data collected after the deafening procedure. In each case the amplitude of the response to each successive pulse in the train (up to 50 ms) is plotted. Data are plotted for three different stimulus levels (indicated on the graph) for each condition. In each case the amplitude of the response to each pulse is normalized to the amplitude of response to the first pulse in the train. We note two differences between the responses before and after deafening. First, the responses before show relatively little alternation, suggesting a more stochastic response pattern. In addition the responses before show a relatively slow decline over time, where the response after deafening demonstrate a relatively constant response (except for the alternation pattern) after the initial pulse. Both of these observation could be consistent predicted effects of functional hair cells, i.e., more stochastic pattern and cumulative adaptation effects.

4 Summary

We plan to investigate the effects of hair cell survival on the response of auditory nerve neurons to electrical stimulation. Our initial studies will assess the effect of the presence of functioning hair cells on the neural response as well as the interaction of acoustic and electrical stimulation when functioning hair cells are present. The preliminary data presented in this QPR demonstrates that with the particular preparation we are using to measure the EAP, we are able to separate direct nerve stimulation from electrophonic response and to assess interactions between acoustic and electrical stimulation (Figures 1 and 2). The ability to temporarily affect hair cell function and to assess those effects with the EAP is demonstrated in Figure 3. Fi-

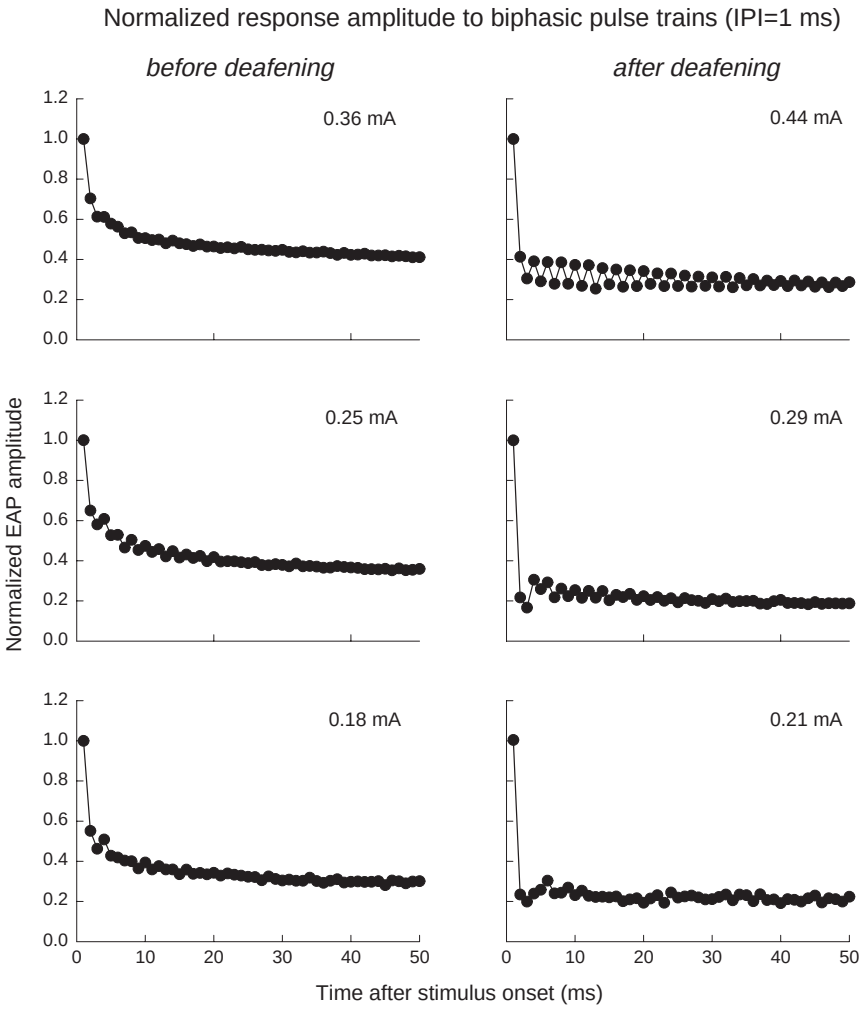
Normalized response amplitude to biphasic pulse trains (IPI=1 ms)
before deafening
after deafening
0.36 mA
0.44 mA
0.25 mA
0.29 mA
0.18 mA
0.21 mA
Normalized EAP amplitude
Time after stimulus onset (ms)

Figure 5:

nally, the results from a permanently deafened animal in Figures 4 and 5 suggest that hair cells may significantly affect both the growth and temporal properties of the response to electrical stimulation.

We stress the preliminary nature of these findings but both the single pulse and pulse train response patterns have demonstrated effects consistent with a more stochastic neural response pattern with functioning hair cells. We will use these findings as a basis to perform more detailed measures of the response patterns with and without functioning hair cells.

References

[1] Brown C.J., Abbas P.J., Borland J., & Bertschy M.R. (1996). Electrically evoked whole nerve action potentials in Ineraid cochlear implant users: Responses to different stimulating electrode configurations and comparison to psychophysical responses. J. Speech Hear. Res., 39, 453-467.

[2] Brown C.J., Abbas P.J., & Gantz B.J. (1998). Auditory nerve potentials recorded using the neural response telemetry system of the Nucleus C124M cochlear implant. Am. J. Oto., 19, 320-327.

[3] Brummett R.E., Brown R.T., & Hines D.L. (1979). Quantitative relationships of the ototoxic interaction of kanamycin and ethacrynic acid. Arch Otolaryngol. 105, 240-246.

[4] Lusted H.S., & Simmons F.B. (1988). Comparisons of electrophonic and auditory-nerve electroneural responses. J. Acoust. Soc. Am., 83, 657-661.

[5] Matsuoka A.J., Abbas P.J., Rubinstein J.T., & Miller C.A. (1998). The neurophysiological effects of simulated auditory prosthesis stimulation. Seventh Quarterly Progress Report N01-DC-6-2111.

[6] McAnally K.I., & Clark G.M. (1994). Stimulation of residual hearing in the cat by pulsatile electrical stimulation of the cochlea. Acta Otolaryngol., (Stockh.) 114, 366-372.

[7] Miller C.A., Abbas P.J., Rubinstein J.T., Robinson B.K., & Matsuoka A.J. (1998a). The neurophysiological effects of simulated auditory prosthesis stimulation. Sixth Quarterly Progress Report N01-DC-6- 2111.

[8] Miller C.A., Abbas P.J., Rubinstein J.T., Robinson B.K., & Matsuoka A.J. (1999a). Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophaisc stimulation. Hear. Res.

[9] Miller C.A., Abbas P.J., & Rubinstein J.T. (1999b). An empirically based model of the electrically evoked compound action potential. Hear. Res.

[10] Miller C.A., Abbas P.J., Rubinstein J.T., Robinson B.K., Matsuoka A.J., & Woodworth G. (1998b) Electrically evoked compound action potentials of guinea pig and cat: response to monopolar, monophasic stimulation. Hear. Res., 119, 142-154.

[11] Morse R.P., & Evans E.F. (1996). Enhancement of vowel coding for cochlear implants by addition of noise. Nat. Med., 2, 928-932.

[12] Moss F., Chiou-Tan F., & Klinke R. (1996). Will there be noise in their ears? Nat. Med., 2, 860-862.

[13] Moxon E.C. (1971). Neural and mechanical responses to electrical stimulation of the cat's inner ear. Doctoral Dissertation, MIT, Cambridge, MA.

[14] Ni D., Shepherd R.K., Seldon H.L., Xu S.-A., Clark G.M., & Millard R.E. (1992). Cochlear pathology following chronic electrical stimulation of the auditory nerve. I: Normal hearing kittens. Hear. Res., 62, 63-81.

[15] NIH Consensus Statement (1995). Cochlear implants in adults and children, 13, No. 2.

[16] Risberg A., Agelfors E., Lindstrom B., & Bredberg G. (1990). Electrophonic hearing and cochlear implants. Acta Otolaryngol., 469, 156-163.

[17] Rubinstein J.T., Wilson B.S., Finley C., & Abbas P.J. (1999). Pseudospontaneous activity: stochastic independence of auditory nerve fibers with electrical stimulation. Hear. Res.

[18] Sewell W.F. (1984). The relation between the endocochlear potential and spontaneous activity in auditory nerve fibres of the cat. J. Physiol., 347, 685-696.

[19] Smith R.L., (1977). Short-term adaptation in single auditory nerve fibers: Some poststimulatory effects. J.Neurophysiol. 40, 1098-1112.

[20] Smith R.L., & Brachman M.L. (1982). Adaptation in auditory-nerve fibers: a revised model. Biol. Cybernetics, 44, 107-120.

[21] Verveen A.A. (1961). Fluctuation in Excitability, Drukkerjj Holland N.V., Amsterdam.

[22] West B.A., Brummett R.E., & Himes, D.L. (1973). Interaction of kanamycin and ethacrynic acid. Arch. Otolaryngol. 98, 32-37.

[23] Wilson B.S. (1997). The future of cochlear implants. British Journal of Audiology, 31, 205-225.

[24] Wilson B.S., Finley C.C., Zerbi M., & Lawson, D. (1995). Eleventh Quarterly Progress Report, Speech Processors for Auditory Prosthesis, NIH Contract N01- 2-2401.

[25] Xu J., Shepherd R.K., Millard R.E., & Clark G.M. (1997). Chronic electrical stimulation of the auditory nerve at high stimulus rates: a physiological and histopathological study. Hear. Res., 105, 1-29.

[26] Yamane H., Marsh R.R., & Potsic W.P. (1981). Brain stem response evoked by electrical stimulation of the round window of the guinea pig. Otolaryngol. Head Neck Surg., 89, 117-124.