The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #5

Reporting Period: May 1, 2002 – July 31, 2002

Contract N01-DC-1-2108

Submitted to Neural Prosthesis Program

National Institute for Neurological Disorders and Stroke

National Institute for Deafness and Other Communication Disorders

National Institute of Health

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ABSTRACT

The principle activities of the team during this reporting period were focused on: 1) experiments and analysis of results on quantifying the selectivity of stimulation of the auditory nerve using electrically evoked, auditory brain stem response (eABR) overlap as the index of selectivity. 2) Histological analysis of chronically implanted cat auditory nerves. 3) Measurement of frequency maps of auditory cortex resulting from acoustic stimulation. 4) Development and *in vivo* evaluations of 'backpack' stimulators to be used in long-term stimulation of chronically implanted auditory nerve via 'Utah Electrode Arrays' . 5) Preliminary attempts at recording brainstem responses evoked with a ball electrode positioned on the auditory nerve in human subjects undergoing resections of acoustic tumors.

1. INTRODUCTION

1.1. PROJECT GOALS

This contract has three specific aims: 1) develop an array of microelectrodes that is suitable for implantation into the auditory nerve, 2) determine the functional potential for this technology to provide a useful sense of hearing, 3) evaluate the risks and benefits of this technology prior to human experimentation. Activities in the first year of this contract concentrate on validating our proposed technique for accessing the auditory nerve, estimating the dimensions of the arrays that can be implanted, and determining the spatial independence of the implanted electrodes. The second year will concentrate on other measures of the functional independence of the electrodes as well as the long-term biocompatibility of the array. The final year of the contract will finish the functional independence studies and center around the chronic electrical stimulation experiments.

1.2. PROGRESS REVIEW TO DATE

Surgical Access: We have demonstrated a viable surgical access that allows placement of the Utah Electrode Array (UEA) into the feline auditory nerve. This allows us to use cats in our acute and chronic experimentation. We have also demonstrated a viable surgical access that allows insertion of the UEA into auditory nerve in cadaveric human temporal bones. These accesses should permit insertion of 20 electrodes in a 1.8mm x 2.2 mm array configuration (for 400 micron spaced electrodes), or 80 electrodes in a 200 micron spaced array.

eABR Electrophysiological Experiments: We have demonstrated that high velocity implantation of the UEA into the auditory nerve can be accomplished without significant harm to the nerve. This was demonstrated by recording electrically evoked auditory brainstem responses (eABR's) that were evoked by currents injected via a UEA that had been implanted into auditory nerve. Stimulation current thresholds for evoked eABR's have been found to lie in 10μA-50μA range. We were able to record eABR's for up to 52 hours in one acutely implanted cat before the experiment was terminated.

Cortical Mapping Experiments: We have demonstrated that we are able to implant UEA's into cat auditory cortex, and that we are able to record single- and multi-unit responses to acoustic stimulation. In our six most recent experiments, we recorded acoustically evoked single- and multi-unit responses from an average of 69 of the 100 electrodes in the implanted array.

Measurements of auditory nerve dimensions in human cadaveric material: We have measured the diameter of the auditory nerve using MRI measurements and compared these estimates with physical measurements of the same nerves. MRI estimates typically underestimate auditory nerve diameter by 32%.

Stimulation selectivity: We have developed a technique by which we can estimate the extent of stimulation overlap in a pair of electrodes implanted into the auditory nerve. The technique uses paired sequential stimulation via two electrodes and monitoring of the eABR recorded with needle electrodes. With short interstimulus intervals (the second stimulus delivered within the refractory period of the first stimulus), stimulus selectively is reflected in the amplitude of the second eABR. We have seen some electrode pairs with virtually no stimulated fiber overlap, and others with considerable overlap.

2. WORK PERFORMED DURING REPORTING PERIOD

2.1. ANIMAL EXPERIMENTS

2.1.1 Stimulation selectivity

One of the primary motivations underlying this contracted research program was the validation of the hypothesis that penetrating electrodes, inserted into the auditory nerve can achieve much more focal stimulation of the auditory nerve than can electrodes on arrays inserted into the cochlea. If this is the case, then it is further postulated that focal stimulation could result in much more selective activation of discrete frequency percepts than could be achieved with cochlear electrodes. Much more selective activation of AI would allow the implantation of higher electrode count arrays, which would recreate a richer auditory perceptual space. We have recently conducted a set of experiments that we feel provides insights into the issue of the selectivity of auditory nerve fiber stimulation.

The experiments are based upon two observations: first, activation of a subpopulation of auditory nerve fibers evokes a measurable eABR, and second, this subpopulation of fibers is refractory to a second stimulus delivered within 350 usecs of the first stimulus. Both of these premises have been reported in the literature (1), and tested in our pilot experiments. Our tentative validation of these premises were described in our progress report #4. If two electrodes are inserted into the auditory nerve, and these two electrodes excite *the identical population* of auditory nerve fibers, then the two eABRs evoked by sequential stimulation via each electrode will be very different. The first stimulus will evoke a measurable eABR. The second stimulus, if delivered within 350 usec of the first will evoke no eABR (the fibers will be refractory). If, on the other hand, the two electrodes excite *completely independent subpopulations* of auditory nerve fibers, then the eABR evoked by the second of the two sequential stimuli will be unaffected by the first stimulus. These hypotheses have also been demonstrated in pilot experiments described in our previous progress report. Thus, the size of the second eABR evoked by paired sequential stimuli delivered through a pair of electrodes inserted into the auditory nerve provide us with an index of independence of fibers excited by currents injected via these two electrodes.

Over this past quarter, we have conducted two additional experiments designed to further validate this approach, and to extend the data set to many pairs of electrodes in UEA's implanted in the cat auditory nerve. We have used our custom built, computer controlled, constant current

stimulator and our custom eABR recording instrument to perform these experiments. We have generated over 10,000 separate data records each of which describes the set of averaged eABR responses evoked by stimulation via a pair of UEA electrodes at particular current levels and at particular interstimulus intervals. While the analysis of this data set is not yet complete, the data validate the findings observed in our preliminary experiments, and described in our previous progress report. The results of these experiments will be described when the analysis of this large data set has been completed (in progress report #6).

2.1.2 Histological studies of implanted cat auditory nerve.

A necessary, but not sufficient, condition upon which an auditory nerve based auditory prosthesis can be built is that a multielectrode array can be implanted into the auditory nerve, and that it will remain implanted in the nerve for prolonged periods. This condition can be (and will be) validated in chronic electrophysiological experiments, or using anatomical studies of nerves that have been implanted with a UEA for a prolonged period (2-7). To achieve this demonstration, we have implanted UEAs into the auditory nerves of thirteen cats, and allowed them free roaming in gang housing for a period exceeding six months for each cat. The animals have been sacrificed using high doses of anesthetics, followed by cardiac puncture and perfusion with Formalin.

In all specimens, at the time of sacrifice, a visual inspection was performed on the site of implantation and of the explanted UEA. In all cases there was no indications of visual hemorrhage into the implanted site as evidenced by both unaided eye examination of implanted site as well as microscopic examination with 40x magnification. None of the explanted UEAs had any broken electrodes and the microelectrode morphology was undistinguishable from unimplanted UEAs under 40x magnification. This indicates that the electrodes did not shatter against the medial side of the modiolus on implantation.

Our anatomical analysis of the specimens has yet to be completed, but we are using three techniques to visualize the electrode array location with respect to the auditory nerve. We have used conventional photography of dissected material, planar X-ray visualization, computed X-ray tomography, and hemotoxylin and eosin staining of decalcified temporal bone samples. Examples of a sample implanted auditory nerve is provided in figures 1a and 1b below.

In order to develop and refine our histological techniques, we have focused our efforts on only a single specimen. After harvesting the temporal bones of this specimen, gross inspection revealed that the UEA was located in the internal auditory canal (see figures 1a and 1b). The implant date of this specimen was October 26, 2001 and the date of sacrifice and dissection was July 10, 2002. Therefore, after approximately eight months post-implantation, the UEA remained visibly implanted into the auditory nerve.

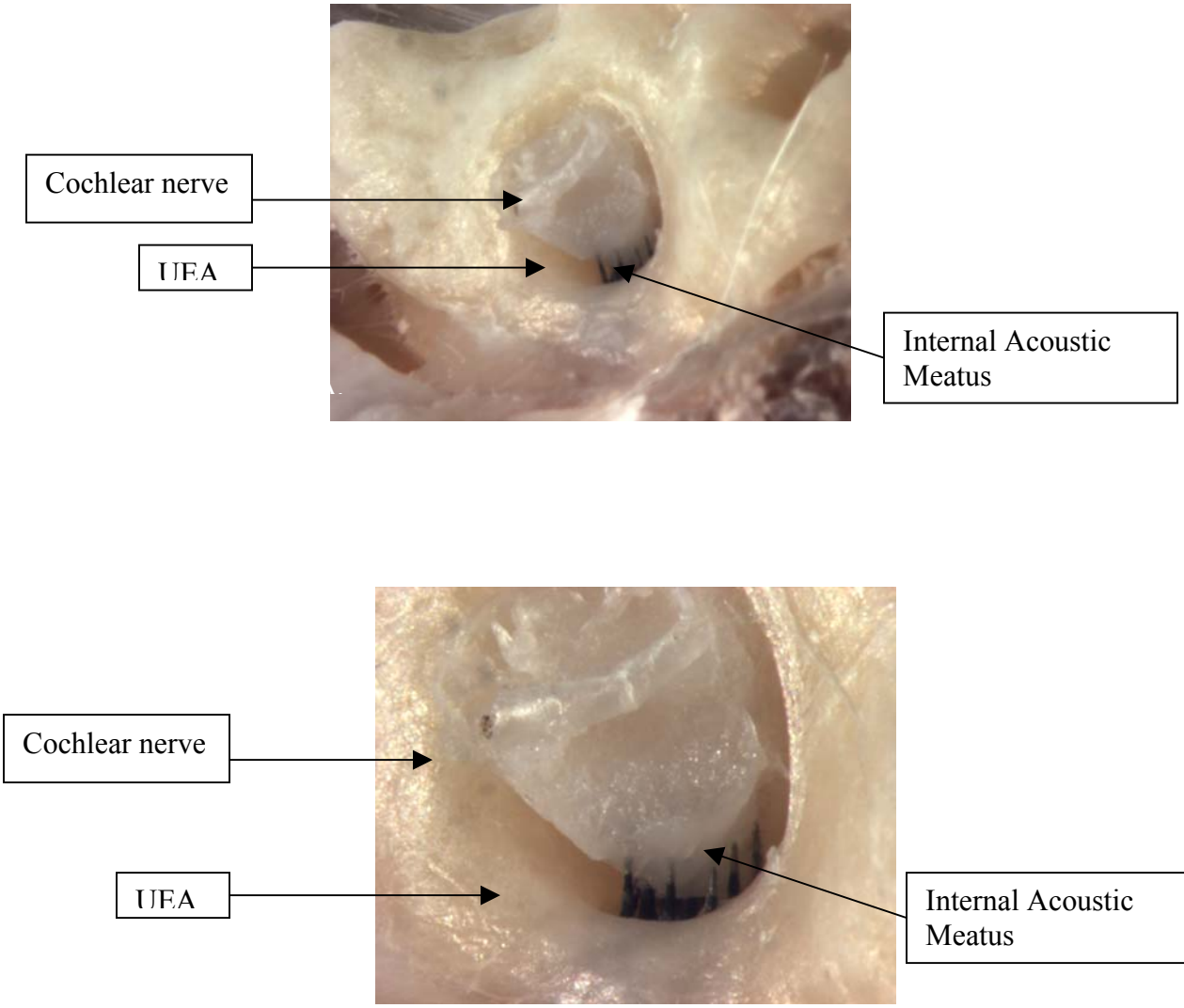

Figure 1. a). Medial view of the right temporal bone (approximately 8.5x magnification). b) Medial view of the right temporal bone (approximately 18x magnification).

To determine the microscopic response of the nerve tissue to long-term implantation, we have developed the following protocol for tissue preparation and analysis. The temporal bones of an implanted and Formalin fixed specimen are harvested by dissection. The temporal bones are then decalcified in a 5 % formic acid solution. The solution is changed every two days. After one week, the tissue is usually decalcified. Endpoint decalcification varies slightly based on bone density and size and is reflected in the mechanical compliance (measured by feel) as the decalcified tissue becomes very flexible. After decalcification, the tissue is dehydrated, embedded in paraffin wax, and cut in 15 μm sections. The sections are then stained with hematoxylin and eosin to reveal the different types of tissue.

Initial results from the tissue sectioning have shown that it is possible to preserve gross structural and cellular detail through the decalcification procedure. The tissue sections clearly show many landmarks of the temporal bone. We plan to continue tissue sectioning as explained above with a goal of visualizing the electrode tracts of the UEA in the cochlear nerve. Visualization of the tracts will verify the presence of the UEA in the nerve over 6-10 month periods of time and offer insights into the response of the tissue to the implant. The tissue sections will then be treated with a variety of histochemical stains that will differentially stain for connective tissue or myelin to determine different tissue responses to the implant.

2.1.3 Unit recordings from cat auditory cortex with UEA.

A second means of establishing the degree of independence of the nerve fibers in the auditory nerve is to map the regions of primary auditory cortex that are activated when currents are injected into the auditory nerve via each of the electrodes implanted into the nerve. As a prelude to this experiment, we have demonstrated that we can map the tonotopic organization of AI using UEA's acutely implanted in AI.

Because of the success of the auditory nerve fiber overlap experiments described in section 2.1.1, the impetus for conducting these experiments has decreased somewhat. However, because the eABR experiments will not allow us to map the frequency space accessed by stimulation of each of the electrodes implanted in the auditory nerve, we will continue to pursue the cortical mapping experiments, but at a later time frame. Another motivation behind this decision is our need to recruit another research assistant who can help us with these experiments. This is a result of the

relocation of Dr. Sri Nagarajan from the University of Utah to the Radiology Department at the University of California School of Medicine in San Francisco. Dr. Nagarajan was responsible for our cortical mapping experiments, and he will continue to provide oversight on these experiments via quarterly visits to the University of Utah, and via telephone. The entire set of auditory mapping instrumentation necessary to conduct these experiments (sound proof chamber, acoustic stimulus generators, custom stimulating software, etc) has remained in Utah, and during this quarter we have conducted one mapping experiment to ensure that this instrumentation is fully functional and complete. We have begun searching for an individual who will be able to carry on the mapping experiments under Dr. Nagarajan's and Dr. Normann's join direction of this project. The recruitment and subsequent training of this individual is expected to take at least six months.

2.1.4 *In vivo* evaluation of backpack stimulators.

We have evaluated our portable stimulator in two cat implantations to date. The percutaneous interconnection of the implanted electrode array with the stimulator has proven to be more difficult than we had originally anticipated. For purposes of evaluation of the portable stimulators, we have implanted the auditory cortex of two cats with 100 electrode Utah Electrode Arrays, and have tried two different transdermal interconnection schemes in an attempt to optimize this percutaneous interconnection. The interconnection schemes differed in the way the lead wires entered the stimulator box: in one design the lead wires entered the end of the stimulator, and in the other design the lead wires entered the top of the box. The implant system consists of a 100 electrode UEA and 16, one mil diameter gold lead wires about 2" long that are connected to an intermediate interconnect board. This interconnect board provides a transition between the delicate wires going to the UEA, and the more robust wires going to the stimulator, and also a site that allows fixation of the implant system to the skull. Sixteen, five-strand copper wires are connected to the opposite end of the interconnect board and these are inserted inside a silicone tube and brought out to a 26 pin connector. The connector mates with a male connector on the stimulator and provides a 'quick connect' function if the cat snags the tube. A Dacron grommet is glued to the silicone tube with 2-part silicone elastomer and provides a region for tissue ingrowth on the tube to secure it to the neck of the cat. Strain relief in the interconnect

system was designed to be achieved by the length of the tube between the tube's exit site on the cat's neck and the stimulator.

The cats were implanted and the interconnect system checked on a periodic schedule. Electrode impedances were monitored to determine lead breakage. Unfortunately, neither design has proven to be satisfactory. The lack of sufficient strain relief in the lead design has lead to wire breakage in both designs, and in catastrophic failure in one design (all multistrand wires broke over the course of one night). The transcutaneous passage of the tube through the skin also appeared to be a problem in both animals: there were signs of infection in the tubes and around the implant sites, even though the cats did not manifest any sign of discomfort.

2.2 HUMAN EXPERIMENTATION

2.2.1 Electrically Evoked ABR

The surgeon on our team (Dr. Shelton) routinely perform evoked potential monitoring in various skull base surgical cases. In three recent acoustic tumor cases, we attempted to obtain ABR recordings using electrical stimulation rather than the typical acoustic stimulation. The facial nerve stimulation probe was used to provide the stimulus at a 0.05 – 0.10 milliamp level. The stimulation rate was 11/sec and the stimulation duration was set at 500 microseconds. One thousand repetitions were averaged. To date, we have not obtained any reliable responses. The first case had difficulty due to problems with stimulus synchronization. All of the cases had hearing that was poor and the ABR may have been unobtainable because of the poor condition of the cochlear nerve due to tumor involvement.

2.3 INSTRUMENTATION and TRANSCUTANEOUS INTERCONNECTIONS

2.3.1 Portable Stimulator.

Our need for a portable stimulator to be used in the 60 hour electrical stimulation requirement of the contract has motivated us to develop a hybrid digital/analog system with colleagues in Spain. Unfortunately, progress in the development has proceeded slowly due to poor availability of VLSI components. This has caused us to design and fabricate a simple hybrid analog/digital

based stimulator in our Utah laboratories. The wiring diagram of the stimulator is shown in figure 2 below.

The stimulator is controlled by a low power PIC microcontroller which is operated in either a sleep mode (8 hours/day) or in stimulation mode (16 hours/day). The PIC produces two sequential pulses on RB0 and RB1 which are fed to the inputs of the differential amplifier. Thus, the output of the stimulator is a +/- 9 volt 100 usec biphasic pulse, delivered at 30 pulses per second. In order to convert this voltage pulse in to a current pulse, each of the 16 stimulated electrodes has a series resistor connected to it. The value of each resistance has been matched to each electrode to deliver either 10 uamp, 30 uamp or 100 uamp pulses to the electrode to which it has been connected. While this is not a true constant-current design, we have adopted its use due to the simplicity of the circuit, its compact size, and long battery life. We have used a blocking capacitor to minimize any non-zero output offset voltages from the op amp. To conserve space and weight, the stimulator is powered by two sets of CR2032, 3VDC button batteries that provide +/- 9VDC. The PIC is powered by a single CR2032 button battery. These 'off the shelf' batteries provide about a 25 day operating life. The case of the stimulator has contact points that allow monitoring of battery voltages and stimulator operation.. The size of the stimulator is 10.3 cm x 6.5 cm x 1.9cm, and the entire system with batteries weighs about 50 grams. The size and weight of the stimulator is easily carried by the implanted cats and appears to be well tolerated by them.

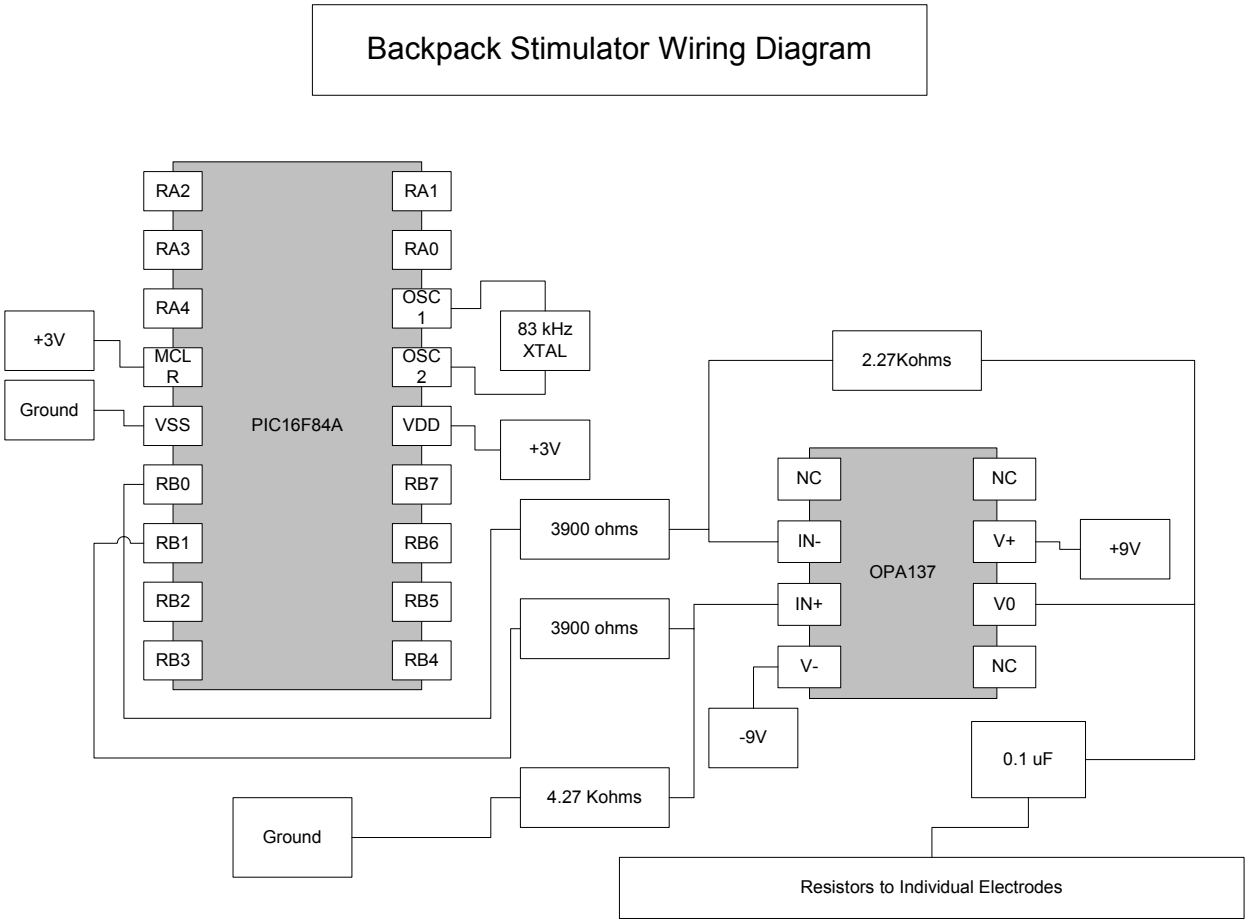

Figure 2. Wiring diagram of the Utah designed portable stimulator.

2.3.2 Cat Backpacks

We have designed and built custom backpacks which carry the portable stimulator. The backpacks, shown in figure 3 a and b are built from fabric enclosed foam, and are secured to the animal by a collar, straps around each forelimb, and a strap around the animals chest. The straps are fully adjustable and provide a secure mounting of the backpack to the animal. The top surface of the backpack contains a 1.5 x 2 inch Velcro patch that is used to mount the stimulator, and a separate Velcro strap that surrounds the mounted stimulator for added security. The bottom of the stimulator contains a Velcro patch that mates to the backpack. The animals that are to be implanted and chronically stimulated are fitted to their backpacks and stimulators and the animals wear the backpack for at least a week prior to its implantation. The animals manifest

no signs of discomfort nor distress when wearing these backpacks. Thus, we are quite satisfied with their design and construction.

Figure 3. a) Side view of backpack. B) top view of backpack and portable stimulator.

3. PLANS FOR NEXT REPORTING PERIOD

3.1. ACUTE ANIMAL EXPERIMENTS

3.1.1 Auditory nerve stimulation selectivity

We will complete the analysis of the two auditory nerve stimulation overlap experiments we have done. Depending upon the results of this analysis, we will likely conduct one or two more such experiments (the eABR thresholds in our last two experiments were higher than typical, but they are still useful in quantifying auditory nerve fiber overlap between pairs of implanted electrode). This experimentation, analysis and manuscript preparation is expected to require significant effort over the next one to two quarters.

3.1.2 Acute AI mapping.

Because of the relocation of Dr. Sri Nagarajan from the University of Utah to the University of California in San Francisco, progress in acute cortical mapping has been slowed. However, we did complete one acute mapping experiment over this quarter, and we are now looking for a graduate student who can carry on this work (still under the co-direction of Dr. Nagarajan and

Dr. Normann). Work in this area is considered to be somewhat less of a priority due to the success of our eABR overlap experiments. We plan to recruit a research assistant who will work on acute cortical mapping during this next one to two quarters.

3.2. CHRONIC ANIMAL IMPLANTS

3.2.1. Passive implants.

We will complete our histological evaluation of the implanted auditory nerves. Histology will be conducted in the pathology department at the University of Utah, at the pathology laboratory at the VA hospital, and/or by Dr Fred Linthicum, Jr. at House Ear Institute who has agreed to participate in the experiments.

3.2.2 Active implants.

We will redesign our chronic stimulation system to make it more robust and less prone to infection. We are considering the use of the implanted electrode array system we have used in our previous chronic recording experiments: a Microtech connector, mounted in a titanium pedestal which is bolted on the top of the animals skull. This has proven to be a robust and infection free approach to percutaneous interconnection in the cat. The only negative with this approach (and the reason we didn't first use this approach) is the loop of wires coursing from the connector to the stimulator. However, we have seen that this doesn't seem to be a significant problem (at least in the two cats implanted to date). We will test this new design in an additional pair of cats that will be implanted in auditory cortex (simply for ease of implantation). If the Spanish portable stimulators are completed during this quarter, we will evaluate them in bench tests, and, if acceptable, replace our in-house stimulators with the superior Spanish design.

3.3 HUMAN EXPERIMENTATION

We will continue our preliminary experiments on electrical stimulation of the human auditory nerve using a ball electrode and monitoring evoked responses with a commercial signal averaging system (Nicolet). This monitoring is used by the surgeons to assess the degree of

auditory nerve function in individuals with tumors in the region of the 8th nerve. While we have not been successful at achieving eABRs in the prior three experiments, we are hopeful that subsequent experiments will allow us to determine threshold currents for direct auditory nerve stimulation. These human experiments will allow us to later place the Utah array acutely in these same types of patients and record ABR responses by stimulating the device. The experiments will also facilitate the development of eABR monitoring capabilities in the noisy environment of the operating room.

4. PUBLICATIONS AND PRESENTATIONS

No publications/presentations have been made over this quarter. However, the PI has been invited to present a platform presentation at the 2003 Asilomar meeting, and we look forward to presenting our work at this venue.

5. DISCUSSION

We are pleased with the progress we have made over the past five quarters. Two new Otolaryngology residents have joined in our work over the past quarter (Dr. Richard Kennedy from Australia, and Dr. Junghwan Park from Korea), and we have a new graduate student and a medical student who will be conducting the histological analysis of our auditory nerve implant material. The recent relocation of Dr. Nagarajan to UCSF will also impact our cortical mapping experiments, but he will continue to advise us on this work both by phone and by quarterly visits to Utah.

We look forward to the chronic auditory nerve stimulation experimentation, and feel that the portable stimulators and the backpacks that support them will provide us with functional systems with which to perform these experiments. We have yet to develop a robust chronic percutaneous interconnect system which will be used in these experiments, and this will be worked on this quarter.

6. LITERATURE CITED

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