The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #1

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Abstract

In this initial reporting period for this contract, the team at the University of Utah has initiated activities in three areas: determining the dimensions of an array of microelectrodes that would fit in a human auditory nerve, developing a transbulla approach to the modiolar portion of the auditory nerve, and validating that an array of microelectrodes can be pneumatically inserted into the auditory nerve of our animal model. At this time, the cadaveric human work is progressing well while the evaluation of the functionality of the nerve after implantation has been completed with observations out to 30 hours post-implant. Principal activities for the upcoming reporting period are addressing the spatial selectivity of microstimulation through our array, developing a "slant" electrode suitable for implantation into the nerve, and initiating long-term chronic implants to assess the structural and materials biocompatibility of the array.

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, the dimensions of the array that will be implanted, and 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

This is the first quarterly progress report.

2. WORK DURING REPORTING PERIOD

3.1. Array Development

The Utah Electrode array is a mature technology in the sense that it has been used by a number of laboratories in addition to the Center for Neural Interfaces at the University of Utah. Modifications to the array for this contract include using a rectangular 3x4 or 5x5 grid of electrodes attached by platinum-iridium wires to a Microtech connector. We have also had to make a number of minor adjustments to the pneumatic inserter to make it fit into the small surgical access. These changes have been to the configuration of the inserter head to make it smaller to that it is possible to visualize the implant positioning.

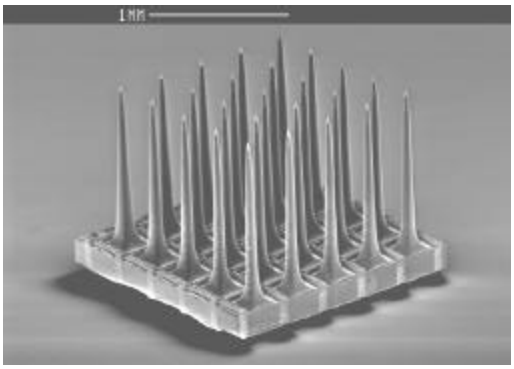

Figure 1: The Utah Electrode Array

3.2. Animal Acute Experiments

Surgical Access in Animal Model

This part of the study was conducted in 6 cats (Felis catus). Animals were treated in accordance with guidelines of the Institutional Animal Care and Use Committee of the University of Utah, Salt Lake City, UT. Anesthesia was induced using a 1:1 combination of tiletamine HCl and zolazapam HCl (9 to 12 mg/kg, intramuscularly). The animal was intubated and general anesthesia maintained by Halothane inhalation (0.5% - 1.5%). Maintenance of the depth of anesthesia and vital signs were periodically assessed. Lactated Ringer's solution was administered intravenously (8-12 mL/kg/hr) through an intravenous cannula in the arm to compensate for blood loss. A warmed water blanket was used to prevent hypothermia. The surgical site was prepared by shaving the ventral and lateral part of the neck. Surgical exploration was done using the transbulla approach in the anesthetized cats. An initial Auditory Evoked Brainstem Response (ABR) was performed to rule out deafness in the cats, the method of performing ABR is described below. The cat was placed in a specially designed head

holder in a left lateral position with the head facing anteriorly and extended; this facilitated surgical access to the tympanic bulla.

Dimensions of the exposed nerve were measured as described in the human temporal bone studies. We also attempted to measure the spontaneous electrical activity in the modiolar nerve using a WPI tungsten microelectrode (0.5 MW impedance at 1 kHz) in 21 different sites and at different depths of the modiolar nerve in one preparation. We were able to obtain spontaneous action potentials in the nerve at all sites and depths. The neural activity was recorded differentially between the WPI electrode and a Ag/ AgCl electrode placed in the middle ear as a reference. The differential signal was amplified 5,000 times using a commercially available system (Neural Signal Acquisition System, Bionic Technologies LLC, Salt Lake City, UT). Each channel was high and low pass filtered with cutoff frequencies at 250 Hz and 7.5 kHz, respectively. The filtering reduces noise and minimizes distortion of the action potential spikes. The filtered signal was digitized at 30,000 samples/sec using a 16-bit ISA card and the data stored for offline unsupervised statistical spike classification using mixture modeling techniques [1, 2, 3, 4]. The sorted spikes were plotted and results compared to published spike characteristics.

Serial ABRs and Electrically Evoked Auditory Brainstem Responses (EABRs) were obtained in three cats to demonstrate nerve survival throughout the surgery. Serial measurements of ABRs were done before the start of the surgery, after exposure of the bulla and after bullostomy. EABRs were obtained by placing a ball electrode (Standard Prass monopolar stimulating probe with a flush 0.5mm tip diameter, Medtronic Xomed Surgical Products, Inc., Jacksonville, FL USA), on the round window, in the scala and on the exposed modiolar nerve. EABRs were also measured by stimulating a single WPI tungsten microelectrode (0.5 MW impedance at 1 kHz) inserted into the modiolar nerve. For all EABRs, the nerve was electrically stimulated with a charge balanced biphasic waveform of amplitudes ranging from 2mA to 350mA with 75mS per phase. The pulse

was generated using a Grass S88K Stimulator and the stimulus was delivered by using a pair of Grass PSIU6 photoelectric stimulus isolation units (Grass Instrument Division, Astro-Med, Inc, West Warwick, RI, USA), the nerve was stimulated cathodically with the return placed in the clavotrapezius muscle. Both the ABR and EABR were measured using a commercial ABR system, Navigator SE (BioLogic Systems Corp, Mundelein, IL, USA). The ABR/ EABR measuring electrodes were placed intradermally as described by Achor et al. [5]; the brainstem response was measured differentially across the vertex and the base of the pinna with a distant ground in the neck. The signal was amplified 100,000 times and signal averaged across 1,024 stimuli. The resultant waveforms were compared with published literature and the waveform peaks identified by two independent experts. Presence of a consistent positive deflection in Wave I and Wave III was defined as threshold, this was done to avoid the variability reported in latency of negative deflection of Wave II [6].

A dummy UEA was implanted in the exposed modiolar nerve to assess the possibility of implantation. In each surgical exposure a UEA of 4x5 (20 electrodes) configuration was carefully positioned on the modiolar nerve using a micromanipulator and implanted using a process of rapid pneumatic insertion [7]. The rapid pneumatic insertion used a ‘spacer’ that facilitates insertion to a predetermined depth of 1 mm into the nerve.

After the experiments, the animals were euthanised using 5 ml of 3M KCl administered IV.

An incision was made just medial to and parallel with the digastric muscle in the ventral aspect of the neck. The incision was approximately 7 cm. long and located directly over the hollow bulla, the tympanic part of the temporal bone. The skin, subcutaneous tissue, platysma and mylohyoid muscle were incised; the bulla was exposed by blunt dissection between the digastric, the styloglossus and hyoglossus muscles. Care was taken not to damage the hypoglossal nerve, the anterior lobules of the sublingual salivary gland, and the internal maxillary vessels. The lingual artery which is lateral to the

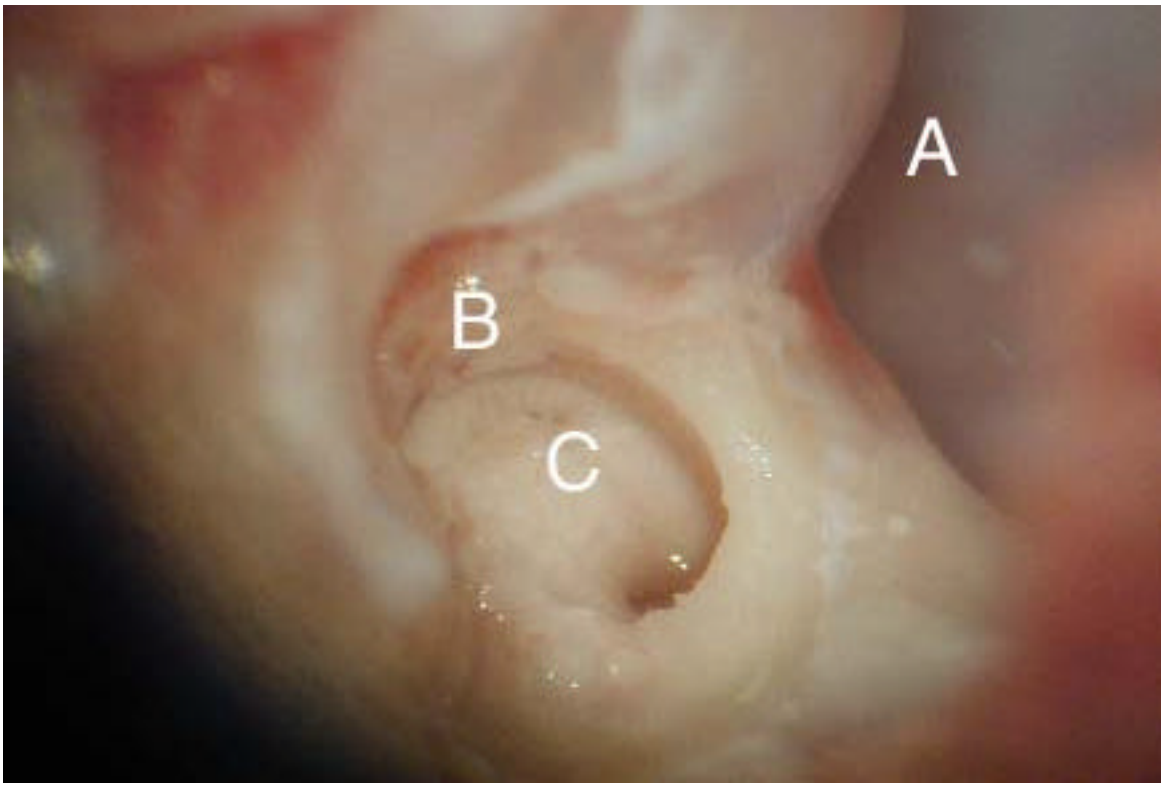

Figure 2: Surgical Access in Cat. (A) Middle Ear cavity. (B) Basal turn of the cochlea. (C) Exposed modiolar portion of CN VIII.

hypoglossal nerve was spared. The base of skull was thus exposed. A 2 cm diameter access in the bulla was made using a rotary burr tool mounted on a dental drill. Saline was used for regular suction- irrigation to prevent dehydration of tissues and heating up of the cutting and diamond burr. The mucosa internal to the bulla was freed with alligator forceps, which allowed visualization of the round window in the posterolateral wall of the bulla. This provided us access to the cavity of the middle ear without damage to the tympanic membrane. The location of the round window was verified by identification of the promontory and the attachment of the stapes to the oval window. The round window was drilled with a diamond burr under a surgical microscope to reach the basal turn of cochlea. The access was expanded by further drilling to expose the modiolar bone. The modiolar bone was thinned out and the bone fragments picked with a Rosen needle to expose the modiolar portion of the VIII nerve. Figure 3 shows a magnified photograph of a typical exposure of the cat modiolar nerve using the above

procedure. The modiolar nerve is seen emerging out of the basal turn of cochlea; we expect this portion of the nerve to have purely auditory fibers. Given these results, the cat was chosen as a good animal model and the transbulla approach was chosen over the middle fossa approach.

Validation of Nerve Functionality

Serial ABR and EABR at different stages of the surgery demonstrates nerve survival during the surgery. Figure 4 shows sample ABR/ EABRs from a cat to suprathreshold stimuli at different stages of surgical exposure. The presurgery ABR was done to rule out any hearing loss in the cat. Although the presence of EABRs after the opening of the modiolus would have been sufficient proof regarding the nerve survival, we recorded EABRs to stimulation at surgical stages before that to pinpoint the stage of failure and validate the stimulation and recording system before modiolar stimulation was attempted. The waveform shapes corresponded to the latencies

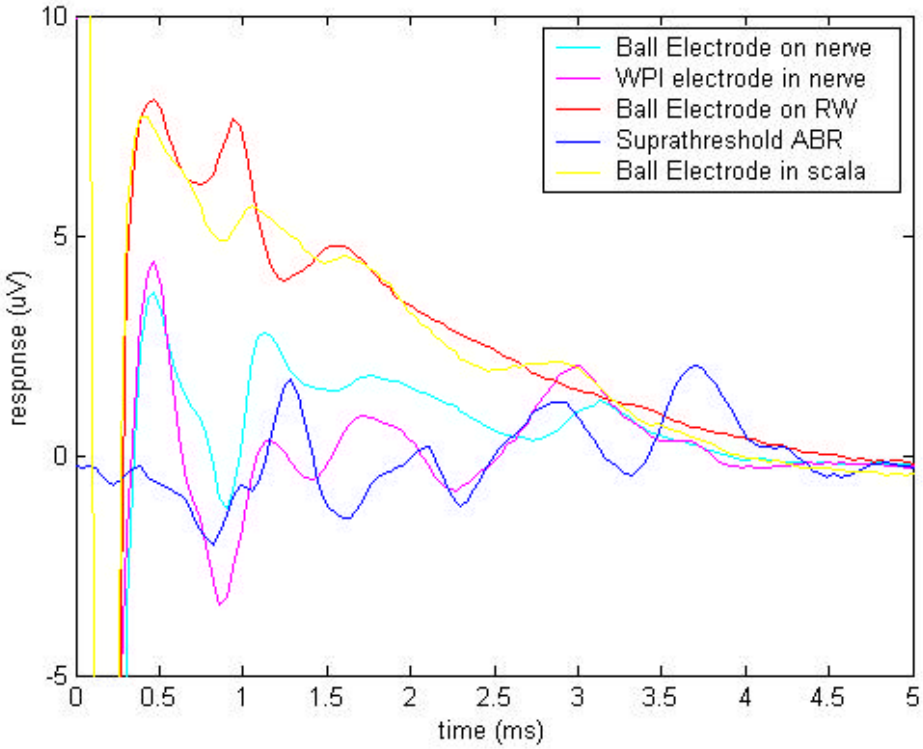

Figure 2: ABR and Serial eABR Recordings. The ABR stimulus was suprathreshold (150% threshold) and the response was averaged over 1024 trails. The EABR shown were recorded by presenting suprathreshold biphasic stimuli with 75 ms per phase at each site. Again responses were averaged over 1024 trials.

suggested by Achor et al [5] and to the waveforms published in Black et al [8] and Simmons et al [9]. The presence of independently identifiable and consistent peaks in the EABR at each stage of the surgery suggests that the nerve was intact at each stage of the surgery. Table 1 shows that the thresholds for stimulation were within limits of published results for the electrodes used [9, 10]. The variation in thresholds in comparison to published data can be attributed to the different biphasic pulse durations used in the experiments and intra species differences.

In our experiments we note that the thresholds decrease as we get closer to the modiolar nerve, with the lowest threshold being for intraneural stimulation using the single WPI electrode. This indicates that the thresholds for intraneural stimulation using the UEA is likely to be close to 8 mA with 75 ms biphasic stimulation pulse.

Table 1 Comparison of stimulation site and thresholds

Location of electrode	***Experiment Thresholds***	***Published thresholds***
Round window using ball electrode	400 μA, 75 μs biphasic	300 μA, 500 μs monophasic [10]
Scala using ball electrode	300 μA, 75 μs biphasic	110 μA [9] 200 μA 500 μs monophasic [10] 100 μA, 100 μs biphasic (using Teflon® coated wires)[6]
Surface of modiolar nerve using ball electrode	150 μA, 75 μs biphasic	—
In modiolar nerve using WPI electrode	8 μA, 75 μs biphasic	—

We were also able to record spontaneous action potentials in one preparation when we attempted to record the modiolar nerve activity. Figure 4 shows the spontaneous action potentials recorded from the nerve. The characteristics of

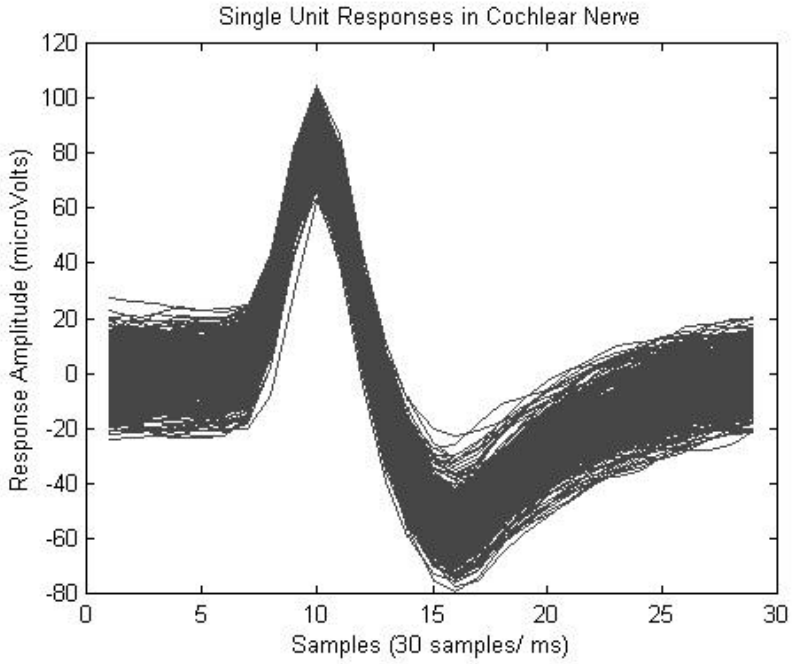

Figure 4: Action Potentials in Auditory Nerve. Spontaneous sorted and time aligned action potentials recorded from the modiolar nerve of a cat using a single tungsten electrode. The response amplitude of the amplified action potentials is shown in microvolts and the time is represented in samples per millisecond. Given the sampling frequency of 30kHz, the time window is 1 ms.

the action potentials were compared to the typical action potentials in published data [11, 12] and we conclude that the spike characteristics are similar to them. Though this is an anecdotal observation, it also indicates nerve survival after surgery.

Non-Functioning UEA In Cat Nerve

The measurement of nerve dimensions was crucial, as we wanted to show that the size of the cat modiolar nerve is comparable to human modiolar nerve. The dimension of the exposed nerve would also dictate the dimensions of the UEA that could be implanted and hence the number of electrodes in the implanted array. The diameter of the exposed nerve was 1.64 + 0.07 mm (n=9) and the length was 2.5 + 0.11mm (n =9) as measured with a WPI electrode mounted over a micromanipulator. We implanted non-

functional but otherwise geometrically accurate UEAs in all exposed modiolar nerves to examine the feasibility of such implantation. This exposure was adequate to accommodate a 4x5 UEA of 400 mm spacing used in the study, without any insertion difficulty. There was an adequate area in which to work and we could gain perpendicular access to the nerve. The inserter spacing at 1 mm allowed us to insert the array to a depth of 1 mm from the nerve surface. The array was explanted and examined for broken electrodes. No broken electrodes were detected. This indicates that the array did not shatter against the medial side of the modiolus on implantation. However, given the exposed nerve dimensions it should be possible to implant 6x10 UEA with 200mm electrode spacing.

3.3. Human Temporal Bone Studies

Human anatomical studies were done in the Temporal Bone Lab of the division of Otolaryngology, Head and Neck Surgery at the University of Utah. Two human temporal bone surgeries were done using an operating microscope and a high-speed drill. The extended facial recess approach was modified to expose the modiolus.

Dimensions of the exposed nerve were measured with a World Precision Instruments (WPI) tungsten microelectrode (World Precision Instruments, Sarasota FL) having shaft diameter of 0.254 mm and a tip diameter of 1-2 mm, positioned with a calibrated micromanipulator.

Surgical procedures were done in 2 human temporal bones to establish access to the human modiolar nerve and to measure the dimensions of the exposed nerve. A post-auricular incision was made and flaps raised, the ear reflected anteriorly and a self retaining retractor used to expose the mastoid, a standard mastoidectomy was performed using a high speed drill and the promontory and the round window exposed by the extended facial recess approach. Next, a cochleostomy was performed by removing the bone of the round window, exposing the basal turn of the cochlea. The modiolar bone was thinned with a diamond burr and the thinned bone picked with an otologic pick to expose the nerve. Figure 2 shows a labeled photograph of

the exposed modiolar nerve in the left temporal bone. The exposure was not significantly more difficult than the procedure for implanting the CI, as both involve the extended facial recess approach, while the CI surgery exposes the scala, our technique is modified to expose the modiolar nerve.
Exposure by such a modified extended facial recess approach yielded a diameter of 2 mm and length of 3mm in two studies. This was adequate to implant the 4X5 Arrays used in this study, however, given the dimensions of the exposed nerve it would have been possible to implant 6x8 arrays (48 electrodes).

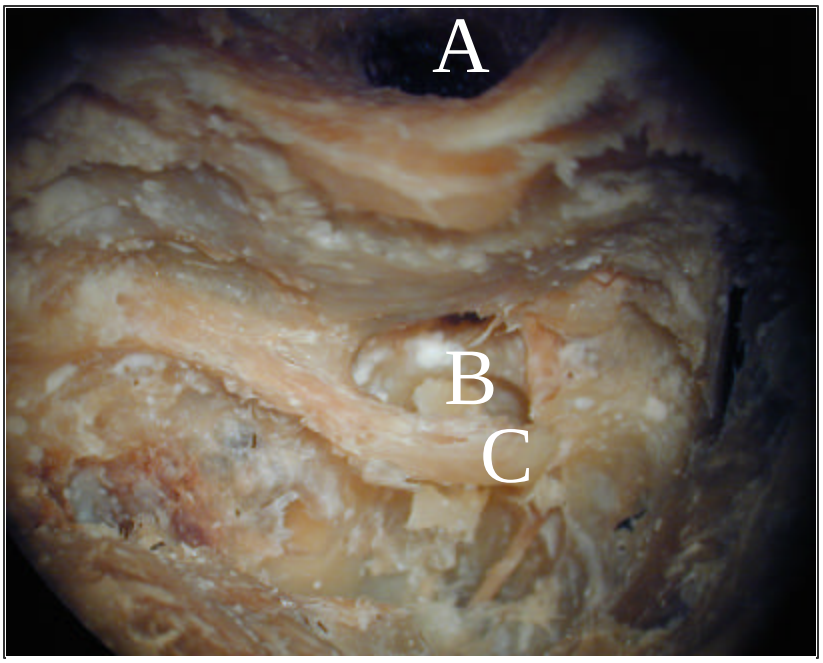

Figure 5: Human CN VIII Access. (A) External ear canal. (B) Cochleostomy. (C) Facial Canal.

3. PLANS FOR NEXT REPORTING PERIOD

3.4. Acute Experiments

3.4.1. CN VIII Stimulation

This quarter we will begin experiments to assess the spatial selectivity of microstimulation through electrodes of our array. Our original proposal, and one which we will continue to pursue, involves mapping evoked activity in primary auditory from stimulation of the auditory nerve. These experiments will be supplemented with experiments suggested by Drs. Terry Hambrecht

and William Heetderks of the NIH. These additional experiments will involve implanting the auditory nerve with an array, then exposing the auditory nerve as it enters the brainstem by means of a posterior fossa approach. Hook electrodes will be used to record compound action potentials resulting from stimulation of the nerve. Waveforms resulting from stimulation through single microelectrodes can then be compared with simultaneous stimulation through pairs of microelectrodes. We expect that these two methods will allow us to evaluate the electrical overlap in the stimulation fields.

We have purchased a programmable two-channel stimulator (STG-1002, Multichannel Systems GmBH) for these experiments and are currently building an analog multiplexing system to interface it to our array and Labview-based control software to synchronize the patterned stimulation and acquisition of the compound action potentials. This system will be integrated into an eABR acquisition system currently in development in order to consolidate all of the systems used in the collection of the data.

3.4.2. Histology

We have attempted an osmium stain of the auditory nerve to determine the distribution of the electrode tips in the nerve. An osmium stain is effective at highlighting changes in the shapes of the axons resulting from implantation of the array of electrodes. Our initial results were disappointing, likely for two reasons: extracting the nerve which is encased in the temporal bone is difficult and the three dimensional organization of the nerve makes cuts in the proper plane all the more important. Our plans in this area will include further osmium stains of both acute and chronic implants as well as other, traditional stains such as hematoxylin and eosin (for encapsulation). We will also need to refine our tissue preparation techniques, such as decalcification of the bone prior to sectioning, to better preserve the tissue and electrode tracks.

4. CHRONIC IMPLANTS

3.4.3. Passive Implants

With the encouraging results from the extended acute implants (>30 hours), we anticipate performing the first chronic implants of passive microelectrode arrays in the upcoming quarter. These implants will last either 6 or 12 months before the nerves are removed for histological analysis. In these experiments, we are principally interested in the response of the nerve fibers to the long-term placement of 20 microelectrodes and the effects of different closing techniques on the encapsulation response. We will study whether placing a Teflon© barrier (FEP, Dupont; Preclude, W.L. Gore and Associates) between the implant and the bone analog (hydroxyapatite) has a significant impact on the encapsulation of the array. A majority of these implants will be performed by a recent addition to the team Tony Owa, an otolaryngology fellow.

3.4.4. Stimulator Development

One of the significant technical issues with this contract will be the 60 hours of stimulation through the electrode array. We have received quotes from Neurocontrol about adapting their FES stimulators for this task but it is uncertain whether the stimulation rates will be sufficient to cause identifiable changes in the tissue. We are currently evaluating two other options in this area. The first is to adapt the multichannel stimulator developed by Phil Troyk to our stimulation requirements. The advantage of this approach is that this particular system was designed to stimulate microelectrodes and so it has sufficient compliance voltage and stimulation frequencies. The system also comes in a small enough package that it is reasonable to presume that a cat would tolerate its presence for the envisioned 8-hours/day of stimulation. The downside of this approach are that it would take a significant amount of time to build and debug the external “glue” logic required to program the stimulators.

We also continue to evaluate a stimulator developed by our collaborators in Spain, led by Dr. Eduardo Fernandez. As of this writing, we have received the prototype stimulator for evaluation. The system runs off of a 9-volt battery and has an expected lifetime of two weeks. The system did generate

trains of pulses on all of the electrodes but a problem with the programmable integrated chip (PIC) did not allow us to change the stimulation parameters. We have been assured that a replacement chip has been sent which will fix the problem. We look forward to a final evaluation of this chip prior to the initiation of the chronic stimulation experiments.

5. PUBLICATIONS

Two publications are in the works from work conducted to date. Arun Badi, M.D., has submitted a manuscript to Annals of Otolaryngology describing the surgical access in cats and work demonstrating the viability of the auditory nerve after the implantation. Todd Hillman, M.D., has also had an article accepted in Laryngoscope describing preliminary work in accessing the auditory nerve in humans. In addition, Dr. Badi has attended two professional meetings where he has presented his preliminary finding to the otolaryngology community.

6. DISCUSSION

For the three months covered by this report, we have made significant progress in determining the dimensions of the arrays that could be implanted into humans. We have also demonstrated that the process of rapidly inserting a number of microelectrodes into the auditory does not significantly impair the bulk function of the nerve for periods up to 30 hours. It will be interesting to see how our closing of the implant site affects these observations especially as a delayed inflammatory reaction resulting in swelling of the nerve could have a significant impact of the viability of the auditory nerve fibers. Although the transbulla approach we have adopted provides a much smaller access to the nerve than others, the ability to manufacture the Utah Electrode Array in a more dense configuration as well as change the length of the electrodes in a graded fashion should allow a significant number of electrodes to be placed in the nerve. Our upcoming results in the area of spatial independence of the electrodes should provide invaluable information of the upper limits of the density of the electrodes.

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